Achieving Cost-Effective Endoscopic Surveillance and Treatment of Barrett's Oesophagus

By

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“The pursuit of knowledge is more valuable that its possession”

- Albert Einstein

ABSTRACT

Oesophageal cancer has one of the lowest five-year survival rates among cancers at approximately 18-20% globally (21% in Australia). Adenocarcinoma is the most common variant among developed nations with majority Caucasian population, of which Barrett's oesophagus is the only known precursor. Oesophageal cancer detected under surveillance, prior to developing symptoms, has a five-year survival rate of more than 90%. This considerable survival benefit has prompted medical societies to recommend routine surveillance with endoscopic examinations for patients diagnosed with Barrett's oesophagus.

Endoscopic surveillance for Barrett's oesophagus, unlike Breast or Colorectal cancer, is not currently funded by Australian Department of Health as a surveillance program. This is likely because it has long been suspected not to be cost-effective. The progression rate from the earliest stage of Barrett's oesophagus (metaplasia/non-dysplasia) to oesophageal adenocarcinoma is estimated at 0.33% annually. Results from cost-effectiveness studies investigating endoscopic surveillance of this precursor condition have been somewhat mixed, although the majority conducted outside of United States have found routine 2-yearly endoscopic surveillance of non-dysplastic Barrett's oesophagus to not be cost-effective. Moreover, a cost-effective alternative has not been suggested. The aims for this thesis were to 1) confirm endoscopic surveillance for Barrett's oesophagus is indeed not cost-effective; 2) find factors of progression that can be used to design risk-stratified endoscopic surveillance strategies; 3) build a Markov cohort model to represent progression of non-dysplastic Barrett's oesophagus to oesophageal adenocarcinoma; 4) perform a cost-utility analysis to find cost-effective alternatives to current endoscopic surveillance programs for Barrett's oesophagus.

A systematic review of the literature was conducted (Chapter 2) to identify cost-effectiveness studies that had attempted to test modified endoscopic surveillance strategies. Of the 10 studies identified, all except one study reported that two-yearly endoscopic surveillance was not cost-effective. Two broadly categorised cost-effective approaches to modifying endoscopic surveillance were identified: 1) deselection of low-risk non-dysplastic Barrett's oesophagus individuals; and 2) early intervention of high-risk Barrett's oesophagus individuals.

A decision analytic Markov cohort model was then designed to simulate the progression of non-dysplastic Barrett's oesophagus to oesophageal adenocarcinoma (Chapter 4). Basic health states included non-dysplastic Barrett's oesophagus, regression of metaplasia (No Barrett's oesophagus), low-grade dysplasia, high-grade dysplasia, oesophageal adenocarcinoma, and death. Costs pertaining to investigations and treatments were sourced from local health network finance data. Quality-adjusted life year (QALY) data were obtained from literature values. Initial estimates of transition probabilities between health states were derived from literature and

calibrated to lifetime risk of high-grade dysplasia and oesophageal adenocarcinoma in a seven-stage process. Calibration targets were acquired from a thorough search of the literature, which included de-novo data synthesis (Chapter 3). One-way and probabilistic sensitivity analysis (1000 Monte-Carlo simulations) were conducted. An incremental cost-effectiveness ratio (ICER) below the willingness-to-pay threshold (WTP) of AU$50,000/QALY was considered cost-effective.

Modifications to strategies were based on 1) reducing the frequency of endoscopic surveillance and/or 2) early endoscopic intervention at low-grade dysplasia on a cohort of individuals with non-dysplastic Barrett's oesophagus. Another set of strategies included subgrouping of the aggregate cohort into low and high-risk subgroups, with differing frequency of surveillance with or without early endoscopic intervention of low-grade dysplasia. Permutations of these options yielded 29 non-risk stratified and 95 risk stratified endoscopic surveillance strategies (total 123 strategies).

In base case scenario, two-yearly endoscopic surveillance for non-dysplastic Barrett's oesophagus was not cost-effective with an ICER of AU$76,658/QALY. None of the strategies reducing surveillance frequency for the aggregate cohort (non-risk stratified) were cost-effective. Even though it was the costliest strategy, endoscopic ablation of low-grade dysplasia was cost-effective in combination with surveillance every 2 years for non-dysplastic Barrett's oesophagus (*undominated AU$45,862/QALY*). Endoscopic ablation with reduced frequency of surveillance (non-risk stratified), interestingly, was not cost-effective with ICER values between AU$71,293/QALY (endoscopy every 3 years for non-dysplastic Barrett's oesophagus) and AU$391,827/QALY (10-yearly for non-dysplastic Barrett's oesophagus).

Visible Barrett's oesophagus segment length is known risk factor of progression to oesophageal adenocarcinoma. Two commonly used thresholds (2 cm and 3 cm) were used to bisect the aggregate cohort into short (low-risk) and long segment (high-risk) Barrett's oesophagus subgroups. Several modified endoscopic surveillance strategies were cost-effective in this group. For the 2 cm threshold, reducing frequency of surveillance of short segment, while maintain 2-yearly endoscopies for non-dysplastic long segment and 12-monthly for low-grade dysplasia Barrett's oesophagus was cost effective for several short-segment intervals namely 5, 6, 7, 8, 9, or 10-yearly (ICER AU$49,665/QALY; AU$47,196/QALY; AU$45,432/QALY; AU$44,099/QALY; AU43,079$/QALY; AU$42,290/QALY respectively). Staying within the 2 cm threshold group, exclusion of short-segment Barrett's oesophagus *completely* from surveillance, and 2-yearly or 3-yearly endoscopies for long segment Barrett's oesophagus individuals was cost-effective.

Fewer but several strategies were cost-effective in the 3 cm threshold group, including 9-yearly or 10-yearly endoscopies for short-segment with 2-yearly for long segment non-dysplastic Barrett's oesophagus (AU$49,287/QALY and AU$47,854/QALY respectively both with 12-monthly endoscopies for low-grade dysplasia). Exclusion of short-segment non-dysplastic Barrett's

oesophagus was also cost effective with 2-yearly endoscopic surveillance for the long-segment subgroup (for both 6-monthly and 12-monthly intervals in low-grade dysplasia, ICER AU$31,163/QALY and AU$40,060/QALY).

Adding endoscopic ablation of low-grade dysplasia to the above risk-stratified reduced frequency of surveillance for short-segment Barrett's oesophagus (5 to 10 yearly) while maintaining 2-yearly or 3-yearly surveillance for long-segment subgroup was cost-effective in every instance for both 2 cm and 3 cm thresholds. The two lowest ICER values (undominated) were for excluding short segment Barrett's oesophagus and 2-yearly endoscopies for long-segment with ablation when individuals reach low-grade dysplasia (***AU$18,688/QALY for 2 cm and AU$13,605/QALY for 3 cm threshold***).

Out of 123 tested strategies, 43 were cost-effective under base parameter conditions. Probabilistic sensitivity analysis, which varies key input parameters to account for error, was run for 1000 simulations. At a WTP threshold of AU$50,000/QALY, ***exclusion of short segment Barrett's oesophagus (2 cm threshold) with 2-yearly endoscopy of long-segment subgroup was cost-effective in 90.3% of the simulations, whereas the 3 cm threshold counterpart of the same surveillance frequency was cost-effective in 9.7% of the simulations***. The other 42 strategies were dominated by these two strategies.

In summary, a risk-stratified modified approach to endoscopic surveillance of Barrett's oesophagus is shown to be cost-effective. This study provides several original contributions to the literature, particularly in its innovative modelling methods as well as integrating the model calibration process with the probabilistic analysis, discussed in Chapter 4. Additionally, development of undetected and risk-grouped states allowed testing multiple risk-factor groups as well as surveillance intervals. This generated 123 permutations of strategies, which was important for 2 reasons: 1) internal validation of the cohort model with respect to consistency in expected model outputs and 2) testing the maximum number of strategies possible to ensure the optimal surveillance frequency is identified. The implications of this research are immediate, as clinical guidelines regarding frequency of endoscopic surveillance can be updated based on the most acceptable cost-effective strategy presented in this study. Secondly, endoscopic ablation of low-grade dysplasia must be given consideration as it was seen to be a dominating strategy across both risk-stratified and non-stratified cohorts.

DECLARATION

I certify that this thesis does not incorporate without acknowledgment any material previously submitted for a degree or diploma in any university; and that to the best of my knowledge and belief it does not contain any material previously published or written by another person except where due reference is made in the text.

Signed 

Date: Friday 9 June 2023

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>
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>
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RESEARCH OUTPUT

Publications

1) Bulamu NB, **Vissapragada R**, Chen G, Ratcliffe J, Mudge LA, Smithers BM, Isenring EA, Smith L, Jamieson GG, Watson DI; Australian Immunonutrition Study Group. Responsiveness and convergent validity of QLU-C10D and EQ-5D-3L in assessing short-term quality of life following esophagectomy. Health Qual Life Outcomes. 2021 Oct 2;19(1):233. doi: 10.1186/s12955-021-01867-w. PMID: 34600554; PMCID: PMC8487554.
2) **Vissapragada R**, Bulamu NB, Brumfitt C, Karnon J, Yazbeck R, Watson DI. Improving cost-effectiveness of endoscopic surveillance for Barrett's esophagus by reducing low-value care: a review of economic evaluations. Surg Endosc. 2021 Jul 26. doi: 10.1007/s00464-021-08646-0. Epub ahead of print. PMID: 34312726.
3) **Vissapragada R**, Bulamu N, Karnon J, Yazbek R, Watson DI. Cost-effectiveness in surgery: concepts of cost-utility analysis explained. ANZ J Surg. 2021 Jan 22. doi: 10.1111/ans.16586. Epub ahead of print. PMID: 33480173.

Presentations

1) Rethinking Barrett’s Oesophagus Surveillance. International Society of Diseases of Esophagus – Australia (ISDEAS). Hobart, Australia. Panel Speaker. March 2023.
2) Radiofrequency ablation of Low-Grade Dysplasia is Cost-Effective for patients with Long-Segment Barrett's Oesophagus. International Society of Diseases of Esophagus. Tokyo, Japan. **Oral Presentation**. September 2022.
3) Early Ablation of High-Risk Barrett’s Oesophagus Low-Grade Dysplasia is Cost-Effective. South Australian Upper Gastrointestinal Annual Dinner. Adelaide, SA. **Invited Key Speaker**. March, 2022.
4) Cost-Utility Analysis of Limiting Endoscopic Surveillance to Long-Segment Non-Dysplastic Barrett’s Oesophagus. RP Jepson and Justin Miller Annual Meeting. **Oral Presentation**. October, 2021 (Adelaide, SA).
5) Cost-Utility Analysis of Limiting Endoscopic Surveillance to Long-Segment Non-Dysplastic Barrett’s Oesophagus. Royal Australasian College of Surgeons, Section of Academic Surgery. Adelaide, Australia. **Oral Presentation**. October 2021.
6) Volatile Organic Compound Profiling for Detection of Esophageal Cancer in Exhaled Breath. **Plenary Talk**. Award: Top 30 Presentation. International Society of Diseases of the Esophagus. September 2020. Toronto, Canada (webinar).
7) Detection of Oesophageal Cancer using Exhaled Breath Analysis. **Oral Presentation.**

8) Royal Australasian College of Surgeons, Section of Academic Surgery, **Oral Presentation.** November 2019. Melbourne, Victoria.
9) Ravi Vissapragada (2019, September). Role of Breath Based Volatile Organic Compounds in Detection of Gastroesophageal Disorders. **Headline Talk**. International Association of Breath Research- Breath Summit. Loughborough, UK.
10) Ravi Vissapragada (2019, September). Role of Breath Based Volatile Organic Compounds in Detection of Gastroesophageal Disorders. **Poster Presentation**. Flinders Cancer Innovation Centre- Research Day. Adelaide, South Australia

Awards

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PREFACE

To say medical practice has changed dramatically in the last few decades would be an understatement of monumental proportions. Whereas once upon a time, a surgical procedure guaranteed a month long post-operative stay, nowadays major bowel resections are sent home within mere days. In this era of burgeoning health care services, the more concerning question is whether this is sustainable and cost-effective.

Medicine in the 20th century was primarily reactionary, intended to treat after the disease has manifested in the patient. Clinical research and improved diagnostics have shown that outcomes can be improved with earlier detection or even prevention. Understanding this, the Medicare Benefits Schedule in Australia has incentivised clinicians to provide preventive, screening, or surveillance care for a plethora of diseases ranging from Diabetes Mellitus to Breast and Colon cancer. But health care costs are high and will likely keep rising. This unfortunately means that within a specified budget, only a finite number of programs can be funded. This dilemma forces us to speculate about the opportunity costs of our actions.

Oesophageal cancer is a rare but often fatal disease that affects ~1500 Australians every year. In Australia, the most common subtype is adenocarcinoma, followed by squamous cell carcinoma. The precursor condition to the adenocarcinoma variant of oesophageal cancer is called Barrett's Oesophagus, which is diagnosed by a combination of visible changes to oesophageal mucosa and histopathological diagnosis of metaplasia or dysplasia of biopsied mucosa. Because of its potential to progress to cancer, it is currently recommended to follow patients with Barrett's oesophagus with endoscopic surveillance. Unlike population-based screening programs such as National Bowel Cancer Screening Program, this currently is not nationally funded. The progression from Barrett's oesophagus to adenocarcinoma of the oesophagus is very low, however, medical societies globally recommend endoscopic follow up of patients with Barrett's oesophagus. The main reason is the morbidity and mortality associated with advanced stage disease of oesophageal adenocarcinoma. Earlier detection through a surveillance program allows endoscopic resection and treatment of this cancer, which not only improves survival immensely, but also drastically reduces the loss of health outcomes from major surgery, chemotherapeutic, and radiotherapy treatments.

Flinders Medical Centre, in conjunction with South Australia Health, have funded a program to perform routine endoscopic examinations on patients with Barrett's oesophagus.

Examining the data from this program has helped define the progression rates of Barrett's oesophagus to oesophageal adenocarcinoma in this cohort of South Australians. It was clear that the conversion of Barrett's oesophagus to adenocarcinoma was very low. This was even lower when only considering the subgroup of patients with small amounts of visible changes in their oesophagus. Cost-effectiveness studies performed by our own group, primarily aimed at investigating whether the practice of routine endoscopic surveillance was sustainable, noted that it was not cost-effective to perform routine 2-yearly endoscopic surveillance on Barrett's oesophagus patients. These studies were performed almost a decade ago, since when there have been advances in endoscopic treatments as well as knowledge of their efficacy. There was a strong incentive to update or rebuild the previously built health economic model with the newly available endoscopic treatments.

The primary goal of this thesis was to advance our current understanding regarding the cost-effectiveness of endoscopic surveillance. A systematic review of cost-effectiveness studies revealed which strategies were seen by other groups to be cost-effective. Intuitively, it was understood that male patients or those with long visible segments of Barrett's oesophagus made up the majority of "progressors." Patients with minimally visible segments of Barrett's oesophagus on endoscopic examination made up more than 60% of the cohort but only accounted a minute percentage of those that progressed to cancer. This thesis explores the idea of a risk-modified endoscopic surveillance, with the aim to reduce low-value care. A new health economic model was developed, which allowed dichotomisation of a cohort of individuals with Barrett's oesophagus into risk factor "positive" and "negative" groups.

A crucial step in ensuring the new health economic model was clinically realistic was calibrating the model outputs to real world data. Model outputs for this health economic model were assumed to be the total number of oesophageal adenocarcinomas arising from a cohort of Barrett's oesophagus patients (also referred to as lifetime incidence). In the quest to obtain these values, there were several realisations. Oesophageal squamous cell carcinoma and adenocarcinoma have different oncogenic origins. Most squamous cell cancers are found in the upper two-thirds of the oesophagus whereas adenocarcinomas are most likely to be in the distal one-third, often near the gastroesophageal junction. Tumours at the junction could be correctly or incorrectly classified as gastric or oesophageal in the national cancer registries. Most registries also do not subtype oesophageal cancers, even though many aspects of management (including prevention) are related to the subtype of cancer. Thus, data from various sources was pooled to create a computation model that would calculate the lifetime incidence of oesophageal adenocarcinoma in the community as

well as a cohort of Barrett's oesophagus patients under surveillance. As an additional benefit, this model allowed calculation of the prevalence of Barrett's oesophagus, which will be important in the future for screening oesophageal cancers.

The main results of the health economic analysis of endoscopic surveillance of Barrett's oesophagus indicated that current recommendations are not cost-effective. Over 100 treatment strategies were tested over the course of this thesis study, of which several cost-effective strategies were identified. The visible length of Barrett's oesophagus seen on endoscopic examination was an excellent determinant of progression to dysplasia and adenocarcinoma. A modified surveillance program primarily monitoring patients with long segment Barrett's oesophagus with endoscopy was seen to be a cost-effective strategy. Modifying a surveillance program based on gender was not seen to be cost-effective. Although controversial in Australian, endoscopic treatment with radiofrequency ablation of Barrett's oesophagus with early dysplastic changes was also seen to be cost-effective, both in a risk-stratified and non-stratified setting.

1 CHAPTER 1- BARRETT'S OESOPHAGUS AND CONCEPTS OF HEALTH ECONOMIC EVALUATIONS

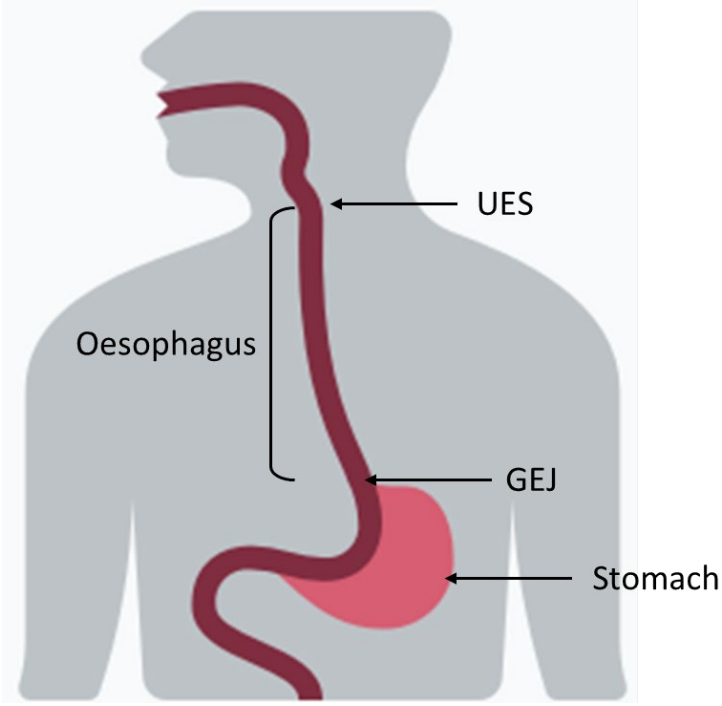
1.1 Chapter Overview

This chapter provides an overview of the two main topics of this thesis: Barrett's oesophagus and cost-effectiveness studies. The first part of the chapter provides a clinical overview of Barrett's oesophagus and oesophageal adenocarcinoma, specifically the challenges pertaining to its diagnosis and surveillance. The second part of the chapter introduces the concepts of economic evaluations and the elements involved in building a health economic model. The two parts are then interfaced to detail the motivation behind studying cost-effectiveness of endoscopic surveillance in Barrett's oesophagus. Parts of this chapter have been published in ANZ Journal of Surgery co-authored by Drs. Norma Bulamu, Roger Yazbek, and Professors Jonathan Karnon, David I. Watson (1).

1.2 Barrett's oesophagus and Oesophageal Adenocarcinoma

Barrett's oesophagus is the premalignant condition to Oesophageal adenocarcinoma. It occurs, usually, in the lower third of the oesophagus, near the gastroesophageal junction (GEJ). The stomach is anatomically separated from the oesophagus with the aid of the lower oesophageal sphincter. The sphincter along with other muscles, guides oesophageal contents into the stomach in a coordinated fashion. It also helps block stomach contents from entering the oesophagus. Barrett's oesophagus arises from this lower third of the oesophagus, especially in patients who experience reflux and are unable to keep stomach and intestinal contents from entering the oesophagus.

Figure 1. Anatomy of the oesophagus and stomach. UES- Upper oesophageal sphincter; GEJ- Gastroesophageal junction



The oesophagus starts at the end of the laryngopharynx. Entry of swallowed contents is controlled by the upper oesophageal sphincter (UES). The UES is made of cervical oesophagus, cricopharyngeus, and inferior pharyngeal constrictor. With the aid of both somatic and autonomic input from glossopharyngeal and Vagus nerves, these muscles open and close to start the process of swallowing (2). Through a coordinated peristaltic effort, the longitudinal and circular muscles of the oesophagus push the contents towards the stomach, until they reach the lower oesophageal sphincter (LES). The LES is a complex unit of muscles that lies, physiologically, at the hiatus created by the diaphragmatic crura. It is approximately 4cm long, spanning partially below the hiatus and above (3). The main function of the LES is to form an anti-reflux barrier against the gastric and intestinal contents.

Loss of this protection against gastric and intestinal contents at the GEJ is the key pathophysiological feature that predisposes patients to chronic gastroesophageal reflux disease (GERD) and Barrett's oesophagus. The oesophagus is made of stratified squamous epithelium. The term stratified signifies flattened epithelial cells, typically designed to withstand a variety of harsh and caustic substances, including gastric acids. However, repeated exposure to gastrointestinal contents, which can be acid or basic, causes cellular differentiation at the levels of exposure. This differentiation from stratified squamous to columnar cells is termed intestinal metaplasia and is a reversible process.

Metaplasia, Dysplasia, and Adenocarcinoma

Histologically, features of intestinal metaplasia, also known as Non-dysplastic Barrett's Oesophagus include villiform patterns, intermediate mucous cells, and goblet cells. Metaplasia can progress to dysplasia, which is irreversible. This is when neoplastic epithelium arises from glands but is confined to the basement membrane. Dysplasia can be further subdivided into low-grade or high-grade. Some centres may recognise an additional subdivision of dysplasia known as indefinite for dysplasia. This speaks to the complexity of diagnosis of dysplasia in Barrett's oesophagus.

Whereas there is relatively less debate about what is histologically considered to be high grade dysplasia (HGD), several studies have reported significant interobserver variability in the diagnosis of low-grade dysplasia (LGD) (4-6). The diagnosis of dysplasia is made when dysplastic cells involve both the crypts and the surface epithelium (4, 7, 8). The reason being that presence of changes in surface epithelium could indicate regenerating epithelium rather than neoplastic changes. However, involvement of crypts is seen to be more related to pro-neoplastic change. For these reasons, several categories of dysplasia have been created, namely indefinite for dysplasia, low grade dysplasia, or high grade dysplasia. Although the definitive histological changes expected in these categories has not been fully agreed upon, it is generally agreed that surface epithelia changes with atypical cytologic features arising from the crypts is important in the diagnosis of low grade dysplasia.

General histological features attributed to dysplasia in not just Barrett's oesophagus, but other gastrointestinal mucosa apply for diagnosis of low grade dysplasia as well. These include changes in the cellular nucleus such as retention of polarity, enlargement, hyperchromaticity, and irregularity. Non-nuclear changes are also described such as reduced number of goblet cells, increased mitosis, and mucin depletion (9). Not all these changes need to be present, which provides histopathologists opportunity to interpret the

degree of dysplasia. This adds to the difficulty in diagnosis as no thresholds have been set for definitive diagnosis of low grade dysplasia. Due to this, significant interobserver variability has been noted in the literature. Cohen's kappa statistic is used to indicate the proportion of agreement that is attributed outside of chance (10, 11). This has been used to identify the interobserver variability between pathologists for diagnosis of low grade dysplasia. The kappa statistic for low grade dysplasia between general pathologists and expert pathologists has been reported as "poor" or "fair" at best, but even between expert gastrointestinal pathologists was not seen to be "high" (6, 8, 12). This underlines a major struggle for centres around the world. Therefore, Australian guidelines now recommend all low grade dysplasia diagnoses must be confirmed by a second pathologist, preferably an expert in gastroenterological histopathology on two occasions at least three months apart (13).

Diagnosis of high grade dysplasia is based on increased presence of architectural, cytological and nuclear changes on endoscopic biopsy of affected oesophagus. A second, confirmatory, endoscopy with biopsy and examination by expert pathologist is required to reduce overdiagnosis, as the consequences of incorrectly labelling a patient with high grade dysplasia could mean unnecessary invasive treatment. Architectural changes include crypt budding, branching, and crowding of dysplastic crypts (14). Cytological and nuclear changes are the same as for all dysplasia mentioned above such as pleomorphism, increased nucleus to cytoplasm ratio, increased number of mitotic events, etc. Importantly, full thickness nuclear stratification in surface extending from the crypts is highly suggestive of high grade dysplasia (14). Additionally, although not quantitatively defined, diagnosis of high grade dysplasia can be made based on presence of number of histological features of dysplasia. This is different to low grade dysplasia, which may contain "some" features mentioned here, whereas high grade dysplasia requires a "high" number of these features, as long as there is no invasion of the basement membrane. The vagueness of these definitions, such as "some" or "high number", invariably leads to incongruency of diagnosis between pathologists. Lastly, evidence of invasion of basement membrane is termed intramucosal adenocarcinoma.

Risk of progression in Barrett's oesophagus

Several factors play a part in progression of Barrett's oesophagus to oesophageal adenocarcinoma. These can be broadly divided into Barrett's stage-related or patient factors. Stages of Barrett's oesophagus are metaplasia (i.e. non-dysplastic Barrett's oesophagus), low grade dysplasia, and high grade dysplasia. Patient factors include demographics such as age and gender, medication use, smoking/alcohol use, obesity, etc.

1.2.1.1 Stage-related risk of progression from Barrett's oesophagus to adenocarcinoma

Risk of progression to adenocarcinoma increases with stage of Barrett's oesophagus. A detailed list of annual progression rates is provided in Table 1. Risk of oesophageal adenocarcinoma in the population can be inferred from its annual incidence, which in Australia varies between 3.8 – 4.4 cases per 100,000 persons. Lifetime risk of oesophageal adenocarcinoma in the general population will be discussed in more detail in later chapters. Presence of intestinal metaplasia in the lower oesophagus is considered to be reversible in most cases and thus has the lowest risk of progression to oesophageal adenocarcinoma. A systematic review and meta-analysis by Desai et al. including 57 studies determined the annual progression from non-dysplastic Barrett's oesophagus was 0.33% (95% CI 0.28 – 0.38%) (15). This included a subset analysis of 10 studies which were deemed to be of the highest quality but also showed a pooled annual progression rate of 0.33%. Since this systematic review and meta-analysis, several large cohort studies have been published, (shown in Table 1) which overall agree with findings of Desai et al.(15)

Even though there is significant variation in reported progression rates from non-dysplastic Barrett's oesophagus to oesophageal adenocarcinoma, it is agreed that the progression is low. The heterogeneity in reporting is likely related to selection bias. We know that several risk factors contribute to progression to oesophageal adenocarcinoma. Some of these risk factors will be outlined later. Generally, however, it is agreed that in a Western-type population, which consists predominantly of Caucasians, the annual progression rate is as stated earlier ~ 0.3%, but much lower ~0.1% in female population. This variation is important to understand, as a study reporting a high number of male patients will likely have a higher annual progression rate, whereas the converse will have a lower progression rate to oesophageal adenocarcinoma.

Table 1. Annual probability of progression in Barrett's oesophagus

Progression from	Annual %	Source and description of study
NDBE to HGD	0.67%(16)	Anaparthy 2013: 1175 NDBE 5 tertiary US centres, 6463 patient years
NDBE to EAC	0.33%(15)	Desai 2012: meta-analysis
	0.19%(17)	Kroep 2015: population model-based estimate (ERASMUS/UWA)
	0.36%(17)	Kroep 2015: Prospective design model
	0.47%(18)	Peters 2019: large population study
	0.32%(19)	Masclee 2014: UK population
	0.36%	Masclee 2014: Dutch population
	0.22%(20)	Krishnamoorthi 2016: large pop study
LGD to EAC	0.54% (21)	Singh 2014: meta-analysis LGD to adenocarcinoma incidence(21). 24 papers.
	1.19% (22)	Kestens 2016: total (1579 patients)
	2.5%(22)	when confirmed by second pathologist (16/161 patients)
	1.01%(22)	when not confirmed (66/1348)
	5.18% (23)	Moole 2016: confirmed by 2 pathologists (reviewed 12 articles = 1532 patient yrs)
LGD to HGD/EAC	1.73% (21)	Singh 2014(21)
	2.1% (22)	Kestens 2016 all patients: combo HGD/EAC incidence
	5.18%(22)	When confirmed (33/161)
	1.85%(22)	When not confirmed (110/1348)
	10.35%(23)	Moole 2016: combined incidences
HGD to EAC	6.58%(24)	Rastogi 2008: meta-analysis
	4.49%(25)	Kambhampati 2020: cohort study
Indefinite for dysplasia to EAC	0.6% (26)	Krishnamoorthi 2019: indefinite for dysplasia to EAC

*NDBE- Non-dysplastic Barrett's oesophagus; HGD- High grade dysplasia; EAC- Oesophageal adenocarcinoma; LGD- Low grade dysplasia;

Progression from high grade dysplasia to oesophageal adenocarcinoma was also calculated from a systematic review and meta-analysis by Rastogi et al. (24) but only included four studies. Nevertheless, the annual progression was determined to be 5.57% (crude incidence) and 6.58% (weighted incidence) from high grade dysplasia to oesophageal adenocarcinoma. Since then, several large cohort studies have been published including Kambhampati et al. estimating it similarly at 4.9% annual progression (25) and 10-year cumulative incidence of 40% with 25-year incidence nearing 80%. While this is considered high, other studies estimate similar incidence rates (27, 28).

While the literature surrounding progression to adenocarcinoma from high grade dysplasia and non-dysplastic Barrett's oesophagus is relatively corroborative, progression from low grade dysplasia to oesophageal adenocarcinoma has been controversial. Singh et al. (21) published evidence of 24 studies estimating the annual progression to be approximately 0.54% (95% CI 0.32 – 0.76%) but expectedly with significant heterogeneity (I^2 = 63%). This speaks towards the challenges in assigning a diagnosis of low grade dysplasia. This is related to two main reasons: 1) the variability in diagnosis of low grade dysplasia based on detection of histological features between pathologists, 2) confirmation of low grade dysplasia by a second endoscopy and expert gastrointestinal pathologist, as detailed in the previous section. The systematic review by Singh et al. (21) examined an important relationship of the percentage of low grade dysplasia (of total Barrett's oesophagus) at the centres. A higher percentage of low grade dysplasia correlated with a lower annual progression rate of low grade dysplasia to oesophageal adenocarcinoma. This is likely because a number of low grade dysplasia were either incorrectly diagnosed or may have downgraded at a follow up examination. Conversely, a lower percentage of low grade dysplasia cases correlated with a higher conversion rate to oesophageal adenocarcinoma. Specifically, a low grade dysplasia/Barrett's oesophagus ratio ~ 0.15 was quoted as a threshold to keep in mind. Centres with higher low grade dysplasia/Barrett's oesophagus ratios were likely to be over diagnosing low grade dysplasia. This could be related to many factors, but chiefly related to how histopathologists were defining low grade dysplasia or whether patients were receiving a repeat endoscopy (with biopsy) to confirm the diagnosis. A subset analysis of 6 studies that reported confirming diagnosis of low grade dysplasia by a second pathologist revealed a 4-fold increase in annual oesophageal adenocarcinoma progression rate of 2.15%. This led to perhaps one of the most important conclusions concerning progression of Barrett's oesophagus to adenocarcinoma, which is that high risk features of dysplasia identified by two expert gastrointestinal pathologists are associated with increased progression to adenocarcinoma.

1.2.1.2 Clinical risk factors of progression of Barrett's oesophagus to oesophageal adenocarcinoma

Several clinical risk factors were compared in a meta-analysis by Krishnamoorthi et al. (29). Male sex, smoking, presence of low grade dysplasia, and length of visible Barrett's oesophagus were associated with increased risk of progression to oesophageal adenocarcinoma. Presence of low grade dysplasia was associated with the highest risk of progression to adenocarcinoma with an odds ratio of 4.25 (95% CI 2.58 – 7.00), albeit with high heterogeneity among 11 studies (I^2 = 87%). Male sex was next highest with an odds ratio of 2.16 (95% CI 1.84 – 2.53) and low heterogeneity in 11 studies. Length of Barrett's oesophagus seen on endoscopy was associated with odds ratio of 1.25 (95% CI 1.16 – 1.36) calculated from 10 studies with moderate heterogeneity (I^2 = 47%). Twelve studies examined age as a risk factor for progression of Barrett's oesophagus to adenocarcinoma, with an odds ratio of 1.027 (95% CI 1.007 – 1.046) per unit increase. Significant heterogeneity was noted (I^2 = 45%).

Diagnostic Tools in Barrett's Oesophagus:

Diagnosis of Barrett's oesophagus requires two elements, 1) presence of endoscopically visible salmon-coloured mucosa in the oesophagus, and 2) presence of intestinal metaplasia or dysplasia on histopathological assessment of mucosal biopsy specimens (30, 31). Presence of intestinal metaplasia is noted as non-dysplastic Barrett's oesophagus, whereas dysplasia can be separated into low grade dysplasia, high grade dysplasia, or indefinite for dysplasia as explained previously. Endoscopic examination is required to visualise salmon-coloured mucosa, and biopsies are required for confirming histological presence of Barrett's oesophagus. This makes endoscopy and biopsy the gold standard test for diagnosis of Barrett's oesophagus. Biopsies are taken every 2 cm in four quadrants as per the Seattle protocol (32, 33).

There are novel diagnostic tools on the horizon, which could in the future reduce the need for invasive and expensive procedures such as endoscopy. Cytosponge-trefoil factor 3 (TFF3) is one such tool, being developed in the United Kingdom as part of the Barrett's ESophagus Trial 3 (BEST3). The trial is aimed at developing a diagnostic test that can be performed in the primary care setting. The Cytosponge-TFF3 is a string with a coated capsule at the end that contains a collection device. The coated capsule is made of a gelatin, while the collection device is made of a polyester, medical grade mesh sphere. The patient swallows the capsule, while the string is secured with the clinician administering the test. After several minutes, the gelatin capsule dissolves in the stomach. The string is gentle withdrawn as the collection device collects cells along the oesophageal mucosa. The cells are then treated with immunohistochemical staining for TFF3, which allows diagnosis of

Barrett's oesophagus. The trial recruited over 13,000 patients in 2 years, who were randomised to the Cytosponge-TFF3 or "standard of care" arms. In the Cytosponge arm, 221 were positive for TFF3, of whom 131 (59%) were confirmed as Barrett's oesophagus by endoscopy (34).

EsophaCap offers a similar diagnostic modality, currently under trial in United States (Johns Hopkins University- NCT04214119). Patients swallow a sponge capsule with an outer covering that dissolves in approximately 10 mins. As the string attached to the capsule is being withdrawn, this then collects tissue and cells from the GEJ. The main difference between Cytosponge and EsophaCap is the proprietary structure of the honeycomb matrix inside the capsule that allows collection of cells from oesophageal mucosa. The cells collected in the capsule are then tested for methylation of gene markers that are specific to Barrett's oesophagus. An added benefit of using DNA methylation is that other diseases can also be tested, such as markers that are atypical for oesophageal cancer or gastric cancer. Currently, five methylation biomarkers are being tested in this ongoing trial, set to conclude in June 2025. These are: p16, HPP1, NELL1, TAC1, and AKAP12. Preliminary results of 80 patients have shown modest promise with 94.4% sensitivity (95% CI 0.71 – 0.99) and 62% specificity (95% CI 0.44 – 0.77) (35). Management of Barrett's oesophagus will be discussed in detail later.

Oesophageal adenocarcinoma

To understand how the management of Barrett's oesophagus has evolved, it is important to first outline the clinically relevant features of oesophageal cancer and, especially oesophageal adenocarcinoma.

1.2.1.3 Epidemiology

Oesophageal cancer has two main subtypes: Squamous cell cancer and adenocarcinoma. Globally, ESCC is still the most common oesophageal cancer subtype, accounting for approximately 84% of the cases (36). Oesophageal adenocarcinoma accounts for approximately 15%, with the remain 1% being leiomyosarcomas, lymphomas, and other rare entities. The highest incidence of oesophageal squamous cell cancer and oesophageal cancer in general is throughout Central Asia and Eastern Africa. Central America, Oceania, and Northern Africa has some of the lowest incidences.

This global trend is not representative of Western-type countries, i.e., those with a predominantly Caucasian population. In the United States, oesophageal adenocarcinoma accounts for 60-65%, where subtypes of oesophageal cancer are recorded routinely (37). Australia for example does not record subtypes of oesophageal cancer, but state-based

records suggest the number is likely to be between 65-75% (38). Regardless of the attributable percentage, the incidence of oesophageal adenocarcinoma has been rising worldwide. This is likely due to the risk factor profile of oesophageal adenocarcinoma. By far the most common risk factor for ESCC is smoking and alcohol consumption. However, the precursor to oesophageal adenocarcinoma is Barrett's oesophagus, which itself is a result of GERD, as previously detailed. Obesity is also a risk factor, as it results in increased intrabdominal pressure causing higher chance of reflux of intestinal contents into the oesophagus. A decrease in percentage of heavy smokers (which is a larger risk factor for squamous subtype) combined with increase in obesity has resulted in oesophageal adenocarcinoma overtaking ESCC for the most common subtype in Western type Caucasian-dominant population.

Male preponderance of Barrett's oesophagus translates to male sex being a risk factor for oesophageal adenocarcinoma as well, accounting for more than two-thirds of the cases. In some studies, the male to female ratio has been seen to be as high as 9:1 (39). These ratios are much lower in non-Caucasian dominant populations such as South American, Caribbean, Asian, and African countries (37). Having familial Barrett's oesophagus or oesophageal adenocarcinoma is another risk factor. These tend to develop earlier and may be seen in patients without symptoms of GERD.

1.2.1.4 Symptoms

Symptoms of oesophageal adenocarcinoma are similar to oesophageal squamous cell cancer. Both are intraluminal cancers, which means by the time patients notice symptoms, it is likely that the cancer has spread at least locally. Barrett's oesophagus is also an asymptomatic disease, so clinical suspicion of oesophageal adenocarcinoma is based on the patient risk-profile as much as symptoms. In fact, symptoms associated with Barrett's oesophagus and oesophageal adenocarcinoma are similar to many other benign oesophageal conditions such as oesophagitis (infective, eosinophilic, or reflux related), Shatzki rings, or achalasia. Ingestion of caustic material may also cause damage to the oesophageal mucosa with dysphagia. Progressive difficulty in swallowing (dysphagia) is the most common symptom associated with oesophageal cancer, but it may be associated with vague symptoms such as weight loss or symptoms of gastroesophageal reflux disease (40).

1.2.1.5 Diagnosis, TNM Staging and Location

Endoscopy with biopsy is the gold standard for diagnosing oesophageal adenocarcinoma. Diagnosis is on the basis of histopathological examination of tissue, which should show glandular differentiation of oesophageal mucosa (41). However, many patients do not present with typical symptoms as presented above. Many patients might present to

their general practice with vague symptoms or atypical swallowing problems. Patients may be investigated for these symptoms with a contrast swallow test or CT chest/abdominal scan (with or without on table oral contrast). In other cases, lesions suspicious for cancer may be found by endoscopists. In these cases, where oesophageal cancer is highly suspected or even diagnosed, an endoscopic ultrasound may be performed additionally, which helps in outlining the tumour spread. Laparoscopy and thoracoscopy have no current role in management of oesophageal adenocarcinoma. However, if the tumour is seen to be infiltrating the gastric cardia, there is a chance that this is gastric in origin. In cases where gastric adenocarcinoma is suspected, it is recommended to check for of peritoneal spread by laparoscopic examination (42).

The TNM (Tumour, Nodal, Metastases) staging is an internationally recognised classification for malignant tumours developed by Union for International Cancer Control (UICC) (43). Nodal and metastatic involvement are usually diagnosed by imaging such as CT or Positron emission tomography (PET) scanning. T-staging can be seen on endoscopic ultrasound or, less commonly, on Magnetic resonance imaging (MRI). This TNM staging identifies the American Joint Cancer Committee (AJCC) I-IV staging for oesophageal adenocarcinoma (44). Patients with any organ related metastasis are considered to be Stage IVb. The rest of the stages depend on the severity of T and N staging.

1.2.1.6 Management of Oesophageal adenocarcinoma

Treatment of oesophageal adenocarcinoma depends on two broad factors: patient related factors and tumour related factors. Establishing the AJCC staging is the first step to management of oesophageal adenocarcinoma. Approximately a third of patients presenting with oesophageal cancer present with metastatic organ or nodal spread, which is stage 4 disease (45). Management of patients with metastatic spread is palliative in nature, focused on improving symptoms and maintaining nutrition. This may include endoscopic procedures to stent areas of narrowing or insertion of feeding/venting tubes. Mostly, it includes management of nausea, vomiting, pain, and or discomfort.

Next most commonly, patients present with Stage II or III spread, which accounts for another third of the patients at diagnosis (45). Patients without distant nodal or metastatic spread can be considered for curative treatment. The main difference in treatment of oesophageal squamous cell carcinoma and oesophageal adenocarcinoma is the number of modalities that can be used in curative treatment. Oesophageal adenocarcinoma is generally found in the distal oesophagus, whereas oesophageal squamous cell carcinoma may be found in the upper two-thirds of the oesophagus. Owing to the technical difficulty of accessing a mid-thoracic organ, morbidity associated with resection of upper oesophageal

cancers is high. However, most oesophageal adenocarcinoma is found in the lower thorax and can be resected in selected individuals. Management of oesophageal cancer requires a multidisciplinary approach and is generally discussed in such a setting(46). Current recommendation for Stage II or III operable oesophageal adenocarcinoma in a patient who is medically fit for surgery is to undergo for neoadjuvant chemoradiotherapy or perioperative chemoradiotherapy with followed by surgical resection (47). Patients found to have pathological lymph nodes positive for cancer may be considered for additional chemotherapy. Medical fitness includes a combination of factors including comorbidities, pre-morbid conditioning, social factors etc which are assessed preoperatively. Pre-operative anaesthetic assessment examining for high-risk comorbidities such as respiratory and cardiovascular disease is also required, as postoperative pulmonary and cardiac complications are common (48, 49).

Patients with early-stage disease (Stage 1) may be suitable for unimodal treatment with resection. Resection can be either through a surgical or endoscopic approach. Five-year survival in patients with T1a and T1b is approximately 90% and 85% respectively. T1b implies cancer spread into submucosal layers, whereas T1a is limited to the lamina propria or muscularis mucosa. The difference in survival between these two stages is due to a small increased chance of nodal spread in T1b cancers (50). As a result, not all Stage 1 cancers can be treated with endoscopic resection. Endoscopic resection can be mucosal (EMR) or submucosal (ESD) and may be followed by ablation using Radiofrequency (RFA) or Argon plasma coagulation (APC), but this requires lifelong follow up with endoscopic examinations.

Surgical resection for oesophageal cancer can be performed using open, minimally invasive, or hybrid approaches. Open approach such as Ivor-Lewis oesophagectomy involves abdominal and thoracic incisions in a two-stage manner. Starting with the abdominal stage, the stomach is carefully prepared as the new conduit for the oesophagus by preserving the gastroepiploic arterial supply over the greater curvature. Then the left gastric artery is ligated, and surrounding nodal tissue is resected. A section of upper stomach, known as gastric cardia and portion of fundus and upper body, is resected along with the oesophagus. The remaining fundus of stomach, body and antrum form the conduit to replace the oesophagus. The next stage of surgery involves thoracic incision, generally through the right side with resection of nodal tissue, oesophagus, and thoracic duct. The remaining oesophagus is then anastomosed with the gastric conduit to complete the operation (51).

Management of Barrett’s oesophagus

Even though the annual progression from non-dysplastic Barrett's oesophagus to oesophageal adenocarcinoma is low, Barrett’s oesophagus is still the precursor condition to oesophageal adenocarcinoma, which has an overall five-year survival of 19% globally. However, this improves to as high as 90% if oesophageal adenocarcinoma is detected in its early stages, such as T1a tumours as discussed earlier. The motivation behind management of Barrett’s oesophagus is based on the poor survival of late stage oesophageal adenocarcinoma. Even though several advances have been made in the field of chemotherapeutic agents and radiation oncology for this cancer, most patients present in the latter stages. Less than 10% of the patients present with T1a cancer, most of which are through an endoscopic surveillance program for Barrett’s oesophagus. It is for this reason that most medical societies recommend routine surveillance of Barrett’s oesophagus.

Guidelines for management of Barrett’s oesophagus vary with the health system, although the underlying principles are the same. Table 2 presents the main differences between recommendations from various medical societies around the world. Patients with the lowest risk of progression, such as those with non-dysplastic Barrett’s oesophagus, undergo endoscopy less frequently, whereas high risk patients such as those with dysplastic features undergo more frequent endoscopic examinations or even treatment. However, several aspects of treatment are still controversial. Endoscopic intervention such as RFA, EMR, or ESD are relatively recent developments that have been slowly adopted into clinical practice over the last 10-15 years. As such, several questions remain unanswered. For example, long term follow-up results for survival and recurrence past 10 years are scarcely available.

It is generally agreed upon that patients with non-dysplastic Barrett's oesophagus require some type of endoscopic surveillance. Both US and UK guidelines are vague in how frequently the surveillance endoscopy must be, but Australian guidelines recommend 2-5 years based on the length of segment(52). Defining short or long Barrett’s oesophagus has been the subject of controversy. Most agree that the maximum length seen should be used when measuring Barrett’s oesophagus in order to diagnose with long segment or short segment, but the cut-off threshold is not always agreed upon. Nearly everyone agrees that any length >3 cm is considered long segment Barrett’s oesophagus, and <2 cm is considered short segment(53). It is between 2-3 cm that the controversies exist(54). Another point of contention is whether an extension of salmon-coloured mucosa under 1cm can be sometimes interpreted by endoscopists to be an irregular z-line.

In Australia, the cut-off for long segment non-dysplastic Barrett's oesophagus is ≥3 cm, for whom endoscopy is recommended every 2-3 years. Short segment non-dysplastic

Barrett's oesophagus may undergo endoscopy every 3-5 years. For patients with low grade dysplasia or indefinite for dysplasia, a repeat endoscopy must be performed in 6 months and pathology confirmed by a second pathologist, preferably an expert in gastroenterological pathology. For high grade dysplasia, the recommendation is to refer to a centre for multidisciplinary discussion and treatment (52). The discussion is based on several factors such as age, family history, and segment length. Evidence of effectiveness of endoscopic ablation treatment (with or without mucosal resection) is provided in a systematic review by Desai et al., that included 9 studies and 774 patients. Recurrence of oesophageal adenocarcinoma and dysplasia was 1.4% and 2.6%. Endoscopic resection alone for high grade dysplasia was inferior for initial effectiveness and recurrence (55).

With the annual progression of non-dysplastic Barrett's oesophagus to oesophageal adenocarcinoma being less than 0.3% in most centres around the world, a very small percentage of patients benefit from regular endoscopic surveillance. Over 20-30 years, this accounts for fewer than a sixth of patients. Over 80+% of patients will never develop high grade dysplasia. A study calculated the number needed to treat (NNT) for surveillance of Barrett’s oesophagus to be 400 annually (56). This is likely a generous estimate, as the authors assumed that the annual progression was 0.5% and half the patients (50%) would benefit from surveillance. If this is recalculated with 0.3% annual progression and 20% gaining a benefit from surveillance, the NNT would be between 1600-1700 annually. For comparison, the NNT for statins is 104 for 5 years (~20 annually), 1374 for colorectal screening with colonoscopy (~275 annually), and 2451 for breast mammograms (~490 annually)(57). By these numbers, the NNT for surveillance of Barrett’s oesophagus is much higher, meaning a high percentage of patients are being treated unnecessarily. However, the question isn’t what ideal NNT must be reached to make surveillance for Barrett’s oesophagus a sustainable practice, but instead, is it a cost-effective practice. To understand how to assess this question, the concepts and principles of economic evaluations are presented below, particularly in how they impact provision of surgical health care services.

Table 2. Differences in global guidelines for endoscopic surveillance in Barrett's oesophagus.

Barrett's Oesophagus Stage	Cancer Council Australia	ACG	AGA	BSG	SFED
Non-dysplastic Barrett's Oesophagus	Segment length < 3 cm, EGD every 3-5 years. Segment length >=3 cm EGD every 2-3 years.	2 EGDs in first year, then every 3 years if no dysplasia	EGD every 3–5 years.	Segment length < 3 cm (with IM), EGD every 3–5 years. Segment length>= 3 cm, EGD every 2-3 years.	Segment length < 3 cm, EGD every 5 years. Segment length 3– 6 cm, EGD every 3 years. Segment length > 6 cm, EGD every 2 years.
Low Grade Dysplasia	Confirm with second expert pathologist. Repeat EGD within 6 months on maximal acid suppression. EGD every 6 months if still LGD	Repeat EGD within 6 months; if no HGD, then every 1 year	EGD every 6–12 months	Repeat EGD within 3 months; if no HGD, then every 6 months	Repeat EGD. If LGD confirmed, EGD 6 months, 1 year, then yearly.
High Grade Dysplasia	Confirm HGD on second EGD. Consider for endoscopic treatment	Repeat EGD within 3 months, then every 3 months or consider endoscopic treatment.	EGD every 3 months in the absence of endoscopic treatment	Consider endoscopic treatment	Repeat EGD. If HGD confirmed, endoscopic or surgical treatment.

Abbreviations: ACG- American College of Gastroenterology; ASGE- American Society for Gastrointestinal Endoscopy; AGA- American Gastroenterological Association; BSG- British Society of Gastroenterology; SFED- French Society of Digestive Endoscopy; BO- Barrett's oesophagus; EGD- oesophago-gastroduodenoscopy; LGD- low-grade dysplasia; HGD- high-grade dysplasia. Adopted from Old et al 2015 (56).

1.3 Cost-effectiveness in Surgical Diseases

Health care in Australia is funded through federal and state resources. As health care costs rise and public health care funding remains constrained, inevitably some programs are prioritised while others are unfortunately discarded. This is referred to as opportunity cost. The opportunity cost of funding, for example, a national screening program, is that several others may not be funded. To maximise health outcomes for a fixed budget, funding agencies require a way of comparing several programs on the same platform. Economic evaluations address this issue by quantifying the effectiveness of a program in comparison to its cost. Health economics emerged from principles of microeconomics and welfare economics in the early 1960s. Dr. Selma Muskin's 1958 book "Towards the Definition of Health Economics" not only dispelled notions of health care expenditure being a burden on the economy but also outlined the long term advantages of investing in supporting health care (58).

The interest in economic evaluations has seen a meteoric rise. A literature search for the term "cost-effectiveness" in PubMed resulted in 1,038 hits in 2000, whereas this number was 8,903 last year in 2020. Whilst there has been an increasing focus on economic evaluations in recent medical literature, governmental and health agencies such as National Institute of Health and Care Excellence (NICE) in the United Kingdom (59), the Pharmaceutical Benefits Scheme (PBS) in Australia (60), and Pharmaceutic Management Agency (PHARMAC) in New Zealand (61) among others, across the last four decades, have relied on these analyses to guide the allocation of public resources.

In the simplest terms, an economic evaluation is a comparative analysis of two or more competing treatment options with regards to their costs/inputs and outcomes/outputs (62-64). Its formal role is to inform decisions for funding such as Medicare Benefits Schedule (MBS) items(65), for procurement e.g. which surgical devices to purchase, or for clinical guidelines such as screening programs(66). In addition, National Health and Medical Research Council (NHMRC) identifies "improving efficiency in resource use" as one of the four types of impact when funding research proposals (67), encouraging researchers to incorporate economic evaluations in project proposals to increase impact.

For the clinical community, it can be argued that the goal of an economic evaluation is not to guide decisions at the patient's bedside but to provide context and contribute to the eventual uptake of new evidence. Specifically, in surgical management, they are not meant to decide which hernia or rotator cuff tear to repair, but rather to broaden our vision and view our health system on a larger scale and inform us whether public health services are

efficiently distributed. For example, knowing that biennial screening for colorectal cancer using faecal occult blood testing is cost-effective in Australia (66) means funding these services are warranted. But knowing current endoscopic surveillance practice for Barrett's oesophagus is not cost-effective (68) encourages clinicians to research new diagnostic modalities(69) or reduce low-value care through risk stratification(70). It can also be used to support pleas to continue cost-effective practices that deliver equitable healthcare access to a much-needed community, such as the Mobile Telemedicine Service and Deadly Ears Program for Indigenous children (71).

Decisions about offering a surgical treatment are based on clinical indications and potential benefits; e.g. cancer survival, improvement in symptoms etc, but treatments that are clinically indicated are not always cost-effective. Consider acute appendicitis, for example: Wu et al., compared the cost-effectiveness of laparoscopic appendicectomy with non-operative management (with antibiotics) in children (72) and adults (73), finding in both cases that antibiotic treatment was more cost-effective. Despite this, most surgeons continue to hold the view that uncomplicated appendicitis is an appropriate indication for appendicectomy. This sentiment is echoed in the field of vascular surgery by Mandavia et al. (74), who concluded that NICE guidelines have not reflected results of cost-effectiveness studies that show elective open repair of aortic aneurysms is more cost-effective than endovascular repair in asymptomatic patients.(75-77) It isn't to say these surgeries should be ceased, but conducting a cost-utility analysis could be a step towards gaining a comprehensive understanding of the factors involved in improving either the costs or outcomes related to the condition.

Although widely used by many funding agencies, clinicians have difficulty evaluating evidence from economic evaluations for their practice. This is due to several reasons. For one, economic evaluations are difficult to interpret as their research design differs from traditional surgical outcome studies. Whereas clinical studies provide outcomes in a known quantity, for example mortality or complication rate, economic evaluations incorporate cost with health outcomes. In order to do this, several assumptions must be made, some of which may be seen as abstract or theoretical. Finally, economic evaluations are fraught with confusing terms, adding to the difficulty in their interpretation.

Introduction to economic evaluations involves breaking down some of the most commonly used terms, as well as presenting an algorithm for its development and use. The cost-utility analysis is the most common type of economic evaluation in health care. It is also the form of economic evaluation recommended by funding agencies such as NICE and PHARMAC (61, 78). The thesis is also based on a cost-utility analysis of surveillance

strategies in Barrett's oesophagus. For these reasons, the remained of the chapter will focus on cost-utility based on a Markov model or decision-analytic model design (79). In this section, we provide the steps necessary to construct a cost-utility analysis with the aim to simplify the underlying terms and processes to facilitate the understanding of cost-utility analyses, including research design, the components of a health model, interpretation of outcomes, and finally calculating uncertainty in a decision-analytic or Markov model.

Types of Economic Evaluations

There are several types of economic evaluations, mainly varying according to their outcome/output value. The type of evaluation depends on which outcomes are being measured. An algorithm for deciding the appropriate study is provided in Figure 2 (80). The underlying principle of economic evaluations is to consider the costs and outcomes of two or more competing treatment strategies. Where the outcomes can be quantified, cost-effectiveness can be calculated through various methodologies. Common types of economic evaluations and their usages are discussed below (81):

1.3.1.1 Cost-minimization analysis

In a situation where the outcomes of all alternatives being compared are assumed to be equivalent and only their respective costs are compared. This is particularly useful when two interventions demonstrate the same level of effectiveness.(82)

1.3.1.2 Cost-effectiveness analysis

A *cost-effectiveness analysis* calculates the differences in costs of comparative strategies against the differences in their outcomes or "effect." The outcome can be represented as natural or physical units e.g., number of cancers identified by a screening program, mortality, cancer recurrence, etc. The outcome used should reflect the objective of the study, while trying to ensure compatibility between other studies.

1.3.1.3 Cost-utility analysis

A *cost-utility analysis* (CUA) is a specialized type of analysis that measures outcomes as QALY. A QALY combines both the quantity and quality of life generated by an intervention into a single measure on a scale of 0 to 1, with a score of 1 being equated to perfect health and 0 being death(83). Unlike cost-effectiveness analyses, a cost-utility analysis measures comparative effectiveness between several health care interventions using QALYs.

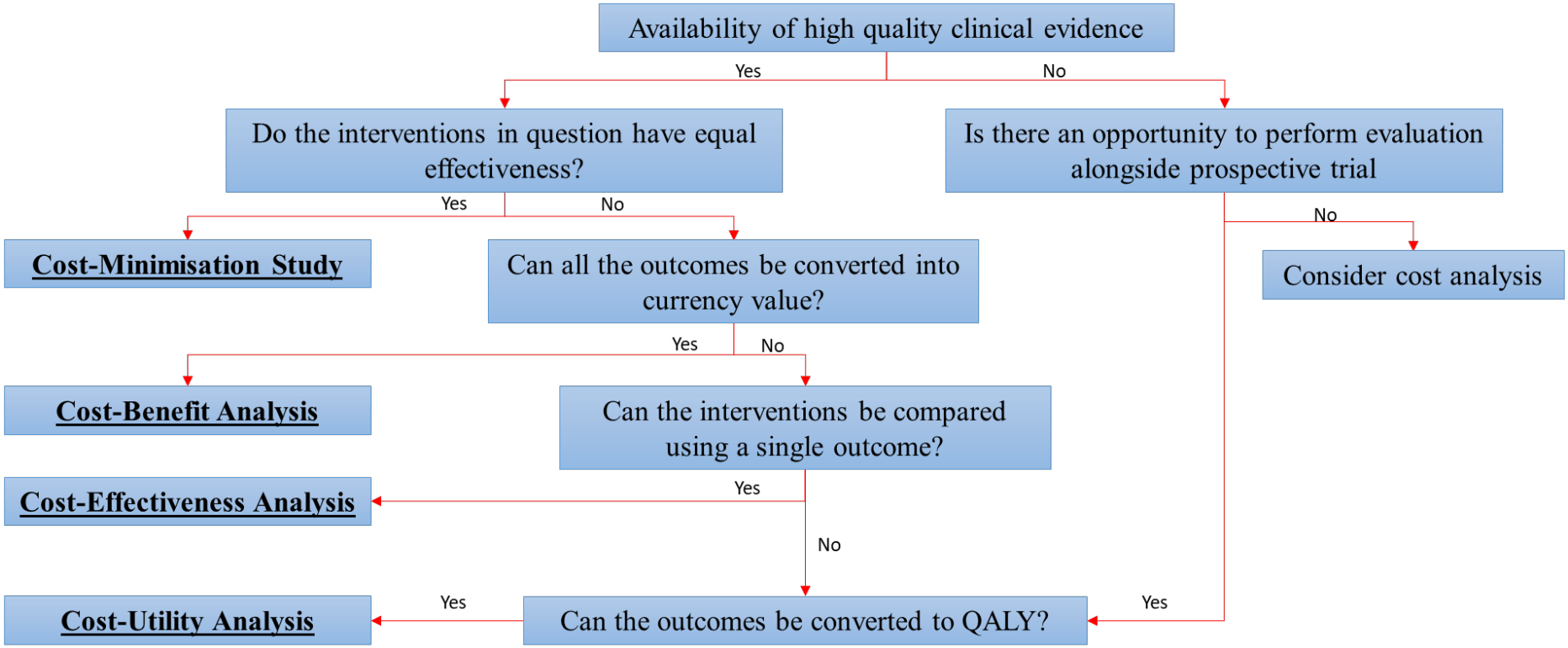
1.3.1.4 Cost-benefit analysis

In *Cost-Benefit Analysis*, the “outcome” is assigned a monetary value, which can be useful when comparing non-related treatments with varying outcomes. With the “outcome” converted to a monetary value, it becomes easier to make a direct comparison. This is routinely used especially in the setting of national budgetary discussions, where one might need to compare benefits of programs in different governmental sectors such as Defence and Health.

1.3.1.5 Cost-consequence analysis

There are instances when the effectiveness of both treatments cannot be represented through QALYs or a common unit of measure. In these cases, a *cost consequence analysis* can be utilized, which simply presents costs and outcomes of each intervention, allowing the decision-maker to form their own conclusions(84).

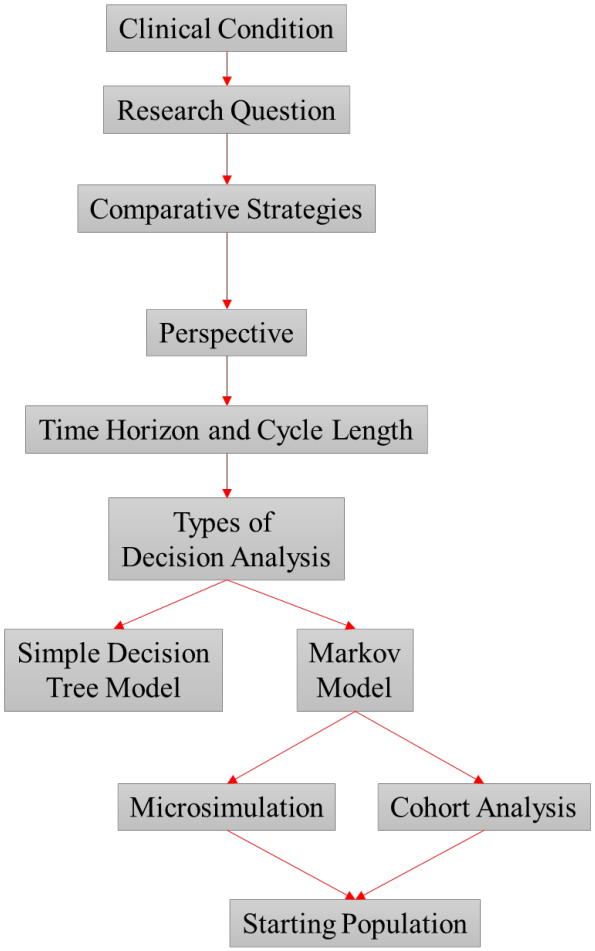
Figure 2. Selecting the right type of Economic Evaluation.



¶ Adopted from "Clarke, P. "Introduction to Cost-Effectiveness Analysis in Health." Centre for Health Policy, Melbourne School of Population and Global Health, University of Melbourne. https://mdhs-study.unimelb.edu.au/short-courses/mspgh-short-courses/introduction-to-cost-effectiveness-analysis-in-health/overview. Date created 23/03/20. Date Accessed 04/05/2020.

Steps in building an economic evaluation

Figure 3. Steps in initiating an economic evaluation



In order to understand what type of clinical condition would benefit from an in-depth analysis of its costs and outcomes, we must understand what resources are involved with provision of surgical care. Running a clinical service requires several resources. These can be broadly divided into personnel, equipment, and space. Sometimes these are shared between several types of clinical services, but other clinical services are specific to one specialty. For example, radiological imaging such as Computed Tomography (CT) has strict requirements for space allocation and shielding to protect both patients and staff from harmful effects of radiation. As such, the resources of personnel, space, and equipment related to this clinical service can essentially be isolated to one department. Other clinical services such as outpatient clinics or inpatient wards, however, share personnel, equipment,

and space from multiple departments. Clinical services such as operating theatres and procedure suites are somewhere in between the preceding two examples, as they are also shared, but to a lesser extent. Equipment required for surgery, for example, is rarely used elsewhere. Staff trained in surgical theatres or endoscopy suits are not usually shared between other departments. Although this is seemingly trivial, it becomes important when funding is allocated to specific services by the local, regional, state, or federal funding agency. Understanding what resources are shared versus standalone for a clinical condition is key to calculating the costs associated with a clinical condition.

Building a computational model of a disease requires access to observed data. This can be in the form of published literature or available databases. In both cases, a number of factors determine accuracy and reliability of the model. The first is the quality of evidence. Systematic reviews and meta-analyses are considered to be the highest level of evidence, as they combine data from multiple sources. This reduces the risk of bias from any one study. In the absence of such studies, large prospective cohort studies can also be used. In addition to quality of reported study, the number of patients being followed up is important in building a model. The outputs of the model reflect the inputs. Large studies or trials are more likely have a portray a more accurate range or confidence interval in which the true value lies. Smaller studies may contain several biases such as selection and observer bias, which when inputted in a model can be amplified producing inaccurate or inconsistent model outputs.

Another factor to consider is whether the studies report an appropriate follow up period. An appropriate follow up period will encompass all clinically relevant changes pertaining to the clinical condition. This can be short in acute conditions, for example acute cholecystitis or appendicitis, where the follow up period may only be weeks or months. In other instances, the clinical condition may take years to develop or evolve. In these cases, longer term data is required. Availability of such data is crucial to building an accurate model of the disease.

Even prior to selecting a condition, a hypothesis of whether a particular treatment algorithm in a clinical condition is cost-effective should be developed. This can be based on previous studies, clinical audits, or even intuition. Peer reviewed studies provide a great starting point for development of the hypothesis but may not always be available. Several aspects of treating a condition can tip off whether cost-effectiveness needs to be studied. A simple way is to look at the number needed to treat or diagnose (85). If we take a hypothetical example of a screening programme, the number needed to diagnose identifies how many patients are diagnosed by being screened compared to how many patients do not. Although this does not indicate cost-effectiveness, one can imagine that a screening test

that is expensive with a high number needed to diagnose would not be cost-effective. Conversely, an inexpensive screening test with a low number needed to diagnose would mean that more patients are identified using relatively fewer resources. This process of generating a research question and hypothesis is critical to building a computation or state-transition model that can help funding agencies make decisions.

Design of Markov models

Traditional scientific research design depends on observations in a controlled environment, whereas cost-utility analyses can vary in design according to the objective of the study. Broadly, economic evaluations can either be modelled or run alongside a trial. The design in part depends on the natural history of the disease-states, timeframe for study completion, requirements for certainty/confidence in the study outcomes (to make a decision), and the availability of clinical evidence. A rare condition that takes several years to be clinically defined is difficult to study through a prospective trial. Conversely, a condition that has low-quality incidence/prevalence data or poorly defined health states is better studied alongside a trial.(86, 87)

Once the clinical condition is clearly defined, a decision-tree model or a Markov-model is designed based on the natural progression of the disease/condition. Simple decision analytic tree models are mainly used for conditions with unidirectional movement through health states. Markov models have special mathematical properties and are better suited for conditions of a recursive nature as they allow forward and backward movement through each stage of the disease also referred to as a health state.(88)

Diseases can be represented through a microsimulation or cohort model. There are several differences between the two (89). A Markov cohort model moves an entire cohort of patients through the model, whereas a microsimulation moves an individual through the model at time. This key difference allows the model to simulate individual patients, which can be helpful in representing a variety of patients or individuals. For example, if the model needs to represent the heterogeneity of varying ages, sex, genetic mutations, etc of a particular type of cancer from a database of patients, a microsimulation model can be useful. The main advantage of cohort models is they are quicker to run (requiring fewer calculations). But unlike microsimulation models, it is more difficult to generate heterogeneity within the cohort. One way around it is to assign different proportions of patients starting in different health states to introduce heterogeneity. The other key advantage of microsimulations is they have memory. Using trackers, individuals simulated through a microsimulation can undergo more specific interventions based on a “memory.” This can be

particularly in a variety of situations such as crossover treatments or varying surveillance/screening intervals.

Definitions of Model Components:

Cost-utility analyses are built on the same scientific principles as empirical studies. As with any type of research, the first step is to generate a *research question*. The research question identifies a clinical condition or indication, for which an eligible population of patients can be clearly defined, the *treatment strategies* to be compared, and the type of economic evaluation to perform. As detailed above, the type of economic evaluation that should be undertaken depends on the available data, units of “effect”, and convertibility of effects to currency. If inadequate high-quality evidence is available, then running alongside a prospective trial is a potential option. If this option is chosen, it is important to comment on missing data or quality of data collected in the methodology.

The *perspective* of the study determines whose costs will be included in the analysis and is critical to reporting outcomes and drawing conclusions (expanded below). Healthcare payer perspective is the most commonly used perspective, which includes costs to a third party such as Medicare in Australia and the National Health Service (NHS) in the United Kingdom. This is different from a healthcare sector perspective, which includes the costs borne of healthcare payer but also patients’ out-of-pocket costs. A societal perspective includes all costs mentioned above but also includes loss of productivity to the patient and carers and any effects the disease condition generates inside and outside of the health system. (90)

The other aspect to define is the *time horizon* which is the total period over which costs and consequences will be measured. The aim is to specify a time horizon that is sufficient to capture all necessary differences in costs and outcomes. Similarly*, cycle length* is the duration between each health state, which is also dependent on the clinical progression of the disease (91). A condition that changes quickly should have a shorter cycle length, to encompass all clinically relevant events.

The time horizon selected for the study also helps in deciding whether *discounting* will be applied to the costs and Quality Adjusted Life Years (QALY). A time horizon of 1-year or less does not require discounting, but over time, the costs and health outcomes decrease in comparison to current costs and outcomes, and thus a fixed annual reduction of value is applied to account for these changes. This is related to a concept known as opportunity cost. It may seem counter-intuitive, as we think that costs should increase over time, but economic principles dictate that our money and health have higher value in present time

than in the future. Imagine, if a study invested AU$1000 in 1980, its present estimated worth would equal AU$4252. Discounting allows us to extrapolate this rise in monetary and health value in the future (92). Discount rates vary widely depending on local economic setting, for example New South Wales Health recommends using 7%, while Australian Institute of Health and Welfare uses 5%, while the United Kingdom uses 3.5% .(91, 93-95) It is therefore recommended to check healthcare agency guidelines on conducting economic evaluations to apply the correct rate.(61, 96)

Defining the clinical condition also aids in defining the health states. Patients/cohort all start in a health state, known as *starting population* or *Markov entry point* and move through the model changing health states depending on events within the model. It is important to represent all possible health states in the model without making the model too complex. Unnecessarily complex models may contain inaccuracies that could be amplified across a longer time horizon.

Model Results

A model of the natural history of the clinical condition is then designed, based on all clinically relevant health states, investigations, and treatment options. A major advantage of Markov models is that it allows recursive health states. Movement between health states depends on ability of disease progression and regression, as well as absorbing states. Death is typically the absorbing state in most disease conditions, but this could differ based on research objectives. It is important to model all potential treatment strategies to be tested at the outset. This allows improvisation and testing of hypothetical treatment strategies, which can be informative of the clinical condition or the model.

Although patients are unable to return from death (termed absorbing state), they can move between the other states. This seemingly trivial detail is quite important because it identifies the recursive nature of the health states, and thus the transitions between these states can be calculated using a Markov chain process. It is a mathematical model that allows us to estimate the probability of transitioning from one state to another, based on a specified sequence of events (i.e. progression of disease).

A cohort analysis allows us to simulate individual patients with homogenous characteristics through our defined disease states (97). The model starts with a cohort of individuals defined by a clinical train. This is termed called the entry point. At this point, the model must decide the type of treatment the cohort will undergo, represented by a *decision node*. Decision nodes indicate different strategies being tested within a model. Each strategy contains a Markov node, which contains several health states. Health states represent the clinically relevant stages of the disease. As an example, in a state transition model of a hypothetical cancer, the relevant health states could be: healthy, early stage cancer, remission, late stage cancer, and death. Each health state can transition to one or more health states, through the aid of a *chance node*. Chance nodes, as implied, are determined by the probability of the event occurring. For example, if treating for cancer, patients can either remain in a cancer state, transition to remission, progress to late-stage cancer, or die. If a patient is in remission, then they can either return to a healthy state or relapse into a cancer state. This keeps occurring until we reach the terminal node, which for our model is death.

A cost-utility analysis involves tallying the costs and QALY associated with health states, investigations, and treatments in the state transition model. Different treatments can then be compared using these costs, for example, in the case of a hypothetical cancer surgical resection versus medical treatment. The total costs and QALYs accrued over the time horizon of the model forms the elements required to calculate the *base-case*

incremental cost-effectiveness ratio (ICER) value. This is calculated using the equation below:

Equation 1. Calculation of Incremental Cost-effectiveness Ratio (ICER)

$$ICER = \frac{(Cost\ of\ Surgical\ Resection - Cost\ of\ Chemoradiotherapy)}{(QALY\ of\ Surgical\ Resection - QALY\ of\ Chemoradiotherapy)}$$

Equation 2. Net monetary benefit

$$Net\ monetary\ benefit = (Effectiveness * Willingness\ to\ pay\ Threshold) - Costs$$

Interpreting Incremental Cost-Effectiveness Ratios:

Interpretation of ICER values is dependent on a concept in health economics known as the Willingness-To-Pay threshold. In everyday vernacular, we understand that a product/service is considered "cost-effective" if its output (i.e., improved health) is desirable at the demanded price. However, it is quite challenging to quantify a product's value, as it is subjective and abstract. In microeconomics, the value of a product is measured in monetary units. This is different from the market value which is the *maximum* price a consumer is willing to pay for the product or service. The same concept is applied to health economics, where the consumer is the health system. Each health system has a threshold above which they consider the treatment alternatives to be less desirable to fund. Previously, willingness-to-pay thresholds were based on GDP per-capita (98), which is now outdated. The rationale was that one QALY is equivalent to production of an average person, in other words, GDP per-capita. This is no longer preferred. The current recommended approach is to estimate the opportunity cost of funding a new intervention or program by calculating incremental changes in healthcare expenditure over time compared to mortality and morbidity outcomes in that same time (99). To state more simply, it is how much a healthcare agency has spent over a period compared to the outcomes it has produced during that same period. Although they are not rigid, willingness-to-pay thresholds are estimated reference values for the health system provider to consider funding. In the United States, the threshold is somewhere between US$50,000 - 100,000 (per QALY), whereas in United Kingdom and Australia, it is roughly £20-30,000 (per QALY) and AU$35-50,000 (per QALY) respectively(98). In New Zealand, there is no set threshold; instead, funding is committed in relation to all proposed interventions in a budgetary period (61). In interpreting the results of a cost-utility analysis, *an ICER that is less than or equal to the willingness-to-pay threshold is considered cost-effective.*

When testing several strategies or interventions, the ICER values can be compared to the base comparator (usually the standard of care or gold standard) and/or they can be compared in an incremental fashion. Comparing to the base strategy can be useful as it gives a snapshot of the incremental cost and outcome values against the control. Equally, comparing to all other strategies is necessary because strategies that provide lower outcomes at similar or higher costs are termed ***dominated***. An ***undominated*** strategy is one that provides improved outcomes albeit at higher costs. If a strategy provides lower outcomes than the cheapest strategy (usually base strategy), then it is termed ***absolutely dominated***. If strategy #3 provides improved outcomes than the base strategy (cheapest), but strategies #4 provides equal outcomes at lower cost than strategy #3, then strategy #3 is termed ***extendedly dominated*** (100).

Uncertainty/sensitivity Analysis:

This initial run of a model based on point estimates of each variable is known as the *base-case analysis* which generates a base-case ICER value. Before we can declare a treatment strategy as being cost-effective, we must calculate the confidence of our results, which is done through *uncertainty analyses* or sensitivity analyses. Although the models are created to be as realistic as possible, they are never perfect and can generate biased outcomes just like empirical experiments. The accuracy of the model is based on the accuracy of the input parameters and model structure. Economic evaluations can assess the error of these input parameters through deterministic and probabilistic sensitivity analyses. Sensitivity analyses vary input variables of the model that may have a greater influence on the results of the model.

Deterministic sensitivity analyses vary key input variables/parameters, uncovering the *main drivers* of the model. These are identified by the researchers to be clinically important input variables and can be an essential clue to understanding the model. In a deterministic sensitivity analysis, these inputs are varied across a range of plausible values, either one at a time (one-way sensitivity analysis), two inputs together (two-way sensitivity analysis), or more as deemed necessary. In our example, this would involve varying the cost of surgery, hospitalization, chemotherapy, radiotherapy, palliative care, etc. The probability of achieving remission after treatment is also likely to be a key factor in determining cost-effectiveness, so this would also be tested. The variation in ICER values can be graphed/plotted, indicating the sensitivity of the model to changes. Varying a key assumption would expectedly change the ICER and cost-effectiveness of the treatment strategy. For example, if probability of achieving remission for surgical resection is reduced to 0.1, this would expectedly change the total costs and QALYs for that arm. A large variation of ICER

does not always indicate a poorly constructed model. Conversely, a narrow margin of ICER values even when varying the key inputs to a large degree may indicate an unrealistic model.

While deterministic sensitivity analyses test variation in ICER values by changing one or two input parameters at a time, a probabilistic sensitivity analysis can plot the resultant ICER values when all input parameters are varied. Typically, this requires running thousands of iterations of the model to allow a wide amount of variation. Each run selects a different set of input parameters (transition rates, costs, utilities, etc.) based on a probability distribution set by us and thus results in a different ICER value. As an example, for the hypothetical model, a specified probability distribution was set for transition rates (gamma), costs (beta), and utility (beta). The results of this can be plotted as a cost-effectiveness acceptability curve. The cost-effectiveness acceptability curve informs us about how the model performs should the model inputs have inconsistencies.

Cost-utility analyses calculate the incremental cost and effects of comparative treatment options to derive an ICER value, for which cost-effectiveness is defined by the willingness-to-pay threshold. Although their design and outcomes are unique, cost-utility analyses are subject to similar critical appraisal as other studies. Accuracy of model design, assumptions, and input parameter values should all be assessed when evaluating the quality of the study. Deterministic sensitivity analyses can help identify key input parameters, whilst probabilistic sensitivity analyses describe the overall uncertainty around the estimated cost-effectiveness of the interventions.

1.4 Aims of the thesis

The main aim of the thesis was to provide conclusive evidence of the cost-effectiveness of Barrett's oesophagus surveillance through endoscopic examination as well as develop strategies to improve it. This was done through a number of steps starting from asking basic questions such as incidence and prevalence of this disease to diving deeper into developing a health economic model. These smaller steps formed the specific aims of the project and listed below:

1) Determine the lifetime incidence of oesophageal cancer and adenocarcinoma in Australia
2) Calculate the community prevalence of the asymptomatic precursor to oesophageal adenocarcinoma known as Barrett's oesophagus
3) Perform a literature review to understand concepts of economic evaluations and their role in surgical practice
4) Perform a systematic review of economic evaluations to understand the factors surrounding cost-effectiveness in endoscopic surveillance of Barrett's oesophagus
5) Delineate the key risk factors for progression from non-dysplastic Barrett's oesophagus to oesophageal adenocarcinoma
6) Develop a decision analytic Markov model to simulate the progression from non-dysplastic Barrett's oesophagus to oesophageal adenocarcinoma
7) Calibrate the model to high quality literature evidence
8) Develop risk stratified and non-risk stratified strategies for improving cost-effectiveness of Barrett's oesophagus surveillance and treatment of low grade dysplasia with radiofrequency ablation
9) Perform deterministic and probabilistic sensitivity analyses to identify optimal cost-effective strategy

Methods and results of these specific aims are presented in chapters below.

2 CHAPTER 2: A SYSTEMATIC REVIEW OF ECONOMIC EVALUATIONS EXAMINING COST-EFFECTIVENESS OF ENDOSCOPIC SURVEILLANCE FOR BARRETT'S OESOPHAGUS

2.1 Chapter overview

This chapter focuses on the first three steps of the algorithm, which are 1) Selecting a clinical condition, 2) developing a research question, 3) collating comparative strategies. Here I present the methods and results of a systematic review of economic evaluations that focuses on reducing the total number of endoscopies performed on a cohort of Barrett's oesophagus individuals. This was done through various methods, from selecting a high risk subgroup for more frequent endoscopic examinations or reducing the frequency of endoscopies for a low risk subgroup. Alternatively, some studies also performed earlier interventions (with endoscopic treatments) for high risk subgroups. Risk stratification was performed using clinical features or biomarkers.

Parts of this chapter have been published in *Surgical Endoscopy* as "Improving Cost-Effectiveness of Endoscopic Surveillance for Barrett's Esophagus by reducing low-value care – a review of economic evaluations" by the following authors: Drs. Ravi Vissapragada, Norma B. Bulamu, Christine Brumfitt, and Roger Yazbek, and Professors Jonathan Karnon and David Watson.

2.2 Studying endoscopic surveillance of Barrett's Oesophagus

Oesophageal Cancer is a lethal condition, with a five-year survival rate of 23.5% in Australia and 17-19% globally (101, 102). Oesophageal adenocarcinoma is the most common subtype in developed nations, accounting for 65-80% of the total cases, depending on the region, and increasing in incidence (103). One of the main factors contributing to low survival rates is late presentation of symptoms. The tumour has mucosal origins but can cause little to no symptoms, in part related to its progressive insidious growth. Due to this and other factors, a third or more of the patients present with Stage IV disease. Treatment at this stage is mainly palliative, with less than 5% surviving past five years and close to 0% surviving at 10 years. Even for patients undergoing treatment with curative intent, the survival is only approximately 50% at five years. At the other end of the spectrum, survival for patient diagnosed with Stage Ia disease is approximately 90%. However, unless patients are under constant surveillance, patients are unlikely to present at this stage. This makes surveillance of any precursor conditions critical in improving the overall survival of this condition.

The pathophysiology, as previously detailed, is postulated to be due to chronic damage caused by refluxing gastric contents, giving rise to Barrett's oesophagus which is characterised by columnar mucosa with intestinal metaplasia primarily in the lower third of the oesophagus. Macroscopically, this is visualised as salmon-coloured mucosa on endoscopic examination. The combination of these two features represents non-dysplastic Barrett's oesophagus, and this is the known precursor to oesophageal adenocarcinoma. Although the progression rate from non-dysplastic Barrett's oesophagus to oesophageal adenocarcinoma is low, between 0.2% to 0.5% annually (17, 19, 20), the low 5-yr survival rates of oesophageal cancer have compelled international societies to endorse routine endoscopic surveillance with endoscopic. However, the effectiveness of surveillance has been questioned. The ideal method of establishing clinical or cost-effectiveness of endoscopic surveillance would be a prospective randomised study. Patients would be randomised to endoscopic surveillance or no surveillance. Clinical effectiveness would be measured with progression to oesophageal adenocarcinoma, mortality, or quality adjusted life years (QALY). However, this is both impractical and highly unethical. For starters, it would have to be conducted over a lengthy period and include a huge cohort of patients. Further, many patients in any non-surveillance arm would likely develop late-stage cancer, which is associated with high morbidity and mortality.

Decision-analytic models, such as those used in economic evaluations like *cost-utility analysis,* are thus useful for assessing potential efficacy and cost-effectiveness using parameters from large epidemiological studies. Modelling negates the need for conducting expensive and potentially unethically trials. Several studies have conducted modelling exercises to establish cost-

effective strategies in Barrett's oesophagus. A 2017 systematic review by Saxena and Inadomi (104) examining the cost-effectiveness of endoscopic surveillance with or without endoscopic eradication treatments in patients with non-dysplastic Barrett's oesophagus and dysplastic BE concluded among other findings that 1) endoscopic eradication is cost-effective in patients with high-grade dysplasia and 2) endoscopic surveillance is cost-effective for *high-risk* patients. Even though the risk was not fully quantified, it is suspected that endoscopic surveillance is likely not to be cost-effective in all patients with non-dysplastic Barrett's oesophagus.

Patients with non-dysplastic Barrett's oesophagus represent a heterogeneous group of individuals, with approximately 30-125x overall greater risk of developing oesophageal adenocarcinoma compared to the normal population (105). There are two potential approaches which might be considered to improve the cost-effectiveness of BE surveillance. The first is to intervene earlier for the highest risk individuals i.e. patients with high-grade dysplasia (106, 107), and this has been shown to be cost-effective (104) and is now reflected in updated clinical guidelines.

Endoscopic eradication for low grade dysplasia, the step before high-grade dysplasia, is more controversial, as the histopathological diagnosis of low grade dysplasia is associated with high interobserver variability (4, 6, 23, 108). There are several reasons why this is the case, but one of the underlying difficulties is agreeing which dysplastic features in which areas constitute low grade dysplasia, as opposed to indefinite for dysplasia, non-dysplastic Barrett's oesophagus, or high grade dysplasia. It is generally agreed that, histologically, surface epithelial changes resembling dysplasia (for e.g., nuclear pleomorphism, high mitotic event counts, etc) alone are not enough to label the specimen as low grade dysplasia. For one, the biopsy taken has likely been in exposure to intestinal contents, which can cause inflammation. Secondly, surface epithelial changes are an expected histological feature of inflammation. And thirdly as surface epithelium of gastrointestinal tract goes through regular apoptotic events, it is likely that many patients with dysplastic features will lose the "dysplastic" or affected epithelium. However, crypts are present between the surface epithelial cells, providing vital support to endoluminal functions. So, changes occurring in the crypts are more likely associated with longer exposure to intestinal contents, which will be present for a longer period of time.

The differences in assessment of what constitutes low grade dysplasia versus other diagnoses causes a change in epidemiological variance in risk of progression to adenocarcinoma. Essentially, different risks of progression to oesophageal adenocarcinoma appear to be associated with different diagnostic standards. A centre that has a low threshold for diagnosing low grade dysplasia will likely see a large number of patients of patients revert to non-dysplastic Barrett's oesophagus after proton-pump inhibitor (PPI) therapy. This group of patients are likely to have a

much lower risk of progression than patients who have persistent low grade dysplasia. Hence, patients with confirmed low grade dysplasia on two occasions by two specialist pathologists are likely to be at greater risk of progression to cancer, and likely to benefit from eradication treatments such as ablation. The addition of the second histopathological review appears to more reliably identify features in low grade dysplasia biopsies that confer higher dysplastic/malignant potential (23). This has been examined across two systematic reviews that conclude similarly (104, 109).

Another approach to achieving cost-effectiveness is to reduce the frequency or even cease surveillance in individuals identified to be at low risk. Approximately 80-90% of patients who have non-dysplastic Barrett's oesophagus will never progress to dysplasia or cancer (107). Our group has previously analysed the cost-effectiveness of a modified endoscopic surveillance (using a hypothetical biomarker) compared to the natural history group and suggested this is likely to be cost-effective at a willingness-to-pay (WTP) threshold of $50,000 per quality adjusted life year (QALY) gained (68). Similarly, we also demonstrated improved cost-effectiveness of endoscopic surveillance by excluding patients with BE lengths of less than 2 cm (70). Other groups have also attempted to improve cost effectiveness by either excluding low-risk individuals or increasing the intervals between surveillance episodes. Hence, a focus on modifying current surveillance recommendations to achieve cost-effectiveness and better clinical outcomes has potential to improve outcomes for individuals with BE, and those at particular risk of progressing to oesophageal adenocarcinoma. A systematic review was conducted to summarise the literature pertinent to the cost-effectiveness of endoscopic surveillance, with special consideration of strategies which aim to achieve cost-effectiveness by reducing the overall number of endoscopies performed.

2.3 METHODS

Databases included:

The following databases were interrogated: MEDLINE, PubMed, EMBASE, The Cochrane Library, CINAHL, Scopus, and Web of Science (Last date of search: 14 April 2020). Two reviewers performed the screening process. Any conflicts were discussed and a third reviewer, if necessary, was involved to reach consensus. The Consolidated Health Economic Evaluation Reporting Standards (CHEERS) checklist prescribed by the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) was used to identify risk of bias (performed by two reviewers: RV/NB).

Study selection criteria:

Included studies were cost-effectiveness analyses of endoscopic surveillance of patients with BE, undertaken from 1975 to 2020, with the specified outcome of QALY or Disability adjusted

life years (DALY). Studies were limited to those that used non-dysplastic Barrett's oesophagus as the starting population and containing at least one strategy varying the interval frequency of endoscopic surveillance or limiting surveillance to a higher risk non-dysplastic Barrett's oesophagus population.

Exclusion criteria:

Studies taking the perspective of the healthcare service sector in low- and middle-income countries were excluded due to differences in health care systems and funding. This approach was taken because the percentage of Gross Domestic Product (GDP) allocated to health care in developed nations such as the UK, Spain, Australia is approximately 9-12%, whereas many Asian countries spend approximately 4-6%. Studies with poorer methodology identified using the Consolidated Health Economic Evaluations Reporting Standards risk of bias tool were also excluded to maintain a high level of evidence quality (110).

Search string strategy:

The search strategy used in Medline database is described in Supplemental Table 3. The study selection followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (111). A completed checklist of the items has also been provided as supplemental data (Table 3).

Table 3. Search String strategy

#	Searches
1	Barrett Esophagus/
2	(barrett* adj2 (esophag* or oesophag* or epithelium)).tw,kf.
3	(column* adj3 (esophag* or oesophag* or epithelium)).tw,kf.
4	or/1-3
5	Esophagoscopy/ or Endoscopy, Gastrointestinal/ or Endoscopy/
6	disease progression/
7	Watchful Waiting/
8	(esophagoscop* or oesophagoscop* or Esophagogastroduodenoscop* or Oesophagogastroduodenoscop* or endoscop*).tw,kf.
9	(surveillanc* or monitor* or screen* or watch*).tw,kf.
10	or/5-9
11	exp economics/
12	(economic* or cost* or sensitivit* analys* or pharmacoeconomic*).tw,kf.
13	quality-adjusted life years/ or "Quality of life"/
14	(Life Qualit* or Quality Adjusted or Adjusted Life or "quality of life" or qol or qoly or qolys or hrqol or qaly or qalys or qale or qales).tw,kf.
15	Markov Chains/
16	(markov adj3 (process* or decision* or chain*)).tw,kf.
17	ec.fs.
18	or/11-17
19	and/4,10,18
20	limit 19 to English language

Study appraisal:

A descriptive/qualitative analysis was performed to assess the quality of cost-effectiveness studies. Quality appraisal was performed using the CHEERS checklist included in Appendix 10.1 (112). The Checklist contains 24 items, which was given a 1 or 0. Any study with fewer than 20 out of 24 was considered to contain a high risk of bias.

Data Extraction, Analysis, and Synthesis:

Model input parameters and incremental cost-effectiveness ratio (ICER) values were extracted each study. Costs of all procedures were converted to a 2018 value of United States Dollar for ease of comparison through an online tool developed by Campbell Collaboration and EPPI-Centre (version 1.6), specifically using the Organisation for Economic Co-operation and Development (OECD) source for purchasing power parities (113). Costs per QALY were calculated using converted costs (converted costs/QALY). A subset of studies that provided probabilistic sensitivity analysis data in the form of a cost-effectiveness acceptability curve were selected for further analysis. Cost-effectiveness acceptability curves depict thousands of bootstrapping simulations, where each simulation represents a different set of model input parameter values. This is based on probability distributions describing the uncertainty around the true values of a model's input parameter values. The x-axis is the willingness-to-pay threshold (WTP) and the y-axis is the probability of cost-effectiveness. The probability of cost-effectiveness is calculated from the percentage of simulations that a strategy produces an ICER value below the WTP (x-axis). In a model testing two strategies, the strategy with greater than 50% probability of cost-effectiveness (at a given WTP), is considered cost-effective (114, 115). To compute this, data points were extrapolated from existing cost-effectiveness acceptability curves in the studies using GetData Graph (Digitizer version 2.26.0.20) (116, 117). The software allows digital copies of graphs to be analysed on a grid to allow approximation of data points used to plot the original curves. This data was combined in Excel and plotted using R (R Foundation for Statistical Computing, Vienna, Austria) and Rstudio (Boston, MA, USA). Results were not combined for meta-analysis due to heterogeneity in model design and parameters between studies, rather they were graphically represented to allow qualitative comparison. Instead, an in-depth narrative synthesis has been produced.

2.4 RESULTS

The study selection process was divided into four stages (Figure 4). A total of 10 studies were included in the data extraction process, with 5 studies that had probabilistic sensitivity analyses results included in sub-group analyses of cost-effectiveness acceptability curves.

Figure 4. Preferred Reporting Items for Systematic Reviews and Meta-Analyses

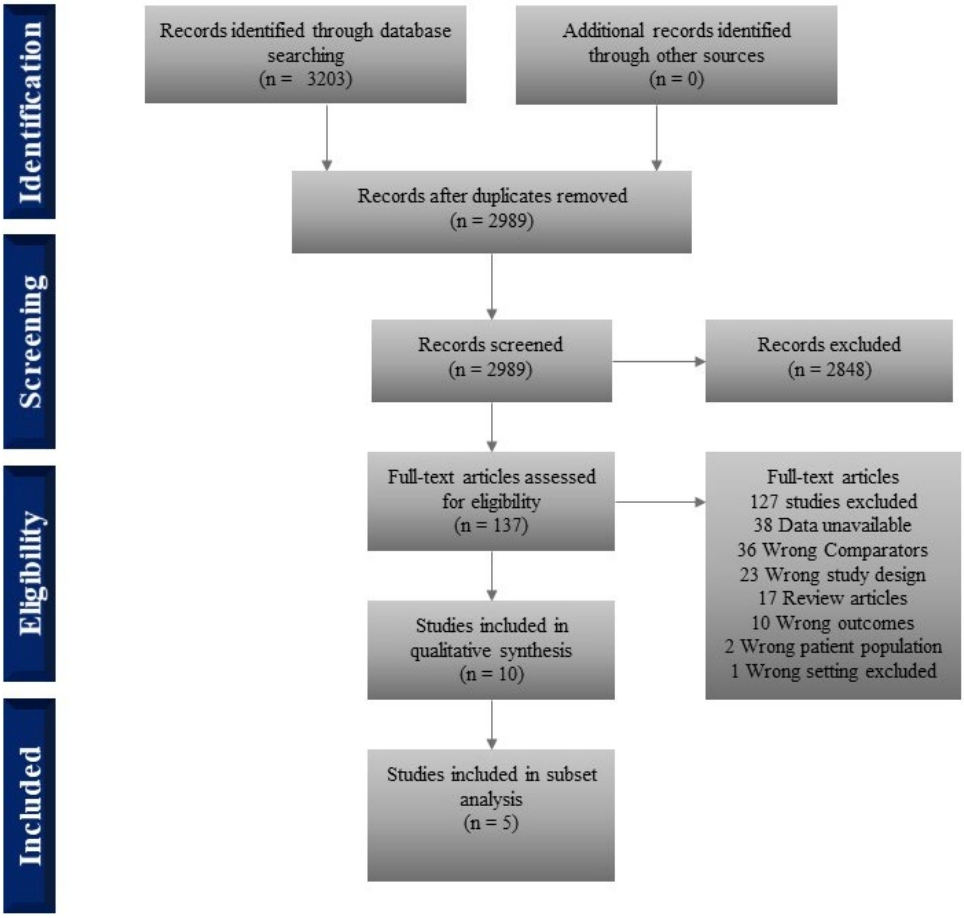


Table 4. List of economic evaluations, interventions, main outcome (incremental cost-effectiveness ratio), and willingness-to-pay threshold

Studies	Currency	Base treatment	Comparator (s)	ICER Currency Per QALY	WTP
1999 Provenzale	USD (1993)	Natural History	EGD Surveillance q5yr	**$98,000 ∓**	$100,000
			EGD Surveillance q4yr	$108,333	
			EGD Surveillance q3yr	$132,222	
			EGD Surveillance q2yr	$197,972	
			EGD Surveillance q1yr	$497,297	
2003 Inadomi	USD (2001)	Natural History	Surveillance for dysplasia only	**$10,440 ∓**	$100,000
			EGD Surveillance q5yr	$596,000	
			EGD Surveillance q4yr	$383,860	
			EGD Surveillance q3yr	$381,543	
			EGD Surveillance q2yr	$414,233	
2006 Garside	GBP (2002)	Natural History	EGD Surveillance q3yr	-£19,318	£20,000
2009 Inadomi	USD 2007	Natural History	Radiofrequency Ablation of NDBE (no surveillance)	$16,286	$100,000
			EGD Surveillance with RFA dysplasia only	NA	
			Radiofrequency Ablation of NDBE (with surveillance)	NA	
2014 Gordon **	USD (2011)	Natural History	EGD Surveillance q2yr	$60,858	$50,000
			Biomarker modified Surveillance #1	**$38,307 ∓**	
			Biomarker modified Surveillance #2	**$48,111 ∓**	
2014 Kastelein**	Euro (2012)	Natural History	EGD Surveillance q5yrs with RFA	**€5,283 ∓**	€35,000
			EGD Surveillance q5yrs with EMR + RFA	-	
			EGD Surveillance q5yrs with Oesophagectomy	-	
			EGD Surveillance q4yrs with RFA	€62,619	
			EGD Surveillance q4yrs with EMR + RFA	-	
			EGD Surveillance q4yrs with Oesophagectomy	-	
			EGD Surveillance q3yrs with RFA	€105,755	
			EGD Surveillance q3yrs with EMR + RFA	-	
			EGD Surveillance q3yrs with Oesophagectomy	-	
			EGD Surveillance q2yrs with RFA	€324,420	
			EGD Surveillance q2yrs with EMR + RFA	-	
			EGD Surveillance q2yrs with Oesophagectomy	-	
			EGD Surveillance q1yr with RFA	-	
			EGD Surveillance q1yr with EMR + RFA	-	
			EGD Surveillance q1yr with Oesophagectomy	-	

2016 Lindblad	USD (2011)	Natural History	EGD Surveillance q2yr	$60,858	$50,000
			2 Step exclusion to eliminate Barrett's Length < 2 cm	**$33,807** ₸	
			Eliminating Barrett's < 3 cm	**$35,785** ₸	
			Eliminating Barrett's < 4cm	$110,583	
2016 Das	USD (2013)	Natural History	EGD Surveillance	**$13, 823**	
			Mutational Load based stratification	**$2,847** ₸	
			Radiofrequency Ablation of NDBE	**$11,417** ₸	
2019 Hao ****	USD (2012)	EGD Surveillance (q3yr)	Biomarker Assay	**$52,483** ₸	$100,000
2020 Omidvari	USD (2015)	Natural History (male cohort)	EGD Surveillance q0; LGD EET (c)	**$2,476** ₸	$100,000
			EGD Surveillance q5yr; LGD EET (c)	**$19,779** ₸	
			EGD Surveillance q4yr; LGD EET (c)	**$32,850** ₸	
			EGD Surveillance q3yr; LGD EET (c)	**$53,044** ₸	
			EGD Surveillance q2yr; LGD EET (c)	$156,313	
			EGD Surveillance q2yr; LGD EET (nc)	$1,105,045	
			EGD Surveillance q1yr; LGD EET (c)	$1,446,520	
2020 Omidvari	USD (2015)	Natural History (female)	LGD only EGD surveillance	**$6,716** ₸	$100,000
			EGD Surveillance q0; LGD EET (c)	**$7,561** ₸	
			EGD Surveillance q5yr; LGD EET (c)	**$36,045** ₸	
			EGD Surveillance q4yr; LGD EET (c)	$118,233	
			EGD Surveillance q3yr; LGD EET (c)	$202,874	
			EGD Surveillance q3yr; LGD EET (nc)	$700,093	

EGD- Esophagogastroduodenoscopy; EMR- Endoscopic Mucosal Resection; EET- Endoscopic Eradication Treatment; NDBE- Non-dysplastic Barrett's oesophagus; LGD- Low Grade Dysplasia; HGD- High Grade dysplasia; EAC- Oesophageal Adenocarcinoma; QALY- Quality Adjusted Life Years; WTP- Willingness to Pay Threshold; (c) LGD confirmed by additional endoscopy; (nc) not confirmed by additional endoscopy

* Esophagectomy for HGD; ** 6 monthly cycles used, instead of annual;

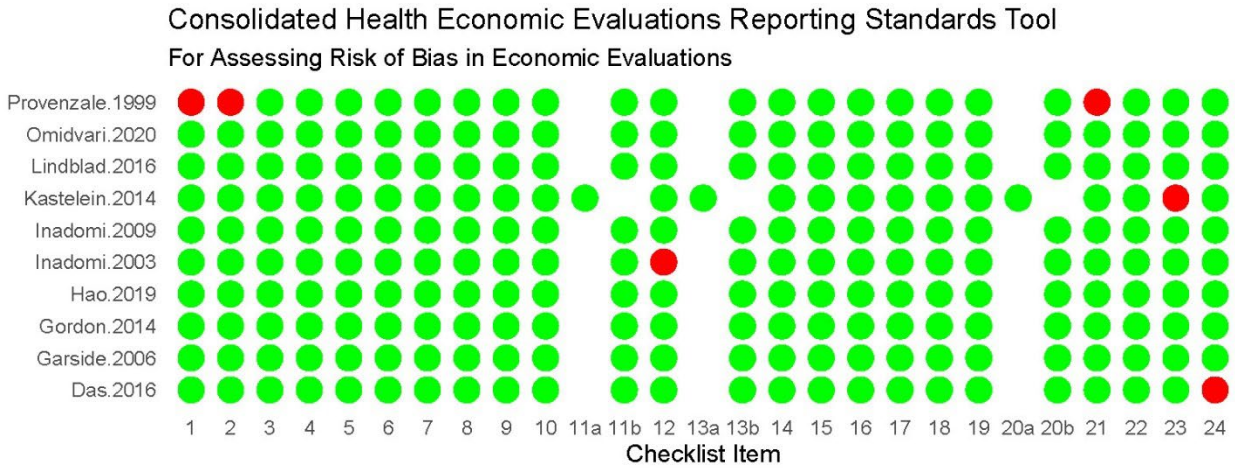
*** HGD/EAC considered one entity → RFA **or** EMR and RFA **or** Neoadjuvant chemoradiation and Oesophagectomy;

**** Time horizon 5 years only; ₸ Cost-Effective Treatments

Critical Appraisal of Studies:

Two reviewers scored all studies; all differences were discussed to reach a consensus. All studies met more than 20 of the checklist items from the CHEERS statement. Thus, the risk of bias was considered to be minimal. Sss xxxx shows the results of the critical appraisal.

Figure 5. Risk of Bias using Consolidated Health Economic Evaluations Reporting Standards Tool



Models and Assumptions:

Model structure and inputs varied widely across all studies. Six studies originated from the United States, two from Australia, one from United Kingdom, and one from Netherlands. All studies except Hao et al (118) used a “no surveillance” strategy of Barrett’s oesophagus as their base strategy, which did not involve endoscopic surveillance, with endoscopy only performed once symptoms developed. This was compared to endoscopic surveillance frequency options or modified surveillance using risk stratification (e.g. using a biomarker, length of Barrett’s segment, etc.). Four studies were conducted before the clinical adoption of endoscopic treatments such as radiofrequency ablation, argon plasma ablation, and endoscopic mucosal resection, and hence did not include endoscopic interventions in their modelling (119-121). Three studies had a male cohort as the starting population (120, 122, 123), while the rest evaluated a mixed population. Only Omidvari 2020 (123) evaluated cost-effectiveness in a female-only cohort.

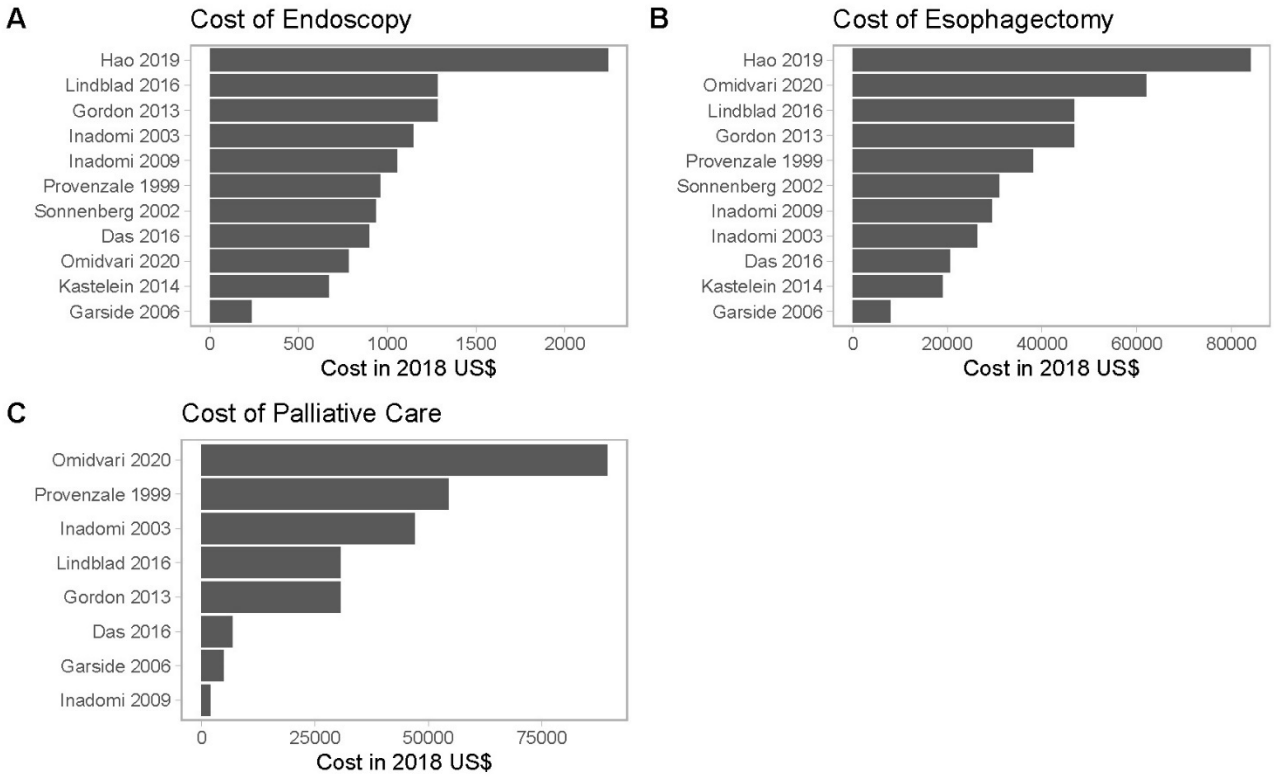
One of the heterogeneities between studies was the definition of health states and procedures. This impacted the model inputs associated with those health states and procedures. For this reason, not all model inputs could be compared. However, the studies that provided similar definitions to procedures and health states were extracted to provide an appreciation of the differences in costing and utilities, which are the elements needed for calculating ICER values (Figures 2 & 3).

Model inputs:

2.4.1.1 Costs and Utilities:

For ease of comparison, the costs were converted to USD 2018, but expectedly varied widely across all models. This is partly due to how the health states were defined, which varied according to the clinical model. The only cost distinctly comparable across all studies was the cost of surveillance endoscopy. Treatment costs for early adenocarcinoma were the next most reported variable; although some studies included costs of medical therapy in this cost, while others referred to this as the cost of esophagectomy and hospital admission. The median cost of a diagnostic endoscopy and biopsy was $960 (interquartile range $839 - $1214), and treatment of early oesophageal adenocarcinoma was $30,852 (interquartile range $23,370 – $46,823). Treatment of oesophageal adenocarcinoma with metastatic disease had the largest variation in cost (Figure 6c) with median of $30,578 (interquartile range $6,279 – $48,790). Figure 6 shows the differences in costs across studies of diagnostic endoscopy and biopsy (Figure 6a) and treatment of early oesophageal adenocarcinoma (Figure 6b).

Figure 6. Common cost inputs (2018 USD) across studies

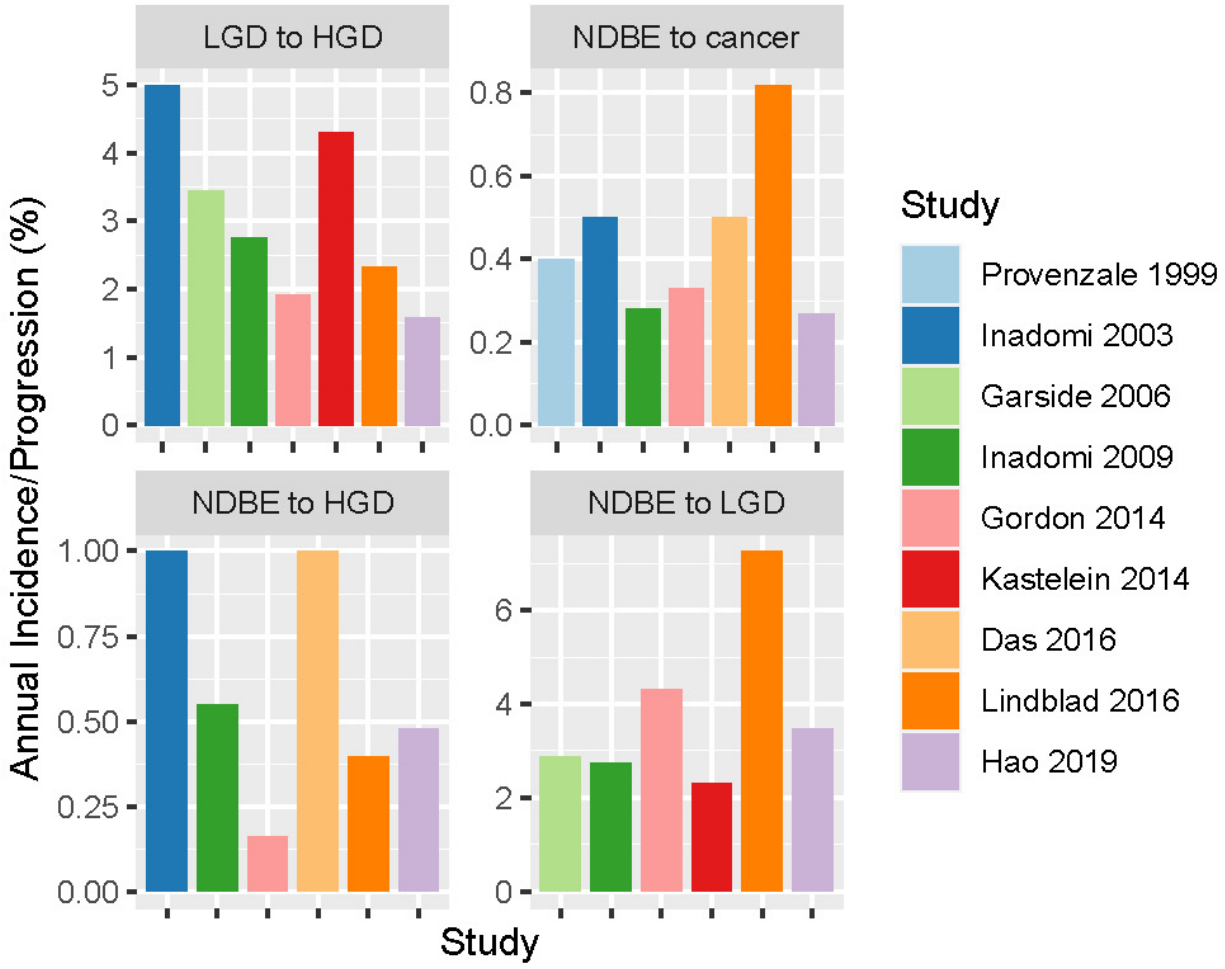


Not all studies reported utility values associated with all health states. The key utility values were extracted. All values had a wide range, early-stage oesophageal adenocarcinoma was seen to have a wide variation with a range of 0.5 to 0.84.

2.4.1.2 Transition rates:

Progression rates were related to the design of the model and local clinical practices. Some studies included a model that allowed the patient or cohort to skip between health states, e.g. non-dysplastic Barrett's oesophagus to high grade dysplasia directly or low grade dysplasia to oesophageal adenocarcinoma. Other models assumed that non-dysplastic Barrett's oesophagus must go through low grade dysplasia before progressing to high grade dysplasia. The transition rates reflect the design of the clinical model used. These values (provided in annual incidence percentage) are summarised in Figure 7. The median (IQR) was 0.45% (0.318% -0.5%) for non-dysplastic Barrett's oesophagus to oesophageal adenocarcinoma, 3.18% (2.78% - 4.1%) for non-dysplastic Barrett's oesophagus to low grade dysplasia, 2.75% (2.11% - 3.875%) low grade dysplasia to high grade dysplasia. These rates reflect the heterogeneity found in the literature (17, 19, 21, 107, 124).

Figure 7. Variation in transition rates across studies



2.4.1.3 Incremental Cost-Effectiveness Ratio:

Table 4 shows a list of the studies included in the systematic review, the base treatment strategy, comparators, the reported ICER value, and the willingness-to-pay threshold for cost-effectiveness specified in the paper. The cost-effective strategies have been identified in bold.

2.4.1.4 Cost-Effectiveness prior to Endoscopic Eradication Treatments:

All studies in this category (Provenzale 1999, Inadomi 2003, Garside 2006 (119-121)) found guideline-recommended endoscopy surveillance was not cost-effective. Garside et al. found that endoscopic surveillance (every 3 years) was not cost-effective compared to non-surveillance arms, noting that endoscopic surveillance cost more and generated fewer QALYs. The other two studies found the ICER values at 2 year and 3-year endoscopic examination intervals were far above their reference WTP threshold (Provenzale- $197,972/QALY for every 2 years; $132,222/QALY for every 3 years/ Inadomi $414,233/QALY for every 2 years; $381,543/QALY for every 3 years) (119, 120).

2.4.1.5 Reducing the frequency of endoscopic surveillance:

Provenzale 1999, Inadomi 2003 and 2006, (119, 120) Kastelein 2014 (125), Omidvari 2020(123) et al. evaluated the cost-effectiveness of reducing the frequency between surveillance periods. In all cases, more frequent surveillance i.e. less than every 3 years was found not to be cost-effective. Provenzale et al. found q5yr to be just under the WTP threshold of $100,000/QALY (ICER $98,000)(119). Kastelein et al. showed endoscopic surveillance every 5 years was only cost-effective when patients received RFA for high grade dysplasia (125).

Omidvari et al. performed an extensive analysis evaluating numerous strategies in three different population models (MISCAN-EAC, EACMo, MSCE-EAC) (123). The strategies were permutations of increasing intervals for endoscopic surveillance, endoscopic eradication treatment at different stages of Barrett's oesophagus (non-dysplastic Barrett's oesophagus, low grade dysplasia, and high grade dysplasia), and confirmation of low grade dysplasia by repeat endoscopy. This was also the only study that evaluated cost-effectiveness specifically in a *female cohort* and found optimal frequency of surveillance to be every five years for women, whereas the optimal strategy for the male cohort was endoscopic surveillance every 3 years with low grade dysplasia eradication (note: low grade dysplasia was confirmed at 2 endoscopies prior to endoscopic eradication treatment). Although this correlates well with incidence data that shows female patients have lower risk of progression to oesophageal adenocarcinoma, current guidelines do not recommend varied surveillance intervals for female patients. As for eradication of dysplasia,

more recent guidelines (NICE, ACG) have approved it for low grade dysplasia as well, but this has not been adopted worldwide.

2.4.1.6 Modified endoscopic surveillance with clinical or biomarker tool:

Four studies (Gordon et al 2014 (126), Lindblad et al 2016 (70), Das et al 2016 (127), Hao 2019 et al (118)) examined use of a risk stratification strategy for selective surveillance of non-dysplastic Barrett's oesophagus patients. Table 5 provides an overview of the base and modified surveillance strategies, risk stratification tools used for selection or exclusion of patients, costs per QALY, ICER values, and the WTP value at which more than 50% of the trials were considered cost-effective. Three studies (Gordon et al 2014, Lindblad et al 2016, Das et al 2016 (70, 126, 127)) modelled natural history as their base strategy, while Hao used endoscopic surveillance (guideline specified) as the base strategy. Guideline specified endoscopic was a common strategy among all studies. When the converted cost/QALY of endoscopic surveillance in studies was compared, it varied widely from $600/QALY (Gordon et al 2014 (126)) to $1957/QALY (Hao et al 2019(118)) (and in broader context $445/QALY in Garside et al 2006(122), data not shown). This is also reflected in cost inputs for the respective studies, as noted in Figure 6. Hao et al (118) reported the highest cost of endoscopy and esophagectomy, while the other studies (Gordon et al 2014, Lindblad et al 2016, Das et al 2016 (70, 126, 127)) had similar cost per QALY and costs of endoscopy and esophagectomy. Even with significant heterogeneity in model structure, inputs, and strategies, all studies applying a risk-stratification endoscopic surveillance showed cost-effectiveness of their primary strategy. Roughly, the excluded proportions of patients were 85.5% for Gordon et al, 77% for Das et al, 77% for Hao, and for Lindblad et al. 37% for <2 cm; 69% for < 3 cm; 75% for <4cm segment of non-dysplastic Barrett’s oesophagus. *In other words, more than a third of patients currently in guideline-recommended endoscopic surveillance programs may need to be excluded to make it cost-effective.*

Table 5. Summary of Studies that modelled a modified surveillance program

Study	Base strategy	Model and Modification to Surveillance	Cost per QALY	ICER	50% Probability CEAC (WTP)
2014 Gordon	Natural History	Base	$217	-	Not reached
		EGD Surveillance	$600	$60,858	
		- Standard Australian guidelines (every 2 years for NDBE, every 6-12 months for LGD, EMR/EET/esophagectomy for HGD)			
		Hypothetical Biomarker			
		- Based on EGD biopsy flow cytometric analysis			
		- 14.5% positive in base case			
		Biomarker Scenario A	$454	**$38,307** ₸	~$41,500/QALY
		- Negative patients excluded from further surveillance			
		- Positive patients are under surveillance every 6-months			
		Biomarker Scenario B	$516		
		- Negative test excluded		**$48,111** ₸	No CEAC
		- Positive test received 6-monthly surveillance for 5 years and 2 yearly after that			
		Biomarker Scenario C	$358	**Dominated** ₸	No CEAC
		- Negative test means exclusion from surveillance			
		- Positive test received ablation therapy			
		Model Features:			
		- Six-month cycles			
		- Starting population 50-year-old male and female with 95% NDBE, 4% LGD, and 1% HGD			
		- Time horizon was 80 years age or death			
		- Included different pathways based on T-staging			
		One-way sensitivity analysis			
		- Key drivers: High proportion of positive biomarker test, decreasing maximum surveillance duration to 5 years (base 30 years)			
		- Not affected by: progression rates of NDBE to LGD/HGD/EAC, costs of endoscopy or esophagectomy			
2016 Lindblad	Natural History	Base	$876	-	
		Two Step exclusion based on NDBE segment length			
		• ***Excluding NDBE < 2 cm*** (37% of total patients; 0.15% incidence of HGD/EAC)	$2263	**$33,807** ₸	~$33,000/QALY
		• ***Excluding NDBE < 3 cm*** (69% of total patients; 0.22% incidence of HGD/EAC)	$1992 $2170	**$35,785** ₸ $110,583	~$42,891/QALY ~$122,000/QALY

		• ***Eliminating NDBE < 4cm*** (75% of total patients; 0.35% incidence of HGD/EAC) Model Features: Same as 2014 Gordon One-way sensitivity analysis: not reported			
2016 Das	Natural History	Base	$794	-	Not reached
		EGD Surveillance • Standard Guidelines surveillance as per ACG (2016) q3-5 years for NDBE, every 1 year for LGD, EET for HGD	$1,303	**$13, 823**	Not reached
		Mutational Load based stratification • Based on LOH of tumour suppressor proteins TP53 and CDKN2A • If no ML, then excluded from surveillance • Low ML received guideline surveillance • High ML received ablation	$1,185	**$2,847** ₸	$4100/QALY
		Radiofrequency Ablation of NDBE • Non discriminant stepwise ablation of all NDBE using HALO procedure Model Features: • One-year cycle • Starting population 50-year-old white ***male*** • Lifetime horizon One-way sensitivity analysis • Key Drivers: Low ML risk factor, Frequency of EGD surveillance, probability of Low ML • Not affected by: cost of ML test, probability of High ML	$975	**$11,417** ₸	Not reached

2019 Hao	EGD	Base: EGD Surveillance • Standard guideline surveillance as per ACG q3 years for NDBE, annually for LGD, and EET for HGD ***Biomarker Assay*** • Based on TissueCypher® Cernostics assay, 3 tiers of risk • Low risk surveillance q5years (77% of patients) • Intermediate risk: Standard guideline surveillance (15%) • High risk: Ablative treatment (8%) • False negative rate of biomarker ○ 16.7% for HGD ○ 8.1% for EAC Model Features: • Time horizon 5 years • Natural history not modelled One-way sensitivity analysis • Key drivers: progression from NDBE to EAC, cost of assay and endoscopy • Not affected by: transition from LGD to EAC	$1,957 $2,013	- **$52,483** ₸	 ~$72,500/QALY

EGD- Esophagogastroduodenoscopy; EMR- Endoscopic Mucosal Resection; EET- Endoscopic Eradication Treatment; NDBE- Non-dysplastic Barrett's oesophagus; LGD- Low Grade Dysplasia; HGD- High Grade dysplasia; EAC- oesophageal Adenocarcinoma; QALY- Quality Adjusted Life Years; WTP- Willingness to Pay Threshold; ML- Mutational Load; LOH- Loss of Heterozygosity; ACG- American College of Gastroenterology; CEAC- Cost-effectiveness acceptability curve

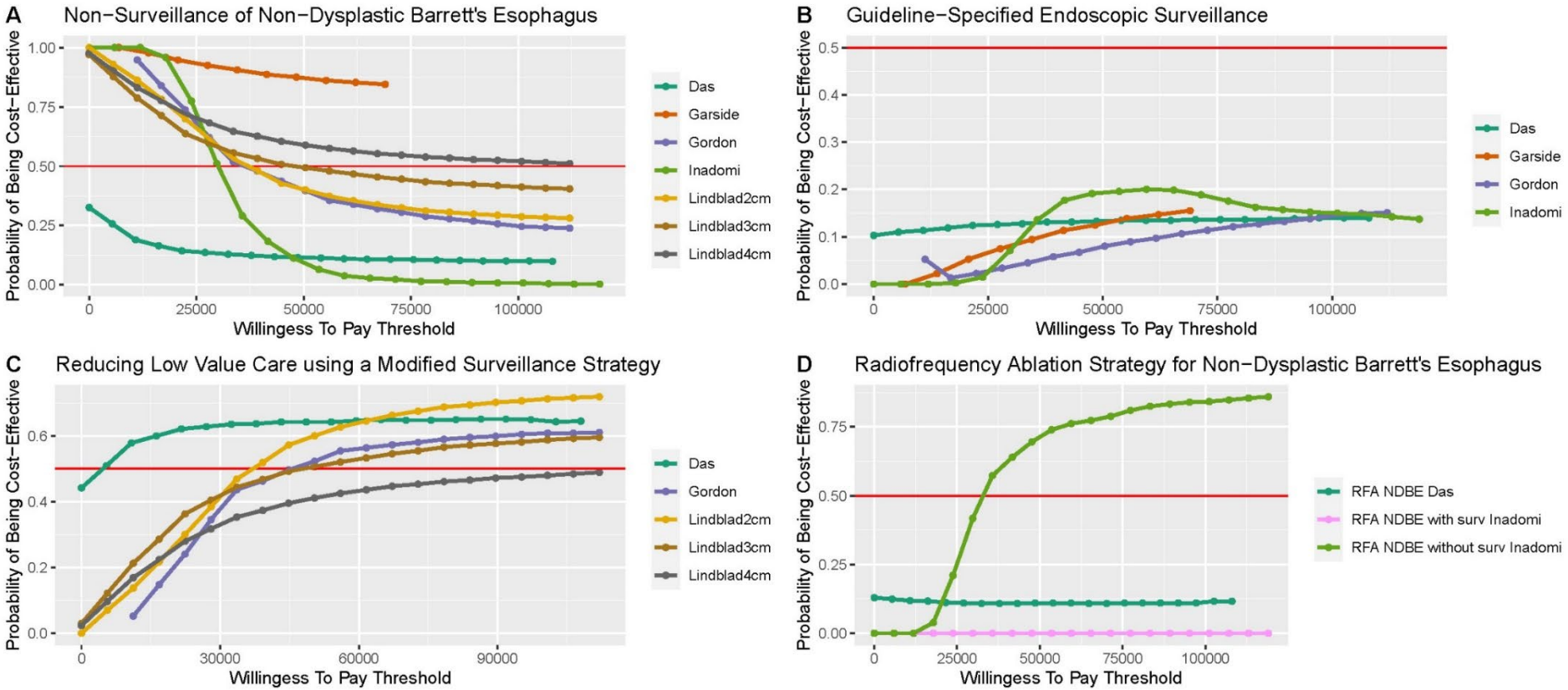
₸ indicates cost-effective treatment strategies

Cost per QALY: Using converted costs (USD 2018)

2.4.1.7 Probabilistic Sensitivity/Cost-Effectiveness Acceptability Curve Analysis:

Probabilistic analysis was performed in nine studies, but six studies provided a cost-effectiveness acceptability curve which was used for further data extraction (Garside 2006, Inadomi 2009, Gordon 2014, Lindblad 2016, Hao 2019 (70, 118, 121, 126, 128)). The cost-effectiveness acceptability curves from Hao was excluded from qualitative comparison because it did not model a no-surveillance scenario as its base strategy. These are re-graphed in Figure 8(a-d); a horizontal line at 50% probability has been drawn to indicate cost-effectiveness of strategy above the line. Each graph represents a treatment strategy. Nearly all studies found a no-surveillance strategy to be cost-effective at low WTP thresholds (Figure 8a), but the converse is true at high WTP thresholds. A modified endoscopic surveillance strategy had the opposite trend, so was not cost-effective at low WTP thresholds, but as the WTP thresholds increased, the cost-effectiveness improved. Most strategies in studies reached >50% probability cost-effectiveness well before $100,000 WTP (Figure 8c), and this is also reflected in Table 5 (last column). Again, the guideline-specified endoscopic surveillance strategy was found to be not cost-effective in most studies (Figure 8b). Therefore, a modified surveillance with endoscopic examination thus is likely to improve cost-effectiveness as it excludes low-risk individuals that do not progress to adenocarcinoma

Figure 8. Probabilistic Sensitivity Analysis comparison through cost-effectiveness acceptability curve analysis.



* Vertical line (red) at 50% probability, above which the treatment strategy is considered cost-effective. Lindblad- Both “non-surveillance” and “surveillance cohort consisted only of individuals greater than or equal to 2, 3, or 4cm length of Barrett’s segment in the oesophagus. RFA NDBE Das- All individuals with non-dysplastic Barrett’s oesophagus underwent radiofrequency ablation. RFA NDBE without surv Inadomi- All individuals with NDBE underwent radiofrequency ablation and were not followed up with endoscopic surveillance. RFA NDBE with surv Inadomi- All individuals with NDBE underwent radiofrequency ablation and were followed up with endoscopic surveillance.

2.5 DISCUSSION:

Approximately 88-92% of the patients under endoscopic surveillance have a finding of non-dysplastic Barrett's oesophagus. The annual progression of non-dysplastic Barrett's oesophagus to oesophageal adenocarcinoma ranges between 0.19%(17) and 0.47% (124). The majority of individuals with non-dysplastic Barrett's oesophagus do not progress to oesophageal adenocarcinoma but are maintained under endoscopic surveillance due to the high risk of a poor outcome associated with advanced oesophageal adenocarcinoma. In 2010 Hirst et al. (109) conducted a systematic review of cost-effectiveness of endoscopic surveillance including 7 studies and concluded that conventional 2 yearly surveillance was not cost-effective unless new technologies that are able to discriminate between high and low risk Barrett's oesophagus are found. Endoscopic eradication treatment strategies have been shown to be effective in multiple trials recently, and this has spurred a change in guidelines for patients with high- and low-grade dysplasia (NICE guidelines, ACG guidelines). A more recent systematic review conducted by Saxena and Inadomi in 2017 (104) also examined the cost-effectiveness of endoscopic surveillance and concluded that endoscopic eradication in patients with high-grade dysplasia is ***cost-effective***, but cost-effectiveness in individuals with low-grade dysplasia depends on the accuracy of the histopathologic diagnosis. They also concluded that endoscopic surveillance could be cost-effective, but only for a *high-risk* population although their study did not quantitatively define this 'risk.' Their review aimed to determine the cost-effectiveness of endoscopic surveillance in the context of identifying and excluding low-risk individuals from surveillance, thereby defining a high-risk group.

A limitation of this study is that comparisons between economic evaluations are difficult because of varied model inputs and contextual differences in institutional practices. For example, the cost of palliative care ranged from ~US$2000-89,000 (2018 value) across the various evaluations. Whilst this variability might suggest that comparisons could be futile (129), common findings across studies may provide supporting evidence for the validity of the reviewed models' outputs. The novel approach of comparing the probabilities of cost-effectiveness at varying willingnesses to pay thresholds for additional QALYs is presented. Despite the different contexts in which the models were developed, the probability curves displayed relatively similar profiles. Figure 8 represents this graphically, indicating that a "no surveillance" option is not a practical strategy from both an economic and public health perspective at most WTP thresholds above US$35,000/QALY (converted 2018 value). Guideline recommended endoscopic surveillance also does not offer a cost-effective solution, as seen in Figure 8b by an inability to reach the 50% probability horizontal line in most studies.

If the “natural history” or no surveillance option is not cost-effective at moderate and high WTP thresholds, and endoscopic surveillance is generally not cost-effective, then it seems logical that the option that splits the difference between these two strategies will likely be cost-effective. This is exactly what is observed, as seen in Figure 8c. Reducing the number of surveillance endoscopies performed by clinical or biomarker-based risk stratification was reported to have high chance of being cost-effective between $10,000/QALY and $45,000/QALY WTP threshold. To achieve this some studies used biomarkers to select or deselect patients (Gordon et al 2014, Das et al 2016, Hao et al 2019 (118, 126, 127)), but others used Barrett’s segment length as a guide (Lindblad et al 2016(70)). The cost-effectiveness of models employing a risk stratification strategy (Table 5) depends at least partially on the proportion of patients being excluded from surveillance. The most cost-effective strategies excluded approximately 60-75% of patients from endoscopic surveillance (Table 5). Patients in this cohort are theoretically at the lowest risk of developing oesophageal adenocarcinoma. Gordon et al and Das et al presented evidence of this in their one-way sensitivity analyses. Varying the proportions of patients with positive/negative risk modifier heavily influences the likely cost-effectiveness. Regarding age vs. risk, this was not considered in the examined studies. However, it should be recognised that older patients have a significantly higher risk of developing oesophageal adenocarcinoma, whereas patients with persistent Barrett’s (without dysplasia) are not seen to be at higher risk(124). This suggests that limiting surveillance to older age groups might be a strategy worth considering for future modelling. Lastly, the American College of Gastroenterology (ACG) currently does not recommend the use of biomarkers to guide endoscopic surveillance, but it is likely that in the future, we will have more reliable biomarkers with robust sensitivity and specificity to support their clinical practice.

2.6 Concluding Remarks

Endoscopic surveillance at current guideline-recommended intervals is not cost-effective. No surveillance is also not cost-effective at thresholds above $35,000/QALY (converted 2018 value). Modifying surveillance programs by eliminating patients at low risk of progression or increasing the surveillance intervals reduces the number of endoscopies performed and can be cost-effective strategies. Several studies provide evidence of cost-effectiveness with reduced frequency of endoscopy in male and female cohorts (119, 120, 123). Others present evidence of cost-effectiveness in risk-stratified endoscopic surveillance programs, but this needs to be further evaluated to ensure appropriate selection and follow up (70, 118, 126, 127).

While it is important to intervene early in patients with high-risk Barrett’s oesophagus, the key to improving cost-effectiveness might require doing less rather than more! Clinical assisted risk-stratification, and possibly in the future biomarker assisted risk-stratification can aid in improving cost-effectiveness and should be explored. In addition, as women are at a much lower risk of

progression to oesophageal adenocarcinoma and reducing endoscopic surveillance in this lower risk group warrants further investigation.

3 CHAPTER 3- DETERMINING LIFETIME INCIDENCE OF OESOPHAGEAL ADENOCARCINOMA AND PREVALENCE OF BARRETT'S OESOPHAGUS

3.1 Chapter overview

The main outputs of a cost-utility analysis are costs and quality adjusted life years (QALY). These outputs are calculated in a Markov cohort model, which accumulates costs and outcomes. Prior to this analysis, there is crucial aspect which must be addressed. Each Markov cohort model must represent the clinical condition it is modelling in a realistic manner, through the clinically relevant and measurable endpoints. These endpoints or model outputs can be any event or health state that is evidenced in the medical literature. In the case of Barrett's oesophagus, there is ample literature about patients in a surveillance program, but this is lacking for those not under endoscopic surveillance. Arguably, if they are known Barrett's oesophagus patients, they are likely to be offered endoscopic surveillance. But equally, most patients that present with oesophageal adenocarcinoma have never been examined endoscopically for Barrett's oesophagus. Knowing that data for the prevalence of Barrett's oesophagus and the total number of cancers within a period are available, we sought to answer two key questions prior to developing our final Markov cohort model: 1) What is the risk of developing oesophageal cancer and adenocarcinoma in the general population? And 2) What is the risk of developing oesophageal adenocarcinoma in patients with Barrett's oesophagus: a) Under surveillance; and b) Not under surveillance (natural history/progression).

The expectation was that these questions would be easily answerable through a literature review, but this was not the case. For one, lifetime risk of oesophageal cancer or adenocarcinoma in the general population had not been reported for Australian population. Most cancer registries (except for USA) in fact did not record subtypes of oesophageal cancer. Also, literature reporting Barrett's oesophagus progression to oesophageal adenocarcinoma had varied follow up periods. And lastly, prevalence rates of Barrett's oesophagus reported by observational studies differed from outputs of computation models. In order to further understand the complexities surrounding model outputs of a Markov cohort model of Barrett's oesophagus progression, a simplified state transition model was created specifically to compute the lifetime risk of oesophageal cancer (all subtypes) and oesophageal adenocarcinoma. The was run in various starting cohorts, i.e. for Australian and American populations (including male only, female only, Barrett's oesophagus only etc). The annual rate of progression in the general population was obtained from cancer registries in the form of age and sex-related incidence. Once the lifetime risk of cancer was calculated, the prevalence of Barrett's oesophagus was back-calculated using an optimisation algorithm. As an additional benefit, age-related prevalence rates of Barrett's oesophagus were also calculated using this optimisation algorithm. The results of this simplified state transition model and the literature surrounding it are presented in this chapter.

3.2 Incidence of Oesophageal Cancer and subtypes

The incidence of oesophageal cancer varies widely across the world. Oesophageal adenocarcinoma and squamous cell carcinoma constitute approximately 90-95% of all oesophageal cancers (130). Small cell carcinoma, large cell carcinoma, leiomyosarcomas, carcinoids, and lymphomas are rare subtypes that make up less than 5% of all oesophageal cancers. The remaining percentage of cancers are reported as undifferentiated/non-characterised (131). Squamous cell is still the predominant variant of oesophageal cancer, accounting for 88% of the cases globally. Many of these cases are found in underdeveloped nations. While the rate of new squamous cell carcinomas of the oesophagus has declined significantly in developed nations, East African and Central Asian countries account for the top 20 countries with the highest incidence of oesophageal cancer (Table 6) (36, 132). Malawi leads this list with 18.7 cases per 100,000, which is threefold higher than most developed nations. It is no coincidence that some of the poorest nations are atop this list. Environmental factors such as access to clean water, storage and processing of food, and wood-burning stoves likely aid ingestion of carcinogenic substances and organisms which increase risk of particular types of cancers (133).

Table 6. Top 20 Countries with Highest Incidences of Oesophageal Cancer (all subtypes). Taken from World Cancer Research Fund

Rank	Country	Incidence of Oesophageal Cancer (Age-standardised rate per 100,000)	Region
1	Malawi	18.7	Africa
2	Mongolia	18.5	Asia
3	Kenya	18.4	Africa
4	Bangladesh	14.8	Asia
5	China	13.9	Asia
6	Zimbabwe	12.4	Africa
7	Tajikistan	11.1	Asia
8	Uganda	10.8	Africa
9	Cape Verde	10.4	Africa
10	Burundi	10.2	Africa
11	Turkmenistan	9.2	Asia
12	Tanzania	8.9	Asia
13	Afghanistan	8.2	Asia
14	Kazakhstan	8.1	Asia
15	Comoros	7.9	Africa
15	Madagascar	7.9	Africa
17	South Africa	7.8	Africa
18	South Sudan	7.6	Africa
19	Somalia	7.5	Africa
20	Botswana	6.9	Africa

* Adapted from https://www.wcrf.org/dietandcancer/oesophageal-cancer-statistics/)

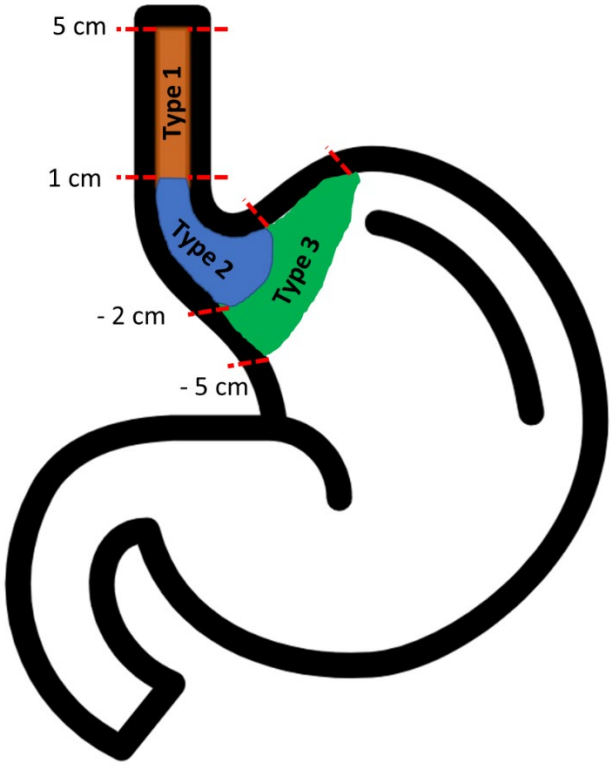
The proportion of oesophageal cancer accounting for the adenocarcinoma variant is based on multiple factors. While smoking, alcohol use, and human papillomavirus are known risk factors for oesophageal *squamous cell carcinoma* in the developed nations, there are several risk factors that relate to poor access to basic amenities of life in the less developed countries. Some have been mentioned above such as clean water as well as food preparation, refrigeration, and storage utility. Preventive medicine and health literacy also play a major part, as knowing about potential exposure to carcinogens can help reduce incidence of cancer itself. In addition, genetic polymorphisms may also play a part in predisposing certain ethnicities to oesophageal cancer, especially squamous cell carcinoma(134).

Most of the data profiling incidence of the subtypes is prospective studies and registry data from the United States. The incidence of oesophageal adenocarcinoma in United States is reported between 2.4 – 2.9 per 100,000, provided by the Surveillance, Epidemiology, End Results (SEER) program, which makes a concerted effort to record this data. However, without access to an accurate record of oesophageal cancer subtypes, estimating the incidence of oesophageal adenocarcinoma in other countries is much more difficult. This is mainly because most national registries cancer combine all oesophageal cancer subtypes, making it difficult to extract an accurate incidence of the adenocarcinoma variant by itself.

The variants of oesophageal cancer have very different origins. Both squamous cell carcinoma and adenocarcinoma still progress through a dysplasia to carcinoma transformation, but pathogenesis of oesophageal adenocarcinoma is more specific, as it involves columnar changes in the squamous epithelium in response to reflux of gastrointestinal contents. This is also why most oesophageal adenocarcinoma is found in the distal third of the oesophagus. Dysplastic transformation in squamous epithelium (without columnar changes) usually happens in the upper two-thirds of the oesophagus and is related to more “traditional” carcinogenic risk factors such as smoking and alcohol use, among others.

The significance of the anatomical location of these tumours further intensifies at the gastroesophageal junction. Tumours at the junction are categorised using a Siewert classification illustrated in Figure 9. Tumours that primarily lie more than 1 cm above the gastroesophageal junction are termed Siewert Type 1. Siewert Type 2 includes any tumours that lie within the gastroesophageal junction or within 1 cm proximally or 2 cm distally to the gastroesophageal junction. Tumours that lie more than 2 cm distal to the gastroesophageal junction are Siewert Type 3 (135). Of course, not all tumours obey these demarcations, but in general, Siewert Type 1 tumours are noted as true oesophageal cancers, whereas Siewert Type 3s are considered gastric cancers. Siewert Type 2 cancers are more difficult but can be classified as either oesophageal or gastric cancers.

Figure 9. Siewert Classification of Gastroesophageal junctional tumours



From a histopathological point of view, Siewert Type 2 tumours are tumours that originate from or near the “true” junction, which means they arise from dysplastic changes to columnar epithelia found at this junction (136). Presence of columnar epithelium at the gastroesophageal junction is normal/physiologic, as it is part of the gastric cardia. This, in theory at least, differs from oesophageal adenocarcinomas, which originate from dysplastic cells more than 1 cm proximal to the gastroesophageal junction. Importantly, dysplastic cells of oesophageal adenocarcinomas have been through metaplastic changes, which are visible on endoscopy. Whether a Siewert Type 2 tumour is classified in cancer registries as oesophageal or gastric is nearly impossible to answer. For this reason, it is important to know what percentage of all adenocarcinomas occurring in this region are classified as Siewert Type 2, which can be anywhere between 4-70% (135, 137-139). But the accuracy of this data is difficult to verify.

3.3 Lifetime Incidence of Oesophageal Cancer and Adenocarcinoma

Annual incidence is the most reported descriptive in cancer statistics. Annual incidence approximates the burden of a particular cancer on the population, in comparison to other cancers or conditions. Patterns of growing and reducing annual incidence can be related to *changes in risk factors*, when compared across appropriate time frames. Obesity and smoking are two such risk

factors associated with a plethora of medical conditions, but more importantly oesophageal cancer. These two risk factors have seen opposite trends in the last few years. While rates of smoking have actually decreased in Australia (140), rates of adult and childhood obesity have increased (141, 142).

Relating present rates of risk factors to the annual incidence of cancer can clarify the interactions between them, but it doesn't provide an accurate analysis. The transformation of solid organ cancers generally involves normal cell → exposure to risk factors → dysplasia → in situ cancer → invasive cancer. This period between normal cell and symptomatic cancer, also known as cancer latency, and can take anywhere from 10-25 years depending on the type of cancer (143). Risk factors are usually provided in prevalence rates, whereas cancers are provided in annual incidence. Annual incidence accounts only for new cases within a 12-month period, whereas prevalence rates include all existing cases at a given cross section. Linking cumulative or lifetime incidence rates of cancers to specific risk factor or precursor condition is feasible, but it requires several variables. These variables are:

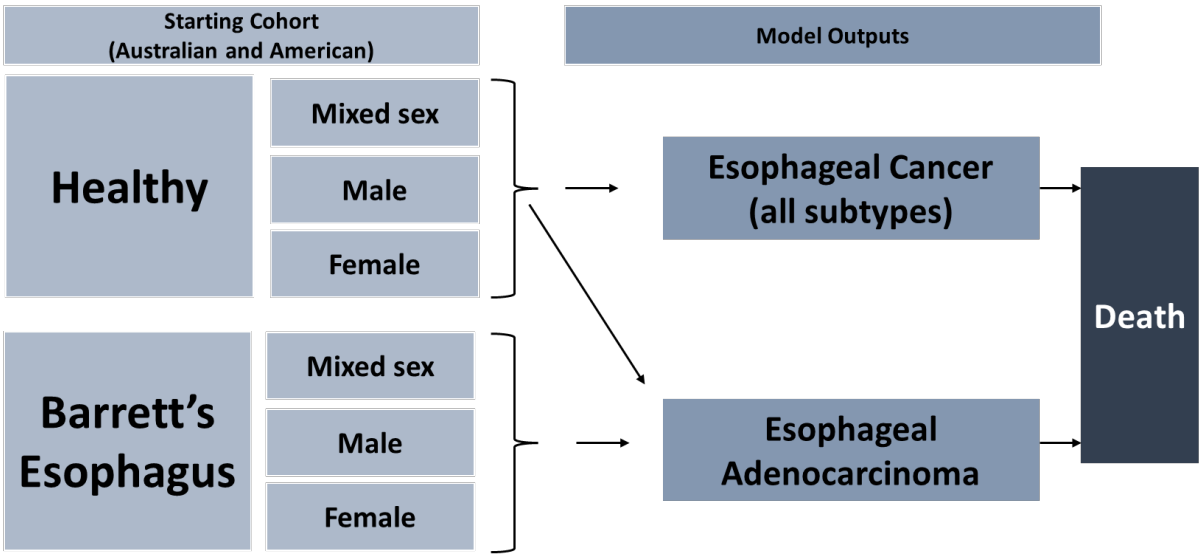
- Cancer incidence at various ages (age-related incidence)
- Cancer related mortality
- Non-Cancer related mortality
- Percentage of group with risk factor or precursor (also known as prevalence)

Using these variables, a computational model was developed that estimated the percentage of the cohort that will develop cancer, over a specified period. The period selected was from birth to 100 years, which estimates the probability of a particular cohort developing oesophageal cancer or adenocarcinoma in their lifetime. In addition, the model estimated key variables such as prevalence at various ages. This is highly advantageous, because otherwise, we would require large observational studies to estimate prevalence for each age group.

Methods: Creating the model

A simplified state transition model was created in TreeAge Pro (version R2.1 2021), simulating progression from healthy state to oesophageal adenocarcinoma. Male, female, and combined sex cohorts in Australian and American (non-Hispanic white) populations were modelled. The model's cycle length was one-year, with a time horizon of 100 years. The model starts at birth of the starting population (age 0). During each cycle there onwards, they either developed oesophageal adenocarcinoma or died. Once an individual in the cohort reaches oesophageal adenocarcinoma, they can either survive or die, thereby completing all movements in the model. Figure 10 shows the starting health states that were used in this model.

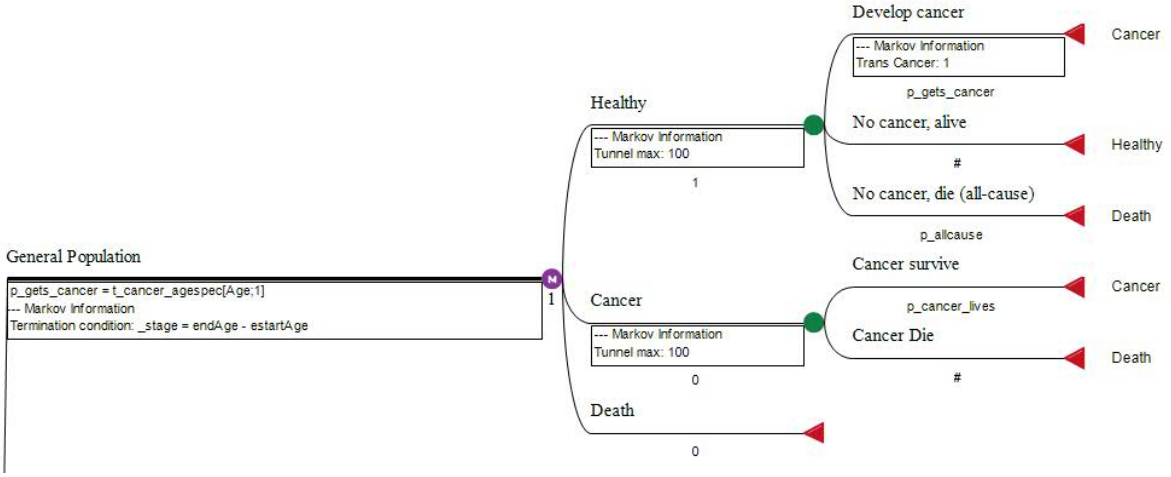
Figure 10. Starting cohorts



* Twelve cohorts were modelled, which were permutations of the initial health states in American (non-Hispanic White) and Australian populations. Model outputs were progression to cancer and death.

Figure 11 shows an example of a healthy cohort representing how the general population would progress through the model. Each cycle is 12 months, in which the cohort can either stay healthy (no cancer, alive), develop cancer (oesophageal cancer or adenocarcinoma), or die from natural causes (no cancer, die- all cause mortality). Patients who develop cancer can either stay alive (cancer survive) or die. The main model output was: Percentage of the cohort that developed cancer from birth to death – also known as lifetime incidence of cancer.

Figure 11. Decision tree showing movement for an individual from the general population through cohort model for calculation of lifetime incidence of oesophageal cancer or adenocarcinoma.



Age and sex-specific incidence data were obtained from Australian Institute of Health and Welfare (AIHW) and Surveillance Epidemiology and End Results (SEER) database. Data collation

and analysis was performed using Rstudio (R version 4.1.0; 2021-05-18). Disease states included Healthy, oesophageal adenocarcinoma, and death (Figure 10). A typical individual in the cohort would be born between year 2000-2016, starting from one of the health states mentioned above and ending in death. The probability of progressing from a healthy state to oesophageal adenocarcinoma depended on the characteristics of the starting population. Progression from a healthy state to oesophageal adenocarcinoma was sourced from observed age specified incidence rate of oesophageal cancer (AIHW database from 2000-2016 (144); SEER database 2000-2017(145)). For male and female populations, age-specified cancer incidence data were available from both AIHW and SEER data. For the Australian population, an assumption was made that oesophageal adenocarcinoma represents 65-80% of all oesophageal cancers (38), as this data was not provided in AIHW cancer registry. The 10-year mortality for oesophageal cancer was sourced from SEER data (from 2000-2017).

The probability of dying each cycle was based on sex and age-related all-cause mortality, and the probability of developing cancer was derived from the age-specified incidence of oesophageal cancer (from AIHW). For Australian data, AIHW was used (Creative commons license 3.0, access date: 15 January 2021) and for American data the SEER database and DevCan software (version 6.7.8.5; download date 2 February 2021)(145-147). When modelling the American population, only White (non-Hispanic) ethnicity cancer incidence rates were used, as this population represented the largest proportion of patients with oesophageal adenocarcinoma and demographically is more closely related to the Australian population. Age and sex specific (non-cancer) mortality was sourced from American and Australian mortality life tables: for the Australian population from the Australian Bureau of Statistics (ABS; access date 6 April 2021) and American population from Social Security data (148). A complete list of model inputs can be found in Table 4.

Table 7. Model Inputs for state transition model calculating lifetime incidence of oesophageal cancer

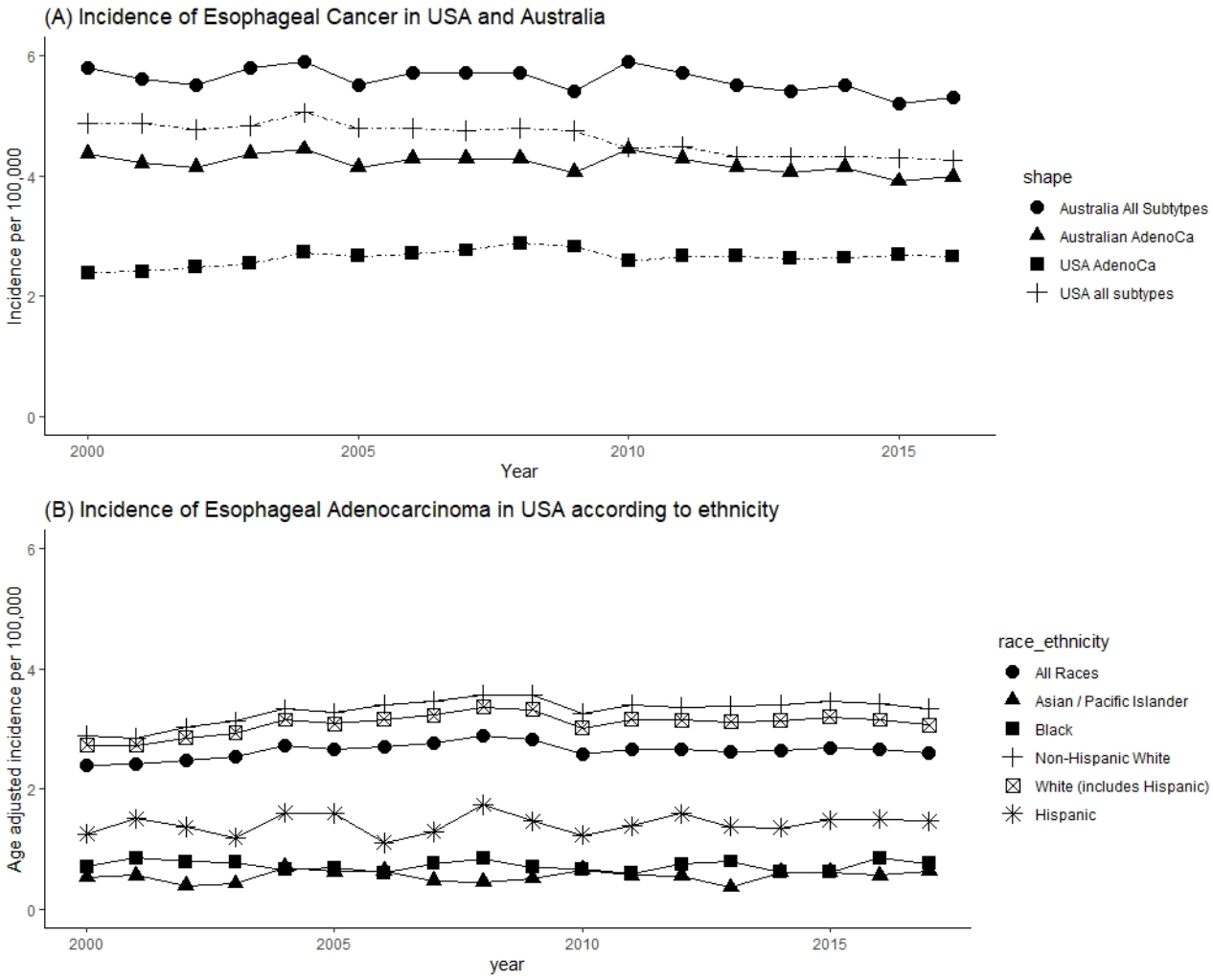
Type of Model Input	Value (Mean +/- SD)	Source
Starting age	0	
Time horizon	100 years (or death)	
Cycle Length	1 year	
All-cause mortality	Weighted average	Australian Bureau of Statistics- Weighted average Life tables (149) USA- Social Security Weight average Life table(148)
Assumed % oesophageal adenocarcinoma (of all oesophageal cancers)	70% +/- 10%	Nguyen 2016 (38) Queensland Oncology Analysis System (OASys) data(150)
Probability of being diagnosed with oesophageal adenocarcinoma (annual)	Age based incidence	AIHW(144) SEER(145, 151)
Chance of survival per annum	Based on oesophageal cancer mortality per year post-diagnosis	SEER(151, 152)

Results

3.3.1.1 Annual incidence of oesophageal cancer

The annual incidence of oesophageal cancer was higher in Australian population (5-6 cases per 100,000 persons) compared to US population (4.5-5 cases per 100,000 persons) seen in Figure 12a. The highest incidence of oesophageal cancer occurred between 80-90 years of life, with male incidence higher than female (data not shown). In the US population, (non-Hispanic) Whites had the highest incidence of oesophageal adenocarcinoma, followed by Hispanic, Black, and Asian/Pacific Islander ethnicities (Figure 12b). The yearly incidence of oesophageal adenocarcinoma was higher in Australians (4.0-4.6 cases per 100,000 persons) than US Whites (3.2-3.5 cases per 100,000) (Figure 12a).

Figure 12. (A) Differences in incidences of oesophageal cancer between USA and Australia (SEER and AIHW sources respectively).



* Solid lines represent Australian data, while the dashed lines represent American data. Incidence of Oesophageal adenocarcinoma is higher in Australia. (B) Differences in age-adjusted incidence of Oesophageal adenocarcinoma in United States between ethnicities. Non-Hispanic white population carries the highest risk, with Black and Asian populations account for the lowest. 3

3.3.1.2 Cumulative incidence of Oesophageal cancer

The state transition model presented in Figure 10 and Figure 11 was run to compute the lifetime risk of oesophageal adenocarcinoma in the general population. The cumulative percentage of cancer cases over a 100-year timeframe was interpreted as a lifetime risk of developing oesophageal cancer. This is representative of all individuals between year 2000-2016 in the Australian population, and all individuals from 2000-2017 in the US white population. In the

Australian cohort, 0.81% developed oesophageal cancer (all subtypes), while 0.61% developed oesophageal adenocarcinoma. In the US (non-Hispanic) Whites population, 0.61% developed oesophageal cancer (all subtypes) and 0.56% developed oesophageal adenocarcinoma (Table 8). Male-only cohort had higher cumulative incidence of oesophageal adenocarcinoma, compared to female-only cohort. In the Australian population, 0.84% of male cohort developed oesophageal adenocarcinoma during the time horizon, compared to 0.4% of female cohort. In US white population, this was 0.4% in the male-only cohort and 0.11% in the female-only cohort.

Table 8. Model outputs: Cumulative percentage of cohort progressing to cancer over the time horizon in the general population (base scenario)

Lifetime Risk (100 years)	All Oesophageal Cancers		Oesophageal Adenocarcinoma only			
	Australian model	United States model	Australian model	United States model	Australian 70%	Australian 80%
General population	0.81%	0.56%	0.61%	0.36%	0.57%	0.65%
Male (general population)	1.20%	0.89%	0.84%	0.40%	0.78%	0.9%
Female (general population)	0.48%	0.25%	0.40%	0.11%	0.37%	0.43%

3.4 Progression from Barrett's to oesophageal adenocarcinoma

Several systematic reviews and meta-analyses have reported both annual progression rate as well as long term progression of non-dysplastic Barrett's oesophagus to oesophageal adenocarcinoma. Gatenby et al 2014 (153) conducted a review of systematic reviews and meta-analysis of long-term progression of patients with Barrett's oesophagus, publishing an estimate of the annual progression rate as well as the individual lifetime risk of adenocarcinoma. Table 6 shows the results of this study, augmented with additional parameters and recent studies. The last entry is data from a local South Australian Barrett's oesophagus study, which compares local data to the synthesised data from several systematic reviews.

Gatenby et al (153) reported in their study that the lifetime risk of developing adenocarcinoma from Barrett's oesophagus was between 1 in 14 (~7.1%) to 1 in 8 (12.5%). Studies examined in this review ranged from 1984 to 2011. Much has changed in the way we manage Barrett's oesophagus through these three to four decades. For one, diagnosis of Barrett's oesophagus itself was not unified until the late 1990s (54). Secondly, in 2008, Society of Thoracic Surgeons (USA) introduced endoscopic ablation and resection into their guidelines for treatment of high-grade dysplasia. There is still controversy surrounding the confirmatory diagnostic criteria for high-grade dysplasia, but there is agreement that endoscopic treatment of lesions at high-grade dysplasia stage for Barrett's oesophagus is indicated. The treatments offered at high-grade dysplasia stage highly influences the overall conversion or progression from non-dysplastic Barrett's oesophagus to oesophageal adenocarcinoma. If the meta-analyses are divided into pre-adoption of endoscopic treatment for high grade dysplasia in Barrett's oesophagus versus post-guideline publishing (2008), we see that there is a markedly higher progression to oesophageal adenocarcinoma is observed in patients with Barrett's oesophagus. In Table 6 arranges the meta-analyses are arranged by year and divided into pre- and post-2010, as most studies within these meta-analyses had recruited patients prior in 2008 prior to guideline changes to include endoscopic treatment for high-grade dysplasia. In the pre-endoscopic treatment era, the lifetime risk of progressing to oesophageal adenocarcinoma is between ~9-13%, whereas post-ablation, this drops to ~6-7%.

Table 9. Literature review of systematic reviews and meta-analyses investigating the cumulative progression from Barrett's oesophagus to oesophageal adenocarcinoma (lifetime risk).

Study Author/Year	Patients (n)	Pt Yrs follow up	Annual incidence	Lifetime EAC Risk	Combined lifetime risk HGD/EAC
Thomas 2007	9469	36635	0.51%	11.30%	20.00%
Gatenby 2008	807	3912	0.59%	13.10%	22.20%
Yousef 2008	11279	47496	0.44%	9.80%	17.50%
de Jonge 2010		78131	0.85%	-	25.50%
Sikkema 2010	14109	61804	0.56%	12.40%	19.10%
Desai 2012	11434	58547	0.32%	7.10%	-
Krishnamoorthi 2018	9660	-	0.23%	6.90%	-
Peters 2019		64537	0.68%	-	20.30%
Local database (current)	1069	5081	0.26%	5.80%	12.53%

*Adapted from Gatenby et al.(153).

This differences in risk pre- and post-endoscopic treatment are critical to building a firm understanding of what occurs in patients without endoscopic surveillance. Prior to endoscopic treatments for dysplastic Barrett's oesophagus, patients would typically undergo endoscopic surveillance without any intervention. This means surveillance is purely observational and does not change the course of their condition. It could be argued that patients under surveillance are treated with proton-pump inhibitors and H2 antagonists. But these treatments are usually initiated for any patient with symptoms and occurs in patients who have not had endoscopy for diagnosis of Barrett's oesophagus as well, i.e., undiagnosed non-dysplastic Barrett's oesophagus patients. According to current guidelines endoscopic treatment is only initiated once patients in a surveillance program develop high-grade dysplasia stage in a surveillance program, as per the current guidelines, endoscopic treatment is initiated. This is contrary to patients with high grade dysplasia *not under* surveillance, who would likely progress undetected to oesophageal adenocarcinoma. The lifetime risk of progression from Barrett's oesophagus to oesophageal adenocarcinoma of 9-13% in pre-endoscopic treatment studies is an important model output for relating any model of Barrett's oesophagus, but specifically the models presented in this thesis. This will be referenced and detailed in other chapters.

3.5 Derivation of Barrett's oesophagus prevalence

The true prevalence of Barrett's oesophagus is difficult to estimate for multiple reasons. Firstly, Barrett's oesophagus is an asymptomatic disease, which means many will remain undetected in the population. Individuals *suspected* of Barrett's oesophagus generally have symptoms of gastro-oesophageal reflux disease or reflux esophagitis, which may only represent a portion of Barrett's oesophagus population, as reported by Vaughan and Fitzgerald (154). It is noted that some patients with Barrett's oesophagus do not experience any symptoms of gastroesophageal reflux disease. Conversely, only a small percentage of patients with gastroesophageal reflux disease will have evidence of Barrett's oesophagus on endoscopy.

A recent systematic review and meta-analysis of 103 studies concluded similarly that the prevalence of Barrett's oesophagus is approximately ~0.96% (95% CI 0.85% – 1.04%) but remarked there was heterogeneity between studies. This is conceivable because diagnosis of Barrett's oesophagus can vary in studies due to factors such as biopsy compliance with Seattle protocol (four quadrant biopsy every 1-2 cm), histological definitions of metaplasia and dysplasia, and sampled population. Calculating prevalence of Barrett's oesophagus amongst patients undergoing endoscopy could be an inaccurate representation of the general population. Most patients will only undergo an endoscopy if they have symptoms or clinical indication. Barrett's oesophagus, being an asymptomatic disease, by itself is unlikely to cause symptoms. The symptoms are more likely related to gastroesophageal reflux disease or oesophagitis. However, even in a randomly sampled asymptomatic population of Swedish adults, the prevalence of Barrett's oesophagus was found to be similar at 1.6% (95% CI 0.8-2.4%) (155), which supports the findings of the meta-analysis.

Once diagnosed with Barrett's oesophagus, patients are placed under surveillance. But the cancers detected from surveillance only account for less than 10% of the total known oesophageal adenocarcinoma cases. The rest of the 90% of individuals diagnosed with oesophageal adenocarcinoma do not have known Barrett's oesophagus. If all cases of oesophageal adenocarcinoma are assumed to arise from pre-existing Barrett's oesophagus, then it is highly likely that there is a larger group of individuals that have undetected Barrett's oesophagus in the general population. This could mean that observed cases of Barrett's oesophagus that are reported in the literature and seen in databases are only the tip of the iceberg. Others studying the role of screening in oesophageal adenocarcinoma have remarked on this issue, hypothesising the true prevalence of Barrett's oesophagus may be closer to 5-6% (128, 154, 156).

To investigate this discrepancy, the simplified computation model was adopted for cohorts of Barrett's oesophagus patients. A decision tree similar to the cohort of healthy individuals

progressing to cancer (seen in Figure 11) was used for progression of Barrett's oesophagus individuals to cancer. The aim, however, was not to calculate the lifetime incidence in patients with Barrett's oesophagus (as this is already known, Table 6), but to back-calculate the prevalence that would explain the observed rate of progression noted in the literature. This was done by tallying all community occurrences of oesophageal adenocarcinoma (shown in Table 5) and dividing by the progression of Barrett's oesophagus (derived from meta-analyses, Table 6).

The cumulative or lifetime incidence of oesophageal adenocarcinoma in general population has been presented earlier. This was an important first step, which aided in calculation of the prevalence of Barrett's oesophagus. But to be able to make these calculations, it was assumed that all oesophageal adenocarcinomas arose from Barrett's oesophagus. Following this assumption, a first equation was derived, which states that over a defined period, the overall progression rate of a patient with Barrett's oesophagus to oesophageal adenocarcinoma is related to the overall risk of developing oesophageal adenocarcinoma in the population over previously defined period divided by the percentage of population with Barrett's oesophagus. This is represented as below:

Equation 3. Progression from non-dysplastic Barrett's oesophagus (NDBE) to Oesophageal Adenocarcinoma (EAC)

$$Lifetime\ Progression\ from\ NDBE\ to\ EAC = \frac{Lifetime\ risk\ of\ EAC\ in\ General\ Population}{Prevalence\ of\ NDBE}$$

If this is the case, then the risk of progression to oesophageal adenocarcinoma for this cohort is the inversely proportional to the prevalence. As the prevalence of a Barrett's oesophagus rises, the probability that a single patient progresses to cancer decreases. The above equation was thus rearranged to calculate the prevalence of Barrett's oesophagus as follows:

Equation 4. Calculating prevalence of Barrett's oesophagus (NDBE) in the general population

$$Prevalence\ of\ NDBE = \frac{Lifetime\ risk\ of\ EAC\ in\ General\ Population}{Lifetime\ risk\ of\ progression\ from\ NDBE\ to\ EAC}$$

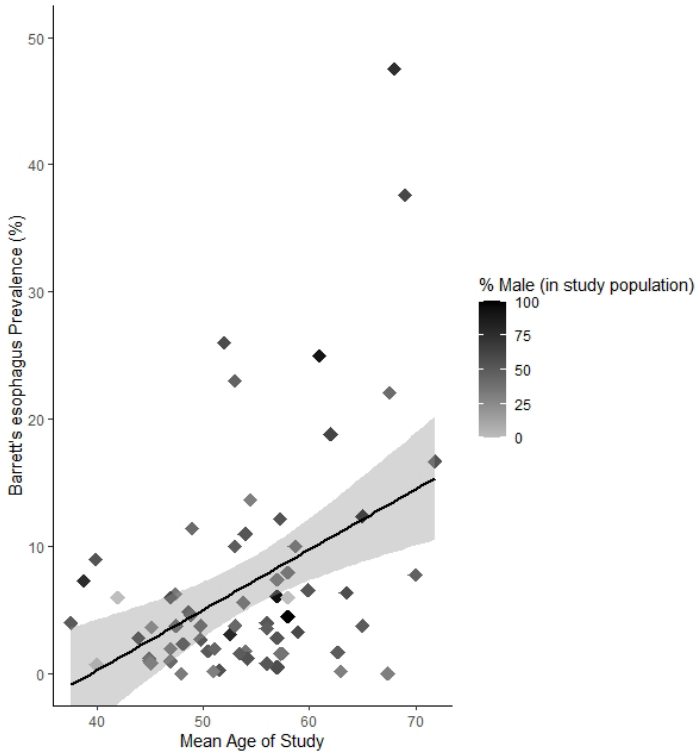
Analysing results of meta-analysis of prevalence of Barrett's Oesophagus

After calculating the lifetime risk of oesophageal adenocarcinoma in the general population through the state transition model presented above and deriving the lifetime risk of progression from Barrett's oesophagus to oesophageal adenocarcinoma from multiple systematic reviews and meta-analyses, the model was modified to calculate the prevalence of Barrett's oesophagus. As with any chronic condition, the prevalence of Barrett's oesophagus varies with different ages. Barrett's oesophagus is extremely rare in children (157), and its prevalence rises with age (158), likely decreasing in the 9th decade of life because of an increase in death (due to all causes). As such, the model was altered with the addition of five age-based prevalence modifier variables for the following clinically relevant age brackets:

- 0 – 29 years
- 30 – 44 years
- 45 – 59 years
- 60 – 74 years
- 75+ years

It was assumed that the prevalence at the lowest age brackets would be the lowest and increase until the last two decades of the model time horizon. This assumption was based on age adjusted prevalence rates, which were found in three studies (158-160). Data provided in a systematic review and meta-analysis by Marques de Sa et al (160) was extracted and analysed for the prevalence of Barrett's oesophagus at different mean ages. Then, a linear regression analysis was performed with prevalence as the outcome variable and mean age group as the predictor. The prevalence was predicted in the five age brackets devised, using a linear regression model from this data (intercept = -18.7205; slope = 0.475). These predicted prevalence values were used as the *initial* estimates for the model.

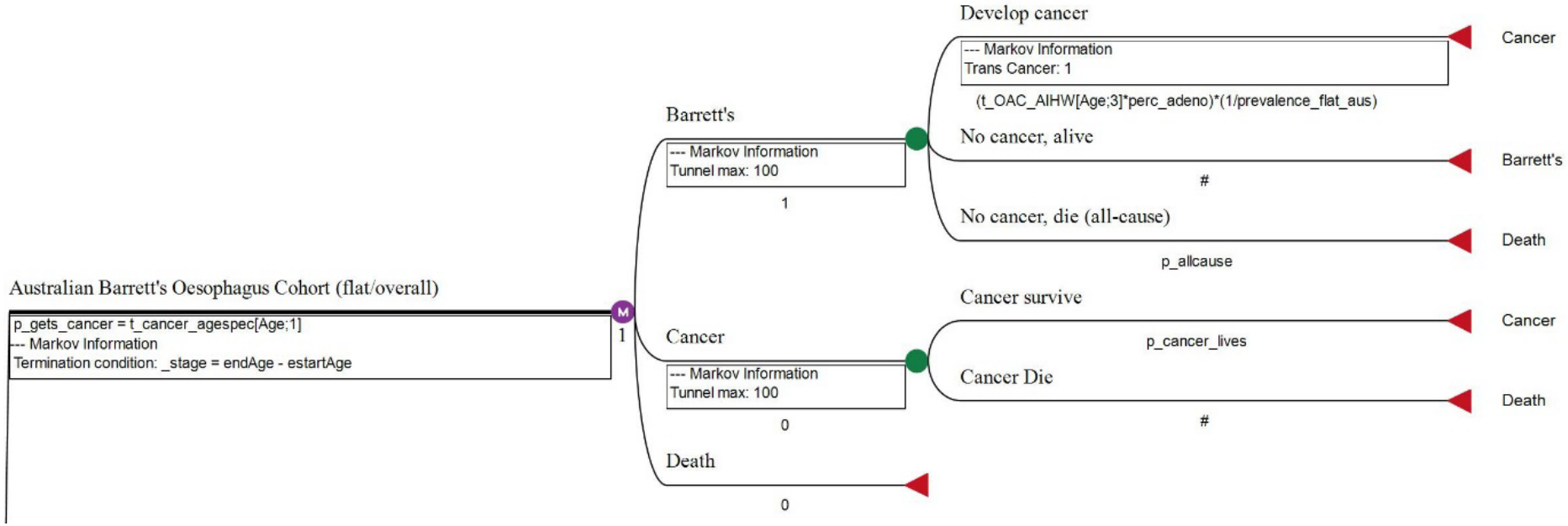
Figure 13. Prevalence of Barrett's Oesophagus reported in 66 studies compared to mean age. Higher prevalence is seen in studies with higher mean ages.



* Black line is a fit of data using linear regression. Percentage of male patients was between 50-75% in most studies.

The model starts with a cohort of individuals with Barrett's oesophagus, which can either stay (No cancer, alive), develop cancer, or die (due to all-cause mortality). Probability of developing cancer is a function of the prevalence of Barrett's oesophagus. For example, if the overall prevalence is assumed to be 1% overall and all oesophageal adenocarcinomas arise from Barrett's oesophagus in this model, then patients with Barrett's oesophagus (when compared to the general population) have 100x higher probability of developing oesophageal adenocarcinoma. Using this, both "flat prevalence" which is the overall prevalence of the cohort as well as age-related prevalence were modelled.

Figure 14. Modified model/decision tree of Barrett's oesophagus progression to oesophageal adenocarcinoma.



The predicted values from linear regression analysis (Figure 13), or initial inputs for the prevalence of Barrett's oesophagus (flat overall percentage and age-based prevalence) were altered to match known long-term progression rates of oesophageal adenocarcinoma (153). Both the "overall cohort" or "flat prevalence" and age-based prevalence rates were calculated through a process referred to as "model calibration." The aim of model calibration is to run the model using different sets of input parameters to see how the model outputs change. Typically, the variables which need to be modified to match a certain output are used in the model calibration process. In this case, those variables were relating to the prevalence were investigated in the calibration. Specifically, 1 variable for "flat prevalence" and 5 variables relating to "age related" prevalence were inputted for calibration.

This was performed using a function provided in TreeAge pro, which employs a constrained Bound Optimization By Quadratic Approximation (BOBYQA) method and was run for minimisation(161). The algorithm requires the initial estimates, a lower, and upper limit, all of which were derived from the systematic review and 2 additional studies, as stated above. The algorithm stops when it reaches convergence. Convergence is a set of criteria which helps the algorithm optimise the model parameters. The criteria for this model were determined to be the model outputs cumulative oesophageal cancer percentage or lifetime risk between 9% and 13%. Resultant iterations were used to calculate the mean and standard deviation of prevalence of Barrett's oesophagus in the community.

Monte-Carlo Simulations:

After estimating the flat and age-based prevalence of Barrett's oesophagus through the calibration process (including error margins), the new rates were inputted into the model. 10,000 simulations were run to confirm accuracy of calibration results. A beta distribution was generated for each of the calibrated variables described above (using mean and standard deviation). Other distributions generated were for the included percentage of adenocarcinoma cases within the overall oesophageal cancer cohort (for Australian data) using a pert distribution (likeliest 75%, minimum value of 65%, and maximum value of 80%) based on expert opinion and available literature (38).

Results

3.5.1.1 Estimated Prevalence of Barrett's oesophagus:

The overall prevalence of Barrett's oesophagus from published meta-analysis was reported at 0.96% (0.85% - 1.07%). Prevalence data from 66 studies with complete data were extracted and plotted against the reported mean age (160) shown in Figure 13. Studies reporting higher mean ages tended to have a higher prevalence of Barrett's oesophagus. A linear regression model was used to predict values of defined age cut-offs namely 30-44 years, 45-59, 60-74 with predicted prevalence of 5.8%, 5.02%, and 12.8% respectively. Age cut-offs under 30 years and over 75 years did not have adequate data and thus did not yield reliable predictive values. The predicted prevalence values were used as initial estimates for model calibration of an age-adjusted Barrett's oesophagus prevalence. Model calibration with stated convergence criteria yielded approximately 2,600 iterations. Resulting mean and standard deviation of prevalence estimates are reported in Table 7.

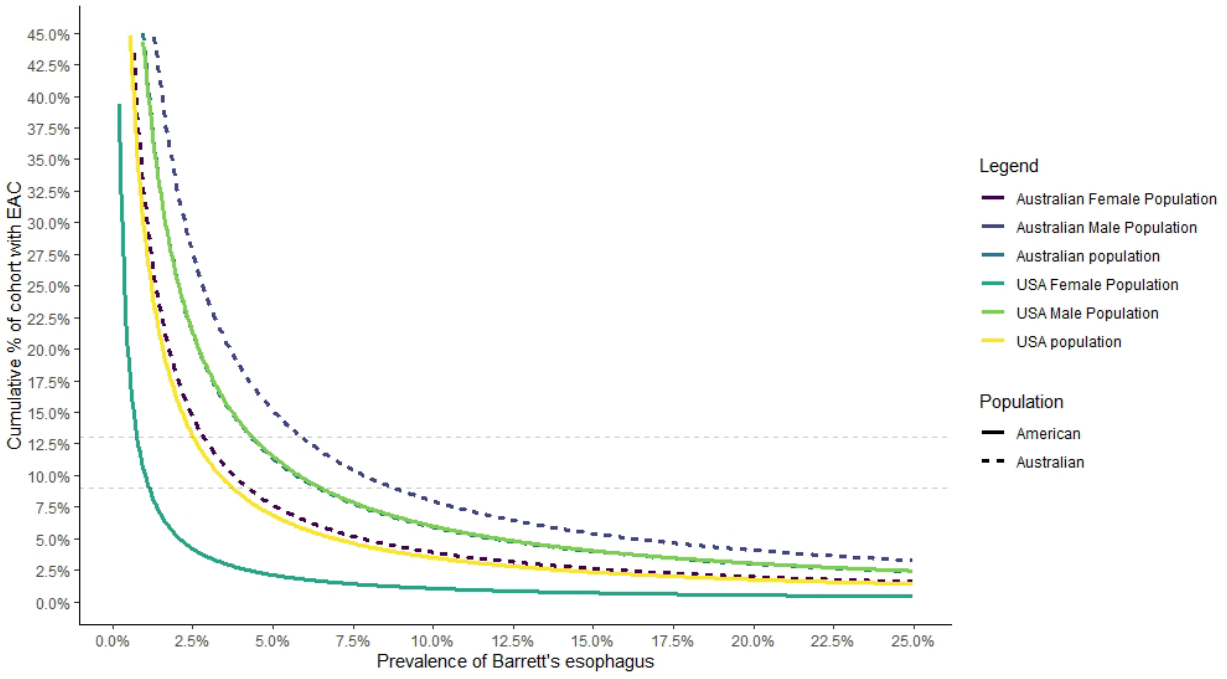
Table 10. Estimated age and sex related prevalence of Barrett's oesophagus in American (non-Hispanic White) and Australian populations.

Population	Non-Age-Specific	Age Specific				
	Overall	Age 0-29 (yrs)	Age 30-44 (yrs)	Age 45-59 (yrs)	Age 60-74 (yrs)	Age 75+ (yrs)
Australian Population						
Combined sex	5.4% +/- 0.6%	0.05% +/- 0.02%	0.9% +/- 0.5%	2.8% +/- 1.2%	7% +/- 3%	12% +/- 4%
Male only	7.4% +/- 0.8%	0.51% +/- 0.18%	1.8% +/- 1.1%	5.4% +/- 2.1%	10% +/- 3%	14% +/- 5%
Female only	3.4% +/- 0.4%	0.06% +/- 0.02%	0.8% +/- 0.4%	1.2% +/- 0.5%	7% +/- 3%	10% +/- 4%
USA population						
Combined sex	3.0% +/- 0.3%	0.06% +/- 0.02%	1.6% +/- 0.7%	3.2% +/- 1.3%	8% +/- 3%	12% +/- 5%
Male only	5.3% +/- 0.6%	0.16% +/- 0.07%	3.2% +/- 1.3%	5.2% +/- 2.5%	11% +/- 5%	10% +/- 4%
Female only	1.0% +/- 0.1%	0.05% +/- 0.01%	0.7% +/- 0.3%	2.2% +/- 1%	5% +/- 2%	7% +/- 4%

3.5.1.2 Overall (flat) prevalence

The relationship between Barrett's oesophagus prevalence and lifetime risk of oesophageal adenocarcinoma for a flat prevalence and age-adjusted prevalence is shown in Figure 4 and Figure 5, respectively. Modelling a flat prevalence percentage for a cohort of Barrett's oesophagus patients revealed an estimated community prevalence rate 2.5-3.7% (mean 3%) for US data and 4.3-6.4% (mean 5.4%) for Australian data (Figure 4). Mean prevalence estimates for subgroups are shown in Table 10. Of note, Australian males had the highest overall prevalence of Barrett's oesophagus at 7.4% (+/- 0.8%), while US females had the lowest at 1% (+/- 0.1%). At a Barrett's oesophagus prevalence value of 0.96% (meta-analysis estimate), the model predicted 44.5% of general Australian population with Barrett's oesophagus and 30% of US population with Barrett's oesophagus would develop oesophageal adenocarcinoma at the end of the time horizon (Figure 4). This is much higher than observed rates of progression from Barrett's oesophagus to adenocarcinoma in the literature and likely implausible.

Figure 15. Progression of a cohort of individuals with Barrett's oesophagus to oesophageal adenocarcinoma (EAC) in American and Australian population based on various prevalence (overall/flat).

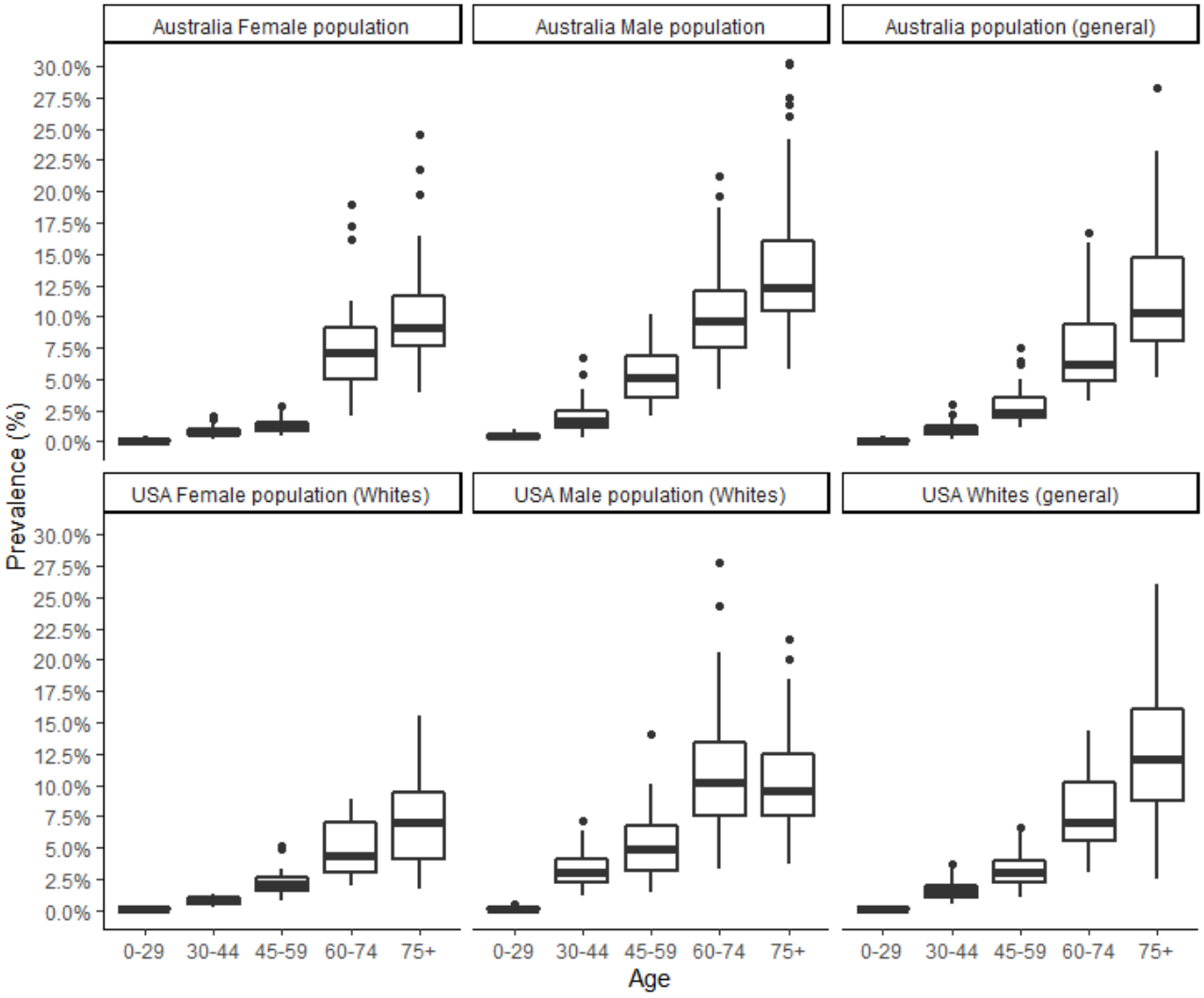


* A high prevalence of Barrett's oesophagus indicates each individual has a lower probability of progression to oesophageal adenocarcinoma, given its observed population incidence.

3.5.1.3 Age-based prevalence estimates

Prevalence, expectedly, increased with age, seen to be minimal in the first 30 years of life and maximum after age 75. For the general Australian population, it was 0.05%, 0.9%, 2.8%, 7%, and 12% for ages 0-29, 30-44, 45-59, 60-74, 75+ respectively. In the US Whites population, the prevalence of Barrett's oesophagus was calculated to be 0.06%, 1.6%, 3.2%, 8%, and 12% again for ages 0-29, 30-44, 45-59, 60-74, 75+ respectively. Female cohorts had lower prevalence of Barrett's oesophagus, with US female population demonstrating the lowest means across all ages (0.05%, 0.7%, 2.2%, 5%, and 7% in ages 0-29, 30-44, 45-59, 60-74, 75+ respectively). Conversely, Australian male cohort had the highest prevalence of Barrett's oesophagus with mean values 0.51%, 1.8%, 5.4%, 10%, and 14% across ages (years) 0-29, 30-44, 45-59, 60-74, 75+ respectively.

Figure 16. Boxplot of calibrated age and sex related prevalence rates of Barrett's oesophagus in Australian and American (non-Hispanic White) populations.



3.6 Discussion

This model estimates the lifetime risk of developing oesophageal cancer and oesophageal adenocarcinoma in Australian and US general, male, and female populations using a state transition model. Working backwards from observed data (i.e., population incidence of oesophageal adenocarcinoma and lifetime risk of conversion from Barrett's oesophagus to oesophageal adenocarcinoma), the model estimated the population prevalence of Barrett's oesophagus to be *approximately 3% (+/- 0.3%) for the white US population and 5.4% (+/- 0.6%) for the general Australian population*. Prevalence of Barrett's oesophagus in female populations was seen to be lower than the male and overall prevalence in both US white and Australian populations. These prevalence estimates are higher than those reported in a comprehensive meta-analysis (160). In addition, an age-based prevalence estimate of Barrett's oesophagus is also calculated from population data, long term cohort data, and age-related prevalence data.

The results of this study highlight an apparent discrepancy between the prevalence of Barrett's oesophagus as reported in the literature, the estimated annual rate of progression, and the incidence of oesophageal adenocarcinoma reported in national cancer databases, an issue that has been raised in several conferences previously. Marques de Sa et al. (160) synthesised data from 103 studies, providing what would seem convincing evidence of Barrett's prevalence ~0.96% (95% CI 0.85% – 1.04%). Only a handful of studies examined the prevalence of Barrett's oesophagus through random sampling, which estimated it to be between 0.5-1% (155, 162, 163). Even though the prevalence of Barrett's oesophagus has been reproducibly reported at ~1%, a sampling bias cannot be ruled out. If the prevalence of Barrett's oesophagus is accurate at ~1%, and all oesophageal adenocarcinoma arises from Barrett's oesophagus, then the estimated lifetime risk of a patient with Barrett's oesophagus developing oesophageal adenocarcinoma would be 44.6% in Australian population and 30% in American population (Figure 4). Such estimates are implausible and do not accord with empirical data. Either the prevalence of Barrett's oesophagus is 4-7x fold higher than current estimations or there is an alternative explanation. The difference between the prevalence of Barrett's oesophagus reported in literature and these estimates represents the individuals with asymptomatic and undetected Barrett's oesophagus in the community. These patients, even though asymptomatic, are still at risk of developing oesophageal adenocarcinoma, albeit at a lower rate. Other computation modelling studies have also concluded similarly that the prevalence of non-dysplastic Barrett's oesophagus must be higher to compensate for the oesophageal adenocarcinoma that are found outside of surveillance programs ~ 5.6%(156, 164, 165).

Within the 103 studies examined in the meta-analysis (160), data extracted from 66 studies is presented revealing a trend for higher prevalence in studies reporting higher mean age Figure

13. As Barrett's oesophagus is often asymptomatic, it is conceivable that its prevalence rises with age (166). This was seen in Rubenstein et al., who conducted a cross sectional study looking at patients undergoing endoscopy, finding a peak in Barrett's oesophagus prevalence in the sixth decade of life (167), a finding which is consistent with the data synthesis from the meta-analysis. This coincides with the peak in oesophageal cancer in the mid-80s, if we assume an incubation period of 15-20 years for oesophageal adenocarcinoma (168). Further evidence of high prevalence rates of Barrett's oesophagus in the sixth decade of life can be found in upper endoscopies performed for patients undergoing colorectal screening programs in USA. Current United States Preventive Services Task Force guidelines recommend individuals above age of 50 years to be routinely screened for colorectal cancer with endoscopy. The prevalence of Barrett's oesophagus in these patients was found to be around 6.8% (169-171), which lies within the range of estimates (Table 9).

A strength of this study lies in drawing from population level data to estimate lifetime risk of oesophageal adenocarcinoma in the general population and merging with best available data on lifetime risk of progression from Barrett's oesophagus to adenocarcinoma. Barrett's oesophagus surveillance is expensive and invasive, performs poorly in cost-effectiveness studies, and only detects 10% or less of the total patients who develop oesophageal adenocarcinoma. Most patients presenting with oesophageal cancer present at late stages, reflecting the asymptomatic nature of its precursor condition. Barrett's oesophagus is considered a silent disease, which means that patients are progressing undetected in the population with or without symptoms of gastro-oesophageal reflux disease. It is likely that this group of individuals have undetected Barrett's oesophagus and screening high risk individuals at the correct age/period could improve the detection rate of oesophageal adenocarcinoma to improve overall survival. The significance of estimating an accurate prevalence and lifetime risk of adenocarcinoma lies in modelling cost-effectiveness analyses for cancer screening or surveillance, especially when considering novel biomarkers, as sensitivity and specificity of tests are often vary with disease prevalence (172).

As with any modelling study, there are limitations surrounding model inputs. Specifically, for this study, there were assumptions that needed to be made and several unknowns which were estimated. Oesophageal cancer subtypes are not reported separately in the AIHW cancer incidence data, or in any public registries in Australia. Adenocarcinoma rates for Australian populations had to be estimated based on scant literature evidence and expert opinion. We assumed that adenocarcinoma represents 70-80% of all oesophageal cancers in Australia based on published studies. This rate was derived from published rates from the States of Queensland (~65%) and South Australia (69.6%) (38, 150). In a subgroup of studies in the meta-analysis (160) from Western countries, the prevalence of Barrett's oesophagus is 2.3% (95% CI 0.42 – 4.2%). Western countries have a predominantly Caucasian population, particularly in the elderly, and it is

likely that this model estimates a higher prevalence due to this feature. Other limitations involved estimation of initial prevalence rates of different age groups by pooling data from other studies. Unfortunately, a meta-regression controlling for fixed and random effects was not in the scope of this study. Instead, a regression analysis was applied to allow us to estimate initial values, which were then calibrated to targets from higher level evidence to mitigate effects of this limitation.

The most reliable figure used in the calculations is likely the incidence of oesophageal cancer, followed by the incidence of oesophageal adenocarcinoma in the SEER database. Other than the inconsistent classification of GOJ adenocarcinomas, for which there is still global dissension, these figures likely capture the cancers as well as it is realistically possible. The progression from Barrett's oesophagus to oesophageal adenocarcinoma was a key factor in determining the prevalence of Barrett's oesophagus. Much of the accuracy of the estimates depended on the accuracy of this progression rate. Data for this were drawn from several meta-analyses. Some of the constituent studies of these meta-analyses were long term prospective cohort studies spanning 30 years, but many were not. Also follow up was imperfect, as it depended on patients who were discharged from surveillance programs to present to the same institution in case of progression. This may be less of an issue in a public health care system such as the Netherlands and the UK, but it certainly is not ideal in US based cohort studies. However, the lifetime progression rate of 9-13% from non-dysplastic Barrett's oesophagus to oesophageal adenocarcinoma was within the confidence interval for most of the observed studies as well as modelling studies (120, 123, 128, 173).

Another major assumption of this study is that all oesophageal adenocarcinoma arises from Barrett's oesophagus. As detailed in Chapter 1, definition of Barrett's oesophagus involves satisfying two conditions 1) presence of salmon-coloured mucosa in the oesophagus, and 2) presence of intestinal metaplasia or dysplasia on biopsy (30, 31). There are, however, some controversial issues involving the categorisation of GOJ adenocarcinomas. As per the Siewert classification, Type 1 is when the centre of the tumour is located more than 1cm proximal to the gastric cardia; Type 2 is if the tumour centre is located within 1cm above the gastric cardia, but less than 2 cm below the gastric cardia; and Type 3 is when the tumour centre is located more than 2 cm below the gastric cardia (137). Type 1 and 2 are generally considered to be oesophageal adenocarcinomas but Type 3 can be sometimes classified as oesophageal or gastric adenocarcinoma. The management of either of these conditions depends less on the origin of the tumour and more on the local extension, nodal spread, and presence of distant metastases in addition to the patient's medical fitness. But the classification or misclassification does alter the calculation of adenocarcinomas arising particularly from Barrett's oesophagus versus columnar epithelium of the gastric cardia. Strictly speaking, diagnosis of Barrett's oesophagus requires extension columnar epithelium above the GOJ which is grossly visible in the form of salmon-

coloured mucosa. Anywhere between 7-35% of the tumours are termed Siewert type 3 (135, 137, 174), which if arising from columnar epithelium in the cardia would not be a result of progression of Barrett's oesophagus. However, it is unknown what percentage of Siewert type 3's recorded in cancer registries are classified under gastric versus oesophageal adenocarcinoma. In fact, most cancer registries of the world do not even distinguish between subtypes of oesophageal cancers. This is an issue almost of a theoretical nature, as the underlying pathological processes still require epithelia to undergo dysplasia prior to adenocarcinoma. But it could also explain the mismatch between the prevalence of Barrett's oesophagus noted in the observational studies and the rates of oesophageal adenocarcinoma. As a theoretical exercise, let us consider two things: 1) Barrett's oesophagus is a subset of the overarching group of the precursors to all GOJ adenocarcinomas, as the requirement that grossly visible oesophageal extension of columnar cells only applies to lesions 1cm above the Z-line and 2) All GOJ adenocarcinomas have been classified as oesophageal adenocarcinomas. In this case, the calculations of prevalence "Barrett's oesophagus" are more reflective of this bigger group of GOJ adenocarcinoma precursor conditions. However, this is extremely difficult to prove as a percentage of cancers of the GOJ will always be inconsistently misclassified. The best we can assume in the modelling exercise is that Siewert Type 3 cancers of the GOJ have been classified as gastric adenocarcinomas, and Siewert Type 1 and 2 cancers have origins related to metaplastic columnar epithelium. If these conditions are true, then the prevalence of Barrett's oesophagus is most certainly higher as indicated by our estimates. Alternatively, Barrett's oesophagus related oesophageal adenocarcinoma are just part of a larger group of precursor conditions that give rise to adenocarcinoma of the GOJ.

An additional limitation is the combination of the above stated limitations. For example, the progression from non-dysplastic Barrett's oesophagus to oesophageal adenocarcinoma is estimated to be between 9-13%. In addition to this estimate having its own margin of error, how this interacts with the population incidence of oesophageal adenocarcinoma is unknown. Ideally, the majority of Siewert Type 3 cancers are listed as gastric adenocarcinomas, in which case, Barrett's oesophagus is likely the underlying precursor to the oesophageal adenocarcinoma incidence noted in the SEER database. This makes the lifetime progression of non-dysplastic Barrett's oesophagus to oesophageal adenocarcinoma reflective of actual progression. But there are several situations this can be untrue:

1) The majority of Siewert Type 3 cancers are recorded as oesophageal adenocarcinomas, but these do not arise from definition specific Barrett's oesophagus, thus progression from Barrett's oesophagus is even lower than 9-13%.
2) Definition of Barrett's oesophagus does not include presence of intestinal metaplasia OR irregular Z-line is considered Barrett's oesophagus. In either case, there are many false positives, hence the progression rate of true positives is higher than 9-13%.

Even if this study estimates the prevalence of the overall entity inclusive of all precursors to oesophageal/GOJ adenocarcinomas or specifically Barrett's oesophagus (which has a narrow definition), it still has widespread implications for how to improve early detection of oesophageal adenocarcinoma.

One of the main implications is our understanding of how oesophageal adenocarcinoma arises. To be precise, this could include anything classified as oesophageal adenocarcinoma and adenocarcinoma of the gastroesophageal junction. This raises several questions. We know both these types of adenocarcinomas arise from columnar epithelium. The question then is *"Does the transformation of columnar epithelium → dysplasia → adenocarcinoma from gastric cardia or at the true gastroesophageal junction due to the same processes as the Barrett's metaplasia → dysplasia → adenocarcinoma in the distal oesophagus?"* However, this may be difficult to prove as the underlying metaplastic and dysplastic segments are rarely seen on surgical specimen after progression to oesophageal adenocarcinoma. For this reason alone, it is difficult to define and characterise the true precursors to oesophageal and gastroesophageal junctional adenocarcinomas. However, if the end goal is to detect precursors of these adenocarcinomas earlier, then this study shines a light on their prevalence, which may avail this population to targeted surveillance or screening opportunities.

3.7 Conclusion

We sought to estimate the lifetime risk of developing oesophageal cancer and adenocarcinoma in the general population and address the current incongruence between low reported prevalence rates of Barrett's oesophagus and observed risks of progression to adenocarcinoma. An age-related rise in prevalence rates can explain the differences noted in the literature, reinforcing the conclusion that most Barrett's oesophagus is undetected in the community. Alternatively, Barrett's oesophagus could be part of a larger group of precursor conditions, which has yet to be characterised. While these estimates are based on population level data and modelling, they remain speculative and do not prove this phenomenon. However, short of performing hundreds or thousands of research endoscopies in a large representative sample of the general population, there are few alternative methods for estimating the true prevalence of Barrett's oesophagus in the community. However, improving the collection of data for national registries is key to more accurate estimates, which needs to be addressed in three key areas: 1) Recognising oesophageal adenocarcinoma as a separate entity and recording subtypes of oesophageal cancer across Australian national cancer registry; 2) Consensus on classification of Siewert 2s and 3s as either oesophageal or gastric adenocarcinomas; 3) Histopathological analysis of non-Barrett's oesophagus related oesophageal/GOJ adenocarcinoma to other potential precursors.

4 CHAPTER 4 – NATURAL PROGRESSION OF BARRETT'S OESOPHAGUS

4.1 Chapter overview

This essence of this thesis is contained within this chapter, which discusses the development and calibration of the decision analytic Markov model simulating the natural history of non-dysplastic Barrett's oesophagus to oesophageal adenocarcinoma. Results from the previous chapter were incorporated in developing a more detailed model. All nodes and branches that were created served a specific purpose, which helped develop a number of interventions/strategies that could be tested. A key concept discussed in detail is development of undetected health states, which allows background progression of Barrett's oesophagus when testing prolonged intervals between endoscopies. Another key concept discussed is splitting the intervention for low and high risk subgroups, which realistically simulates clinical practice. Lastly, a detailed stepwise calibration process is demonstrated, which ensures the model outputs resemble published literature data and also helps determine confidence intervals of transition probabilities.

4.2 Background

A cost-utility analysis is the comparison of costs and utilities (QALY) between two (or more) strategies. A decision analytic Markov cohort model was developed to analyse the expected costs and QALYs for various endoscopic surveillance strategies for Barrett's oesophagus. The base strategy, against which all active strategies were compared, was the natural history of Barrett's oesophagus, which was defined as "no surveillance". The initial step was to build a state transition model of the natural progression from Barrett's oesophagus to oesophageal adenocarcinoma.

Events in Barrett's Oesophagus Progression

The transformation from physiologic squamous oesophageal mucosa to adenocarcinoma undergoes many smaller steps. These can be summarised in a number of ways. On a cellular level, a portion of metaplastic cells can undergo genetic and epigenetic alterations *(mutative phase)*. Loss of regulatory control in these cells then increases proliferative ability of the mutated cells *(proliferative phase)*. As the cells proliferate, their chance of spread increases *(metastatic phase)* (175). While this is an accurate portrayal of events, there are little to no data available on the rates of transition between these cellular stages of transformation from metaplasia to adenocarcinoma. And since Barrett's oesophagus is an asymptomatic disease, it is difficult to describe its clinical stages. Symptoms experienced by patients are likely a result of refluxing gastrointestinal contents rather than progression of Barrett's oesophagus stages. Thus, it is impossible to classify patients based on clinical features solely. Currently, the only way to classify Barrett's oesophagus is through endoscopic examination and histopathological analysis of biopsies. Individuals with Barrett's oesophagus can progress from a non-dysplastic (also referred to as metaplasia) to low grade dysplasia, high grade dysplasia, intramucosal adenocarcinoma (only detectable through surveillance), symptomatic oesophageal adenocarcinoma, or death. Non-dysplastic Barrett's oesophagus can also *regress* spontaneously, which is seen by either absence of intestinal metaplasia on histology and/or absence of visible salmon coloured mucosa in the oesophagus (176, 177). For this reason, the health states in the Markov cohort model were created to reflect these commonly used stages of Barrett's oesophagus. Previous economic evaluation models had employed similar health states (presented in Chapter 2, Table 4).

Defining the states in this manner had other advantages. Many of the transition probabilities lacked observed data. Calculating the community incidence of oesophageal adenocarcinoma aided in calculation of these transition probabilities. In the previous chapter, we were able to link the community lifetime incidence of oesophageal adenocarcinoma to untreated (but under surveillance) Barrett's oesophagus in the pre-endoscopic treatment era to estimate the prevalence of this asymptomatic precursor to oesophageal adenocarcinoma. This helped develop calibration

targets for two important cohort model outputs: cumulative percentage of cohort progressing to high-grade dysplasia and oesophageal adenocarcinoma.

4.3 Methods

A Markov cohort model was constructed using TreeAge Pro (version 2021 R2.1 Williamstown, Massachusetts) to simulate progression and regression of Barrett's oesophagus from metaplasia (non-dysplastic Barrett's oesophagus) to oesophageal adenocarcinoma. A diagrammatic representation of these stages of Barrett's oesophagus and how they pertain in specific to the Markov model is provided in Figure 17. Cancer states were modelled as clinically relevant stages of oesophageal adenocarcinoma because variables such as costs, utility, and probability of survival were cancer stage dependent. Figure 18 shows an example of the decision tree for the initial health state (non-dysplastic Barrett's oesophagus).

Briefly, the steps involved in building a decision analytic Markov cohort model included: defining the clinically relevant health states i.e., non-stratified (aggregate cohort) and risk-stratified health states (low and high risk), building a decision tree within the Markov model (with all anticipated treatment modalities as branches), loading with initial model inputs (derived from literature/observed data), and finally calibrating the model to the lifetime risk of oesophageal adenocarcinoma and high-grade dysplasia Monte-Carlo simulations were run for to ensure the calibrated transition probabilities yielded model outputs within expected ranges. In addition, risk-stratified states were built into the cohort model, which could be defined through pertinent variables.

Undetected health states

Only roughly 10% of the individuals with oesophageal adenocarcinoma are detected through a surveillance program for Barrett's oesophagus. The rest of the approximate 90% of oesophageal adenocarcinoma present with symptoms concerning for oesophageal cancer, at which point approximately 33% already have distant spread of the cancer. The pathophysiological process in these patients is still the same, as they arise from Barrett's oesophagus, progressing *undetected* through metaplasia, dysplasia, and intramucosal adenocarcinoma before developing symptoms consistent with oesophageal adenocarcinoma. Because a substantial percentage of individuals progress undetected meant that any modelling exercise required understanding the progression of Barrett's oesophagus progressing *undetected* in the community (not under surveillance). This poses a conundrum, that has been alluded to in Chapter 3. Without any clinical symptoms or signs to diagnose or even suspect Barrett's oesophagus, endoscopy remains the only way to stage Barrett's oesophagus. Since it is impossible to know the progression of this asymptomatic condition without invasive surveillance, we ultimately assumed that the natural

progression of Barrett's oesophagus is the same as patients under surveillance, provided no treatment has been instituted.

Previous health economic models have employed a similar strategy in assuming individuals not under surveillance progress similarly to those under endoscopic surveillance. Although this study made a similar assumption, additional steps were taken to ensure the outputs of the Markov cohort model would match observed data. A thorough search of the literature described in Chapter 3 helped formulate expected model outputs for the cumulative percentage of the "no surveillance" cohort (starting with non-dysplastic Barrett's oesophagus) progressing to oesophageal adenocarcinoma. There were several motivations behind developing and calibrating the model with "undetected" Barrett's oesophagus stages as health states. The majority of patients presenting with oesophageal adenocarcinoma have never been diagnosed with Barrett's oesophagus, exposing the indolent nature of Barrett's oesophagus. This cohort of community individuals is essentially the current standard of care because neither a screening nor surveillance program is currently funded in Australia. Thus, the natural history of Barrett's oesophagus (no surveillance) was selected as the base strategy against which all other strategies were compared.

Two broad groups of strategies tested in this study were: 1) reduced frequency of endoscopic surveillance and 2) early endoscopic treatment of high-risk individuals. To simulate individuals with reduced frequency of endoscopic surveillance, the model needed to allow these individuals to progress or regress *undetected* until the time of their next endoscopic examination. A decision tree within the Markov model (Figure 18) was designed in such that undetected health states could undergo endoscopy to move into a "diagnosed" state. If a health state does not undergo endoscopy, it was defaulted to a "no surveillance" option, in which case the underlying health state would be progress through undetected states, as they await their next endoscopy.

The application of this approach can be demonstrated through the following example. Consider a strategy to reduce the frequency of endoscopic surveillance to every 10 years instead of every 2 years. Individuals enter the model with having just been diagnosed with non-dysplastic Barrett's oesophagus. For the next 10 years, they then circulate through undetected states, where they can continue progressing or regressing from the starting state to absence of metaplasia (No Barrett's oesophagus) to dysplasia, oesophageal adenocarcinoma, death, etc. The progression between these states assumes the natural progression of Barrett's oesophagus. 10 years after their first endoscopy, the model would divert these individuals from "no surveillance arm" to "endoscopic surveillance" arm (Figure 18). The stage of Barrett's oesophagus on the 10^{th} year is dependent on the probability of progression during this time period. Data for this type of transition was not readily available, as most surveillance programs have shorter intervals between endoscopies. Knowing the long term (lifetime) progression of Barrett's oesophagus helped derive

the probability of progression every cycle, using a seven-stage calibration process described later in this chapter. Without the creation of undetected states, strategies with longer intervals between endoscopies could not be tested. Using this methodology of keeping the undetected states progressing in parallel, the effect of increasing the interval between endoscopic examinations to 10 years (or any interval) was able to be tested with need for observed data.

Non-Stratified and Risk-Stratified Health States

The first priority of this study was to ensure progression or regression of Barrett's oesophagus was accurately represented through a Markov cohort model, which has been detailed in the previous sections. Secondarily, it needed to be adaptable to represent different risk factors without changing the overall characteristics of the cohort. There were two reasons for not changing the overall characteristics of the cohort: 1) Transition probabilities of low and high risk subgroups, which are not available as observed data, could be calibrated to match the characteristics of the aggregate cohort; and 2) non-risk stratified strategies could be compared to risk-modified endoscopic surveillance.

To achieve this, ***one*** *set of non-risk stratified* and ***two*** *sets of risk-stratified* health states were created. Non-stratified states represented the aggregate cohort of individuals with non-dysplastic Barrett's oesophagus. Risk-stratified states were health states that represented low and high-risk subgroups within this aggregate cohort. The sum of the starting populations in risk-stratified health states would equal the aggregate cohort. The benefit of this type of classification was that low and high-risk subgroups could be subjected to different treatments such as *endoscopic surveillance, no surveillance,* or *a combination of both*. Combination of both refers to reduced frequency of endoscopic surveillance (more than every 2 years for non-dysplastic Barrett's oesophagus). During the cycles where no endoscopic examination is performed, the cohort lies in undetected states as explained in the above section.

Classification of health states is depicted in Figure 17, while the decision tree within the Markov model depicting surveillance options is shown in Figure 18. Results of the systematic review of economic evaluations in Chapter 2 demonstrated that routine 2-yearly endoscopic surveillance was not cost-effective for all individuals with Barrett's oesophagus (178), but it could be cost-effective for a subset of individuals with increased risk of progression to oesophageal adenocarcinoma. Several studies modelled a high-risk group, selecting them for modified surveillance or intervention. Risk stratification in these cases was through a hypothetical or an existing biomarker (68, 127, 179). It is important to note that no biomarker is currently approved for surveillance in Barrett's oesophagus patients. Only one study modelled limiting surveillance to long segment Barrett's oesophagus to improve cost-effectiveness, testing different thresholds for definition of long segment Barrett's oesophagus (70). This was also the only clinical risk factor

based modified surveillance interval or intervention. Notably, all cost-utility analyses in the literature investigating risk modified strategies modelled for separate cohorts, for example, cost effectiveness of endoscopic surveillance in male or long-segment Barrett's oesophagus only. It may be reasonable to assume that if endoscopic surveillance is not cost-effective for the aggregate (non-risk stratified) cohort but is the for the high-risk cohort, that it is overall cost-effective to exclude the low-risk cohort. There are a few disadvantages to this approach. Firstly, the negative outcomes of the excluded low-risk sub-cohort are not considered. Secondly, as the low-risk cohort is entirely excluded from the analysis, the only a "zero" frequency of endoscopic surveillance can be inferred. Lastly, the optimal permutation of surveillance interval for low and high-risk subgroups cannot be determined. For example, let us consider Lindblad et al.(70), who concluded 2-yearly endoscopic surveillance is cost-effective for long segment Barrett's oesophagus (while excluding the short-segment Barrett's oesophagus entirely from the analysis). It may be possible that a 10-yearly surveillance interval for short segment Barrett's oesophagus is cost-effective if the frequency of surveillance for long-segment Barrett's oesophagus was to be reduced to every 3 years.

In order to test this interplay, both the low and high-risk subgroups were included within the same cohort. Identical sets of health states were created and labelled as non-stratified or risk-stratified, representing various stages of Barrett's oesophagus stated above. This was based on the concept that any given cohort can be subdivided into groups with varying characteristics. The aggregate cohort accounts for 100% of the starting population as well as 100% of the model outputs. This cohort was sub-grouped according to a risk factor or risk factor profile. Each subgroup represented a proportion of the aggregate cohort. Starting proportions for these subgroups are presented in Table 11. As an example, we know that males with Barrett's oesophagus represent approximately 65% of all individuals with Barrett's oesophagus, but also have odds ratio of ~ 2.5x chance of progressing to oesophageal adenocarcinoma according to the literature (29). Expectedly, the male and female subgroups will have different model outputs, such as percentage of cohort developing oesophageal adenocarcinoma, owing to the varying progression rates. Their combined model outputs, such as percentage of cohort developing oesophageal adenocarcinoma, would be the same as the aggregate cohort. Model outputs of high-grade dysplasia and oesophageal adenocarcinoma were calibrated to the observed progression in the aggregate group to derive appropriate transition probabilities for the Barrett's oesophagus states. This was instrumental in adapting the model to low and high-risk subgroups, giving the ability to generate 122 permutations of clinically relevant surveillance strategies.

Presence and Absence of Intestinal Metaplasia

The initial health state in the Markov cohort model was also the first stage: non-dysplastic Barrett's oesophagus. It is synonymous with metaplastic Barrett's oesophagus. Individuals enter the model after being diagnosed with the first stage of Barrett's oesophagus. This is diagnosed

through endoscopic examination and biopsy of salmon coloured mucosa in the oesophagus and *presence of metaplasia* on histology (i.e., columnar epithelial changes). Columnar epithelium is indigenous to gastrointestinal tract, which is in contrast to the pale pink colour of normal oesophageal mucosa containing squamous stratified epithelium. Historically, the diagnosis of Barrett's oesophagus only required identification of visible salmon coloured mucosa on endoscopy, but international guidelines now recommend that intestinal metaplasia must be present on histology for this diagnosis to be made (30, 52, 180). This means there is a category of individuals with endoscopically visible changes to their oesophageal mucosa *without intestinal metaplasia* on histology. In theory, because these individuals do not meet criteria for a diagnosis of Barrett's oesophagus, they do not need endoscopic surveillance. Practically, however, inadequate biopsies over the area of visible changes could potentially miss histological metaplasia. Current practice guidelines stress the importance of four-quadrant biopsies every 2 cm of visible changes, as per the Seattle protocol (32, 33, 181). Even with this rigorous biopsy protocol, there is a chance that metaplasia or dysplasia is missed due to overlying inflammation from oesophagitis (182, 183). Furthermore, previously metaplastic (or non-dysplastic) Barrett's oesophagus could have naturally regressed. For these myriad reasons, in the model, patients with only visible changes in the oesophagus but without metaplasia were required to have two consecutive negative biopsies prior to removal from surveillance. *Absence of intestinal metaplasia* was termed "No Barrett's oesophagus" and also the second health state in the Markov cohort model.

Dysplastic Barrett's oesophagus

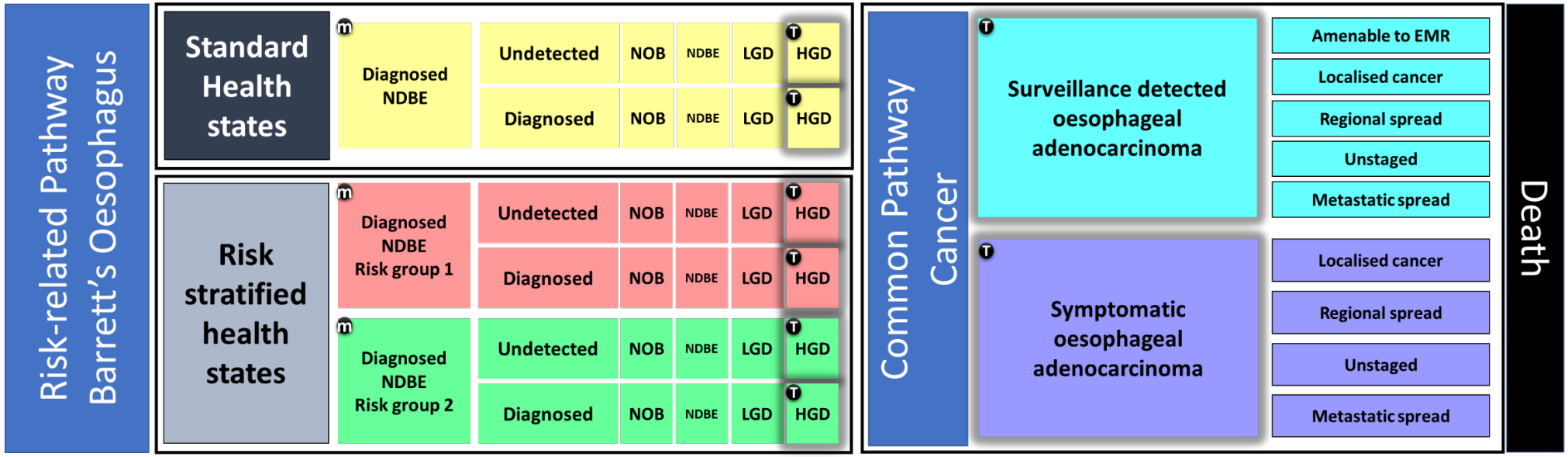
Individuals with non-dysplastic Barrett's oesophagus can also progress to dysplastic Barrett's oesophagus. Dysplastic Barrett's oesophagus can be further divided into low grade and high grade. The differences in diagnostic criteria, non-consensus among expert gastrointestinal pathologists, along with interobserver variability for low grade dysplasia have been outlined in previous chapters (4-6, 23). Previously a diagnosis of dysplastic Barrett's oesophagus signified merely increasing frequency of endoscopic examination, which was relatively innocuous as major complications from endoscopy are rare. With the advent of endoscopic ablative treatments, patients could potentially be committed to an unnecessary procedure with a larger side effect profile. This has prompted medical societies to devise more stringent criteria for diagnosing low grade and high-grade dysplasia. Australian, U.K., and U.S. guidelines recommend a histopathological examination revealing any grade of dysplasia must be confirmed by a second endoscopy and another expert gastrointestinal pathologist (30, 31, 52). Accordingly, for these health states, an additional endoscopy within 6 months after the initial diagnosis of either high- or low-grade dysplasia was modelled in the surveillance arm. For low grade dysplasia, U.S. and U.K. guidelines recommend endoscopic ablative therapy (provided no contraindication with patient

factors), but Australian guidelines have not yet adopted this. Hence, endoscopic ablation for low grade dysplasia was modelled separately and is the topic of discussion in a latter Chapter.

Oesophageal adenocarcinoma

Undetected Barrett's oesophagus states could progress to oesophageal adenocarcinoma but are only detected once they develop symptoms. Once an individual developed symptoms due to oesophageal adenocarcinoma, the cancer was assumed to be one of four stages: Localised cancer, regional spread, unstaged, or distant spread. The percentage of individuals that would be diagnosed in each of these stages was derived from Surveillance, Epidemiology, End Results database (151), as was the annual mortality for these stages. These values are provided in Table 15. Symptomatic oesophageal adenocarcinoma was different to intramucosal carcinoma, which is an asymptomatic condition and was only detectable through endoscopic surveillance. Individuals with dysplastic Barrett's oesophagus can either regress to metaplasia or progress to intramucosal adenocarcinoma or regress to metaplasia (non-dysplastic status). When high grade dysplasia or intramucosal carcinoma was detected, patients under endoscopic surveillance would undergo endoscopic treatment. High grade dysplasia would undergo radiofrequency ablation, whereas patients with surveillance detected intramucosal carcinoma would undergo endoscopic mucosal resection as well as ablative treatment. Patients post endoscopic treatments currently require lifelong endoscopic surveillance. This is because existing literature evidence is inadequate to form guidelines regarding safe cessation of endoscopic surveillance for these patients. Despite treatment with endoscopic ablation, a small percentage of dysplastic Barrett's oesophagus or intramucosal carcinomas can further progress to invasive oesophageal adenocarcinoma.

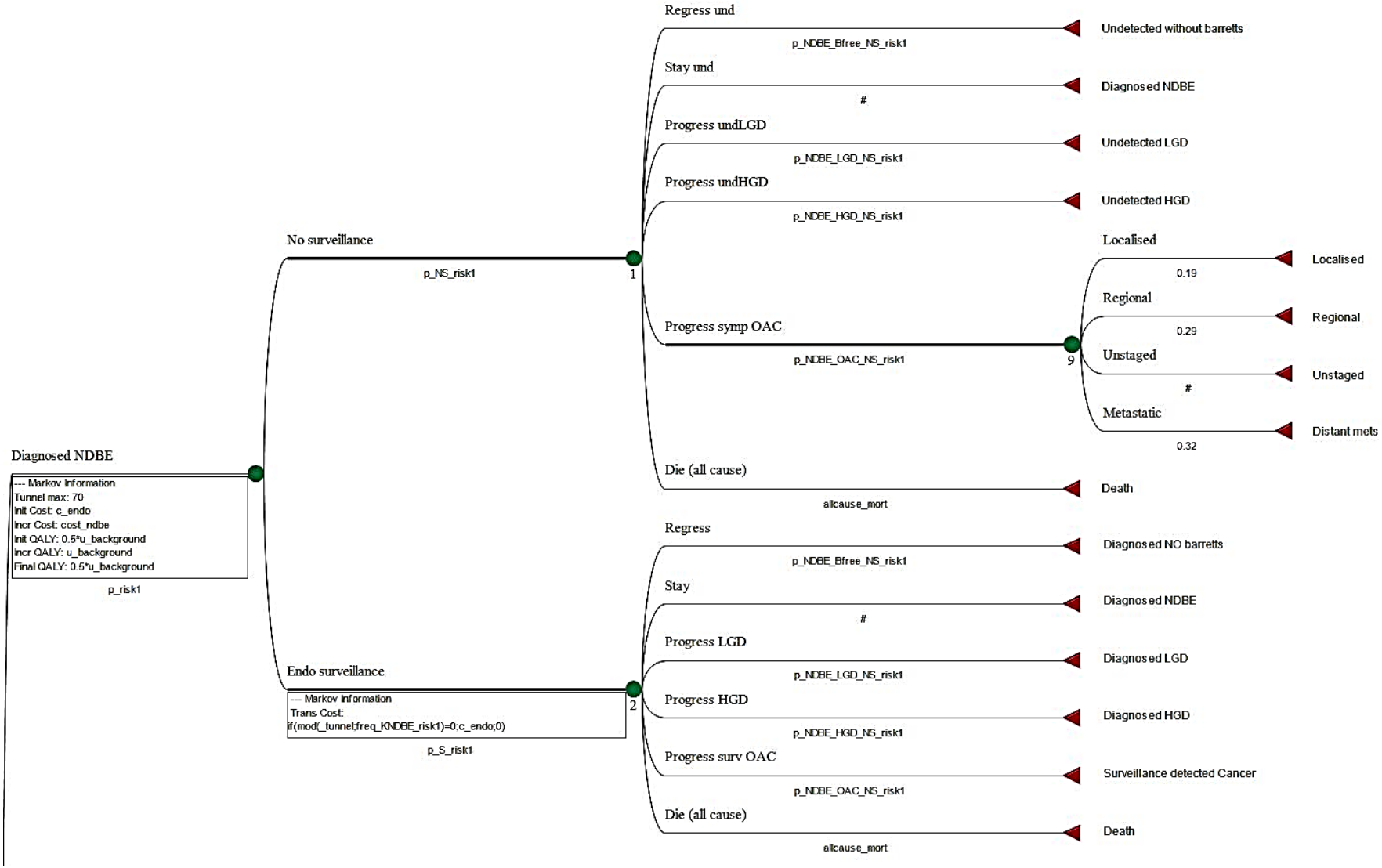
Figure 17. Health states in Markov cohort model of progression of Barrett's Oesophagus to esophageal adenocarcinoma. Starting point of the model is indicated by (m) and calibration targets by (T). Initial proportions are representations of prevalence of risk factor in Barrett's Oesophagus surveillance programs.



Legend: No metaplasia/Barrett's Oesophagus (NOB); Non-dysplastic Barrett's Oesophagus (NDBE); Low-Grade Dysplasia (LGD); High Grade Dysplasia (HGD); Endoscopic mucosal resection (EMR); Standard health states = Aggregate health states

Figure 18. Movement from starting cohort (non-dysplastic Barrett's oesophagus) to other health states.

NDBE- non-dysplastic Barrett's oesophagus; und- Undetected; LGD- Low grade dysplasia; HGD- High grade dysplasia; symp EAC- Oesophageal adenocarcinoma detected by symptomatic presentation; surv EAC- Oesophageal adenocarcinoma amenable to endoscopic resection (detected by surveillance)



Cohort characteristics and movement between health states

The starting population was 50-year-old mixed gender individuals diagnosed with non-dysplastic Barrett's oesophagus. In non-stratified health states (aggregate cohort), 100% of starting cohort was defined by this population of 50-year-old individuals. For risk-stratified states, the proportion of the cohort starting in each of the risk subgroups was based on observed data (Table 11). Two types of known risk factors were used for this study, namely length of Barrett's oesophagus segment and gender. Each risk factor dichotomised the group into a low and high-risk subgroup i.e., male or female; segment length over/under a threshold. For segment length, two commonly used thresholds across endoscopic surveillance guidelines (2 cm and 3 cm) were used to bisect the cohort. Starting populations (shown in Table 11) and proportions were derived from a combination of sources, either literature values (70) and/or a South Australian Barrett's oesophagus Surveillance Study cohort. Transitions between Barrett's oesophagus health states were confined to the assigned group i.e., low-risk subgroup states could not jump to high-risk subgroup states. If the cohort of patients progressed further than Barrett's oesophagus, they entered the *common pathway health states*, which is comprised of stages of oesophageal adenocarcinoma. (Figure 17). A diagnosis of cancer was irreversible, even if complete remission was achieved. Transition probabilities for low and high risk-stratified states varied accordingly, while transition probabilities between *common pathway* states were the same for all cohort subgroups.

Table 11. Starting population of patients according to scenario.

	Starting population %		
Scenario/Strategy name	**Non-stratified**	**Risk group 1**	**Risk group 2**
Aggregate cohort	100%	0%	0%
Segment length (2 cm threshold)			
Low risk- Short segment NDBE		62.5%	
High risk- Long segment NDBE			37.5%
Segment length (3 cm threshold)			
Low risk- Short segment NDBE		75.0%	
High risk- Long segment NDBE			25.0%
Gender			
Low risk- Female		35.0%	
High risk- Male			65.0%

Legend: Non-dysplastic Barrett's Oesophagus (NDBE)

4.3.1.1 Movement between undetected and diagnosed states

The model starts with patient diagnosed as non-dysplastic Barrett's oesophagus (Figure 18). From here, individuals can either undergo surveillance or no surveillance. Patients *not* under endoscopic surveillance progress through Barrett's oesophagus in "undetected" health states, whereas patients under routine 2 yearly endoscopic surveillance circulate through "diagnosed" states. Individuals with prolonged endoscopic intervals transition to an undetected state at the

subsequent cycle until their next surveillance endoscopy. As an example, a cohort/individual assigned to 10-yearly endoscopic examination would start in the “diagnosed” non-dysplastic Barrett’s oesophagus state on cycle 1. Between year 1 and 10, the cohort is assigned to “no surveillance” and thus would cycle through “undetected states” progressing or regressing according to the transition probabilities between the undetected health states. At year 10, a portion of this cohort would remain in undetected non-dysplastic Barrett’s oesophagus, while others could have progressed or regressed. The health state at year 10 would then be detected by endoscopic examination and the cohort would move into the respective “diagnosed” health state. This simulates what would happen in a practical environment, as an individual could potentially progress to dysplasia or cancer between their endoscopic examinations.

Whether the cohort undergoes surveillance or “no surveillance” is determined by a mathematical function known as “modulo.” The modulo function is the absolute value of the remainder after division of two numbers. The result is termed “modulus.” The function calculation was performed as stated below:

Equation 5. Use of modulo function to determine if the cohort is due for endoscopic examination as per surveillance interval

$$if(mod(Cycle\ number, Surveillance\ Interval) = 0) \rightarrow Endoscopy)$$

$$if(mod(Cycle\ number, Surveillance\ Interval) > 0) \rightarrow No\ Surveillance)$$

The cycle number *modulo* surveillance interval was used to determine whether the cohort was due for an endoscopic examination or continue under “no surveillance.” For example, if the surveillance interval is 8 cycles (4 years), and the model is in cycle 21, then 21 modulo 8 = 3. In this case, the no surveillance option would be selected. When the cycle number reaches a product of factor surveillance interval, then the modulus becomes 0. For the above example, this would be cycle 24.

4.3.1.2 Movement through Risk-related and Common Pathway

The model was split into a risk-related pathway and a common pathway. The risk-related pathway included stages of Barrett’s oesophagus, while the common pathway was made of cancer states. In the base case (no surveillance), the model started with a diagnosis of non-dysplastic Barrett’s oesophagus, after which the cohort either remained in the starting state (Diagnosed non-dysplastic Barrett’s oesophagus), regressed (Undetected-No metaplasia/ No Barrett’s oesophagus) or progressed (undetected low-grade dysplasia/undetected high-grade dysplasia (Figure 18). However, if the cohort progressed further than high grade dysplasia, they were diagnosed with symptomatic adenocarcinoma, at which point they had either *localised, regionally spread, unstaged, or metastatic cancer*. Once a patient had a confirmed diagnosis of oesophageal adenocarcinoma, they entered the common pathway. This reflected the progression of patients

through various stages of cancer (Figure 17). Patients with metastatic cancer are offered palliative treatment while other stages receive curative treatment. Curative treatment consisted of tri-modality (neoadjuvant chemo and radiotherapy followed by surgery). Lastly, all patients could die of either cancer-related non-cancer related causes. In the non-cancer states, death rates were defined by lifetables (age related, all-cause mortality). In the cancer states, death was defined by stage-based survival data from Surveillance, Epidemiology, End Results database for esophageal cancer for 10 years (shown in Table 16, Chapter 5). If patients were alive 10-years post cancer diagnosis, all-cause mortality was applied for the remaining time horizon.

Model characteristics

4.3.1.3 Cycle length and Time horizon

The Markov cycle length was set at 6 months with a time horizon of 35 years. Cycle length was selected based on the smallest interval between endoscopies, which was 6 months. Surveillance starting age was 50 years old, which meant model terminated at 85 years of age or death. This was selected based on evidence that indicated cessation of surveillance around 81 years of age is cost-effective (173).

4.3.1.4 Input parameterisation

Transition probabilities were derived from systematic reviews and meta-analyses and large cohort studies. If literature sources were unreliable or unavailable, observed data were used to determine these outcomes through a local database of South Australian Barrett's oesophagus Surveillance Study individuals. Transition probabilities for Barrett's stages (risk-related pathway) were derived through a calibration process, described in detail below. The reason these values were calibrated was because literature values for undetected and risk-stratified health states were unavailable. All-cause mortality data was extracted from the Australian Bureau of Statistics Life tables (2017-2019) (149). Stage based esophageal cancer mortality was extracted from the Surveillance, Epidemiology, and End Results Program (SEER) database, shown in Chapter 5, Table 16 (151). This is an open-access database that collects data related to demographics, diagnosis, and mortality of cancer patients in the United States. The program is supported by Division of Cancer Control and Population Sciences under National Cancer Institute (part of National Institutes of Health).

The initial estimates Risk factor-based health state transitions literature estimates for transition probabilities for segment length of endoscopically visible Barrett's oesophagus were derived from Lindblad et al (70), whereas gender related from Omidvari et al. (123). The local database of South Australian Barrett's oesophagus patients contained 18 years of prospectively collected data from 1,059 patients diagnosed with Barrett's oesophagus at initial endoscopy and enrolled into a routine surveillance program. Patients were removed from the program if more than

two consecutive endoscopic examinations show absence of Barrett's oesophagus (no metaplasia and dysplasia on histology). Data were collected from March 2003 - March 2021 including demographics, diagnosis by Barrett's oesophagus stage, and circumferential and maximum length of Barrett's segment. Descriptive and statistical analysis was carried out with Rstudio (R version 3.6.3 2020-02-29) (184). Specifically, survival analysis and Cox-proportional hazard models were performed for estimating risk of progressing to high grade dysplasia or esophageal adenocarcinoma (using "survival" and "survminer" packages). Ethical approval for the use of the Barrett's oesophagus surveillance database was obtained from Southern Adelaide Human Research Ethics Committee (AUD/20/SAC/138). Further details of this dataset can be found in Appendix 10.2.

4.3.1.5 Assumptions

Building a Markov cohort model to represent clinical conditions requires assumptions to be made. The assumptions made for this study and their justifications are given below:

- All adenocarcinoma arises from Barrett's oesophagus: This has been discussed in Chapter 3. All current evidence suggests Barrett's oesophagus is the only precursor to oesophageal adenocarcinoma.
- All patients have been accurately diagnosed through surveillance: Endoscopic examination with histopathology of biopsies per the Seattle protocol is the gold standard for diagnosing Barrett's oesophagus. Only patients with ≥1cm of salmon-coloured mucosa were deemed to have Barrett's oesophagus. Irregular Z-line was not included. Since there is no alternative way of diagnosing Barrett's oesophagus, we assumed it is 100% accurate.
- Patient attendance/adherence to endoscopy as well as endoscopy proceduralist compliance to Seattle biopsy protocol is 100%: Misclassification models exist in the literature, but the rate of incorrect diagnosis would be similar across all strategies and was not deemed an important variable to introduce.
- Routine Surveillance intervals: Individuals with non-dysplastic Barrett's oesophagus have endoscopic examinations every 2 years as part of routine endoscopic surveillance; individuals with low grade dysplasia have 12 monthly endoscopies; individuals with high grade dysplasia and intramucosal cancer (stage T1a) will have endoscopic treatment. individuals with no metaplasia on 2 consecutive endoscopic biopsies will be considered not to have Barrett's oesophagus and will be excluded from endoscopic surveillance at that time point.
- All Barrett's oesophagus stages are asymptomatic: These stages are metaplasia, dysplasia, and intramucosal oesophageal adenocarcinoma. Symptoms associated with Barrett's oesophagus are usually related to gastroesophageal reflux itself or inflammation caused by refluxing. There are no symptoms pertaining specifically to Barrett's oesophagus

or even indicative of Barrett's oesophagus. Consequently, QALY value of Barrett's oesophagus stages was assumed to be the same as age adjusted background QALY. Endoscopic intervention and diagnosis of dysplasia or cancer resulted in decrease in QALY and was adjusted temporarily.

- All individuals who progress to high grade dysplasia or intramucosal carcinoma under surveillance will be detected at their next endoscopy: Individuals under two yearly endoscopic surveillance in the model conditions were not able to progress to symptomatic oesophageal adenocarcinoma without intervention. A small percentage progressed to oesophagectomy if endoscopic intervention fails, but the model did not allow individuals under routine two yearly endoscopic surveillance to go directly from Barrett's oesophagus to oesophageal adenocarcinoma with localised, regional, or distant spread.
- Individuals not under surveillance will only be detected with cancer when symptomatic: This is reflective of the real world, as if an individual with Barrett's oesophagus is not under surveillance, the only way of suspecting oesophageal adenocarcinoma is when they present with symptoms.
- Anyone that develops cancer would develop it within the time horizon of the model: The model starts at age 50 and ends after 70 cycles or 35 years. We assumed any oesophageal adenocarcinoma developing in these individuals would be between 50-85 years. This is a reasonable assumption to make considering the latency period for oesophageal adenocarcinoma is approximately 15-20 years.
- Once an individual has high grade dysplasia, their chance of progressing to symptomatic oesophageal adenocarcinoma does not vary in risk subgroups: In the aggregate group, the transition probability of high-grade dysplasia to symptomatic oesophageal adenocarcinoma was estimated through the calibration process. In the risk subgroups, this transition probability was not calibrated. This is because once high-grade dysplastic features are reached, the individual is no longer considered a "low-risk." The risk of developing oesophageal adenocarcinoma is independent of their risk profile.
- Treatment for high grade dysplasia is radiofrequency ablation: Treatment for stage T1a cancer is endoscopic mucosal resection and radiofrequency ablation. After treatment, patients were followed with endoscopies until time horizon or death.
- Age specific all-cause mortality is applied until cancer is detected. After diagnosis with cancer, survival is dependent on stage appropriate 5-year survival rates. After 5 years, mortality assumed normal population age specific mortality.

Stepwise calibration

Modelling undetected states and risk-related states for Barrett's oesophagus has not been previously reported in the literature. How the addition of undetected states would thus affect the

model outputs was unknown. In order to accurately simulate the natural history of Barrett's oesophagus, the non-stratified (aggregate cohort) and risk-stratified cohorts (low and high risk subgroups) were calibrated to known targets derived from literature. A point of note, only the Barrett's stages contained non-stratified and risk-stratified health states. Cancer states were part of the common pathway. These states did not require calibration, as observed data was available for these states. An optimisation algorithm (available in TreeAge Pro) was used to systematically alter transition probabilities between stages of Barrett's oesophagus. The initial values and ranges were based on data (observed/modelled) and parameterisation described above. Ranges were specified for each transition probability to ensure the results remained within literature reported values.

Each time a model input was changed, the iteration was recorded, along with the model outputs produced. These model outputs were matched to targets, which were observed data from large cohort studies and ensured validity of the model. This was carried out in a modified seven-step process based on Vanni, Karnon and colleagues (185, 186) detailed below.

4.3.1.6 Stage 1: Parameters varied in calibration process

All transition probabilities relating to progression or regression from metaplasia to oesophageal adenocarcinoma for patients in the no surveillance arm were included in the calibration process.

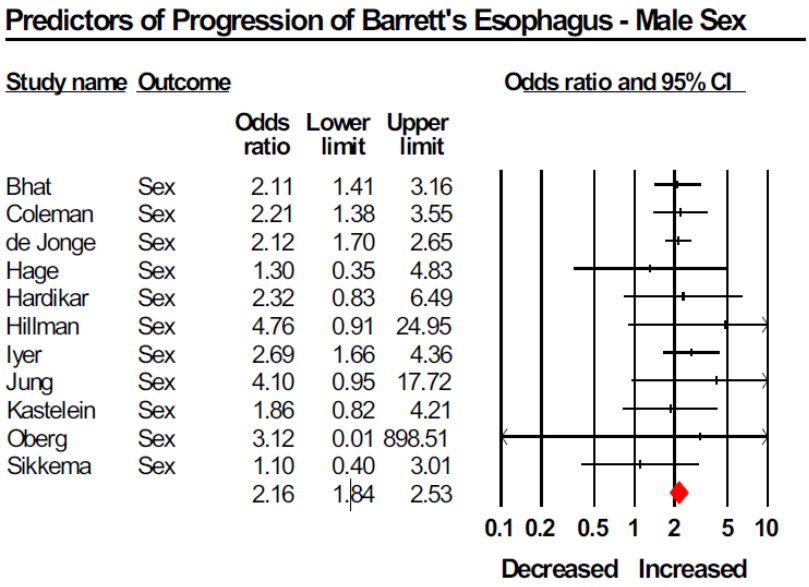
4.3.1.7 Stage 2: Calibration targets

Observed data from systematic reviews/meta-analysis (29) or high-quality cohort studies were pooled and selected as calibration targets (15, 17, 21, 106, 153). The primary targets for model outputs were lifetime risk of high-grade dysplasia or esophageal adenocarcinoma from non-dysplastic Barrett's oesophagus (indicated with "T" in Figure 17) estimated at 16% and 11% respectively. The model output targets for risk-stratified subgroups depended on comparative risk of progression to adenocarcinoma found in the literature. This was derived from hazard ratios from published literature (15, 187) and/or local data (South Australian Barrett's oesophagus database). Model outputs of high-grade dysplasia and oesophageal adenocarcinoma were known from observed/reported data in the form of meta-analyses, but the proportion of individuals in risk-stratified states was not available.

Results of estimated calibration targets (Table 16), model outputs Table 14, and probabilistic sensitivity analysis (Figure 20) are shown. Between March 2003 and March 2021, 1059 patients had started with a diagnosis of non-dysplastic Barrett's oesophagus and had adequate data for inclusion in analysis, followed for a total of 5081 patient years. A Cox regression analysis was used to identify odds ratio of progression from non-dysplastic Barrett's oesophagus to high grade dysplasia or oesophageal adenocarcinoma for between low and high-risk factors. This

showed patients with more than 2 cm Barrett's segment length had 5.46 times higher risk to develop high grade dysplasia or adenocarcinoma. For gender, a meta-analysis reported hazard ratio for male: female as 2.13 HR (95% CI 1.84-2.53)(29). There were several concerns with using values from this meta-analysis. Firstly, there was significant heterogeneity between studies, with the upper limit as high as 25x and lower limit under 0.3x (measures of heterogeneity not reported in meta-analysis)(29). Some studies reported very high hazard ratios, such as Oberg et al, lower limit was 0.01 and upper limit was 898.51(188). Similarly, Hilman et al reported hazard ratio of 0.91 to 24.95(189).

Figure 19. Gender related progression of Barrett's Oesophagus to oesophageal adenocarcinoma. From Krishnamoorthi et al. systematic review and meta-analysis (29)



Additionally, the data synthesis in the meta-analysis combined retrospective and prospectively obtained data. This causes discrepancies in follow-up which can impact the final rate of progression and thus hazard ratio of a risk factor. The final reason for not using the exact value of 2.13 as the odds ratio was the number of patients for each study was not provided in the meta-analysis. This does not impact the results of the meta-analysis, but it effects the transition probabilities generated from the calibration process. Theoretical knowledge dictated that the Barrett's oesophagus cohort has approximately 2x as many males and account for 3-4x as many cancers (compared to females). An odds ratio of between under 2.5x (according to the ranges of the meta-analysis Figure 19) resulted in lower transition probabilities between male risk-stratified Barrett's oesophagus health states. This was contradictory to literature values in economic evaluations (123, 173) and other studies (190). Ultimately, an odds ratio of 2.5 was used to calculate the calibration target for gender-related model outputs of high-grade dysplasia and oesophageal adenocarcinoma, derived from South Australian Barrett's oesophagus cohort database (using cox-proportional hazards model- Appendix 10.2).

Point of note: the proportion of patients per risk group heavily influences the transition probabilities estimated by the calibration process. As an example, in a starting cohort of gender stratified non-dysplastic Barrett's oesophagus patients, we know that approximately 35% of them are female. We also know that females constitute ~3.1% of the starting cohort that develop oesophageal adenocarcinoma, which is ~1 in 12 females over the time horizon. However, if only 10% of starting non-dysplastic Barrett's oesophagus cohort constituted of females, and they still accounted for ~ 3.1% of the oesophageal adenocarcinoma across the time horizon, then the risk of progression from non-dysplastic Barrett's oesophagus for each female would be higher, approximately 1 in 3 females. Conversely, if females made up 50% of the starting non-dysplastic Barrett's oesophagus cohort, then the rate of progression from non-dysplastic Barrett's oesophagus would be lower, approximately 1 in 16 females. In order to accurately estimate the transition probabilities of risk-stratified groups, the hazard ratios of progression from non-dysplastic Barrett's oesophagus to oesophageal adenocarcinoma *and* the proportions of the initial cohort had to be *derived from the same source* or reported observed data (29, 187). When proportion data were not available or risk related data were unreliable, local data (South Australian Barrett's oesophagus database) provided both starting proportions and hazard ratios for subgroup calibration targets. A list of targets used is provided in Table 12.

Table 12. List of calibration targets used. Calibration only performed in no surveillance arm. Percentage signifies fraction of cohort that progressed to the specified state. Proportion of cohort refers to the proportion that started in each of the risk group.

	Target HGD	Target EAC	Hazard Ratio	Starting Cohort	Evidence
No surveillance	16%	11%	-	100%	Gatenby(153)
Gender					
Female	4.57%	3.14%	1	35%	Local data
Male	11.43%	7.86%	2.5	65%	Krishnamoorthi (29) Melquist(190)
Total	16%	11%			
Length					
Short <= 2 cm	2.46%	1.69%	1	62.5%	Local data
Long > 2 cm	13.54%	9.31%	5.46	37.5%	
Total	16%	11%			
Short < 3 cm	2%	1.38%	1	75%	Coleman 2014 (187) Local data
Long => 3 cm	14%	9.63%	7	25%	
Total	16%	11%			

Legend: High Grade Dysplasia (HGD), Oesophageal adenocarcinoma (EAC)

4.3.1.8 Stage 3: Measure of Goodness of Fit

Each iteration of the calibration process results in model outputs that were compared to the targets seen in Table 12. In order to select the iterations that most closely represents the calibration targets, the distance from the iteration model output to the calibration target was calculated. This was performed using a weighted sum of squared differences method using the following formula:

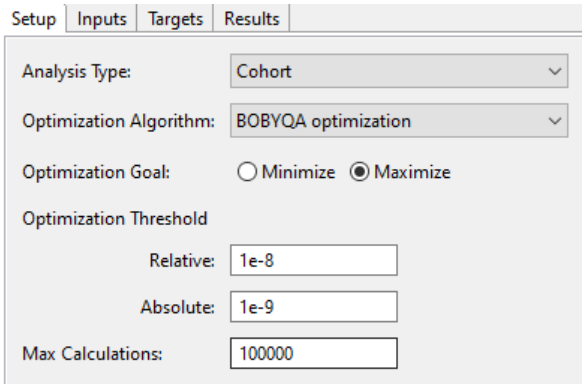
Equation 6. Calculation of Euclidean distance between model output and calibration target

$$\sum_{X=1}^{10}((Model\ output\ X - Target\ X) * Weight)^2$$

$$((Model\ output\ 1 - Target\ 1) * Weight)^2 + ((Model\ output\ 2 - Target\ 2) * Weight)^2 + \ldots + ((Model\ output\ 10 - Target\ 10) * Weight)^2$$

The distance calculated by the above equation was a measure of how closely the algorithm was able to optimise the input parameter sets. The algorithm ended when the input parameters were optimised to generate model outputs within a specified distance of the targets. This specified distance will be referred to as the optimisation threshold, shown being set in Figure 20.

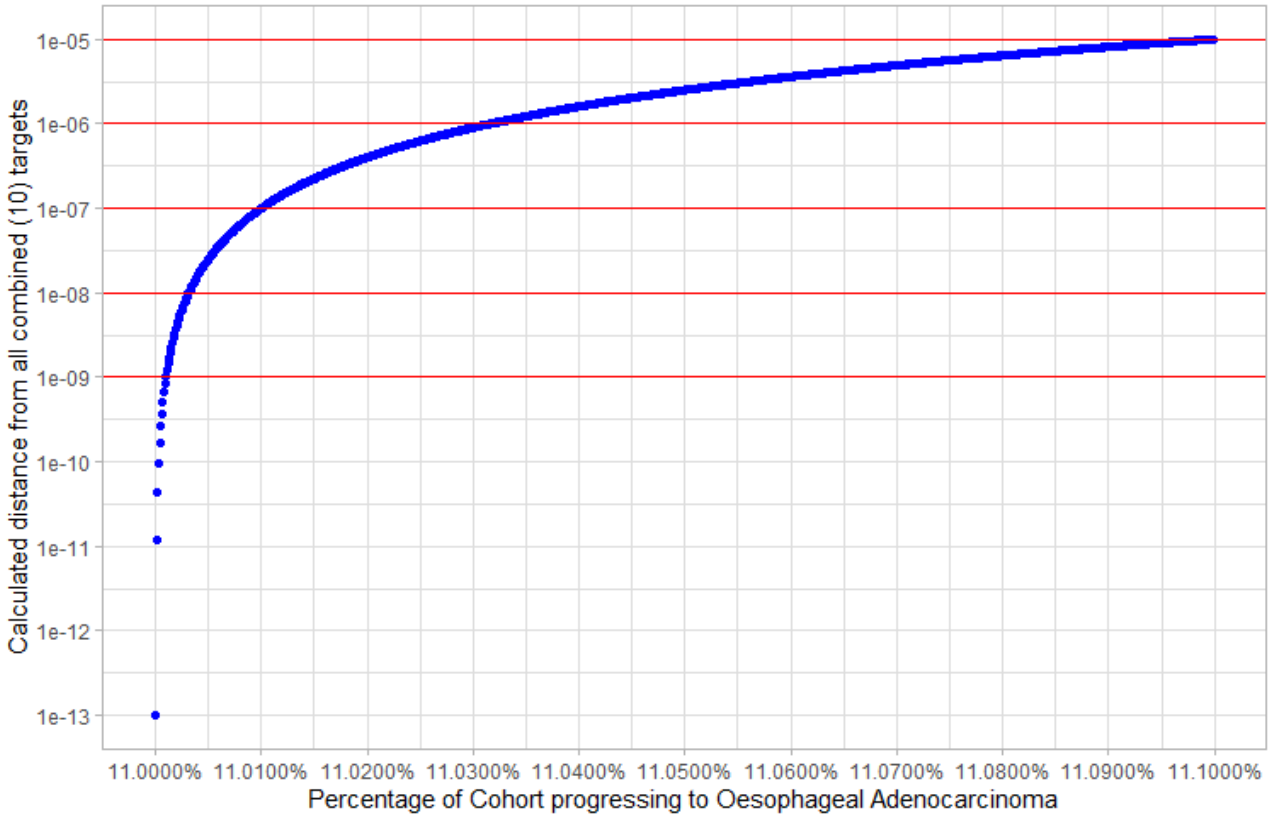
Figure 20. Optimisation threshold setup



The aim of the optimisation process was to achieve enough input parameters sets within a convergent criteria, that a probabilistic analysis could be run. In order to do this, the optimisation algorithm had to achieve 16% of the aggregate cohort progressing to high grade dysplasia and 11% to oesophageal adenocarcinoma. Setting a smaller threshold enabled the algorithm to continue optimising until the model outputs were closer to the absolute distance nearing 0. Choosing a larger threshold would force the optimisation algorithm to end prior to nearing 0, which would mean inadequate number of convergent sets would be available for probabilistic analysis.

Setting an optimisation threshold was based on a theoretically understanding of the distance formula. The distance between one target and one model output is inversely exponentially related the combined distance between all targets and all model outputs (per iteration). This is demonstrated in Figure 21.

Figure 21. Relationship between distance between 1 target and over distance between 10 targets



As seen in the Figure 21, a change from 11.00% to 11.01% results in nearly a 100x difference in the distance for all 10 targets combined. Thus, the absolute threshold was set to $1x10^{-9}$ to enable the algorithm to continue optimisation over 10,000 parameter sets were generated. Point of note: The purpose of calculating the distance between all iterative model outputs and model targets was to run the optimisation algorithm enough to achieve a large set of parameters, of which the convergent sets would be extracted. It is independent to convergence criteria, which is defined in Stage 5.

4.3.1.9 Stage 4: Parameter search strategy

Model calibration was performed using a constrained Bound Optimization by Quadratic Approximation (BOBYQA) method run for minimisation (161). This algorithm requires an initial value, initial step, lowest and highest values. These values are shown in Figure 19. The *initial step* is the increment at which the calibration software adjusts the input parameters. The highest and lowest values were limits of expected values beyond which the input parameter is considered

unrealistic and helps focus the algorithm when adjusting the model input parameters to match desired model outputs. When data was unavailable, initial step, lowest, and highest values were based on informed clinical experience. Most values were found using a combination of literature sources of systematic reviews and meta-analyses, large cohort studies, or published economic evaluations using similar health states. If the transition probabilities were unavailable through these sources, it was extracted from South Australian Barrett's oesophagus database. This was performed using multistate modelling (R Multi state modelling msm package version 1.6.9). The initial value, initial step, lowest value, and highest value are provided in Figure 20.

Figure 22. Calibration optimisation algorithm input parameters for 70 transition probabilities.

Index	Variable	Initial Value	Initial Step	Lower Bound	Upper Bound
1	p_Befree_NDBE_NS_female	0.104397	0.0001	0.01	0.2
2	p_Befree_NDBE_NS_long2	0.144405	0.0001	0.001	0.2
3	p_Befree_NDBE_NS_long3	0.146431	0.0001	0.001	0.2
4	p_Befree_NDBE_NS_male	0.103876	0.0001	0.005	0.2
5	p_Befree_NDBE_NS_risk1	0.101797	0.0001	0.01	0.2
6	p_Befree_NDBE_NS_short2	0.097737	0.0001	0.01	0.2
7	p_Befree_NDBE_NS_short3	0.099148	0.0001	0.01	0.2
8	p_Befree_LGD_NS_female	0.001335	0.00001	0.0001	0.003
9	p_Befree_LGD_NS_long2	0.00282	0.00001	0.0001	0.01
10	p_Befree_LGD_NS_long3	0.003939	0.00001	0.0001	0.01
11	p_Befree_LGD_NS_male	0.001177	0.00001	0.0001	0.01
12	p_Befree_LGD_NS_risk1	0.000909	0.00001	0.0001	0.005
13	p_Befree_LGD_NS_short2	0.000349	0.00001	0.0001	0.003
14	p_Befree_LGD_NS_short3	0.000642	0.00001	0.0001	0.003
15	p_Befree_HGD_NS_female	0.00018	0.000001	0.00001	0.0005
16	p_Befree_HGD_NS_long2	0.000348	0.000001	0.00001	0.005
17	p_Befree_HGD_NS_long3	0.000478	0.000001	0.00001	0.005
18	p_Befree_HGD_NS_male	0.000145	0.000001	0.00001	0.001
19	p_Befree_HGD_NS_risk1	0.000146	0.000001	0.00001	0.005
20	p_Befree_HGD_NS_short2	0.00011	0.000001	0.00001	0.005
21	p_Befree_HGD_NS_short3	0.000056	0.000001	0.00001	0.005
22	p_NDBE_Bfree_NS_female	0.082966	0.0001	0.005	0.2
23	p_NDBE_Bfree_NS_long2	0.094733	0.0001	0.005	0.2
24	p_NDBE_Bfree_NS_long3	0.107911	0.0001	0.005	0.2
25	p_NDBE_Bfree_NS_male	0.083194	0.0001	0.005	0.2
26	p_NDBE_Bfree_NS_risk1	0.082568	0.0001	0.005	0.2
27	p_NDBE_Bfree_NS_short2	0.067801	0.0001	0.005	0.2
28	p_NDBE_Bfree_NS_short3	0.067678	0.0001	0.005	0.2
29	p_NDBE_LGD_NS_female	0.019978	0.0001	0.005	0.05
30	p_NDBE_LGD_NS_long2	0.031753	0.0001	0.005	0.12
31	p_NDBE_LGD_NS_long3	0.035863	0.0001	0.005	0.12
32	p_NDBE_LGD_NS_male	0.022422	0.0001	0.005	0.12
33	p_NDBE_LGD_NS_risk1	0.020715	0.0001	0.005	0.05
34	p_NDBE_LGD_NS_short2	0.005785	0.0001	0.001	0.05
35	p_NDBE_LGD_NS_short3	0.006587	0.0001	0.001	0.05
36	p_NDBE_HGD_NS_female	0.000821	0.00001	0.0004	0.006
37	p_NDBE_HGD_NS_long2	0.001564	0.00001	0.0004	0.04
38	p_NDBE_HGD_NS_long3	0.005876	0.00001	0.0004	0.04
39	p_NDBE_HGD_NS_male	0.001004	0.00001	0.0004	0.04
40	p_NDBE_HGD_NS_risk1	0.000572	0.00001	0.0004	0.006
41	p_NDBE_HGD_NS_short2	0.000494	0.00001	0.0004	0.006
42	p_NDBE_HGD_NS_short3	0.000491	0.00001	0.0004	0.006
43	p_NDBE_OAC_NS_female	0.000489	0.00001	0.0002	0.005
44	p_NDBE_OAC_NS_long2	0.000841	0.00001	0.0002	0.01
45	p_NDBE_OAC_NS_long3	0.00265	0.00001	0.0002	0.01
46	p_NDBE_OAC_NS_male	0.000471	0.00001	0.0002	0.01
47	p_NDBE_OAC_NS_risk1	0.000454	0.00001	0.0002	0.005
48	p_NDBE_OAC_NS_short2	0.000212	0.00001	0.00001	0.005
49	p_NDBE_OAC_NS_short3	0.000214	0.00001	0.00005	0.005
50	p_LGD_HGD_NS_female	0.022997	0.0001	0.001	0.05
51	p_LGD_HGD_NS_long2	0.022781	0.0001	0.001	0.15
52	p_LGD_HGD_NS_long3	0.038356	0.0001	0.001	0.15
53	p_LGD_HGD_NS_male	0.0286	0.0001	0.001	0.15
54	p_LGD_HGD_NS_risk1	0.029039	0.0001	0.001	0.07
55	p_LGD_HGD_NS_short2	0.011131	0.0001	0.001	0.05
56	p_LGD_HGD_NS_short3	0.011691	0.0001	0.001	0.05
57	p_LGD_OAC_NS_female	0.004631	0.0001	0.001	0.05
58	p_LGD_OAC_NS_long2	0.00609	0.0001	0.001	0.05
59	p_LGD_OAC_NS_long3	0.00784	0.0001	0.001	0.05
60	p_LGD_OAC_NS_male	0.006682	0.0001	0.001	0.05
61	p_LGD_OAC_NS_risk1	0.006284	0.0001	0.001	0.05
62	p_LGD_OAC_NS_short2	0.001797	0.0001	0.001	0.05
63	p_LGD_OAC_NS_short3	0.001989	0.0001	0.001	0.05
64	p_LGD_reg_NS_female	0.097295	0.001	0.01	0.2
65	p_LGD_reg_NS_long2	0.000789	0.00001	0.00001	0.2
66	p_LGD_reg_NS_long3	0.000755	0.00001	0.00001	0.2
67	p_LGD_reg_NS_male	0.079832	0.001	0.01	0.2
68	p_LGD_reg_NS_risk1	0.075939	0.001	0.01	0.2
69	p_LGD_reg_NS_short2	0.0928	0.001	0.01	0.2
70	p_LGD_reg_NS_short3	0.090171	0.001	0.01	0.2

4.3.1.10 Stage 5: Convergence criteria

This was determined as within 90% of the calibration targets (Table 12). Multiple runs of the calibration algorithm resulted in over 10,000 iterations. The iterations were combined, and only those which resulted in the model outputs that lay within 90% of the calibration target were selected.

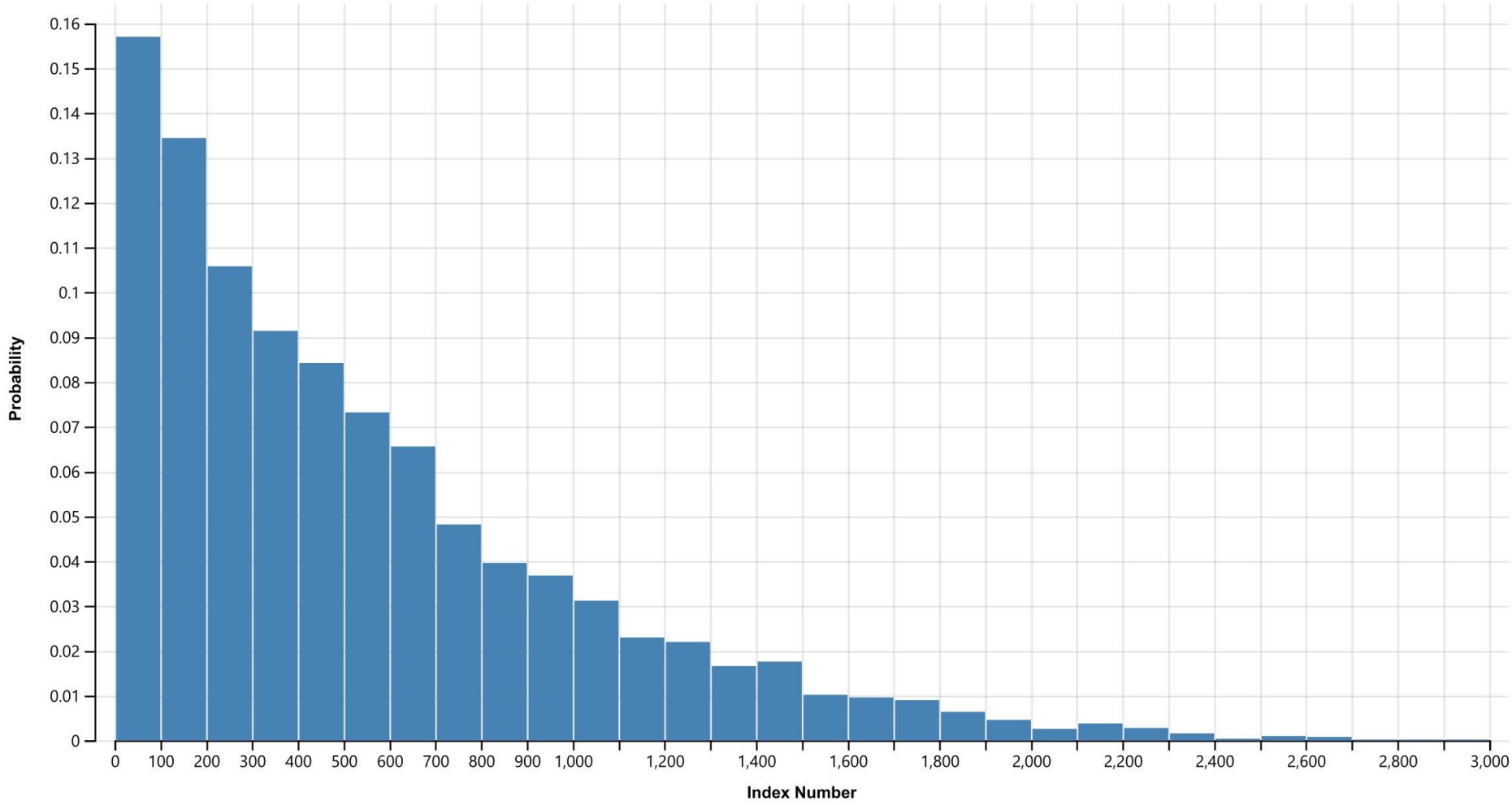
4.3.1.11 Stage 6: Termination of calibration process

The BOBYQA iterative search strategy was run until a low sum of squared differences was achieved ($<10^{-9}$). Out of the 10,187 iterations, 4358 were within 10% of calibration targets. Targets, transition probabilities, and the results of calibration were discussed with and confirmed by group of clinicians and health economists.

4.3.1.12 Stage 7: Integration of calibration process and probabilistic sensitivity analysis

Each of the 4,358 resultant input parameter sets lay within 90% of the mean of the 10 calibration targets and can be seen in Figure 22. These were arranged by ascending Euclidean distance (Equation 5), with an index value to indicate rank within the convergent input parameter sets. The lowest distance value was the first entry (index value 1) and highest as the last (index value 4358). A Pert distribution was created, which generated an integer between 1 and 4358. This type of distribution requires four parameters/values: minimum, likeliest, maximum, and shape. The minimum and the likeliest were defined as index value 1(lowest goodness of fit), while the maximum was 4358. Lastly, a shape that roughly mimics the distribution of the expanded sum of squared differences was chosen (shape = 6). The distribution thus would preferentially sample the parameters sets that were closer in distance to the calibration targets. The distribution is shown in Figure 20.

Figure 23. Pert sampling distribution. Based on the distribution of the distance of each calibration iteration from its calibration targets. X-axis is the index number which refers to a convergent set of transition probabilities. Y-axis is the frequency of occurrence during random sampling.

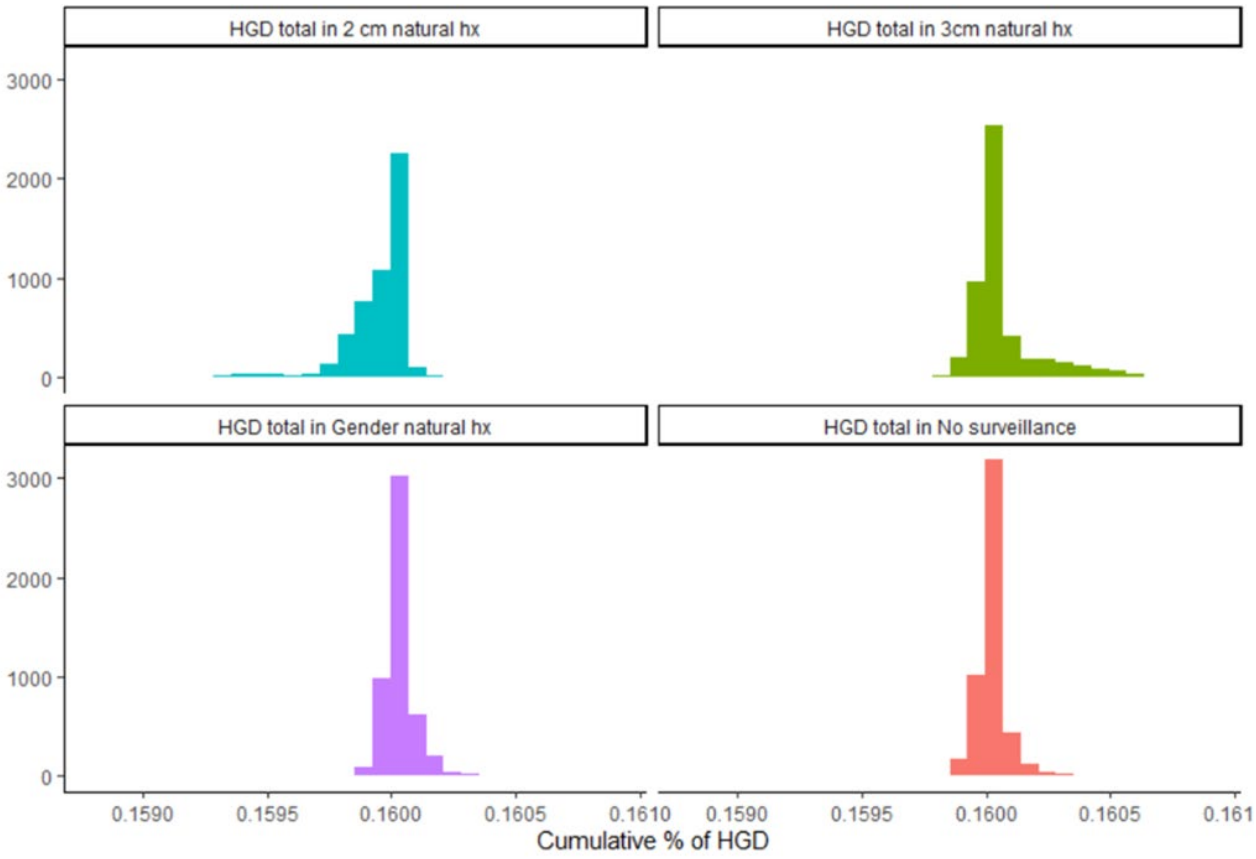


4.4 Results

Estimated Transition Probabilities

Calibration using these targets allowed estimation of transition probabilities between risk-stratified subgroup health states, which were within anticipated ranges Table 13. Transition probabilities for progression to high-grade dysplasia or oesophageal adenocarcinoma were expectedly highest for long segment Barrett's oesophagus (>=3 cm) and lowest for its complement short segment group (<3 cm). Conversely regression from low-grade dysplasia to non-dysplastic Barrett's oesophagus was highest with short segment (<=2 cm) and female subgroup, and lowest for long segment subgroup (>2 cm and >=3 cm of Barrett's oesophagus length). Of further note, transition probabilities of non-dysplastic Barrett's oesophagus to oesophageal adenocarcinoma were highest for long segment Barrett's oesophagus (>=3 cm) at 0.53% annually compared. In comparison, the same transition probability in long segment (>2 cm) was 0.17%, which is a third of patients with >= 3 cm Barrett's oesophagus. non-dysplastic Barrett's oesophagus to high-grade dysplasia transition probabilities were, again, expectedly highest in patients with >=3 cm Barrett's oesophagus segment length (1.18% annually) followed by >2 cm segment length (0.31% annually). Probabilistic analysis with 5,000 simulations showed a narrow distribution of calibrated model outputs, lying within 90% of selected calibration targets. Distribution of high grade dysplasia among the grouped health states is shown in Figure 22.

Figure 24. Histogram of Probabilistic Sensitivity Analysis (5000 simulations) showing distribution of High-Grade Dysplasia is confined within a 90% confidence interval, with highest distribution at a cumulative 16% of total cohort. Legend: High Grade Dysplasia (HGD)



Integration of calibration process with probabilistic analysis

In the 5000 simulations of the base strategy of “no surveillance” (simulating natural history of Barrett’s oesophagus) for non-stratified and risk-stratified groups, the cohort started at age 50 and was followed for a total of 35 years (70 six-monthly cycles), with individuals exiting the model at death or age 85. A cumulative 16% of cohort developed high grade dysplasia and 11% of the overall cohort progressed to oesophageal adenocarcinoma. At the end of cycle 70, 14.3% of the cohort had eventually regressed to having no Barrett’s oesophagus, while 17.1% remained in the non-dysplastic state, 3.4% in low grade dysplasia, 4.8% in high grade dysplasia. The rest of the ~60% of the cohort had died, of which 10.7% were cancer-related deaths, which are similar to published rates from SEER(151). In the length-based subgroups, 2.46% and 1.7% progression of high grade dysplasia and adenocarcinoma was seen in patients with 2 cm or less segment of Barrett’s (starting population 62.5% of cohort), while patients with greater than 2 cm of Barrett’s segment (37.5% of cohort) saw 9.31% and 13.5% progression in adenocarcinoma and high grade dysplasia respectively (Table 14). Patients with 3 cm or less Barrett’s oesophagus segments (75% of starting population) had 1.33% and 2.1% and those with longer than 3 cm (25% of cohort) had 9.6% and 14% adenocarcinoma and high grade dysplasia respectively. Table 14 shows the results of 5000 simulations, showing stable model outputs in both non-stratified and risk-stratified health states.

Table 13. Probabilities of progression in Barrett's oesophagus stages for aggregate cohort as well as subgroups. Values in annual percentages from the best fitting model.

Risk-related health states	No surveillance	Female	Male	Short (2 cm)	Long (2 cm)	Short (3 cm)	Long (3 cm)
No Barrett's to NDBE	21.47%	22.05%	21.94%	20.57%	31.19%	20.88%	31.67%
No Barrett's to LGD	0.18%	0.27%	0.24%	0.07%	0.56%	0.13%	0.79%
No Barrett's to HGD	0.03%	0.04%	0.03%	0.02%	0.07%	0.01%	0.10%
NDBE to No Barrett's	17.24%	17.32%	17.37%	14.04%	19.91%	14.02%	22.84%
NDBE to LGD	4.19%	4.04%	4.54%	1.16%	6.45%	1.32%	7.30%
NDBE to HGD	0.11%	0.16%	0.20%	0.10%	0.31%	0.10%	1.18%
NDBE to EAC	0.09%	0.10%	0.09%	0.04%	0.17%	0.04%	0.53%
LGD to HGD	5.89%	4.65%	5.80%	2.24%	4.61%	2.35%	7.82%
LGD to EAC	1.26%	0.93%	1.34%	0.36%	1.22%	0.40%	1.57%
LGD to NDBE	15.80%	20.47%	16.64%	19.48%	0.16%	18.90%	0.15%
HGD to EAC	3.8%	-	-	-	-	-	-

Legend: No Barrett's (nil intestinal metaplasia), Non-dysplastic Barrett's Oesophagus (NDBE) to Low-Grade Dysplasia (LGD), High Grade Dysplasia (HGD), Oesophageal adenocarcinoma (EAC)

Table 14. Model outputs of Probabilistic sensitivity analysis undergoing no surveillance for non-stratified and risk-stratified health states. Model outputs are given as percentage of cohort in mean and standard deviation.

	HGD	Adenocarcinoma	Localised cancer	Regional spread	Unstaged cancer	Distant Metastases
No surveillance	16.0% (0.006%)	11.0% (0.008%)	2.1% (0.002%)	3.2% (0.002%)	2.2% (0.002%)	3.5% (0.003%)
Length (2 cm threshold)	16.0% (0.013%)	11.0% (0.021%)	2.1% (0.004%)	3.2% (0.006%)	2.2% (0.004%)	3.5% (0.007%)
Group 1- 2 cm or less	*2.5% (0.005%)*	*1.7% (0.025%)*				
Group 2- more than 2 cm	*13.5% (0.023%)*	*9.3% (0.007%)*				
Length (3 cm threshold)	16.0% (0.014%)	11.0% (0.008%)	2.1% (0.002%)	3.2% (0.002%)	2.2% (0.002%)	3.5% (0.003%)
Group 1- less than 3 cm	*3.2% (0.015%)*	*2.2% (0.023%)*				
Group 2- 3 cm or more	*12.8% (0.015%)*	*8.8% (0.017%)*				
Gender	16.0% (0.007%)	11.0% (0.013%)	2.1% (0.002%)	3.2% (0.004%)	2.2% (0.003%)	3.5% (0.004%)
Group 1- Female	*4.6% (0.010%)*	*3.1% (0.012%)*				
Group 2- Male	*11.4% (0.006%)*	*7.9% (0.007%)*				

Legend: Non-dysplastic Barrett's Oesophagus (NDBE) to Low-Grade Dysplasia (LGD), High Grade Dysplasia (HGD)

4.5 Discussion

Summary

The focus of this chapter was to describe the development of the decision analytic Markov cohort model simulating progression of Barrett's oesophagus to oesophageal adenocarcinoma. Clinically relevant health states reflecting stages of Barrett's oesophagus were defined, with identical non-overlapping sets for non-stratified and risk-stratified states. These states could transition within stages of Barrett's oesophagus. If the cohort progressed past Barrett's oesophagus, then they would enter the common pathway which include stages of oesophageal adenocarcinoma. Initial model inputs were derived from literature when possible. Rest of the data was sourced from a prospectively followed cohort of individuals in South Australia. Model calibration to high confidence targets was performed for natural progression (no surveillance) of Barrett's oesophagus for accurate representation of the disease process. This was performed for the aggregate cohort as well as the risk-based subgroups, simultaneously. Cohort was dichotomised using two categories of risk factors: Gender (male/female); endoscopically visible Barrett's oesophagus (2 cm threshold and 3 cm threshold)

The decision tree pertaining to potentially cost-effective treatment strategies were also developed in this chapter. These included increasing the surveillance interval as well as endoscopic intervention for dysplastic Barrett's oesophagus. It was important to calibrate the model with these arms included, as it ensured the outputs generated from the aggregate cohort as well risk-factor based subgroups were consistent. This had several advantages. Firstly, the subgroups were representative of the risk factor used to dichotomise the overall cohort, i.e., the risk of progressing or regressing from non-dysplastic Barrett's oesophagus was reflective of the risk-factor based subgroup. Secondly, the combined model outputs of dichotomised risk-subgroups were identical to the aggregate cohort. This meant varying the management of the aggregate cohort would generate the same model outputs as enacting the same management in the risk-subgroups. For example, if the aggregate cohort was assigned to a 5-yearly endoscopy, and each of the gender-subgroups (male and female) were assigned to 5-yearly endoscopy as well, all final model outputs would be identical. And lastly, it allowed varying the management for the subgroups (increasing surveillance intervals or introducing endoscopic interventions), while knowing that the model outputs are a result of the difference in management, rather than incongruencies in the decision tree arms.

A malleable model

Previously, a model of progression in Barrett's oesophagus was developed by collaborators (70, 126). This evaluated cost-effectiveness of selective endoscopic surveillance using either a biomarker or length of Barrett's segment (2 cm, 3 cm, and 4cm thresholds). The first thought was

to update this model with the latest recommended treatment strategies. The motivation to build a de-novo model, instead of updating an existing one, was three-fold. Firstly, guidelines for management of Barrett's oesophagus have changed significantly since the previous model was developed. Secondly, in the previous model, each strategy arm had a different decision tree, which generated varying model outputs and was not calibrated to known literature values. It was unclear whether the different outputs were due to differences in decision tree structure or the transition probabilities. Lastly, varying the decision trees for each strategy limited the number of strategies that could be tested. This is because each strategy that needed to be tested required an independent design and calibration.

This cohort model was built de novo to test a risk-stratified approach to endoscopic surveillance for non-dysplastic Barrett's oesophagus patients. Our main aim was to answer the question whether endoscopic surveillance is cost-effective in a subgroup of patients with risk factor A compared to risk factor B. The calibrated models presented in this paper should facilitate such analyses by including risk groups as a part of the base strategy. Another key difference in this model was building undetected states mirroring Barrett's oesophagus states, which allows testing the effect of lengthening surveillance intervals for an entire cohort or subgroup.

Model Robustness

The strength of this decision analytic Markov cohort model lies in designing 1) risk-stratified alongside non-stratified health states; 2) undetected health states alongside "diagnosed" states; and 3) non-overlapping Barrett's oesophagus stages that combine towards a common pathway once oesophageal adenocarcinoma is reached. This is the first study modelling the natural history of Barrett's oesophagus through undetected states and a risk-stratified Markov cohort process. Other studies have opted to change the aggregate cohort entirely rather than develop risk-stratified and non-stratified states in parallel. Also, rather than model *specific* risk factors, such as length of Barrett's oesophagus segment, gender, obesity, smoking etc, building generic risk-stratified health states helped test a broader number of variables. Theoretically, this model could be adopted to test any dichotomised (or even trichotomized) risk factor subgroups. In this case, only three groups of risk factors have been tested. This is because these were the only ones with accurate data available from both the literature and South Australian Barrett's oesophagus cohort database. As more persuasive literature becomes available, more risk factors could be tested in the same model without changing its structure.

Another strength is the calibration process which generated accurate model outputs underlining features of robust model performance. Key to this process was accurately defining the risk group proportions and their hazard ratios for progression, which allowed the calibration process to estimate the appropriate transition probabilities between various states. The calibration

was also performed simultaneously with the aggregate cohort as well as subgroups, which helped in comparing differences in transition probabilities estimated by the calibration process. This was then integrated into the probabilistic sensitivity analysis, which generated credible model outputs.

Limitations

One of the challenges of this study was selecting the correct inputs to simulate the natural progression of community Barrett's oesophagus i.e., patients not undergoing endoscopic surveillance. It is impossible to estimate the unobserved progression of a silent disease such as Barrett's oesophagus without active surveillance. Endoscopy is the only way to observe, as it is the only currently available modality for diagnosis. Therefore, any conjecture of the natural progression of Barrett's oesophagus would have to be extrapolated from endoscopic surveillance data. It could be argued, however, if a Barrett's oesophagus surveillance program simply observes and does not intervene, this group would theoretically progress similarly to Barrett's oesophagus patients in the community not under surveillance. Such an opportunity was available, as endoscopic treatments for Barrett's oesophagus have only been recently added into guidelines of care. For this reason, we opted to use meta-analyses prior to 2008, which mainly included patients who had not routinely received treatment for high grade dysplasia. Gatenby et al. provided data from several meta-analyses performed pre-2010 that estimated the lifetime risk of developing adenocarcinoma from Barrett's to be between 9-13% (153), which has been discussed previously in Chapter 3.

The main limitation for most economic evaluations is its model inputs. Transition probabilities provided in Table 13 were compared to the literature to ensure they were within expected ranges. Our confidence in the accuracy of transition probabilities for progression or regression of Barrett's oesophagus states was based on two factors: comparison with inputs from previous economic evaluations and model calibration to literature values. We ultimately decided 16% for high grade dysplasia and 11% for adenocarcinoma were the most appropriate target as they estimated the most clinically plausible transition probabilities when compared to high quality economic evaluations. The model was initially trialled with many permutations of calibration targets of high-grade dysplasia and oesophageal adenocarcinoma. Reasons for rejecting these were mostly based on the credibility of the transition probabilities between health states. For example, calibration target of 18% for high grade dysplasia and 13% for oesophageal adenocarcinoma resulted in a transition probability of 0.03% annually between non-dysplasia to oesophageal adenocarcinoma, whereas the transition probability from non-dysplasia to high grade dysplasia was estimated at 0.27% annually. This contradicted values from previously published economic evaluations(70, 128, 173, 191-193). A transition probability of 0.27% from non-dysplastic health state to high grade dysplasia is also 9x the transition probability of non-dysplasia to oesophageal adenocarcinoma, which was likely to be false.

Compared to the literature, our model predicted a similar overall progression rate from non-dysplastic Barrett's oesophagus to oesophageal adenocarcinoma, at approximately 0.314% annually. A meta-analysis by Desai et al. estimated the annual rate of progression at 0.3% (15). This is testament to the rigorous search for high level evidence-based model inputs and calibration targets. It also reflects the advantages of meticulously following a model calibration protocol (185, 186). Point of note: the reported transition probability of 0.09% in Table 13 of non-dysplastic Barrett's oesophagus to oesophageal adenocarcinoma is different to the overall annual progression of these states. The reported 0.09% refers to the single transition from non-dysplastic health state to adenocarcinoma, whereas the overall 0.314% annual progression rate refers to the cumulative percentage of individuals with non-dysplasia progressing to oesophageal adenocarcinoma divided by the time horizon. We were also reassured when our model outputs matched other Barrett's oesophagus and oesophageal adenocarcinoma models in the literature (123, 128). The model also accurately estimated cumulative cancer deaths ~10.7%, which is similar to SEER lifetime mortality rates after developing esophageal cancer (145). This is corroborated by Australian cancer incidence data suggests that cancer incidence and cancer deaths for esophageal cancer from year to year are roughly equal (194).

4.6 Summary

Risk factors that predispose patients to Barrett's oesophagus are unfortunately on the rise. With increasing incidence of obesity and gastroesophageal reflux disease, we will no doubt continue seeing a rise in patients with Barrett's oesophagus. Even though only a small portion of these patients will develop oesophageal adenocarcinoma, the morbidity and mortality associated with late-stage cancer increases costs to the health care payer, while providing only marginal improvement in quality of life compared to untreated patients (195). Furthermore, oesophageal adenocarcinoma disproportionately affects older Caucasian men, which is still the majority ethnicity in many developed nations. New treatments such as endoscopic mucosal resection and radiofrequency ablation may be able to help, but these depend on early detection, which can only be done accurately through endoscopic examination. Thus, an improved method of selecting individuals for surveillance and perhaps deselecting low risk individuals for non-surveillance is necessary. The next 2 chapters will discuss the results cost-utility analysis performed on the basis of this model.

5 CHAPTER 5- COST EFFECTIVENESS OF NON-RISK STRATIFIED REDUCTION IN FREQUENCY OF ENDOSCOPIC SURVEILLANCE IN BARRETT'S OESOPHAGUS

5.1 Background

In previous decades, surveillance of Barrett's oesophagus entailed endoscopy and biopsy of lesions or areas with potential for adenocarcinoma. Patients detected with oesophageal adenocarcinoma would be investigated for oesophageal resection. Endoscopic interventions such as mucosal resections or ablative devices were in the experimental phases through much of the 2000s. The success of endoscopic treatment for high grade dysplasia and intramucosal carcinoma noted in the literature has led to changes in guidelines by medical societies. However, recommendations for surveillance frequency with endoscopic examination of non-dysplastic Barrett's oesophagus are vague (Table 2). It is agreed that the frequency should be between 2 and 5 years for non-dysplastic Barrett's oesophagus, and between 6-12 months for low grade dysplasia. The U.K, Australian, and U.S. guidelines suggest confirmation of all dysplasia with a second endoscopic examination with biopsies with endoscopic treatment for confirmed high grade dysplasia. Treatment of low-grade dysplasia doesn't currently have global consensus, as current evidence is inadequate. To date, there are only 2 randomised controlled studies and with 263 patients (196, 197). The rest of the evidence comes from national registries and retrospective studies. The U.K. and U.S. guidelines suggest it could be treated with radiofrequency ablation (30, 198), but Australian guidelines recommend continued surveillance (52).

These aspects of ambiguity in the guidelines for non-dysplastic and dysplastic Barrett's oesophagus were tested as strategies in this cost-utility analysis. Specific design features of the model helped form the strategies that could be tested for cost-effectiveness (detailed in Chapter 4). For example, building a decision tree within each health state assigning endoscopic surveillance or "no surveillance" helped test the effect of varying intervals between endoscopies for various stages of Barrett's oesophagus. Creation of "undetected" and "diagnosed" states allowed of progression of individual through stages of Barrett's oesophagus until the time of their next endoscopy. Creation of low and high-risk subgroups allowed assigning different surveillance intervals for each subgroup, which has not been published in the literature. This chapter discusses tools used to generate the strategies along with model inputs pertinent to endoscopic surveillance. Lastly, results of the cost-utility analysis for the non-risk stratified group of strategies are discussed.

5.2 Methods

The complete structure of the Markov cohort model developed in TreeAge Pro, along with decision trees is described in Chapter 4. The primary aim of this thesis was to find cost-effective strategies for endoscopic surveillance of Barrett's oesophagus. Individuals with Barrett's oesophagus have varying risk of progression to oesophageal adenocarcinoma. Both the literature and local database of Barrett's oesophagus individuals indicated that female gender and short segment length were important discriminators of progression. Intuitively, to find cost-effective

strategies, low risk individuals needed to have reduced frequency of endoscopic surveillance (every 4-10 years), while the high risk individuals would remain at guideline recommended surveillance frequency (every 2-3 years). Permutations of these aspects helped generate 123 strategies to find the optimal, cost-effective, endoscopic surveillance/treatment strategy for Barrett's oesophagus. The main themes relating to the strategies were:

1) Reducing endoscopic surveillance interval for the entire cohort (no risk stratification)
2) Increasing interval between endoscopies for both low and high risk sub-cohorts
3) Endoscopic treatment of low grade dysplasia

All decision trees within the Markov model were created in the base strategy (natural history/no surveillance) and calibrated to known targets for derivation of transition probabilities. Generating new strategies involved cloning the base strategy, applying a surveillance frequency or endoscopic treatment (depending on type of strategy), and substituting the appropriate transition probabilities. This chapter discusses which strategies were generated from altering surveillance frequency and treatment options, along with the model outputs (costs, utilities, incremental cost-effectiveness ratio, etc) of modifying the surveillance of Barrett's oesophagus for the aggregate cohort.

Base case scenario

The base case scenario involved a cohort of 50-year old individuals diagnosed with non-dysplastic Barrett's oesophagus progressing without any surveillance. Every Barrett's oesophagus health state had a decision tree (within the Markov model) with two branches: no surveillance (natural progression) or endoscopic surveillance (Figure 25). Routine surveillance was defined as endoscopy every 2 years for non-dysplastic individuals, every 6 months for low grade dysplasia, with high grade dysplasia given endoscopic treatment with radiofrequency ablation +/- endoscopic mucosal resection. All high grade dysplasia underwent a confirmatory endoscopy within 3 months prior to endoscopic treatment. Post endoscopic treatment, individuals had lifelong endoscopic surveillance (every 12 months). The frequency of surveillance for non-dysplastic Barrett's oesophagus or low-grade dysplasia was altered using a mathematical function (modulo) described in Equation 4.

Oesophageal adenocarcinoma detected through surveillance endoscopy was assumed to be amenable to endoscopic mucosal resection. The costs, utilities, and success rates of endoscopic resection and ablation are related to T1a lesions (Table 15 and Table 17).

Figure 25. Structure of decision tree within Markov model that enables varied frequency of endoscopic surveillance for different risk groups.

*Legend: LGD- low grade dysplasia; NDBE- Non-dysplastic Barrett's oesophagus; p_NS_risk1, p_S_risk1, p_NS_dysp_risk1, p_S_dysp_risk1- variables indicating probability of "no surveillance"; freq_KNDBE and freq_LGD- variables to control interval between endoscopic examinations)

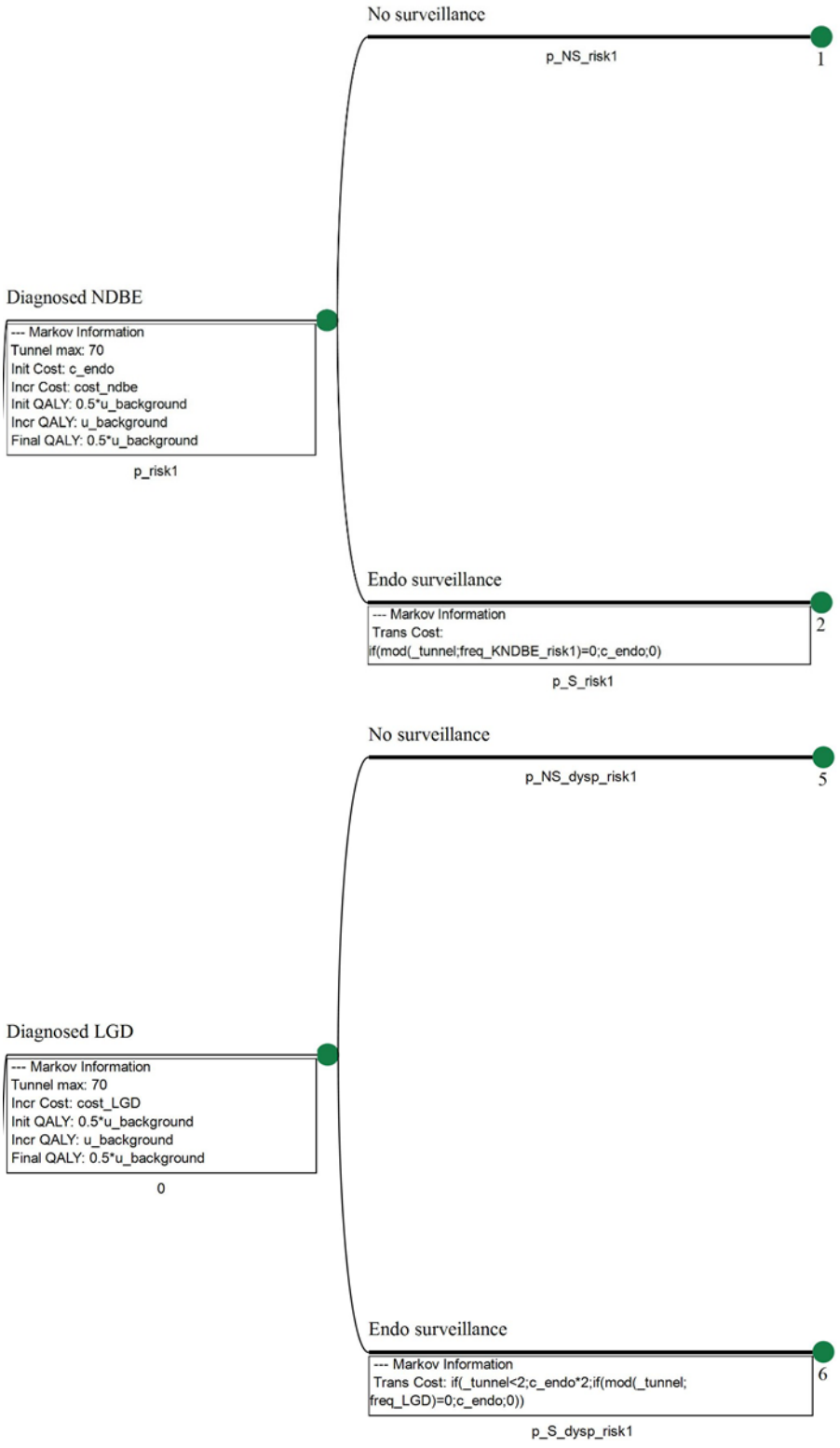


Table 15. Transition probabilities in common pathway from observed data in the literature

Description	Mean value	Standard deviation	Ref
Probability of complication post endoscopic treatment (RFA or EMR)	20%	14%	(199)
Probability of requiring re-treatment with RFA and/or EMR (HGD and EAC)	8.8%	11.9%	(200, 201)
Probability of HGD progression to adenocarcinoma post endoscopic treatment	1%	0.6%	(201, 202)
Probability of LGD progression to HGD post endoscopic treatment	0.5%	0.08%	(200, 202, 203)
Probability of requiring re-ablation of LGD lesion	9.66%	0.82%	(204-206)
Mortality post endoscopic treatment	0.6%	0.09%	(203)
Localised cancer	19%	-	(151)
Regional spread	29%	-	(151)
Unstaged cancer	20%	-	(151)
Distant spread	32%	-	(151)
Background mortality (age dependent)	Life-Tables		(149)

* RFA- Radiofrequency ablation; EMR- endoscopic mucosal resection; HGD- high grade dysplasia; EAC- oesophageal adenocarcinoma; LGD- low grade dysplasia

Table 16. Ten Year Oesophageal Adenocarcinoma mortality (SEER)

Year	HGD-T1aEAC	Localised	Regional	Unstaged	Distant mets
1	0.010	0.306	0.384	0.649	0.713
2	0.010	0.424	0.591	0.784	0.874
3	0.020	0.489	0.679	0.831	0.926
4	0.020	0.533	0.730	0.852	0.944
5	0.021	0.567	0.764	0.869	0.954
6	0.021	0.591	0.783	0.881	0.957
7	0.021	0.608	0.797	0.889	0.961
8	0.021	0.624	0.810	0.893	0.963
9	0.022	0.640	0.824	0.900	0.965
10	0.022	0.651	0.833	0.908	0.968

* SEER- Surveillance Epidemiology End Results; HGD- high grade dysplasia; T1aEAC- T-stage 1a oesophageal adenocarcinoma;

Costs

Costs were applied either “per cycle” or “per event.” Per cycle costs were associated with a health state. For Barrett’s oesophagus stages, this included costs such as maintenance of database of Barrett’s oesophagus patients, which comprised of the salary of a database manager, software licenses, office space and renewables. Cancer related costs and cost of maintaining a database of Barrett’s oesophagus patients were acquired from a previous study from Flinders Medical Centre (68), which was reported as 2011 US dollars in the publication. This amount was adjusted using the consumer price index to 2020 Australian dollar value (92).

Other per cycle costs were related to treatment of cancer, which occurs over several months. For this reason, the cost was distributed over 2 cycles. Cancer without distant spread was assigned to curative treatment. Curative treatment constituted (neoadjuvant) chemotherapy and radiotherapy, followed by surgical resection. Costs related to metastatic cancer (distant spread) were related to palliative management. Costs of cancer related treatments were adjusted with the consumer price index from a previous Australian based study (68, 70, 207). Costs were included in both one-way and probabilistic sensitivity analysis. For one-way sensitivity analysis, the low and high were approximately 50% lower and higher than the base parameter. In the probabilistic analysis, gamma distribution was generated using the mean and standard deviation.

Endoscopy for surveillance was defined as oesophago-gastro-duodenoscopy with Seattle protocol biopsy (32, 33) and was a per-event cost. The costs encapsulated an outpatient day admission procedure, inclusive of procedural, anaesthetic, medication, and nursing costs. This did not include the cost of maintaining the database of patients that require follow up. Mean cost for a single endoscopy was AU$1,390 (standard deviation AU$418) for 1,064 endoscopies performed between 2013-2019 (5 financial years). 73 patients with radiofrequency ablation with mean cost of AU$10,032 (standard deviation AU$2,330). 78 patients with endoscopic mucosal resection with a mean of AU$13,996 (standard deviation AU$4100). There were 58 admissions for complications post endoscopic treatment costed AU$12,322 (standard deviation AU$3580). Cost of maintaining the database of Barrett’s oesophagus per patient was calculated at AU$188 (adjusted using consumer price index).

Utilities

Utility values were assigned to health states, whereas disutility values were assigned to events (Table 17). Stages of Barrett’s oesophagus were considered asymptomatic, so were assumed to have the same quality of life as background utility. Background utility was derived from Viney et al. (208) and was adjusted for age (weighted for ~ 60% male population). In cancer states, the utility depended on both the age, as well as the stage of cancer. The amount of quality of life lost by cancer was subtracted from the background utility of at age diagnosis. Temporary disutility values

were assigned to endoscopic treatments and complications associated with endoscopic treatments.

Table 17. Costs and Utilities. Costs are in Australian Dollars (2020) annual amounts. The utility values are 6 monthly subtracted per cycle from the health state

	Cost (AU$ annual)	Ref
Cost of an endoscopy	$1,390	SA database
Cost of maintaining database (per individual annually)	$185	(68) Gordon 2014 (CPI adjusted)
Cost of radiofrequency ablation	$10,000	SA database
Cost of endoscopic mucosal resection	$14,000	SA database
Cost of complication post endoscopic intervention	$12,300	SA database
Cost of curative treatment (trimodality)	$95,450	(68, 207)
Cost of palliation	$15,700	(68, 207)

	QALYs	Ref
Background utility	Age Dependent	(68, 208) Viney 30
Surveillance detected cancer	Background utility - 0.08	(68, 209) Sullivan 34
Localised Cancer (no nodal spread)	Background utility - 0.168	(68, 210) Garside 32, Gerson 33
Regional Spread	Background utility - 0.235	(68, 209, 210) de boer 31
Metastatic cancer	Background utility - 0.3	(68, 209, 210) de boer 31
Unstaged Cancer	Background utility - 0.235	(68)
Disutility for complication post endoscopic intervention (1 cycle)	-0.05	(68)
Disutility associated with endoscopic intervention (1 cycle)	-0.035	(68)

*Trimodality- Neoadjuvant chemoradiotherapy followed by surgical resection; Endoscopic mucosal resection- includes cost of radiofrequency ablation

Changing variable definitions to change strategy modes

The decision tree within the Markov cohort model along with variable definitions allowed testing off > 100 strategies. Figure 26 shows an example of typical variable definitions at the Markov node to generate the strategy "5-yearly endoscopic surveillance for Female sub-cohort with 3-yearly endoscopic surveillance for Male sub-cohort." Defining these variables was performed in a stepwise manner listed below. The steps refer to the number within the blue circle in Figure 26.

1. The first variable to be defined is p_risk 1,2, and 3 (blue circle #1). This variable refers to the starting population within each sub-cohort. When testing strategies on the aggregate cohort, p_risk1 was defined as 1 (100%), whereas for risk-stratified strategies, the starting percentages shown in Table 11 were used. The sum of these three variables must always equal to 1. Here, in this example, it is defined by p_female and p_male, which are 0.35 and 0.65 respectively. p_risk1 has been defined as 0, to exclude it from the analysis. Derivation of starting percentages of subgroups has been discussed in Chapter 4.
2. The transition probabilities of each of the Barrett's oesophagus states were defined separately for each sub-cohort. 10 transition probabilities per sub-cohort (shown next to blue circle #2) were derived from calibration process described in Chapter 4. Figure 26 shows "risk2 health states" has been assigned female transition probabilities and "risk2 health states" have been assigned male transition probabilities. Risk1, risk2, and risk3 health states run in parallel and have no overlap during stages of Barrett's oesophagus. In other words, individuals cannot jump between risk1, risk2 and risk3 health states.
3. Frequency of endoscopic surveillance for all participating starting populations (in this case p_risk2 and p_risk3) was set by defining freq_NDBE and freq_LGD. The number seen in the figure is number of cycles between each endoscopic examination (cycle = 6 months).
4. See below
5. #4 and #5: p_NS_risk and p_S_risk variables allowed switching between surveillance and non-surveillance cycles involved using the "_tunnel" function that counts the number of cycles the cohort is passing through the node. In this example, for the female sub-cohort, endoscopy would be administered every 10^{th} cycle (5 years) and every 6^{th} cycle (3 years) for male sub-cohort. Importantly, if high grade dysplasia is detected when p_S_risk is activated, then endoscopic treatment with ablation would be instituted after confirmation of high grade dysplasia
6. See below
7. #6 and #7: These two steps define the frequency of endoscopies for low grade dysplasia. In this case, it was every "1" cycle (6 months).
    a. Default option "1" meant low grade dysplasia would receive 6-monthly endoscopies. Setting freq_LGD to 2 meant the cohort would undergo 12-monthly endoscopies.

b. p_S_ablate_2ndscope: A portion of the cohort would either be downstaged to non-dysplastic state, upstaged to high grade dysplasia, or confirmed with low grade dysplasia. This variable ensured a second endoscopy was performed prior to ablation of low grade dysplasia. Default setting was “1.”
c. p_S_ablateLGD: Setting it as “1” meant the strategy involved ablation of low grade dysplasia. Setting at “0” meant surveillance only with endoscopy for low grade dysplasia.

Ablation therapy was administered when high-grade dysplasia was detected through endoscopy and confirmed with a second endoscopy. Undetected high grade dysplasia progressed or remained in a state of dysplasia according to calibrated transition probabilities until an endoscopy was performed. Low-grade dysplasia endoscopic treatment would only be instituted if the strategy specifically was testing cost-effectiveness of this ablation therapy (through variable p_S_ablateLGD). The default option was to continue endoscopic surveillance 6-monthly, but this could be changed to 12-monthly. The decision tree for surveillance of low grade dysplasia is also shown in Figure 27. Figure 28 demonstrates further the aspects involved in treatment of ablation of low grade dysplasia. Those that progressed to high grade dysplasia while under treatment for low-grade dysplasia would then go on to receive endoscopic treatment for high grade dysplasia.

Figure 26. Variables defined at Markov node.

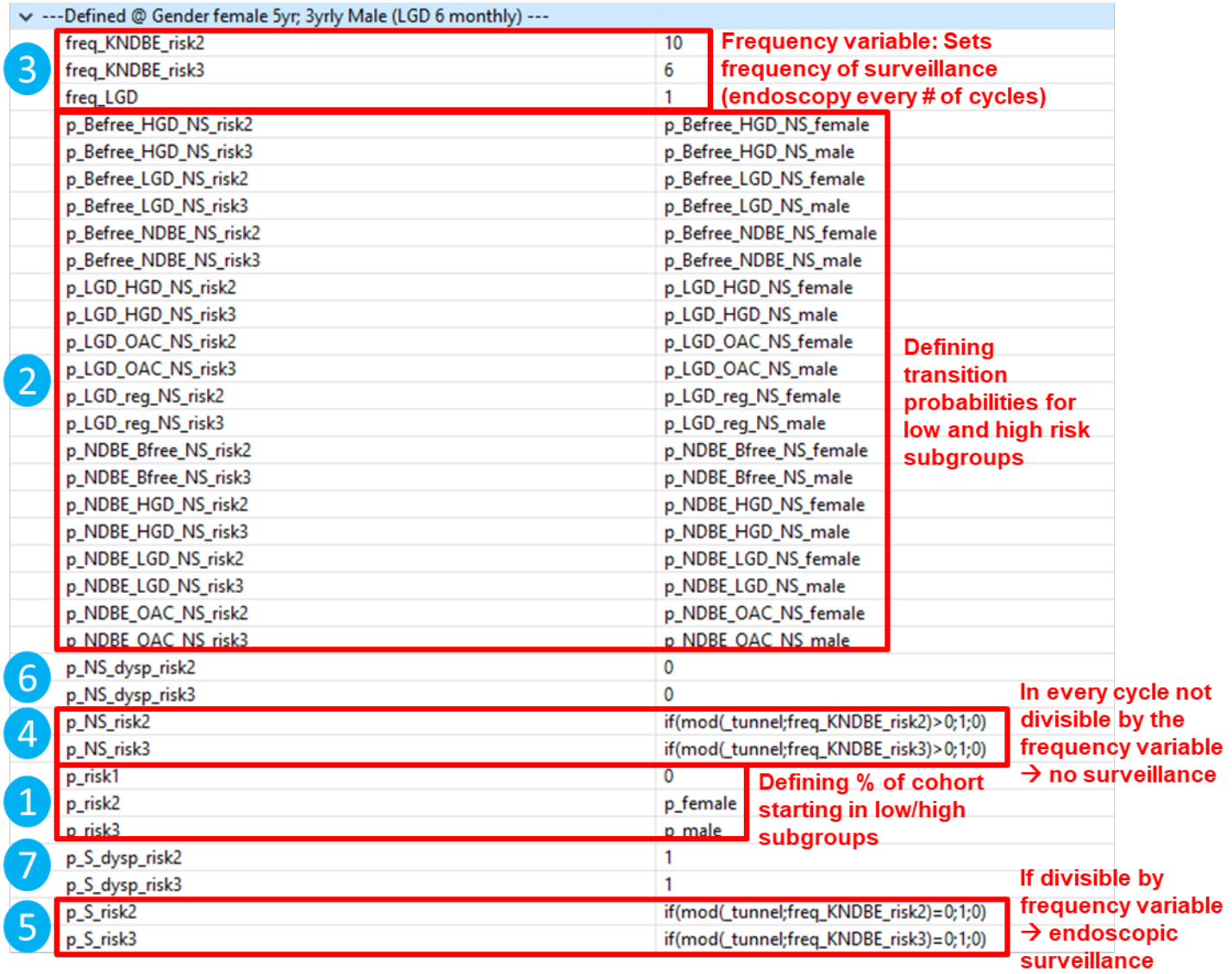


Figure 27. Progression under surveillance and no surveillance of Low-grade dysplasia

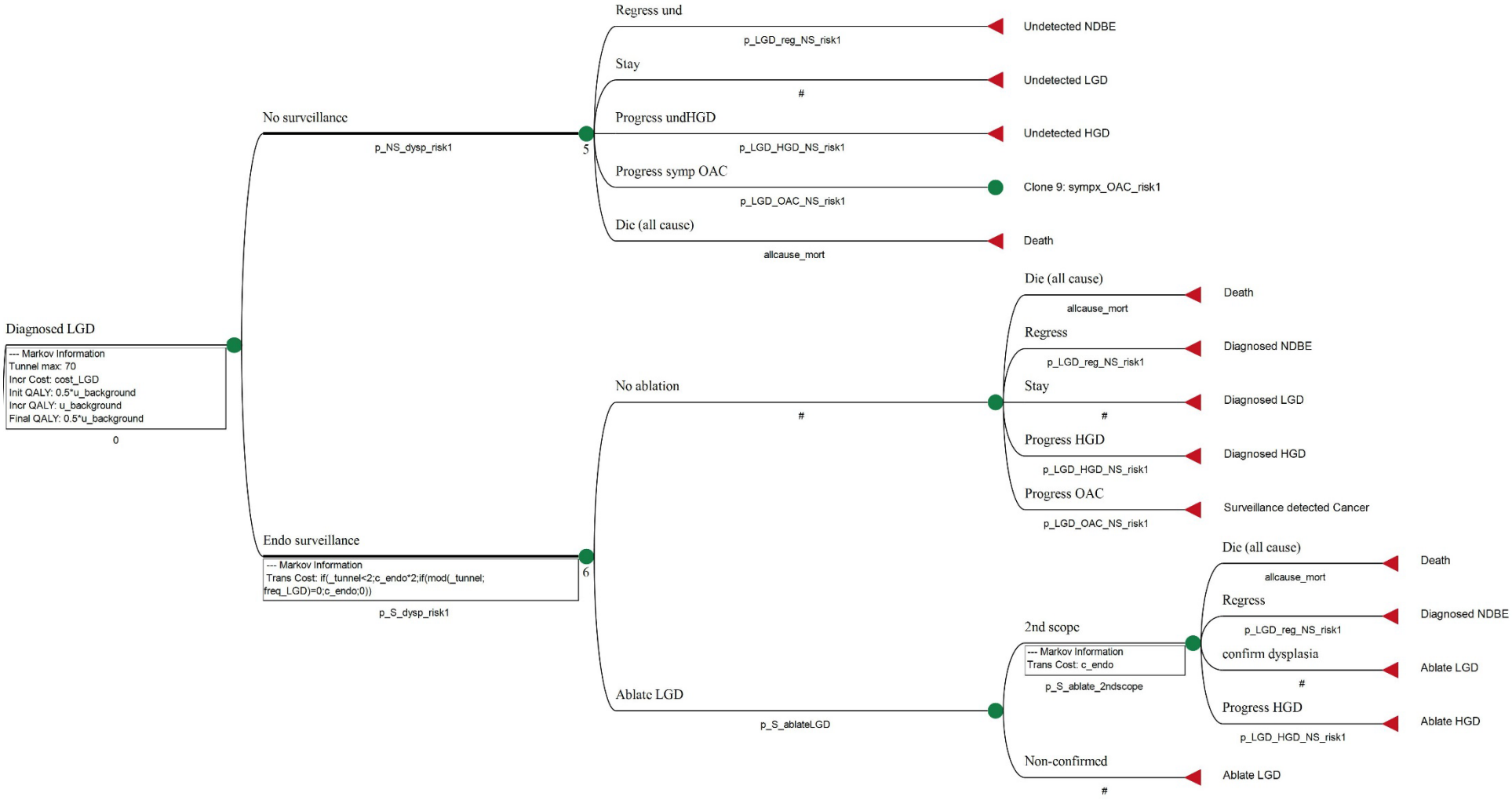
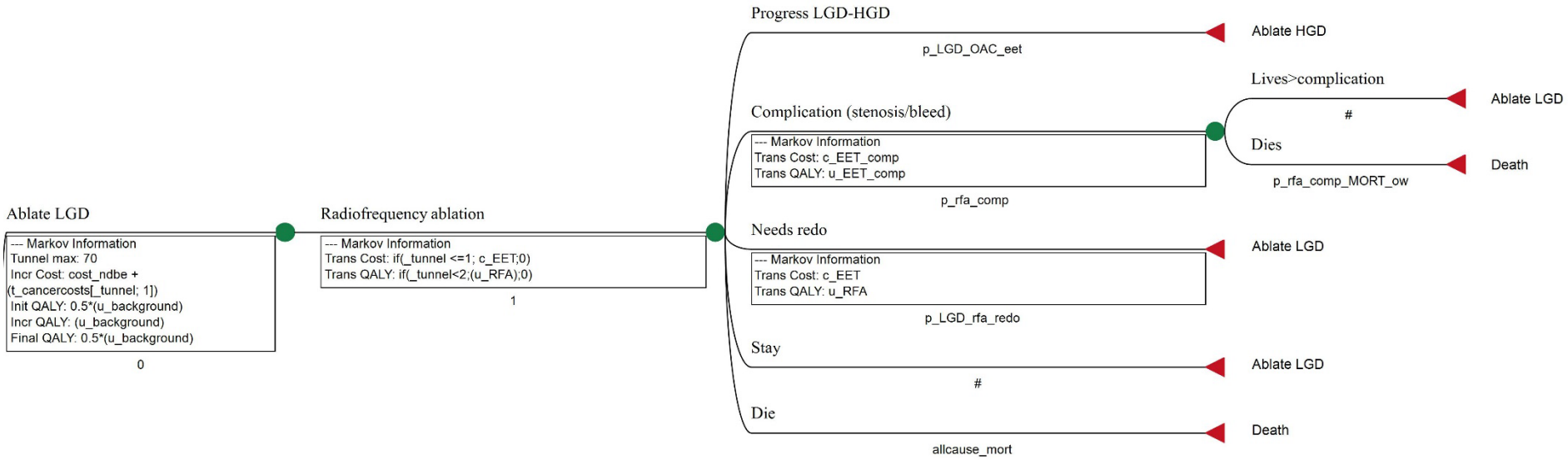


Figure 28. Endoscopic treatment of Low-grade dysplasia



Generating strategies

Strategies were divided into groups as shown in Figure 29. A list of all strategies is provided in Table 22. Initially, they were categorised into a non-stratified versus risk-stratified approach. In the non-stratified group of surveillance strategies, the aggregate cohort was assigned to 1) a reduced frequency endoscopic surveillance, 2) early intervention with ablation of low-grade dysplasia, or 3) a combination of both. Surveillance frequency for non-dysplastic Barrett's oesophagus was varied from every 2 years to 10 years, whereas low-grade dysplasia surveillance was either 6 or 12-monthly. Of particular note, all dysplasia (low or high grade) was confirmed by a second endoscopy. This meant in strategies where low-grade dysplasia was treated with endoscopic ablation, frequency of surveillance for low grade dysplasia was according to the treatment algorithm for ablation, which is shown in Figure 28 and Figure 29. At the second endoscopy, either the lesion was confirmed and treated, or it was upstaged to high-grade dysplasia or downstaged to non-dysplastic Barret's oesophagus.

In the risk-stratified group of strategies, the aggregate cohort was dichotomised into a low-risk and high-risk subgroup. Both groups could be assigned to varied surveillance frequency, endoscopic ablation of low-grade dysplasia, or a combination of both. As an example, for short segment Barrett's oesophagus, surveillance frequency was altered between 4 yearly to 10 yearly, whereas long segment Barrett's oesophagus included 2 yearly or 3 yearly endoscopy for non-dysplastic Barrett's oesophagus with 6-12 months intervals for low grade dysplasia. Short segment Barrett's oesophagus could also be "excluded" from surveillance entirely, in which case, it would follow a similar path to "no surveillance" (natural progression).

Only clinically relevant permutations of strategies were included in the cost-utility analysis. For example, the frequency of surveillance of high-risk subgroups was always higher than low-risk subgroups. This is because a reduced frequency of endoscopic surveillance for high-risk subgroup with a higher frequency surveillance for low risk would not be clinically appropriate. The surveillance frequency of the high-risks subgroup had to be at least the same or higher (in frequency) compared to the low-risk subgroup. A list of all 123 strategies included in the analysis is provided in Table 22 below.

Figure 29. Algorithm for modification of endoscopic surveillance strategies.

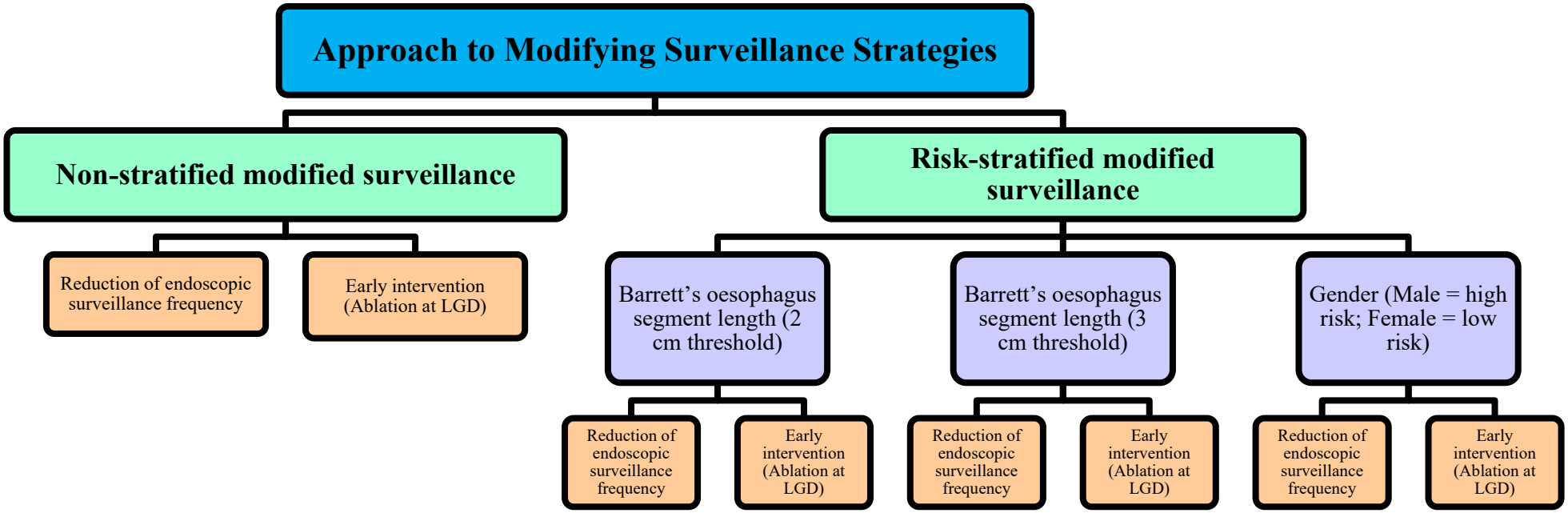


Table 18. List of all strategies

	Base strategy
1	Natural history/ No surveillance

Non-risk Stratified Strategies

	Modifying Frequency of Endoscopic Surveillance for Aggregate Cohort
2	Endoscopic surveillance 10 yearly for all (LGD 6 monthly)
3	Endoscopic surveillance 10 yearly for all (LGD 12 monthly)
4	Endoscopic surveillance 9 yearly for all (LGD 6 monthly)
5	Endoscopic surveillance 9 yearly for all (LGD 12 monthly)
6	Endoscopic surveillance 8 yearly for all (LGD 6 monthly)
7	Endoscopic surveillance 8 yearly for all (LGD 12 monthly)
8	Endoscopic surveillance 7 yearly for all (LGD 6 monthly)
9	Endoscopic surveillance 7 yearly for all (LGD 12 monthly)
10	Endoscopic surveillance 6 yearly for all (LGD 6 monthly)
11	Endoscopic surveillance 6 yearly for all (LGD 12 monthly)
12	Endoscopic surveillance 5 yearly for all (LGD 6 monthly)
13	Endoscopic surveillance 5 yearly for all (LGD 12 monthly)
14	Endoscopic surveillance 4 yearly for all (LGD 6 monthly)
15	Endoscopic surveillance 4 yearly for all (LGD 12 monthly)
16	Endoscopic surveillance 3 yearly for all (LGD 6 monthly)
17	Endoscopic surveillance 3 yearly for all (LGD 12 monthly)
18	Endoscopic surveillance 2 yearly for all (LGD 6 monthly)
19	Endoscopic surveillance 2 yearly for all (LGD 12 monthly)

	Modifying surveillance frequency and add Ablative therapy for Low grade dysplasia
20	Ablate LGD with Endoscopic surveillance 10 yearly for all
21	Ablate LGD with Endoscopic surveillance 9 yearly for all
22	Ablate LGD with Endoscopic surveillance 8 yearly for all
23	Ablate LGD with Endoscopic surveillance 7 yearly for all
24	Ablate LGD with Endoscopic surveillance 6 yearly for all
25	Ablate LGD with Endoscopic surveillance 5 yearly for all
26	Ablate LGD with Endoscopic surveillance 4 yearly for all
27	Ablate LGD with Endoscopic surveillance 3 yearly for all
28	Ablate LGD with Endoscopic surveillance 2 yearly for all
29	Ablate LGD with Dysplasia only surveillance

Risk-stratified Strategies

	Gender stratified
30	Gender Female = 10 yearly; male 2 yearly (LGD 6 monthly)
31	Gender Female = 10 yearly; male 2 yearly (LGD 12 monthly)
32	Gender Female = 9 yearly; male 2 yearly (LGD 6 monthly)
33	Gender Female = 9 yearly; male 2 yearly (LGD 12 monthly)
34	Gender Female = 8 yearly; male 2 yearly (LGD 6 monthly)
35	Gender Female = 8 yearly; male 2 yearly (LGD 12 monthly)
36	Gender Female = 7 yearly; male 2 yearly (LGD 6 monthly)
37	Gender Female = 7 yearly; male 2 yearly (LGD 12 monthly)
38	Gender Female = 6 yearly; male 2 yearly (LGD 6 monthly)
39	Gender Female = 6 yearly; male 2 yearly (LGD 12 monthly)
40	Gender Female = 5 yearly; male 2 yearly (LGD 6 monthly)
41	Gender Female = 5 yearly; male 2 yearly (LGD 12 monthly)
42	Gender Female = 5 yearly; male 3 yearly (LGD 6 monthly)
43	Gender Female = 5 yearly; male 3 yearly (LGD 12 monthly)
44	Gender Female = 4 yearly; male 2 yearly (LGD 6 monthly)
45	Gender Female = 4 yearly; male 2 yearly (LGD 12 monthly)

46	Gender Female = 3 yearly; male 2 yearly (LGD 6 monthly)
47	Gender Female = 3 yearly; male 2 yearly (LGD 12 monthly)
48	Gender Exclude Female; male 3 yearly (LGD 6 monthly)
49	Gender Exclude Female; male 3 yearly (LGD 12 monthly)
50	Gender Exclude Female; male 3 yearly (LGD 6 monthly)
51	Gender Exclude Female; male 3 yearly (LGD 12 monthly)

	Length stratified (3 cm threshold)- modifying surveillance frequency only
52	3 cm Length- 10yearly< 3 cm; 2 yearly => 3 cm (LGD 6 monthly)
53	3 cm Length- 10yearly< 3 cm; 2 yearly => 3 cm (LGD 12 monthly)
54	3 cm Length- 9yearly< 3 cm; 2 yearly => 3 cm (LGD 6 monthly)
55	3 cm Length- 9yearly< 3 cm; 2 yearly => 3 cm (LGD 12 monthly)
56	3 cm Length- 8yearly< 3 cm; 2 yearly => 3 cm (LGD 6 monthly)
57	3 cm Length- 8yearly< 3 cm; 2 yearly => 3 cm (LGD 12 monthly)
58	3 cm Length- 7yearly< 3 cm; 2 yearly => 3 cm (LGD 6 monthly)
59	3 cm Length- 7yearly< 3 cm; 2 yearly => 3 cm (LGD 12 monthly)
60	3 cm Length- 6yearly< 3 cm; 2 yearly => 3 cm (LGD 12 monthly)
61	3 cm Length- 6yearly< 3 cm; 2 yearly => 3 cm
62	3 cm Length- 5yearly < 3 cm; 3 yearly => 3 cm (Australia) (LGD 6 monthly)
63	3 cm Length- 5yearly < 3 cm; 3 yearly => 3 cm (Australia) (LGD 12 monthly)
64	3 cm Length- 5yearly< 3 cm; 2 yearly => 3 cm (AUSTRALIAN) (LGD 6 monthly)
65	3 cm Length- 5yearly< 3 cm; 2 yearly => 3 cm (AUSTRALIAN) (LGD 12 monthly)
66	3 cm Length- 4yearly < 3 cm; 3 yearly => 3 cm (Australia) (LGD 6 monthly)
67	3 cm Length- 4yearly < 3 cm; 3 yearly => 3 cm (Australia) (LGD 12 monthly)
68	3 cm Length- 4yearly< 3 cm; 2 yearly => 3 cm (AUSTRALIAN) (LGD 6 monthly)
69	3 cm Length- 4yearly< 3 cm; 2 yearly => 3 cm (AUSTRALIAN) (LGD 12 monthly)
70	3 cm Length- Exclude < 3 cm (no surv); 3 yearly =>3 cm (LGD 6 monthly)
71	3 cm Length- Exclude < 3 cm (no surv); 3 yearly =>3 cm (LGD 12 monthly)
72	3 cm Length- Exclude < 3 cm (no surv); 2 yearly =>3 cm (LGD 6 monthly)
73	3 cm Length- Exclude < 3 cm (no surv); 2 yearly =>3 cm (LGD 12 monthly)

	Length stratified (3 cm threshold)- modifying surveillance frequency and ablative therapy for low-grade dysplasia
74	Ablate LGD with 3 cm Length- 10 yearly < 3 cm; 3 yearly => 3 cm
75	Ablate LGD with 3 cm Length- 10 yearly < 3 cm; 2 yearly => 3 cm
76	Ablate LGD with 3 cm Length- 9 yearly < 3 cm; 3 yearly => 3 cm
77	Ablate LGD with 3 cm Length- 9 yearly < 3 cm; 2 yearly => 3 cm
78	Ablate LGD with 3 cm Length- 8 yearly < 3 cm; 3 yearly => 3 cm
79	Ablate LGD with 3 cm Length- 8 yearly < 3 cm; 2 yearly => 3 cm
80	Ablate LGD with 3 cm Length- 7 yearly < 3 cm; 3 yearly => 3 cm
81	Ablate LGD with 3 cm Length- 7 yearly < 3 cm; 2 yearly => 3 cm
82	Ablate LGD with 3 cm Length- 6 yearly < 3 cm; 3 yearly => 3 cm
83	Ablate LGD with 3 cm Length- 6 yearly < 3 cm; 2 yearly => 3 cm
84	Ablate LGD with 3 cm Length- 5 yearly < 3 cm; 3 yearly => 3 cm
85	Ablate LGD with 3 cm Length- 5 yearly < 3 cm; 2 yearly => 3 cm
86	Ablate LGD with 3 cm Length- Exclude < 3 cm (no surv); 3 yearly =>3 cm
87	Ablate LGD with 3 cm Length- Exclude < 3 cm (no surv); 2 yearly =>3 cm

	Length stratified (2 cm threshold)- modifying surveillance frequency only
88	2 cm Length- Exclude <= 2 cm (no surv); 3 yearly >2 cm (LGD 6 monthly)
89	2 cm Length- Exclude <= 2 cm (no surv); 3 yearly >2 cm (LGD 12 monthly)
90	2 cm Length- 10 yearly <= 2 cm; 2 yearly > 2 cm (LGD 6 monthly)
91	2 cm Length- 10 yearly <= 2 cm; 2 yearly > 2 cm (LGD 12 monthly)
92	2 cm Length- 9 yearly <= 2 cm; 2 yearly > 2 cm (LGD 6 monthly)
93	2 cm Length- 9 yearly <= 2 cm; 2 yearly > 2 cm (LGD 12 monthly)
94	2 cm Length- 8 yearly <= 2 cm; 2 yearly > 2 cm (LGD 6 monthly)
95	2 cm Length- 8 yearly <= 2 cm; 2 yearly > 2 cm (LGD 12 monthly)
96	2 cm Length- 7 yearly <= 2 cm; 2 yearly > 2 cm (LGD 6 monthly)
97	2 cm Length- 7 yearly <= 2 cm; 2 yearly > 2 cm (LGD 12 monthly)
98	2 cm Length- 6 yearly <= 2 cm; 2 yearly > 2 cm (LGD 6 monthly)
99	2 cm Length- 6 yearly <= 2 cm; 2 yearly > 2 cm (LGD 12 monthly)
100	2 cm Length- 5 yearly <= 2 cm; 3 yearly > 2 cm (LGD 6 monthly)
101	2 cm Length- 5 yearly <= 2 cm; 3 yearly > 2 cm (LGD 12 monthly)

102	2 cm Length- 5 yearly <= 2 cm; 2 yearly > 2 cm (LGD 6 monthly)
103	2 cm Length- 5 yearly <= 2 cm; 2 yearly > 2 cm (LGD 12 monthly)
104	2 cm Length- 4 yearly <= 2 cm; 3 yearly > 2 cm (LGD 6 monthly)
105	2 cm Length- 4 yearly <= 2 cm; 3 yearly > 2 cm (LGD 12 monthly)
106	2 cm Length- 4 yearly <= 2 cm; 2 yearly > 2 cm (LGD 6 monthly)
107	2 cm Length- 4 yearly <= 2 cm; 2 yearly > 2 cm (LGD 12 monthly)
108	2 cm Length- Exclude <= 2 cm (no surv); 2 yearly >2 cm (LGD 6 monthly)
109	2 cm Length- Exclude <= 2 cm (no surv); 2 yearly >2 cm (LGD 12 monthly)

	Length stratified (2 cm threshold)- modifying surveillance frequency and ablative therapy for low-grade dysplasia
110	Ablate LGD with 2 cm Length- 10 yearly <= 2 cm; 3 yearly > 2 cm
111	Ablate LGD with 2 cm Length- 10 yearly <= 2 cm; 2 yearly > 2 cm
112	Ablate LGD with 2 cm Length- 9 yearly <= 2 cm; 3 yearly > 2 cm
113	Ablate LGD with 2 cm Length- 9 yearly <= 2 cm; 2 yearly > 2 cm
114	Ablate LGD with 2 cm Length- 8 yearly <= 2 cm; 3 yearly > 2 cm
115	Ablate LGD with 2 cm Length- 8 yearly <= 2 cm; 2 yearly > 2 cm
116	Ablate LGD with 2 cm Length- 7 yearly <= 2 cm; 3 yearly > 2 cm
117	Ablate LGD with 2 cm Length- 7 yearly <= 2 cm; 2 yearly > 2 cm
118	Ablate LGD with 2 cm Length- 6 yearly <= 2 cm; 3 yearly > 2 cm
119	Ablate LGD with 2 cm Length- 6 yearly <= 2 cm; 2 yearly > 2 cm
120	Ablate LGD with 2 cm Length- 5 yearly <= 2 cm; 3 yearly > 2 cm
121	Ablate LGD with 2 cm Length- 5 yearly <= 2 cm; 2 yearly > 2 cm
122	Ablate LGD with 2 cm Length- Exclude <= 2 cm (no surv); 3 yearly >2 cm
123	Ablate LGD with 2 cm Length- Exclude <= 2 cm (no surv); 2 yearly >2 cm

5.3 Results: Non-risk stratified endoscopic surveillance strategies

As stated previously, the starting cohort was 50-year-old individuals who were diagnosed with non-dysplastic Barrett's oesophagus, the cost of which was included in the analysis. In the base strategy, "No surveillance/natural history" these individuals progressed without any surveillance, unless they presented with symptomatic oesophageal adenocarcinoma. Under base parameter conditions, natural progression (no surveillance) of the aggregate cohort of non-dysplastic Barrett's oesophagus costed AU$6,745 and resulted in 24.219 QALYs (per individual). The ICER values presented throughout this these were calculated comparing these base model outputs versus all other strategies' outputs (using Equation 1, page 30).

28 strategies were tested in the non-stratified endoscopic surveillance group. 18 of these strategies involved reducing frequency of endoscopic surveillance, and 10 strategies included combining reduced frequency of endoscopic surveillance as well as endoscopic ablation of low-grade dysplasia (when detected). Surveillance intervals ranged from 2 yearly to 10 yearly for non-dysplastic Barrett's oesophagus, and 6-12 monthly for low-grade dysplasia. The same frequency of surveillance was tested for non-dysplastic Barrett's oesophagus for early intervention with endoscopic ablation of low-grade dysplasia (2 yearly to 10 yearly), resulting in 10 modified ablation strategies.

Two-yearly endoscopic surveillance for non-dysplastic Barrett's oesophagus

5.3.1.1 Base parameter results

Endoscopic surveillance of non-dysplastic Barrett's oesophagus every 2 years costed AU$33,070 with for 6-monthly endoscopies low grade dysplasia and AU$29,398 for 12-monthly and resulted in 24.5570 QALYs (for both) with an ICER of AU$77,405/QALY and AU$67,797/QALY (for 6 monthly and 12 monthly respectively). In both instances, 6.2% of total cohort progressed to oesophageal adenocarcinoma, with all cancers amenable to endoscopic resection, resulting in ~2.8% cancer-related mortality due to cancer for the entire cohort. This was much lower than 10.7% cancer related death rate for the no-surveillance/ natural progression base strategy.

The current Australian guidelines are vague in specifying what is the best interval for non-dysplastic Barrett's oesophagus individuals, and as a result, many institutions may still be performing endoscopic examinations every 2 years for all individuals with non-dysplastic Barrett's oesophagus. The 2 yearly endoscopic surveillance for non-dysplastic Barrett's oesophagus with 6-monthly for low-grade dysplasia is the shortest interval between endoscopies tested in this study. The outputs of this strategy, such as percentage of cohort progressing to cancer, cumulative

number of QALYs, cancer-related mortality serve as a benchmark against which other treatment strategies are compared to.

5.3.1.2 One way sensitivity analysis

One way sensitivity analysis of cost and utilities for 2-yearly endoscopic surveillance for non-dysplastic Barrett's oesophagus (6-monthly for low-grade dysplasia) is shown in Figure 30 as a tornado diagram. A tornado diagram represents, from top to bottom, the variable that generated the biggest change in ICER values to the variable that caused little or no effect on the ICER value. Models are considered to be sensitive to variables that cause a substantial change in ICER value. Conversely, they are not sensitive to variables that cause minimal changes in ICER values.

The cost of a single diagnostic endoscopy was the most sensitive variable but lowering it to AU$800 was not enough to lower the ICER value under the willingness to pay threshold (AU$50,000/QALY). This is consistent with the way the model was designed. Endoscopic examination is likely the most recurring event in the model and thus changing its cost *would* cause a substantial change in ICER values. Similarly, the model was also sensitive to costs related to maintaining a database of Barrett's oesophagus individuals. As this variable affects the entire cohort, it is conceivable that the model is sensitive to this cost as well. For strategies modifying surveillance intervals alone, the model was not as sensitive to costs and utilities associated with endoscopic treatment (both endoscopic mucosal resection and radiofrequency ablation), complication from endoscopic treatment, or treatment of adenocarcinoma. This is also consistent, as these events are relatively rare compared to events such as endoscopies. Therefore, changes in variables associated with them is unlikely to result in large changes for model outputs.

One way sensitivity analysis was also demonstrated for the transition probability between high-grade dysplasia and symptomatic oesophageal cancer for non-risk stratified strategies aiming to reduce frequency of endoscopic surveillance (seen in Figure 30). The x-axis represents annual progression of high-grade dysplasia to symptomatic oesophageal adenocarcinoma. The y-axis represents the ICER value for each change in transition probability. Horizontal dashed lines have been drawn to indicate the window in which ICER values were considered cost-effective (under the willingness to pay threshold of AU$50,000/QALY). Any points lying between the horizontal dashed lines are considered to be cost-effective, compared to natural history/no surveillance strategy. A vertical line represents the base value ~3.8%, which was derived through the calibration process described in Chapter 4. For 2-yearly endoscopic surveillance, natural progression from high grade dysplasia to oesophageal cancer greater than 4.7% resulted in improved cost-effectiveness below willingness to pay threshold of AU$50,000/QALY.

Prolonged endoscopic surveillance intervals

5.3.1.3 Base parameter results

Endoscopic surveillance frequency was modified from every 3 years to 10 years for non-dysplastic Barrett's oesophagus and 6-monthly or 12-monthly for low-grade dysplasia. This yielded 16 strategies. Primary outcomes of costs and utility values (QALYs), shown in Table 18. Other model outputs, such as percentage of cohort developing oesophageal adenocarcinoma and high grade dysplasia can be seen in Table 19. None of the 16 strategies resulted in an ICER value below the willingness to pay threshold of AU$50,000/QALY. 3-yearly endoscopic surveillance for non-dysplastic Barrett's oesophagus and 6-monthly for low-grade dysplasia was the costliest at AU$23,761 and resulted in 24.314 QALYs (ICER AU$180,256/QALY). This strategy also resulted in 6.7% of the cohort progressing to oesophageal adenocarcinoma, of which 3.5% were detected through surveillance. Cancer-related mortality was 4.6% (compared to 2.3% in 2-yearly endoscopy interval).

Endoscopy every 10 years for non-dysplasia and 12-monthly for low-grade dysplasia cost the least AU$11,657 resulting in 24.215 QALYs (ICER -AU$1,190,630). This strategy resulted in 9% of the cohort progressing to oesophageal adenocarcinoma, with only 1% detected through surveillance. Consequently, cancer-related mortality was 8.2% at the end of the time horizon. A prolonged surveillance interval of 9 years or greater was dominated by the base strategy (no surveillance/ natural history). Even though the prolonged surveillance interval meant fewer endoscopies and thus lower additional cost, this was at the cost of not being detected with early oesophageal adenocarcinoma through the surveillance program. The reduced outcomes (QALYs) are likely due to the disutility associated with treatment of high-grade dysplasia with endoscopic ablation. Not all high-grade dysplasia progresses to oesophageal adenocarcinoma. In order to overcome the disutility accrued by treatment of high-grade dysplasia, it is likely that an optimal number of cancers must be detected and treated early through the surveillance. Endoscopic examinations every 9 or 10 years may not be avoiding enough progression from dysplasia to symptomatic adenocarcinoma in order to counter the disutility associated with endoscopic treatment (and associated complications). Surveillance intervals of 8 or lower avoided enough advanced oesophageal adenocarcinoma to have a slightly improved outcome (QALY) compared to no-surveillance/natural history base strategy, albeit at an ICER value much greater than the willingness-to-pay threshold years (ICER = AU$2,438,389/QALY).

Table 19. Cost and QALY rankings table: Reducing frequency of endoscopic surveillance for aggregate group. Incremental cost-effectiveness ratio values are calculated using costs and utilities from "Natural history." Costs and QALY are accumulated over time horizon for entire cohort

Strategy	Cost		QALY		ICER	NMB
Natural history/ No surveillance	$6,745	(incr)	24.219	(incr)	$0	$1,204,219
Endoscopy 10 yearly for NDBE (LGD 6 monthly)	$11,887	$5,142	24.215	-0.004	Dominated	$1,198,870
Endoscopy 10 yearly for NDBE; (LGD 12 monthly)	$11,657	$4,912	24.215	-0.004	Dominated	$1,199,101
Endoscopy 9 yearly for NDBE (LGD 6 monthly)	$12,491	$5,747	24.218	-0.002	Dominated	$1,198,394
Endoscopy 9 yearly for NDBE; (LGD 12 monthly)	$12,186	$5,441	24.218	-0.002	Dominated	$1,198,700
Endoscopy 8 yearly for NDBE (LGD 6 monthly)	$13,264	$6,520	24.222	0.003	$2,438,389	$1,197,833
Endoscopy 8 yearly for NDBE; (LGD 12 monthly)	$12,859	$6,114	24.222	0.003	$2,286,790	$1,198,238
Endoscopy 7 yearly for NDBE (LGD 6 monthly)	$14,266	$7,521	24.229	0.009	$800,955	$1,197,167
Endoscopy 7 yearly for NDBE; (LGD 12 monthly)	$13,730	$6,985	24.229	0.009	$743,860	$1,197,703
Endoscopy 6 yearly for NDBE (LGD 6 monthly)	$15,588	$8,843	24.239	0.020	$447,509	$1,196,364
Endoscopy 6 yearly for NDBE; (LGD 12 monthly)	$14,880	$8,135	24.239	0.020	$411,684	$1,197,072
Endoscopy 5 yearly for NDBE (LGD 6 monthly)	$17,382	$10,638	24.255	0.035	$299,742	$1,195,356
Endoscopy 5 yearly for NDBE; (LGD 12 monthly)	$16,449	$9,704	24.255	0.035	$273,443	$1,196,289
Endoscopy 4 yearly for NDBE (LGD 6 monthly)	$19,918	$13,173	24.278	0.059	$222,948	$1,194,000
Endoscopy 4 yearly for NDBE; (LGD 12 monthly)	$18,689	$11,944	24.278	0.059	$202,152	$1,195,229
Endoscopy 3 yearly for NDBE (LGD 6 monthly)	$23,761	$17,016	24.314	0.094	$180,256	$1,191,923
Endoscopy 3 yearly for NDBE; (LGD 12 monthly)	$22,145	$15,401	24.314	0.094	$163,141	$1,193,538
Endoscopy 2 yearly for NDBE; (LGD 12 monthly)	$29,398	$22,654	24.553	0.334	$67,797	$1,198,435
Endoscopy 2 yearly for NDBE (LGD 6 monthly)	$32,609	$25,864	24.553	0.334	$77,405	$1,195,224
Endoscopy 2 yearly for NDBE; (LGD 12 monthly)	$29,398	$22,654	24.553	0.334	$67,797	$1,198,435

* Costs are in Australian Dollars (2020 value) per cohort of 1. Incremental cost-effectiveness ratio (ICER) units are AU$/QALY. incr- incremental

Table 20. Model outputs: Reduced frequency of endoscopic surveillance for aggregate group.

			Stages of Oesophageal Adenocarcinoma					Deaths	
Strategy	EAC	HGD	Surv det	Localised	Regional	Unstaged	Metastatic	Cancer deaths	Non-Ca deaths
Natural history/ No surveillance	11.0%	16.0%	0.0%	2.1%	3.2%	2.2%	3.5%	10.7%	49.4%
Endoscopy 10 yearly for NDBE (LGD 6 monthly)	9.0%	16.0%	1.0%	1.5%	2.3%	1.6%	2.5%	8.2%	49.9%
Endoscopy 10 yearly for NDBE; (LGD 12 monthly)	9.0%	16.0%	1.0%	1.5%	2.3%	1.6%	2.5%	8.2%	49.9%
Endoscopy 9 yearly for NDBE (LGD 6 monthly)	8.7%	16.0%	1.2%	1.4%	2.2%	1.5%	2.4%	7.8%	50.1%
Endoscopy 9 yearly for NDBE; (LGD 12 monthly)	8.7%	16.0%	1.2%	1.4%	2.2%	1.5%	2.4%	7.8%	50.1%
Endoscopy 8 yearly for NDBE (LGD 6 monthly)	8.4%	16.0%	1.5%	1.3%	2.0%	1.4%	2.2%	7.4%	50.3%
Endoscopy 8 yearly for NDBE; (LGD 12 monthly)	8.4%	16.0%	1.5%	1.3%	2.0%	1.4%	2.2%	7.4%	50.3%
Endoscopy 7 yearly for NDBE (LGD 6 monthly)	8.1%	16.0%	1.7%	1.2%	1.9%	1.3%	2.0%	6.9%	50.5%
Endoscopy 7 yearly for NDBE; (LGD 12 monthly)	8.1%	16.0%	1.7%	1.2%	1.9%	1.3%	2.0%	6.9%	50.5%
Endoscopy 6 yearly for NDBE (LGD 6 monthly)	7.8%	16.0%	2.0%	1.1%	1.7%	1.1%	1.8%	6.4%	50.8%
Endoscopy 6 yearly for NDBE; (LGD 12 monthly)	7.8%	16.0%	2.0%	1.1%	1.7%	1.1%	1.8%	6.4%	50.8%
Endoscopy 5 yearly for NDBE (LGD 6 monthly)	7.4%	16.0%	2.4%	0.9%	1.4%	1.0%	1.6%	5.9%	51.0%
Endoscopy 5 yearly for NDBE; (LGD 12 monthly)	7.4%	16.0%	2.4%	0.9%	1.4%	1.0%	1.6%	5.9%	51.0%
Endoscopy 4 yearly for NDBE (LGD 6 monthly)	7.0%	16.0%	2.9%	0.8%	1.2%	0.8%	1.3%	5.3%	51.3%
Endoscopy 4 yearly for NDBE; (LGD 12 monthly)	7.0%	16.0%	2.9%	0.8%	1.2%	0.8%	1.3%	5.3%	51.3%
Endoscopy 3 yearly for NDBE (LGD 6 monthly)	6.7%	16.0%	3.5%	0.6%	0.9%	0.6%	1.0%	4.6%	51.6%
Endoscopy 3 yearly for NDBE; (LGD 12 monthly)	6.7%	16.0%	3.5%	0.6%	0.9%	0.6%	1.0%	4.6%	51.6%
Endoscopy 2 yearly for NDBE (LGD 6 monthly)	6.2%	16.0%	6.2%	0.0%	0.0%	0.0%	0.0%	2.8%	52.0%
Endoscopy 2 yearly for NDBE; (LGD 12 monthly)	6.2%	16.0%	6.2%	0.0%	0.0%	0.0%	0.0%	2.8%	52.0%

* Values displayed as percentage of cohort developing the model outputs (per cohort of 1). EAC- Total % of cohort developing Oesophageal adenocarcinoma (surveillance and symptomatic combined); HGD- Total % of cohort with high grade dysplasia; Surv det- Surveillance detected

5.3.1.4 One way sensitivity analysis

One way sensitivity analysis for multiple variables was performed all 16 strategies. Effect of varying natural progression from high grade dysplasia to oesophageal adenocarcinoma is shown in Figure 31. An increase in the transition probability of natural progression of high grade dysplasia to greater than 6.0% annually (from base value of 3.8%) improved cost-effectiveness of several strategies: surveillance every 3 years, 4 years, 5 years, and 6 years. At an annual progression rate of high-grade dysplasia to symptomatic oesophageal adenocarcinoma above ~ 7.5%, all strategies aiming to reduce frequency of endoscopic surveillance through a non-risk stratified approach were seen to be cost-effective. This is consistent and intuitive, as a higher percentage of high grade dysplasia converting to oesophageal adenocarcinoma worsens outcomes, reducing total QALYs. Hence, endoscopic surveillance at both high and low frequencies is desirable to avoid cancer related morbidity and mortality.

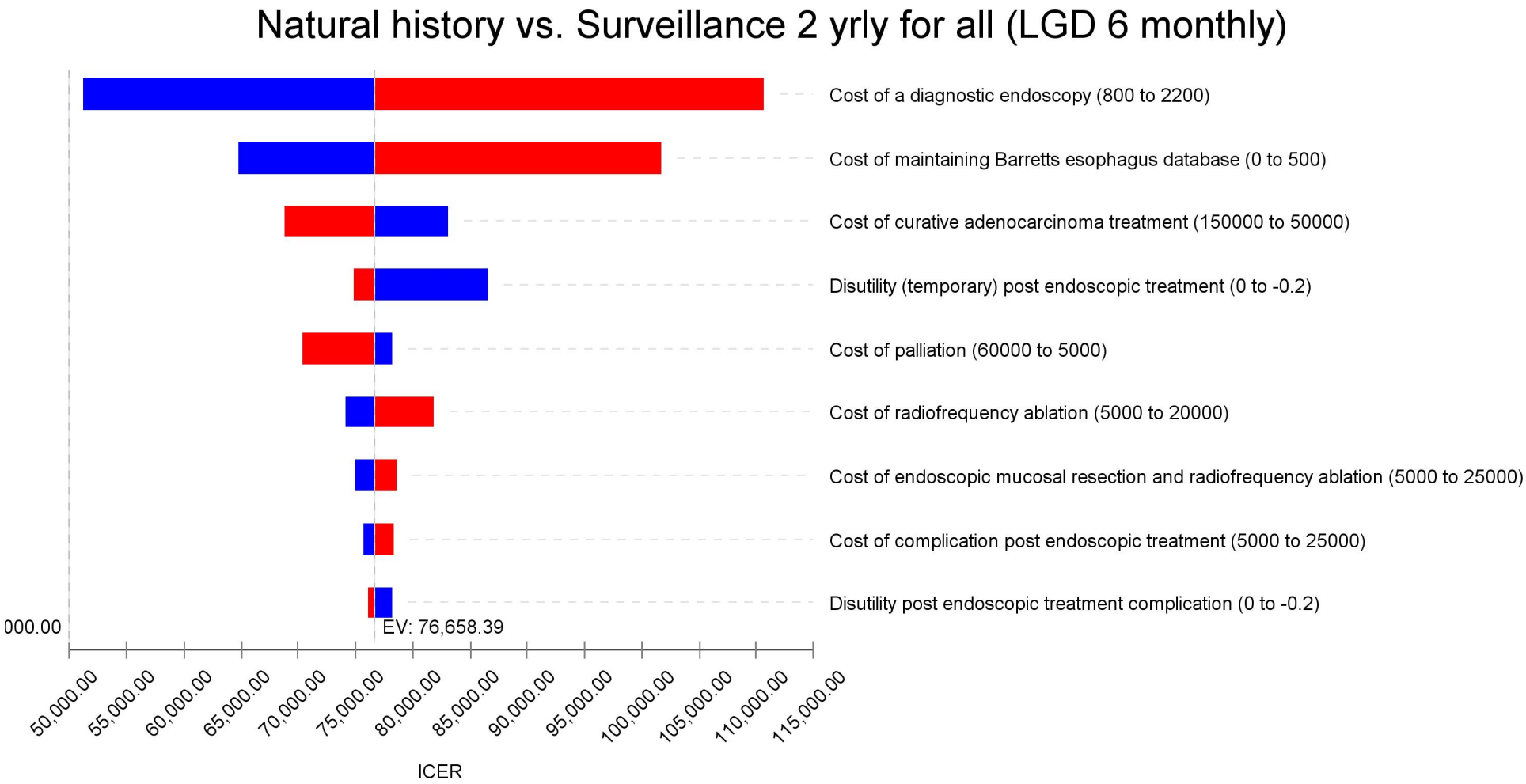
Variation in the transition probability of progression from high grade dysplasia to oesophageal adenocarcinoma after endoscopic mucosal resection and ablation (as seen in Figure 32) was also tested in one-way sensitivity analysis. The transition probability was varied from 0% to 40%. Interestingly, increased rates of progression post treatment did not result in reduced cost-effectiveness, but instead plateaued Figure 32. Closer examination of the data revealed that, in high frequency surveillance strategies, even though a higher percentage of the cohort progressed to oesophageal adenocarcinoma, they were being treated with either endoscopic or surgical resection at early stages of cancer (localised spread). This meant better long-term outcomes, which improved the “effectiveness.” The added benefit of early detection balances out the extra cost of endoscopic and or surgical treatment. For the reduced frequency surveillance strategies, the percentage of individuals affected by the increased progression to cancer post endoscopic ablation of high grade dysplasia was lower than high frequency surveillance strategies, which meant the total cost-effectiveness did not change.

A 2-way sensitivity analysis was conducted between the two transition probabilities discussed above: natural progression of high grade dysplasia and progression post endoscopic treatment of high grade dysplasia to oesophageal adenocarcinoma. Cost-effectiveness depended on the type of strategy used. For routine 2-yearly endoscopic examination for non-dysplastic Barrett’s oesophagus (6 monthly for low-grade dysplasia), as long as the annual rate of natural progression of high grade dysplasia to cancer was > 6.14%, the strategy was cost-effective under WTP AU$50,000/QALY. However, for surveillance every 5-years for non-dysplastic Barrett’s oesophagus (6 monthly for low-grade dysplasia), as long as the annual rate of progression was less than or equal to the annual rate of progression for endoscopically treated high grade dysplasia to adenocarcinoma, it was cost-effective under WTP AU$50,000/QALY. At even more prolonged surveillance intervals (endoscopy every 10 years), the cost-effectiveness depended more on the

transition probability of natural progression from high grade dysplasia to cancer rather than the probability of progression post endoscopic treatment. When the natural progression of high grade dysplasia to cancer was above 8.2%, it is likely that even the few individuals receiving endoscopic examinations had improved outcomes in the surveillance program, making even a 10-yearly endoscopic surveillance program cost-effective.

Tornado diagrams of 2 strategies, endoscopic surveillance every 5 years and 10 years for non-dysplastic Barrett's oesophagus are shown in Figure 31 and Figure 32 (respectively). In both these strategies, disutility associated with endoscopic treatment was the most sensitive variable but did reduce ICER values under the willingness to pay threshold.

Figure 30. One way sensitivity analysis (Tornado diagram) for No surveillance (natural progression) versus 2-yearly non-dysplastic/ 6 monthly low grade dysplasia endoscopic surveillance.



* Values in “red” indicate an increase in the value of the variable. Values in “blue” indicated decrease in variable value. Vertical dashed line indicates willingness to pay threshold (AU$50,000/QALY). ICER- incremental cost-effectiveness ratio; LGD- low grade dysplasia; EV – expected value of ICER; WTP- willingness to pay threshold

Figure 31. One way univariate sensitivity analysis: Transition probability between high-grade dysplasia and symptomatic oesophageal adenocarcinoma. Verticle dashed line represents base parameter, horizontal dashed lines represent cost-effectiveness ($0/QALY < willingness to pay threshold < $50,000/QALY).

* Please note the y-axis has been limited to -AU$100,000/QALY to +AU$500,000/QALY

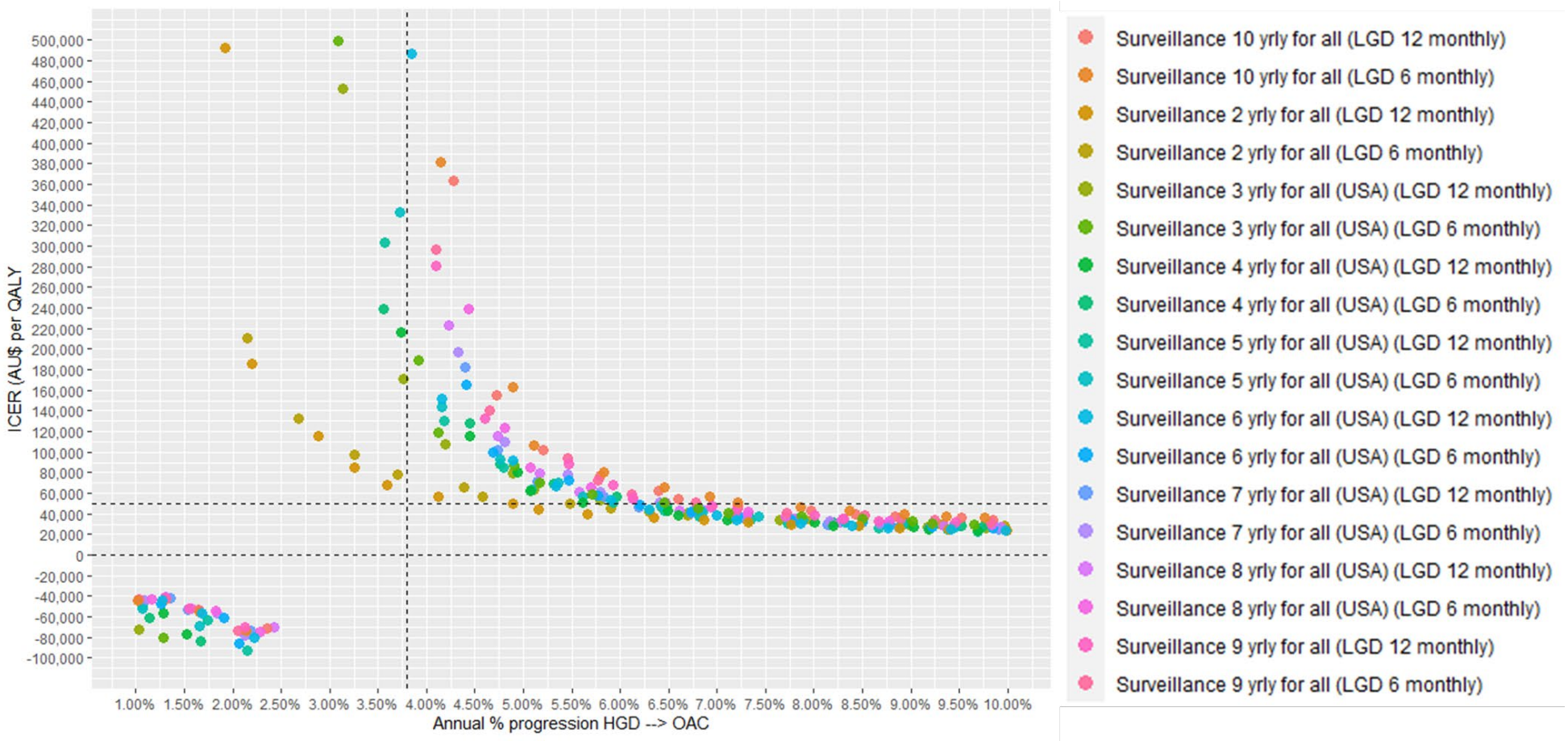


Figure 32. One way sensitivity analysis of progression to oesophageal adenocarcinoma post endoscopic mucosal resection and ablation

* Please note the y-axis has been limited to -AU$100,000/QALY to +AU$1,000,000/QALY

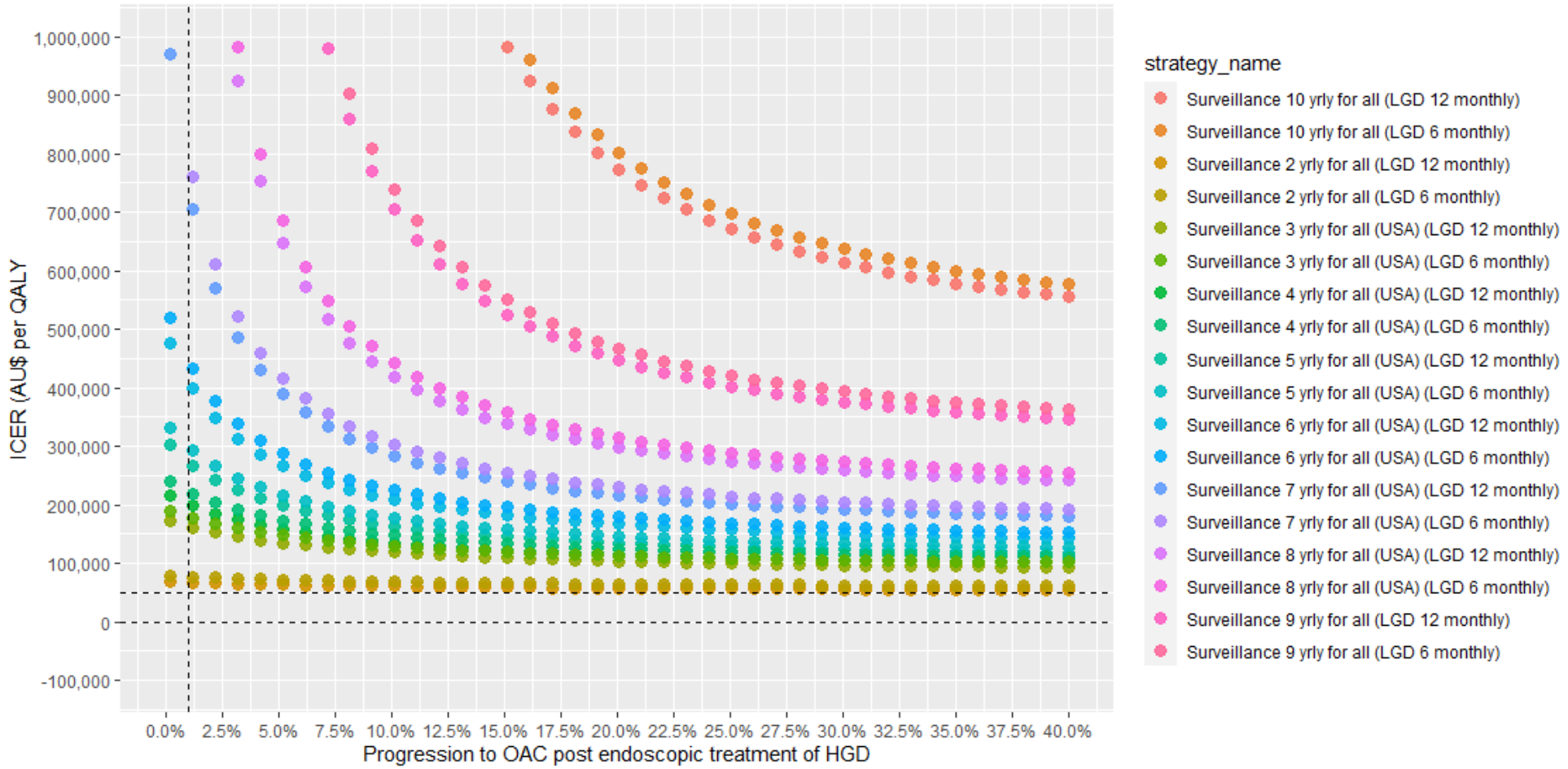


Figure 33. One way sensitivity analysis (Tornado diagram) for No surveillance (natural progression) versus 5-yearly non-dysplastic/ 12 monthly low grade dysplasia endoscopic surveillance.

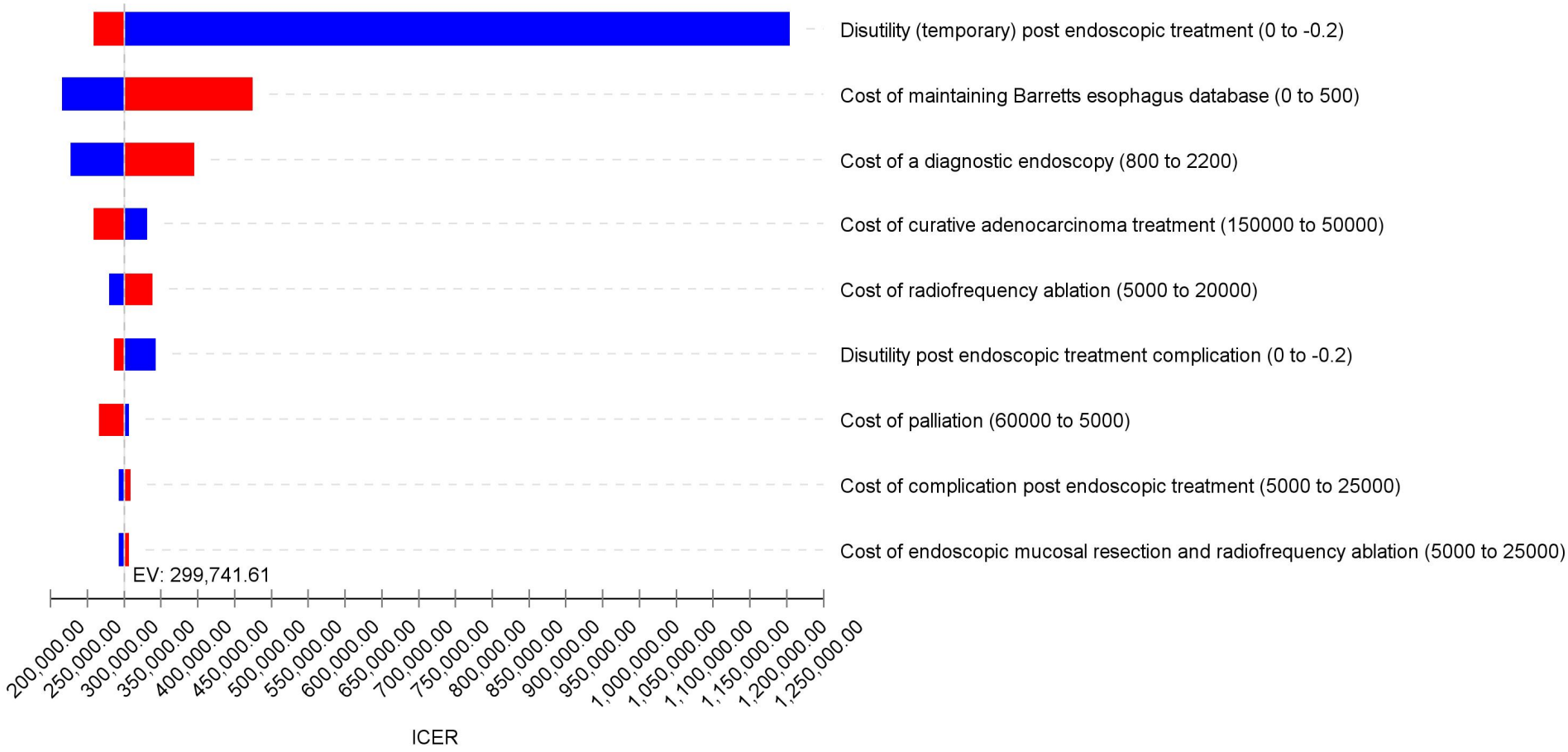
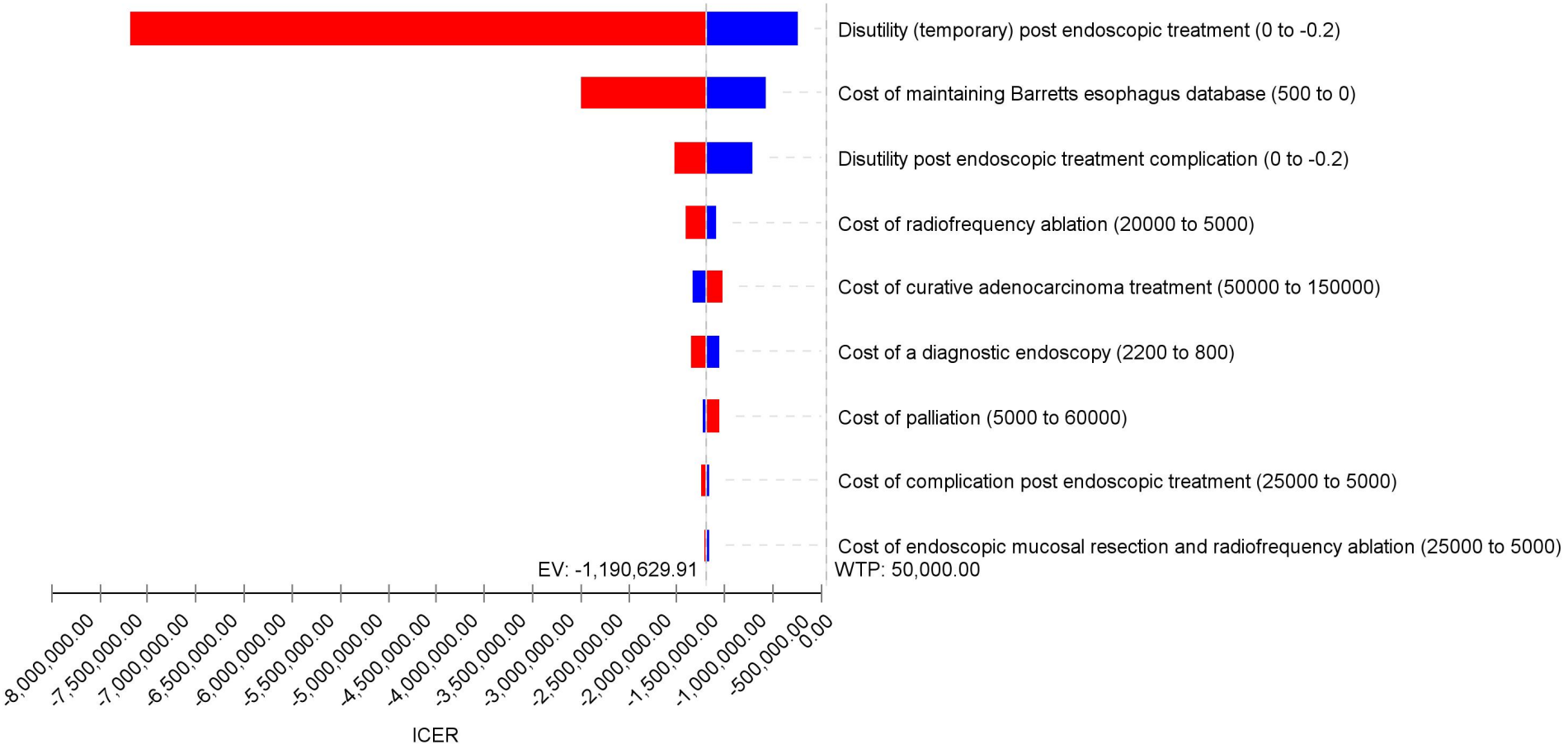


Figure 34. One way sensitivity analysis (Tornado diagram) for No surveillance (natural progression) versus 10-yearly non-dysplastic/ 12-monthly low grade dysplasia endoscopic surveillance.



5.3.1.5 Probabilistic sensitivity analysis

All key variables were varied in the probabilistic analysis using a combination of single variable distributions as well as sets of transition probability parameters extracted from the calibration process described in Chapter 4. 1000 Monte-Carlo simulations were performed, the results of which were analysed and graphed. Incremental cost and utility values were calculated with natural history/no surveillance as the base strategy and plotted on a cost-effectiveness plane (shown in Figure 35). Points under the willingness to pay threshold line (AU$50,000/QALY) indicated cost-effective ICER for that simulation. As seen in the figure, surveillance with prolonged intervals (≥ every 5 years) are concentrated around the vertical dashed black line (incremental QALY gain = -0.1 to +0.05), with an incremental cost between AU$10,000 – $20,0000. This meant the additional cost associated with endoscopic surveillance resulted in no additional gain in QALY outcomes at these surveillance intervals (compared to “no surveillance” strategy). Surveillance every 3 or 4 years resulted in some incremental QALY gain (0.05 - 0.2), but the incremental costs were too high to make this cost-effective. A small percentage of the simulations of the surveillance interval - endoscopic surveillance every 2 years for non-dysplastic Barrett’s oesophagus - were found to be cost-effective in the probabilistic sensitivity analysis. For this surveillance interval, 12-monthly endoscopy for low grade dysplasia was cost-effective in 17.9% of the simulations, whereas 6-monthly surveillance for low grade dysplasia was seen to be cost-effective in 7.3% of the simulations. An even smaller percentage of strategies with reduced frequency of endoscopic surveillance were seen to be cost-effective (≤0.1%). The percentages of simulations found to be cost-effective under this threshold are displayed as a bar chart, shown in Figure 36.

Results of the probabilistic analysis were also plotted on a cost-effectiveness acceptability curve (Figure 37). The graph depicts the percent of simulations the endoscopic surveillance strategy was most cost-effective at different willingness to pay thresholds (0-AU$100,000/QALY). Hence, none of the surveillance strategies that were less cost-effective can be seen. No surveillance (natural history) was seen to be cost-effective in 100% of the simulations until ~AU$30,000/QALY. Between willingness to pay thresholds of AU$30,000/QALY – AU$67,797/QALY, no surveillance was still cost-effective in more than 50% of the simulations. For willingness to pay thresholds above ~AU$68,000/QALY, endoscopy 2 yearly for non-dysplasia and 12-monthly for low grade dysplasia was cost-effective in more than 50% of the simulations.

Figure 35. Probabilistic sensitivity analysis scatter plot on incremental cost-effectiveness plane for non-stratified reduction in frequency of endoscopic surveillance in the aggregate cohort.

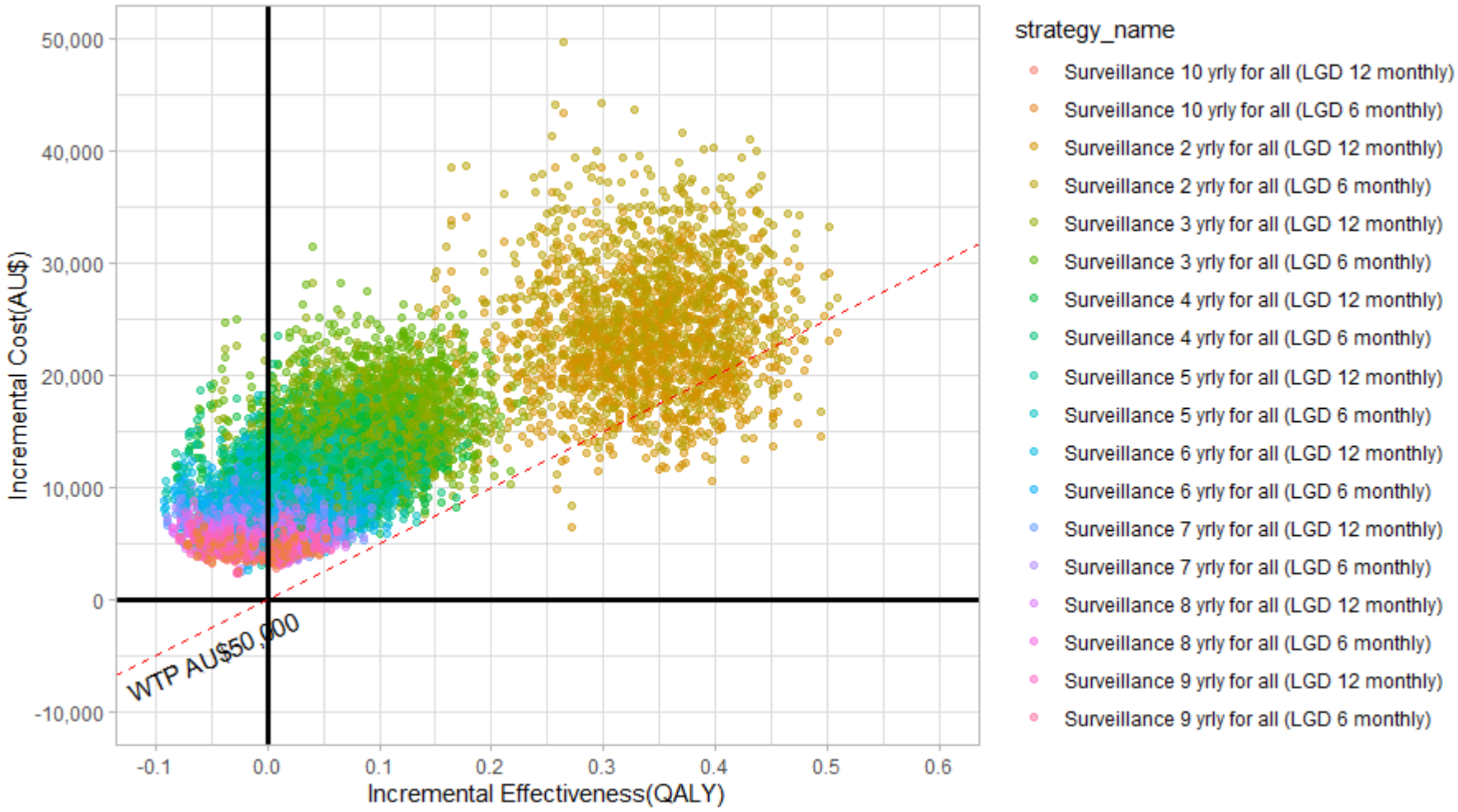
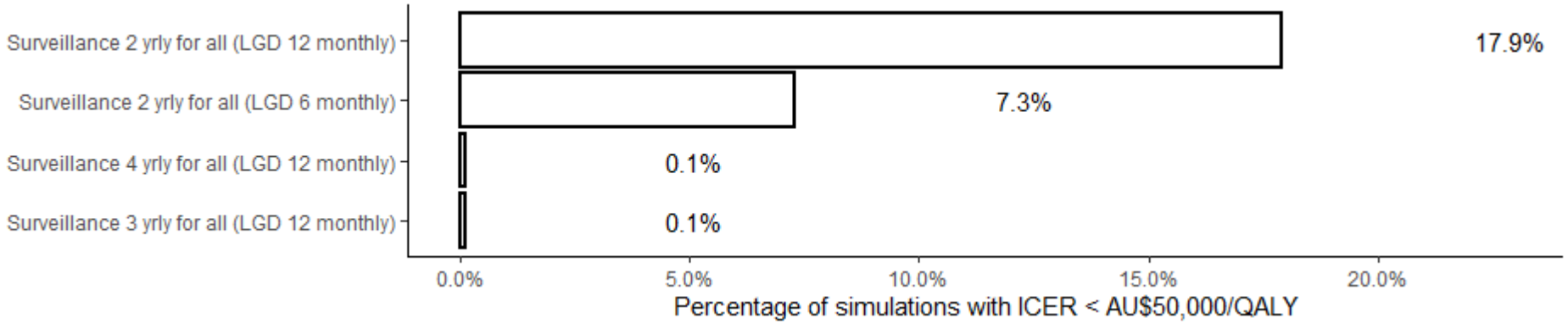
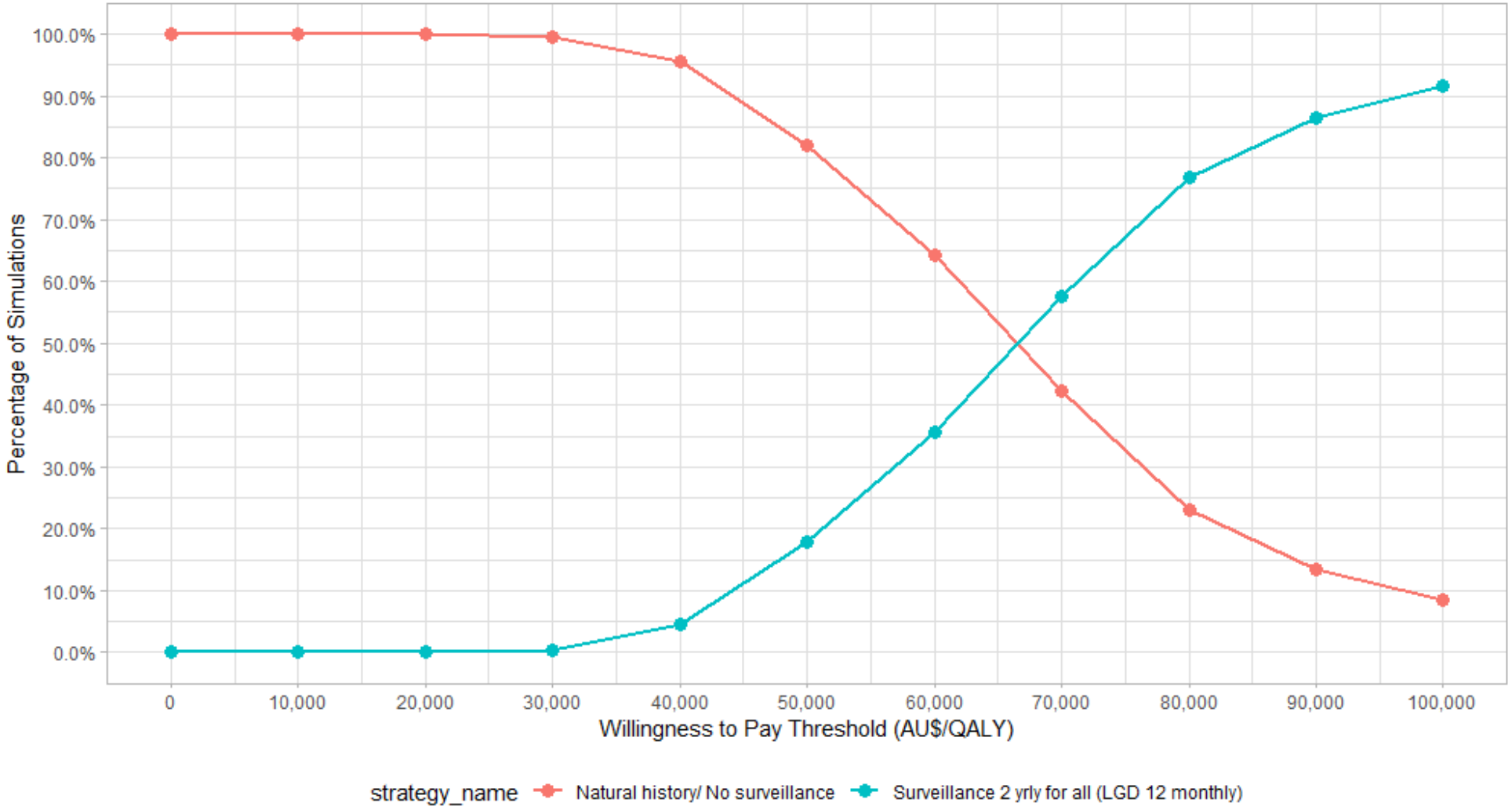


Figure 36. Probabilistic sensitivity analysis showing strategies with incremental cost-effectiveness ratio (ICER) of less than willingness-to-pay threshold (WTP) of AU$50,000/QALY.



* X-axis shows the percentage of simulations that had ICER < WTP

Figure 37. Cost-effectiveness acceptability curve for all strategies reducing frequency of surveillance in the aggregate group



Endoscopic ablation of low grade dysplasia

5.3.1.6 Base parameter results

Ablation of low grade dysplasia was tested in combination with several surveillance intervals. 10 strategies were derived from altering surveillance intervals between 2 and 10 years for non-dysplastic Barrett's oesophagus. When low-grade dysplasia was detected, a second endoscopy was performed to confirm diagnosis prior to treatment with endoscopic ablation. Endoscopic ablation of low grade dysplasia combined with 2-yearly surveillance of non-dysplastic Barrett's oesophagus frequency was the *only* cost-effective and undominated strategy, costing AU$38,743 (incremental cost = AU$31,998) but resulting in ~24.9 QALY (incremental QALY = 0.698), giving an ICER value of AU$45,863/QALY (compared to no surveillance). Even though this was the costliest of all 123 strategies, it was cost-effective because it generated the highest number of QALYs. By intervening earlier at low grade dysplasia, this strategy resulted in only 10.6% of the cohort progressing to high grade dysplasia, and 2.3% to oesophageal adenocarcinoma. Cumulatively, 0.46 endoscopic treatments with ablation for low grade dysplasia occurred per individual. Interpreting this figure is convoluted, as it does not mean that 46% of the cohort underwent ablation. Because an individual could receive multiple ablation treatments, it meant that the cumulative number of endoscopic ablative treatments averaged to approximately 0.46 per individual.

Combining ablation of low grade dysplasia with reduced frequency of surveillance (≥ every 3 years) had high costs but did not produce enough QALYs to be cost-effective. Reducing the frequency of surveillance from every 2 years to every 3 years (for non-dysplastic Barrett's oesophagus) reduced the cost to AU$27,764 but also had reduced outcomes ~24.5 QALYs (ICER = AU$71,293/QALY). The cumulative number of endoscopic treatments with ablation were approximately 0.28 per cohort, which is 40% fewer than the 2-yearly surveillance frequency. It also resulted in 12.5% of the cohort progressing to high grade dysplasia, with 4.3% progressing to oesophageal adenocarcinoma (compared to 11% in no-surveillance) and 3.4% cancer-related mortality. At the lowest surveillance frequency tested (10-yearly for non-dysplastic Barrett's oesophagus), the total cost per cohort was AU$12,538 (incremental cost of ~AU$5,800 compared to no surveillance) with outcomes of 24.4 QALY (incremental QALY ~ 0.01), equating to an ICER of AU$391,827/QALY. This is likely a result of most individuals progressing to oesophageal adenocarcinoma undetected due to the prolonged intervals between endoscopies, evidenced by 15.4% of the cohort progressing to high grade dysplasia, 8.6% oesophageal adenocarcinoma. Additionally, a higher percentage of individuals progressed to symptomatic cancer states rather than detected through surveillance, which led to increased cancer-related mortality (8%) and overall reduction in QALY outcomes.

As a theoretical exercise, cost-effectiveness of “dysplasia only” surveillance was also tested. In this case, individuals seen to have dysplasia (low grade or high grade) at their index endoscopy would receive ablation therapy (after confirmation by second endoscopy). This was seen to be cost-effective at AU$18,761/QALY. It costed only AU$8,608 (AU$1,864 more than no-surveillance) and resulted in 24.3 QALYs. Even though it was a cost-effective strategy, 10% of the cohort progressed to oesophageal adenocarcinoma, and all but 0.2% of the cancers were detected through the surveillance. This resulted in 9.7% cancer-related deaths. The other cost, utilities, and ICER values of the rest of the strategies are shown in Table 21.

Table 21. Costs and utilities of endoscopic treatment of low-grade dysplasia (per cohort of 1). Incremental cost-effectiveness ratio values are calculated using costs and utilities from "Natural history."

Strategy	Cost		QALY		ICER	NMB
Natural history/ No surveillance	$6,745	(incr)	24.219	(incr)	$0	$1,204,219
Ablate LGD with Endoscopic surveillance 10 yearly for all	$12,538	$5,793	24.234	0.015	$391,827	$1,199,165
Ablate LGD with Endoscopic surveillance 9 yearly for all	$13,365	$6,620	24.245	0.026	$258,925	$1,198,877
Ablate LGD with Endoscopic surveillance 8 yearly for all	$14,428	$7,683	24.261	0.041	$185,943	$1,198,602
Ablate LGD with Endoscopic surveillance 7 yearly for all	$15,805	$9,060	24.283	0.064	$141,439	$1,198,362
Ablate LGD with Endoscopic surveillance 6 yearly for all	$17,602	$10,857	24.316	0.097	$112,499	$1,198,187
Ablate LGD with Endoscopic surveillance 5 yearly for all	$19,979	$13,234	24.362	0.142	$92,976	$1,198,102
Ablate LGD with Endoscopic surveillance 4 yearly for all	$23,203	$16,458	24.426	0.206	$79,747	$1,198,080
Ablate LGD with Endoscopic surveillance 3 yearly for all	$27,764	$21,020	24.514	0.295	$71,293	$1,197,941
Ablate LGD with Endoscopic surveillance 2 yearly for all	$38,743	$31,998	24.917	0.698	**$45,863**	$1,207,105
Ablate LGD with Dysplasia only surveillance	$8,608	$1,864	24.319	0.099	**$18,761**	$1,207,322

* Costs are in Australian Dollars (2020 value). Incremental cost-effectiveness ratio (ICER) units are AU$/QALY. incr- incremental

Table 22. Model outputs of endoscopic ablation of low-grade dysplasia (per cohort of 1).

			Stages of Oesophageal Adenoca					Deaths		
Strategy	**EAC**	**HGD**	**Surv det**	**Loca lised**	**Reg ional**	**Unsta ged**	**Meta static**	**Cancer deaths**	**Non-Ca deaths**	**Ablation**
Natural history/ No surveillance	11.0%	16.0%	0.0%	2.1%	3.2%	2.2%	3.5%	10.7%	49.4%	0%
Ablate LGD with endo surv 10 yearly for NDBE	8.6%	15.4%	0.7%	1.5%	2.3%	1.6%	2.5%	8.0%	50.1%	5%
Ablate LGD with endo surv 9 yearly for NDBE	8.3%	15.2%	0.9%	1.4%	2.1%	1.5%	2.4%	7.6%	50.3%	6%
Ablate LGD with endo surv 8 yearly for NDBE	7.8%	15.0%	0.9%	1.3%	2.0%	1.4%	2.2%	7.1%	50.5%	8%
Ablate LGD with endo surv 7 yearly for NDBE	7.3%	14.7%	1.1%	1.2%	1.8%	1.2%	2.0%	6.5%	50.8%	10%
Ablate LGD with endo surv 6 yearly for NDBE	6.7%	14.3%	1.2%	1.0%	1.6%	1.1%	1.8%	5.8%	51.2%	13%
Ablate LGD with endo surv 5 yearly for NDBE	6.0%	13.8%	1.3%	0.9%	1.4%	0.9%	1.5%	5.1%	51.6%	17%
Ablate LGD with endo surv 4 yearly for NDBE	5.2%	13.3%	1.4%	0.7%	1.1%	0.8%	1.2%	4.3%	52.0%	22%
Ablate LGD with endo surv 3 yearly for NDBE	4.3%	12.5%	1.4%	0.6%	0.8%	0.6%	0.9%	3.4%	52.4%	28%
Ablate LGD with endo surv 2 yearly for NDBE	2.3%	10.6%	2.3%	0.0%	0.0%	0.0%	0.0%	1.0%	53.3%	46%
Ablate LGD with Dysplasia only surveillance	10.0%	15.7%	0.2%	1.9%	2.8%	2.0%	3.1%	9.7%	49.9%	4%

** LGD- Low grade dysplasia; NDBE- non-dysplastic Barrett's oesophagus; EAC- Total % of cohort developing Oesophageal adenocarcinoma (surveillance and symptomatic combined); HGD- Total % of cohort with high grade dysplasia; Surv det- Surveillance detected;

5.3.1.7 One way sensitivity analysis

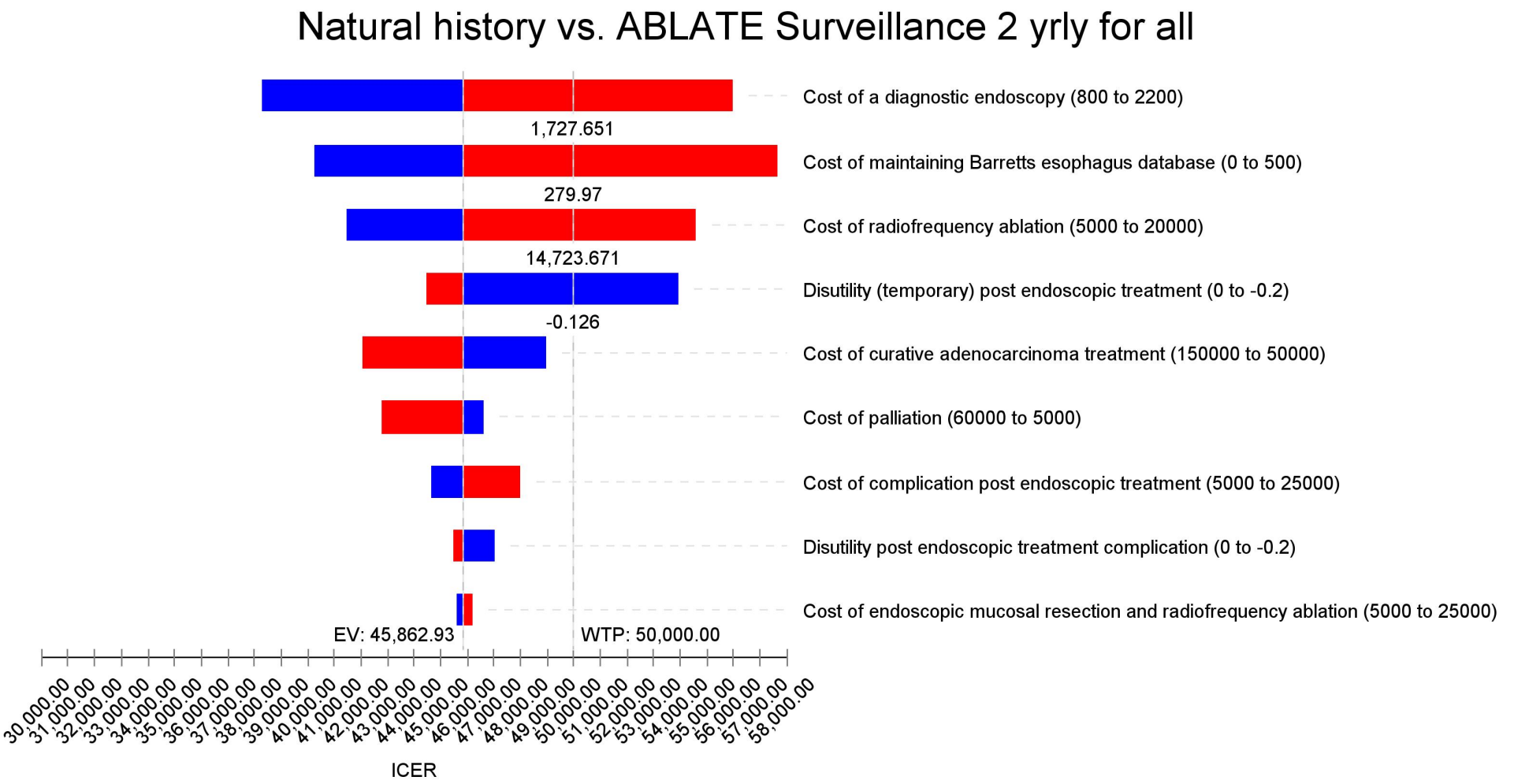
One way sensitivity analysis was performed for several variables shown as a tornado diagram in Figure 37 and Figure 38. The following variables were sensitive to the cost-effectiveness of endoscopy every 2 years (for non-dysplasia) followed by ablation of low grade dysplasia in decreasing order of sensitivity:

1) Cost of a diagnostic endoscopy
2) Cost of maintaining a database for individuals under surveillance
3) Cost of endoscopic ablation
4) Disutility associated with endoscopic ablation

Endoscopy every 2 years for non-dysplasia with ablation of low grade dysplasia was the only cost-effective strategy under base parameter conditions, but if the cost of endoscopy were to rise to ~AU$1,728, it would no longer be below the willingness to pay threshold of AU$50,000/QALY. The base cost of a diagnostic endoscopy was AU$1,390, so a 24% difference in cost (AU$338) would be unlikely. Raising the cost of maintaining a database for follow up of individuals in the surveillance program rose to AU$280 (base = AU$163) per annum, also increased the ICER value above the willingness to pay threshold. This is less plausible, as it is a 78% increase from the base cost. Similarly, if the cost of radiofrequency ablation rose to AU$14,724 (base parameter = AU$10,000, 47% increase), the ICER value would increase to above AU$50,000/QALY.

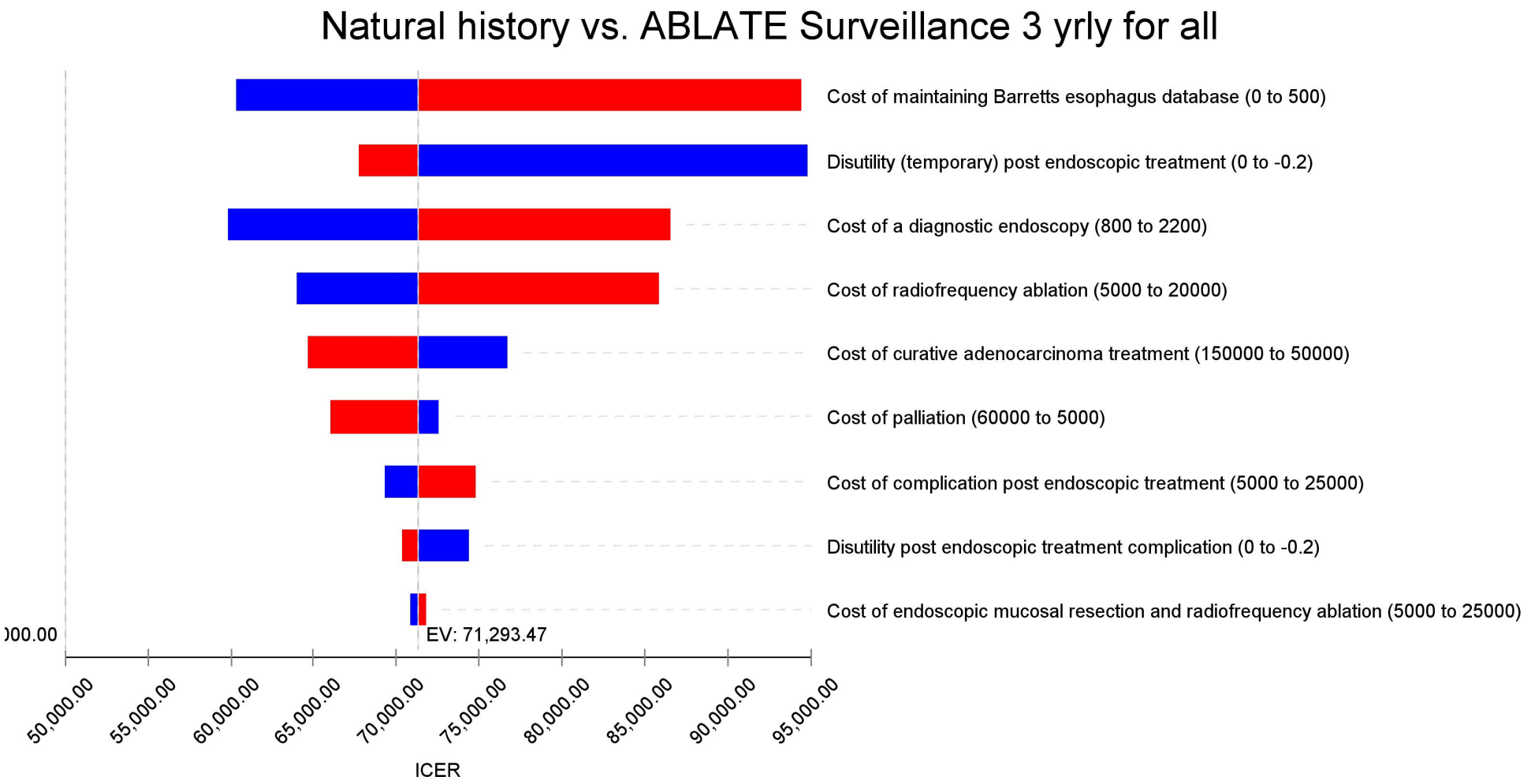
For strategies with reduced surveillance frequency (between 3 yearly – 10 yearly), the model was still sensitive to the costs related to endoscopic examination, but it was more sensitive to the changes in costs of maintaining a database of Barrett's oesophagus individuals, followed by temporary disutility associated with endoscopic ablation treatment (Figure 38 and Figure 39). Yet, none of the variables within the ranges tested through one-way sensitivity analysis improved ICER values below the willingness to pay threshold.

Figure 38. Tornado diagram: No surveillance versus 2-yearly endoscopic surveillance (non-dysplastic Barrett's oesophagus) and ablation of Low grade dysplasia



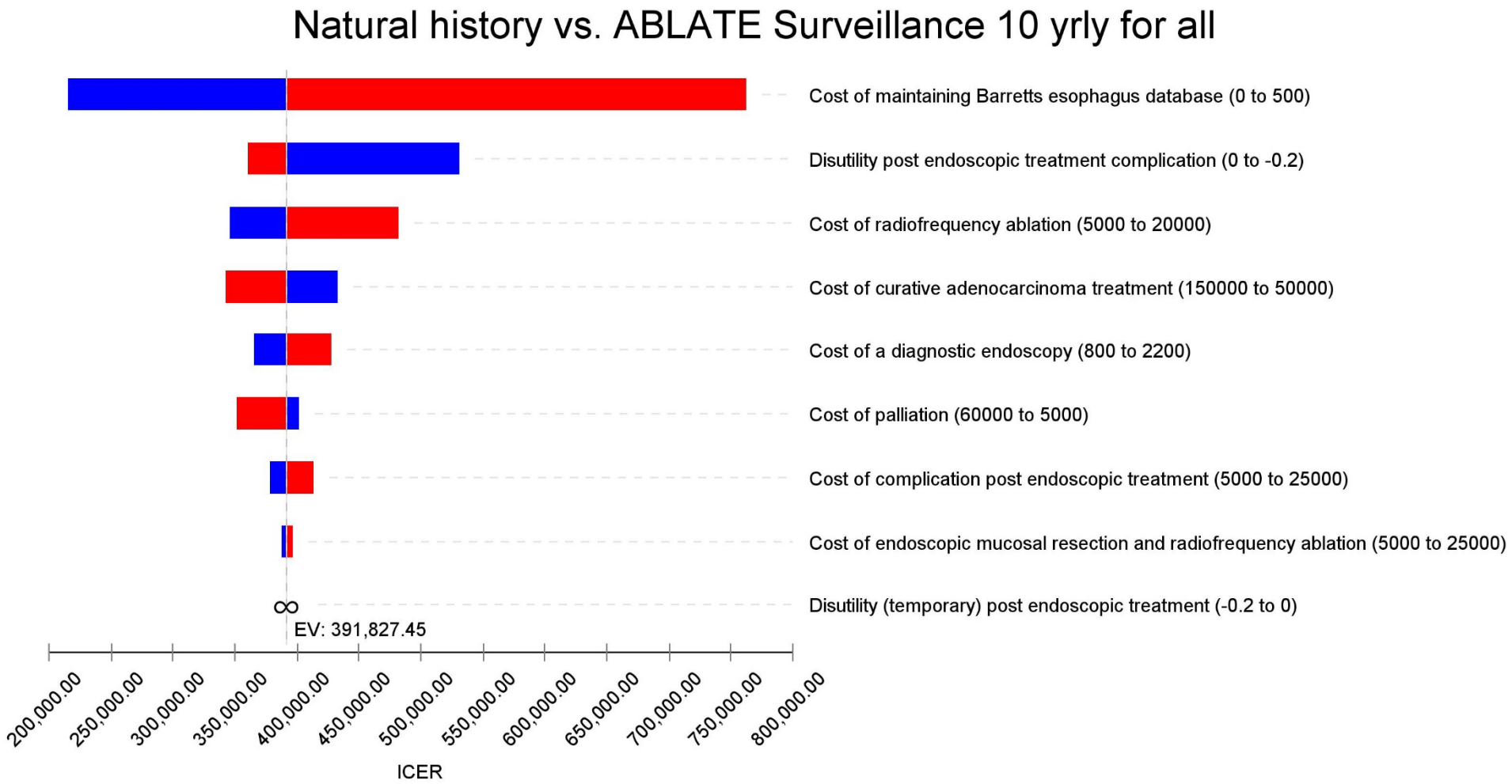
* Values in "red" indicate an increase in the value of the variable. Values in "blue" indicated decrease in variable value. Vertical dashed line indicates willingness to pay threshold (AU$50,000/QALY). ICER- incremental cost-effectiveness ratio; LGD- low grade dysplasia; EV – expected value of ICER; WTP- willingness to pay threshold

Figure 39. Tornado diagram: No surveillance versus 3-yearly endoscopic surveillance (non-dysplastic Barrett's oesophagus) and ablation of low grade dysplasia



* Values in "red" indicate an increase in the value of the variable. Values in "blue" indicated decrease in variable value. Vertical dashed line indicates willingness to pay threshold (AU$50,000/QALY). ICER- incremental cost-effectiveness ratio; LGD- low grade dysplasia; EV – expected value of ICER; WTP- willingness to pay threshold

Figure 40. Tornado diagram: No surveillance versus 10-yearly endoscopic surveillance (non-dysplastic Barrett's oesophagus) and ablation of Low grade dysplasia



* Values in "red" indicate an increase in the value of the variable. Values in "blue" indicated decrease in variable value. Vertical dashed line indicates willingness to pay threshold (AU$50,000/QALY). ICER- incremental cost-effectiveness ratio; LGD- low grade dysplasia; EV – expected value of ICER; WTP- willingness to pay threshold

5.3.1.8 Probabilistic sensitivity analysis

Probabilistic sensitivity analysis showed the endoscopy every 2 yearly for non-dysplastic Barrett's oesophagus with ablation therapy for low grade dysplasia was cost-effective in 73.9% of the simulations (Figure 40 and Figure 41). A negligible percentage of simulations were cost effective when the endoscopic surveillance frequency was reduced. Specifically, surveillance interval of 3-years between endoscopies (for non-dysplasia) was cost-effective in 2.7% of the simulations; 4-years in 1% of the simulations; and 5-year interval in 0.2% of the simulations.

Dysplasia only surveillance was also included as a strategy in the analysis, as an experimental strategy. This was seen to be cost-effective in 100% of the simulations. This approach is highly selective, including only those individuals who are diagnosed with dysplasia on the index endoscopy for surveillance. After confirmation of dysplasia, these individuals would receive endoscopic ablation therapy, therefore drastically reducing their chance of progressing to cancer. Even though this only included a small percentage of the entire cohort, most if not all under this strategy received ablation therapy. This resulted in low overall costs and gain of QALYs for those treated, making it cost-effective at an ICER value ~AU$18,760/QALY. It is important to note that this strategy was *externally dominated*, meaning other strategies were able to produce better outcomes/QALYs. The relevance of undominated, externally dominated, and absolutely dominated strategies is discussed in detail in Chapter 7.

Results of the probabilistic analysis are also displayed as a cost-effectiveness acceptability curve in Figure 43. At low willingness to pay thresholds i.e., between AU$18,000/QALY and AU$45,000/QALY, endoscopic surveillance and ablation for dysplastic Barrett's oesophagus only (excluding non-dysplasia from surveillance entirely) was cost-effective in >50% of the simulations. Endoscopic surveillance for non-dysplastic Barrett's oesophagus with ablation for low-grade dysplasia was seen to be the most cost-effective strategy above willingness to pay thresholds of ~AU$46,000/QALY.

Figure 41. Probabilistic sensitivity analysis for ablative strategies in the aggregate group. Red dashed line indicates willingness to pay (WTP) threshold of AU$50,000/QALY.

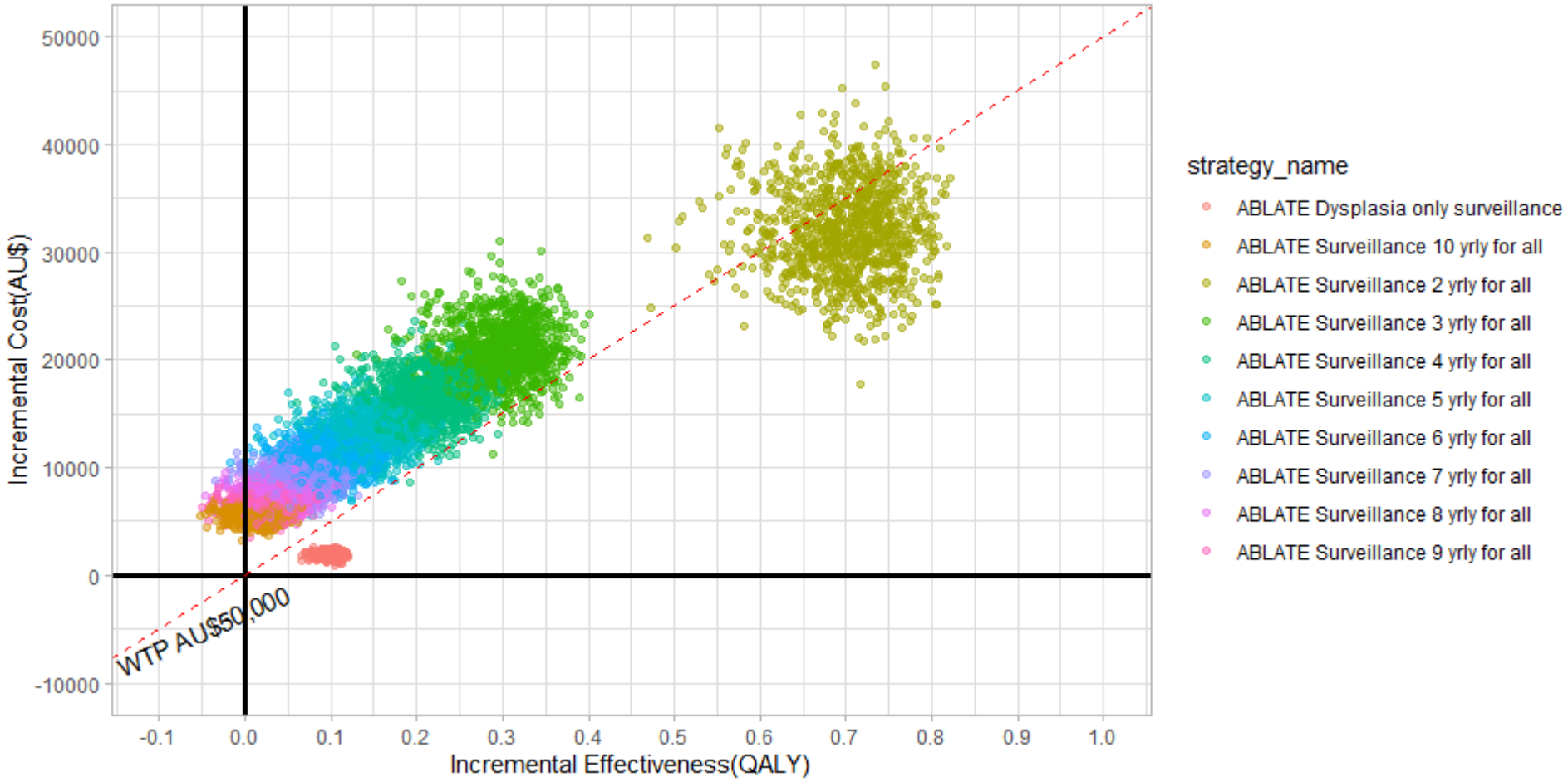


Figure 42. Probabilistic sensitivity analysis showing percentage of simulations which were cost-effective as a bar graph.

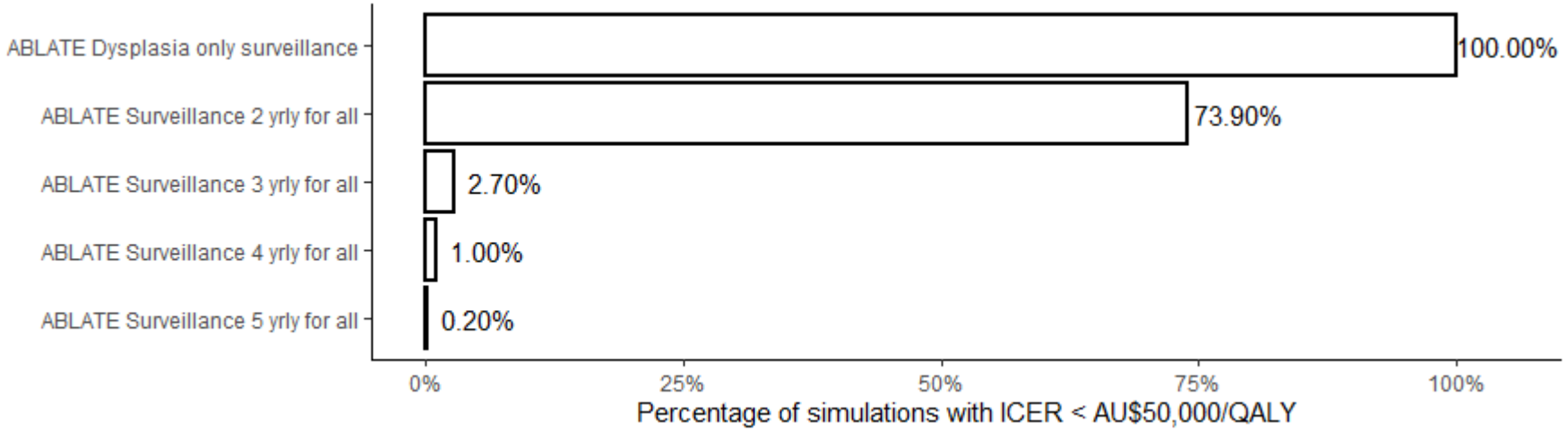
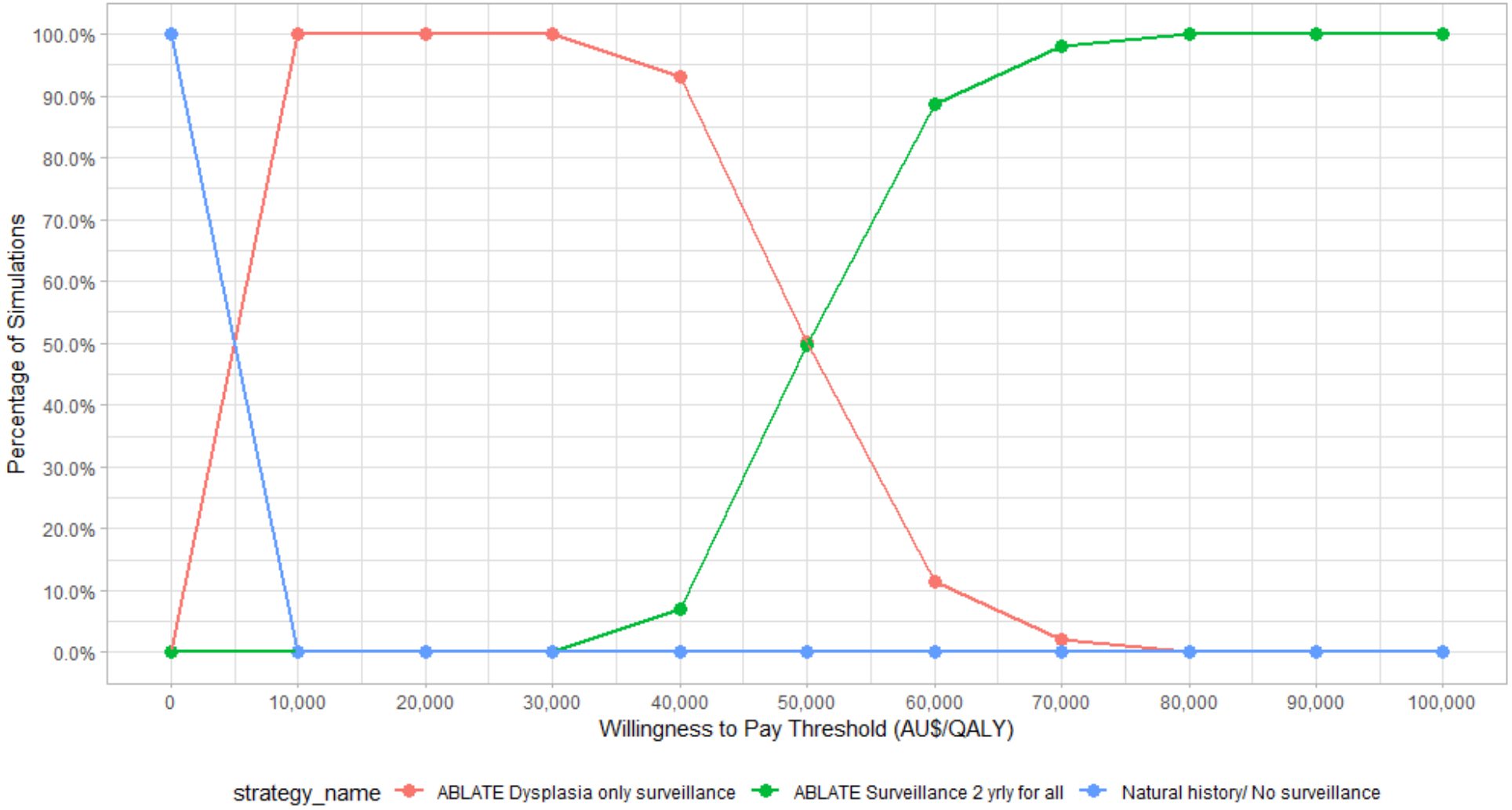


Figure 43. Cost-effectiveness acceptability curve for all strategies using radiofrequency ablation of low-grade dysplasia in the aggregate group



5.4 Discussion

The aim of this chapter was to present the initial results of the cost-utility analysis, specifically for strategies that did not use risk-stratification to assign different surveillance intervals between endoscopies. Lack of global consensus for surveillance intervals between endoscopies exists for non-dysplastic Barrett's oesophagus and to a lesser degree for low grade dysplasia. For this reason, surveillance intervals were altered between 2 – 10 years for non-dysplastic Barrett's oesophagus and between 6 – 12 months for low grade dysplasia. The combination of these two alterations resulted in 18 strategies. Adding endoscopic ablation therapy for low grade dysplasia generated a further 10 strategies in the non risk-stratified group of strategies.

Out of the 18 strategies that tested various surveillance intervals between endoscopies for both non-dysplastic and dysplastic Barrett's oesophagus, none were cost-effective at the willingness to pay threshold of AU$50,000/QALY under base parameters. In the probabilistic sensitivity analysis, surveillance every 2 years for non-dysplastic Barrett's oesophagus was cost-effective in 17.9% of the simulations when endoscopy was limited to every 12 months for low grade dysplasia and in 7.3% of the simulations when performed every 6 months. But when low grade dysplasia was treated with endoscopic ablation, it made this strategy cost-effective with an ICER value of AU$45,863/QALY under base parameters. In the probabilistic sensitivity analysis, this was seen to be cost-effective in almost 74% of the simulations.

There were several interesting results within the 28 strategies presented. Firstly, addition of radiofrequency ablation of low grade dysplasia was not expected to be cost-effective, especially in the group of non-risk stratified strategies. It costs nearly 7.5x as much as an endoscopy and biopsy, is associated with a disutility, often has complications (~20% of the cases) and is also associated with mortality. By all accounts, this seemed to be a strategy that would increase the costs, add disutility, while in avoiding only a small number of oesophageal adenocarcinomas. Adding to this, the strategy involving endoscopy every 2 years for all non-dysplastic Barrett's oesophagus with 6-monthly for low grade dysplasia was *not cost-effective* costing an overwhelming AU$32,600 while producing 24.56 QALY. It seemed counter-intuitive that adding ablation treatment to this strategy would make it cost-effective. However, the extra cost of endoscopic ablation of low grade dysplasia to this strategy was only ~AU$6,100 but more importantly produced an extraordinary 0.36 more QALYs.

The second interesting result was that reducing the frequency of endoscopic surveillance for non-dysplastic Barrett's oesophagus did not prove to be cost-effective but increasing the interval to 12-monthly for low grade dysplasia reduced costs without worsening outcomes. It was originally hypothesised that reducing the frequency of surveillance would lower the ICER values

until reaching a plateau at a certain surveillance interval, after which the ICER values would rise again. Upon further examination of the model, this phenomenon was not observed because the reduction in costs from 2-year to 3-year endoscopies was not enough to compensate for the QALY lost. Even reducing the frequency by 1 year resulted in 6.7% of the cohort progressing to oesophageal adenocarcinoma (compared to 6.2% in 2-yearly strategy), which resulted in poorer outcomes.

Thirdly, supplementing a reduced frequency of surveillance with endoscopic ablation of low grade dysplasia was expected to improve cost-effectiveness, as the costs related to endoscopies for non-dysplastic Barrett's oesophagus would be reduced to offset the costs of endoscopic ablative therapy for low grade dysplasia. However, this was not seen to be the case. Ablation of low grade dysplasia was only cost-effective if a significant portion of cancers were able to be avoided. Increasing the duration between surveillance endoscopies allowed a portion of the cohort to progress undetected to oesophageal adenocarcinoma, not receiving the benefit of endoscopic ablation treatment at low or high grade dysplasia. This in turn reduced the benefit of performing ablation therapy in the form of QALYs.

All three of these points indicated that focusing on increasing outcomes, not reducing costs was the key to improving cost-effectiveness. It is no coincidence that the only strategy found to be cost-effective from the 28 strategies altering both surveillance frequencies and offering earlier ablation was also the costliest. The cost of ablation at earlier stages of dysplasia was justified because of the gain of QALY from preventing advanced oesophageal adenocarcinoma.

One-way and probabilistic sensitivity analysis served two purposes. The first was to ensure the model behaved in a way that simulated realistic clinical events, as a form of internal validity. For example, the model was expected to be sensitive to certain model inputs, because they recur regularly for the entire cohort. Cost of endoscopy and cost of maintaining a database for Barrett's oesophagus individuals are inputs that affect all that underwent endoscopic surveillance. Expectedly, strategies that had high frequency of endoscopic surveillance, increasing the cost of an endoscopy increased the numerator of the ICER equation (Equation 1) without changing the denominator (QALYs), making this strategy less cost-effective (Figure 30). In strategies with reduced frequency of endoscopic surveillance, such as every 10 years, the cost of an endoscopy is not as commonly recurring, and thus an increase in cost does not make the ICER value fluctuate profoundly (Figure 34).

The second purpose of the sensitivity analyses was to understand the drivers of cost-effectiveness for Barrett's oesophagus surveillance and treatment. Initially, it was hypothesized that the effectiveness of endoscopic treatment for intramucosal carcinoma or dysplastic Barrett's

oesophagus would be a major driver of cost-effectiveness. Instead, the ICER value was relatively unaffected by varying the progression to cancer post endoscopic treatment of high grade dysplasia (Figure 32). This was suspicious, as it went against the initial hypothesis. On closer examination, it was revealed that even though the progression to cancer after endoscopic treatment was high, the individuals under surveillance were closely monitored and thus underwent definitive treatment at early stages of oesophageal adenocarcinoma. This ensured superior outcomes compared to individuals that were not under surveillance, who otherwise would progress to advanced cancer stages. 2-way sensitivity analysis of these two transition probabilities (progression to adenocarcinoma from high grade dysplasia under surveillance and not under surveillance) confirmed this finding. When the transition probability of natural progression of high grade dysplasia to adenocarcinoma was higher than transition probability of progression to cancer post endoscopic treatment, the strategies with frequent endoscopies were more cost-effective, which is clinically realistic.

Effectiveness of endoscopic therapy for low grade dysplasia was demonstrated in a meta-analysis by Qumseya et al in 2017 (203). This analysis included 19 studies, comprising of 2 randomised controlled trial studies (196, 211), several national registries and large retrospective studies totalling 2,746 patients. Patients receiving radiofrequency ablation had a relative risk of 0.14 (95% CI 0.04 – 0.45) compared with endoscopic surveillance alone. Of note: Only 11 studies out of the 19 in this meta-analysis reported confirming dysplasia on a second endoscopy. Regardless, evidence from this meta-analysis sparked a conversation about ablation of low grade dysplasia as a viable alternative to surveillance. However, it was not adequate to recommend it over the current standard of surveillance alone.

Cost-effectiveness of low grade dysplasia has also been studied in the literature as well. Phoa et al (212), Pollit et al. (213), and Omidvari et al. (123) all showed that ablation of low grade dysplasia was a cost-effective treatment strategy. The central theme in all literature pertaining to low grade dysplasia has been the interobserver variability of histopathological diagnosis, which is why it must be confirmed on a second endoscopy by an expert gastrointestinal pathologist. Inflammatory changes can appear similar to dysplasia, which subside with time in many individuals once reflux control is optimised. A confirmatory endoscopy (after 3 months) can downstage a small percentage of patients, while others may show more definitive signs of dysplasia and allowing them to be upstaged to high grade dysplasia. The remaining patients are considered to be confirmed with low grade dysplasia, which can either undergo ablation or continued surveillance. These features were built into the model (Figure 27). All low grade dysplasia that was assigned for ablation, required a second endoscopy, which allowed upstaging/downstaging of individuals. Confirmation of low grade dysplasia at the second endoscopy is also likely to select individuals with higher probability progressing to adenocarcinoma. This explains why the outcomes involving a

high frequency of endoscopic surveillance (every 2 years) with ablation of low grade dysplasia was seen to be more cost-effective compared to strategies with reduced frequency of surveillance (in which a much smaller percentage of the cohort underwent ablation).

The other factor that played a part in reduced outcomes (QALY) was the arbitrary nature of selecting individuals that underwent ablation upon reaching low grade dysplasia. Reducing the frequency of endoscopic surveillance meant a percentage of individuals would progress undetected to low grade dysplasia and stay undetected until due for their endoscopy. These individuals are all at the same risk of progressing to cancer. The longer the interval between surveillance endoscopies, the higher the percentage of individuals that do not benefit from earlier intervention for dysplastic Barrett's oesophagus. However, if the individuals that underwent less frequent endoscopies had lower progression rates compared to the individuals that underwent more frequent endoscopies, then this would likely result in a cost-effective strategy.

5.5 Conclusion

In summary, the cost-utility analysis of non-risk stratified approaches revealed that endoscopic ablation of low grade dysplasia in Barrett's oesophagus is cost-effective for 2-yearly surveillance interval. The additional cost of endoscopic ablation is rewarded with improved outcomes in avoiding progression to cancer. Indiscriminately reducing endoscopic surveillance may lead to cost savings, but the resulting decrease in quality-adjusted life years (QALYs) due to disease progression is non-commensurate. Results of risk-stratified strategies are discussed in the next Chapter.

6 CHAPTER 6– COST EFFECTIVENESS OF REDUCING FREQUENCY OF ENDOSCOPIC SURVEILLANCE IN A LOW-RISK SUBGROUP OF BARRETT'S OESOPHAGUS

6.1 Background

The aim of the previous chapters was to develop a Markov cohort model in order to conduct a cost-utility analysis of various forms of endoscopic surveillance and treatment in individuals with Barrett's oesophagus. The main hypothesis of this study was that current endoscopic surveillance of Barrett's oesophagus is not cost-effective, but there is a version that could be cost-effective. The main elements of risk surrounding Barrett's oesophagus are age, gender, and segment length. Modifiable risk factors such as smoking, alcohol use, and obesity have are known to have increased risk of progression to oesophageal adenocarcinoma as well (29). Other risk factors such as epigenetic alterations may play a role in distinguishing between low and high risk individuals (214). Unfortunately, there were far too many risk factors to be tested in the duration of one study. Testing risk-based surveillance intervals with gender and Barrett's oesophagus segment-length as risk factors alone produced over 120 surveillance strategies discussed in this thesis.

Review of the literature (Chapter 1) and analysing the local dataset (South Australian Barrett's Oesophagus Study- Appendix 10.2), it was postulated that the progression of non-dysplastic Barrett's oesophagus is low because it is comprised of a majority subgroup of individuals with low risk of progression. Surveillance for this subgroup is unlikely to identify and treat many oesophageal adenocarcinomas. The second part to this hypothesis was that a minority subgroup of high-risk individuals makes up the majority of oesophageal adenocarcinoma cases, for whom surveillance is indicated and required to improve outcomes. The variation in risk between progressors (to cancer) and non-progressors is attributable to certain risk factors, which can be exploited for targeted surveillance.

Indirect evidence of this hypothesis is provided by Gaddam et al. 2013 (215) Peters et al. 2019 (124), who examined the risk of progression in individuals with consecutive diagnosis of non-dysplasia on endoscopic examination and biopsy of visible Barrett's oesophagus. Both studies involved large prospective cohorts of Barrett's oesophagus patients from the U.S and concluded that annual risk of developing oesophageal adenocarcinoma was reduced in those with 2 or more consecutive findings of non-dysplastic Barrett's oesophagus. Gaddam et al. surmised this feature (persistence of non-dysplasia over >2.28 endoscopies compared to persistence > 1.75 endoscopies) could be calculated to an odds ratio 0.67 (95% 0.51 – 0.91; $p < 0.01$). Peters et al. claimed for every year without progression, the risk decreased by 14%. There are several limitations to these studies that must be taken into account, such as imbalanced follow up in the longer-term group, not controlling for known risk factors, etc. Yet, these two studies had a combined 14,000+ patients. At the least, it warrants investigation of a low-risk subgroup of individuals that are very unlikely to progress to cancer but continue receiving endoscopies every few years. As a risk factor, persistence of non-dysplasia is likely the product of several risk factors

or confounders. It is likely that those that progress early have predisposing factors. Some risk factors have been well reported, while others such as epigenetic causes have yet to be delineated.

The maximum amount of visible Barrett's oesophagus segment length is intuitively the most significant factor of progression to adenocarcinoma (187, 216). Segment length of Barrett's oesophagus signifies a higher predisposition of the individual to transform squamous oesophageal mucosa to columnar type mucosa that resembles the rest of the gastrointestinal tract. A longer segment of visible salmon coloured mucosa means larger area of metaplasia and a higher probability of some of the metaplastic cells undergoing further transformation to dysplasia and adenocarcinoma. This is well supported in the literature, including several systematic reviews and meta-analysis (29, 106{Desai, 2012 #4)}. Long segment Barrett's oesophagus in surveillance programs constitutes less than one-third of the patients in a surveillance program but contributes to more than 70% of the cases of adenocarcinoma. Pohl et al (216) reports of the patients that progressed to T1a oesophageal adenocarcinoma, 573 patients belonged to the long segment Barrett's oesophagus group, while only 240 patients had short segment (excluding patients with less than 1cm of visible Barrett's oesophagus). Perhaps, the only variable not agreed upon is the threshold for what is considered to be long segment. It is agreed anything greater than 3 cm can be safely labelled as long segment, and anything less than 2 cm is definitely short segment. However, length between (and including) 2-3 cm is contentious. Australian guidelines indicate segment lengths greater than or equal to 3 cm should be considered long segment Barrett's oesophagus (52).

Another risk factor that has appeared in multiple studies is male gender, especially looking at the number represented in surveillance programs as well as oesophageal adenocarcinoma databases. Prevalence of Barrett's oesophagus in men is two to threefold compared to women (190). There is even more disparity in the incidence of oesophageal adenocarcinoma, with male incidence being 6-8 times higher than female (45). Within surveillance programs, two meta-analyses calculating odds ratio of risk of progression draw similar conclusions, although the difference seems to be less dramatic. Krishnamoorthi et al (29) combined data from 11 studies (11,434 patients), calculating the 2.16 OR (95% CI 1.84 – 2.53) and Melquist et al. (190) included data from 10 studies (19,337 patients) calculating female versus male odds ratio ~ 0.44 (95% CI 0.3 – 0.65). Inverting the odds ratio for the second study, indicates this approximates to a male to female odds ratio of 2.27 (95% CI 1.53 – 3.33).

Using these two risk factors (segment length and gender) as a basis for subgrouping Barrett's oesophagus individuals, I hypothesised that a reduced surveillance frequency for the low risk subgroup while maintaining routine endoscopic surveillance schedule for the high risk subgroup

would result in a cost-effective option. The cost-effectiveness of risk-stratified reduced endoscopic surveillance is presented in this Chapter.

6.2 Methods

Details of various aspects of the model have been discussed in previous chapters. Specifically, Chapter 4 discussed the development, structure, and calibration of unobserved transition probabilities. Chapter 5 discussed the remaining model inputs and the cost-effectiveness of reducing frequency of endoscopic surveillance for the aggregate group in the absence of risk stratification. In this chapter, two clinical risk factors are considered, namely, gender and endoscopically visible Barrett's segment length (bisected using two thresholds 2 cm and 3 cm into short and long segment Barrett's oesophagus). Several willingness to pay thresholds are discussed throughout the results, but only the AU$50,000/QALY threshold was considered cost-effective. The additional thresholds relate to global health systems where willingness to pay thresholds could be higher or lower.

Risk based surveillance strategies contained many aspects, such as intervals between low and high risk, non-dysplastic and dysplastic Barrett's oesophagus, which expanded into words can become confusing to follow. A notation was designed to improve clarity and avoid repetitive terms. When alluding to a strategy, square brackets were used with three characteristics of the strategy separated by a semicolon. The three aspects were as follows: (Low risk subgroup name) ***# yearly*** (years between endoscopies for non-dysplasia); (High risk subgroup name) ***# yearly*** (years between endoscopies for non-dysplasia); (low risk dysplasia ***# months*** between endoscopies). As an example, take the strategy:

$$8\ yearly\ female;\ 2\ yearly\ male;\ (LGD\ 12\ monthly)$$

The low risk subgroup is listed first (female), which will undergo endoscopy every 8 years. The high risk subgroup (male) will then undergo endoscopy every 2 years. Should either of the risk subgroups reach low grade dysplasia, they will undergo 12 monthly endoscopies.

A note in particular for the length-based risk-stratified surveillance strategies, a threshold specifying what defines short and long segment is provided for the short segment (low-risk) subgroup. It can be assumed that the complement of that definition refers to the long-segment (high risk) Barrett's oesophagus subgroup. For example, if short segment Barrett's oesophagus was defined as [≤2 cm], long segment can be assumed to be "not" [≤2 cm], which is [>2 cm].

Gender-based modified endoscopic surveillance involved varied intervals for non-dysplastic Barrett's oesophagus between female (low risk) and male (high risk) subgroups. Surveillance frequency for low grade dysplasia was not altered between groups, instead only testing 6- and 12-month intervals (for both groups). For the female subgroup, endoscopic surveillance frequency was varied between 0-10 years and between 2-3 years for male subgroup. An interval of zero years refers to exclusion of the female subgroup from surveillance. This generated 22 permutations, which were tested in this study. The same intervals were tested in the segment length subgroups yielding 22 strategies for each threshold (2cm and 3cm).

Routine surveillance frequency was considered to be every 2 years for non-dysplastic and 6 monthly for dysplastic (low grade) Barrett's oesophagus, while reduced surveillance was considered anything greater than a 2-year interval between endoscopies. All surveillance strategies had a "reduction in endoscopies (%)" calculated. The calculation was based on tracking the number of times an endoscopy "node" had been selected and is presented as a percentage compared to "routine surveillance" strategy: 2 yearly for non-dysplastic Barrett's oesophagus with 6 monthly endoscopies for low grade dysplasia. Since this was the most rigorous interval and previously the guideline recommended interval, it served as a benchmark in comparing how many endoscopies each modelled endoscopic surveillance strategy was able to reduce.

6.3 Reduced frequency of Endoscopic Surveillance

Gender based endoscopic surveillance frequency

6.3.1.1 Base case parameters

Results of costs, utilities and calculated ICER values are shown in Table 23, whereas other model outputs such as progression to high grade dysplasia and oesophageal adenocarcinoma are given in Table 24. Notation of each strategy is per description in Methods section. None of the 22 strategies were cost-effective at a willingness to pay threshold below AU$50,000/QALY. ICER values ranged from AU$64,916/QALY [No surv female; 2 yearly male; LGD 12 monthly] to AU$226,111/QALY [5 yearly female; 3 yearly male; LGD 6 monthly)].

The least costly strategy was, expectedly, to exclude the female (low risk) subgroup from surveillance with the male (high risk) subgroup being offered endoscopy every 3 years [No surveillance female; 3 yearly male; LGD 12 monthly]. Total cost per cohort was AU$16,808, with an incremental cost of AU$10,063 and ICER value of AU$170,413 compared to no surveillance (natural history). This combination of surveillance intervals also resulted in the highest reduction in number of endoscopies performed, ~88% compared to two-yearly endoscopies for the aggregate cohort. However, 7.9% of the cohort progressed to oesophageal adenocarcinoma, of which only

31.6% were detected through surveillance and 81% ended in mortality (6.4% of cohort = cancer related deaths).

The most effective endoscopic surveillance strategy was [3 yearly female; 2 yearly male; LGD 6 monthly] resulting in 24.469 QALYs (incremental = 0.25 QALYs) but was also the costliest (AU$29,505 total; AU$22,761 incremental) resulting in an ICER value of AU$91,068/QALY. This was uncoincidentally the strategy with the smallest intervals between endoscopies for both subgroups (3 yearly for female; 2 yearly for male) enabling a 28.8% reduction in endoscopies. NB: The reported percentage in reduction of endoscopies is in comparison to 2-yearly endoscopies for non-dysplasia with 6 monthly endoscopies for low grade dysplasia. 6.3% of the total cohort progressed to oesophageal adenocarcinoma, with 84.1% being detected through surveillance and 52.4% of the cancers resulting in mortality (~3.3% of cohort = cancer related deaths).

The endoscopic surveillance strategy with the lowest ICER value was [No surveillance female; 2 yearly male; LGD 12 monthly]. This strategy excluded the female (low risk) subgroup from all surveillance, while maintaining 2 yearly endoscopies for male (high risk) subgroup. This cost AU$21,657 ($14,913 incremental costs) and produced 24.45 QALYs (0.23 incremental QALYs) with an ICER of AU$64,916/QALY. 7.5% of the cohort progressed to oesophageal adenocarcinoma, of which 58.7% were detected through surveillance and 66.7% ended in mortality (5% of cohort = cancer related deaths).

Table 23. Cost and QALY rankings table: Reducing frequency of endoscopic surveillance for gender subgroups. Incremental cost-effectiveness ratio values are calculated using costs and utilities from "Natural history."

Strategy	Cost		QALY		ICER	NMB
Natural history/ No surveillance	$6,745	(incr)	24.219	(incr)	**$0**	$1,204,219
No surv female; 2 yearly male; (LGD 12 monthly)	$21,657	$14,913	24.449	0.23	**$64,916**	$1,200,792
10 yearly female; 2 yearly male; (LGD 12 monthly)	$23,276	$16,532	24.446	0.227	**$72,778**	$1,199,045
9 yearly female; 2 yearly male; (LGD 12 monthly)	$23,444	$16,699	24.447	0.227	**$73,410**	$1,198,894
8 yearly female; 2 yearly male; (LGD 12 monthly)	$23,660	$16,916	24.447	0.228	**$74,134**	$1,198,712
No surv female; 2 yearly male (LGD 6 monthly)	$23,822	$17,078	24.449	0.23	**$74,340**	$1,198,628
7 yearly female; 2 yearly male; (LGD 12 monthly)	$23,946	$17,202	24.449	0.229	**$74,963**	$1,198,491
6 yearly female; 2 yearly male; (LGD 12 monthly)	$24,331	$17,586	24.451	0.232	**$75,914**	$1,198,216
5 yearly female; 2 yearly male; (LGD 12 monthly)	$24,866	$18,121	24.455	0.235	**$77,034**	$1,197,860
4 yearly female; 2 yearly male; (LGD 12 monthly)	$25,644	$18,899	24.46	0.241	**$78,443**	$1,197,366
3 yearly female; 2 yearly male; (LGD 12 monthly)	$26,865	$20,120	24.469	0.25	**$80,504**	$1,196,595
10 yearly female; 2 yearly male (LGD 6 monthly)	$25,498	$18,753	24.446	0.227	**$82,558**	$1,196,823
9 yearly female; 2 yearly male (LGD 6 monthly)	$25,686	$18,941	24.447	0.227	**$83,266**	$1,196,652
8 yearly female; 2 yearly male (LGD 6 monthly)	$25,930	$19,185	24.447	0.228	**$84,081**	$1,196,442
7 yearly female; 2 yearly male (LGD 6 monthly)	$26,253	$19,509	24.449	0.229	**$85,016**	$1,196,184
6 yearly female; 2 yearly male (LGD 6 monthly)	$26,688	$19,944	24.451	0.232	**$86,089**	$1,195,858
5 yearly female; 2 yearly male (LGD 6 monthly)	$27,291	$20,547	24.455	0.235	**$87,344**	$1,195,434
4 yearly female; 2 yearly male (LGD 6 monthly)	$28,161	$21,416	24.46	0.241	**$88,889**	$1,194,849
3 yearly female; 2 yearly male (LGD 6 monthly)	$29,505	$22,761	24.469	0.25	**$91,068**	$1,193,955
No surv female; 3 yearly male; (LGD 12 monthly)	$16,808	$10,063	24.278	0.059	**$170,413**	$1,197,108
No surv female; 3 yearly male (LGD 6 monthly)	$17,875	$11,130	24.278	0.059	**$188,487**	$1,196,041
5 yearly female; 3 yearly male; (LGD 12 monthly)	$20,016	$13,272	24.284	0.065	**$205,549**	$1,194,176
5 yearly female; 3 yearly male (LGD 6 monthly)	$21,344	$14,599	24.284	0.065	**$226,111**	$1,192,848

* Costs are in Australian Dollars (2020 value) per cohort of 1. Displayed in descending ICER value. Incremental cost-effectiveness ratio (ICER) units are AU$/QALY. incr- incremental; no surv- no surveillance

Table 24. Model outputs: Gender-based risk-stratified reduced frequency of endoscopic surveillance.

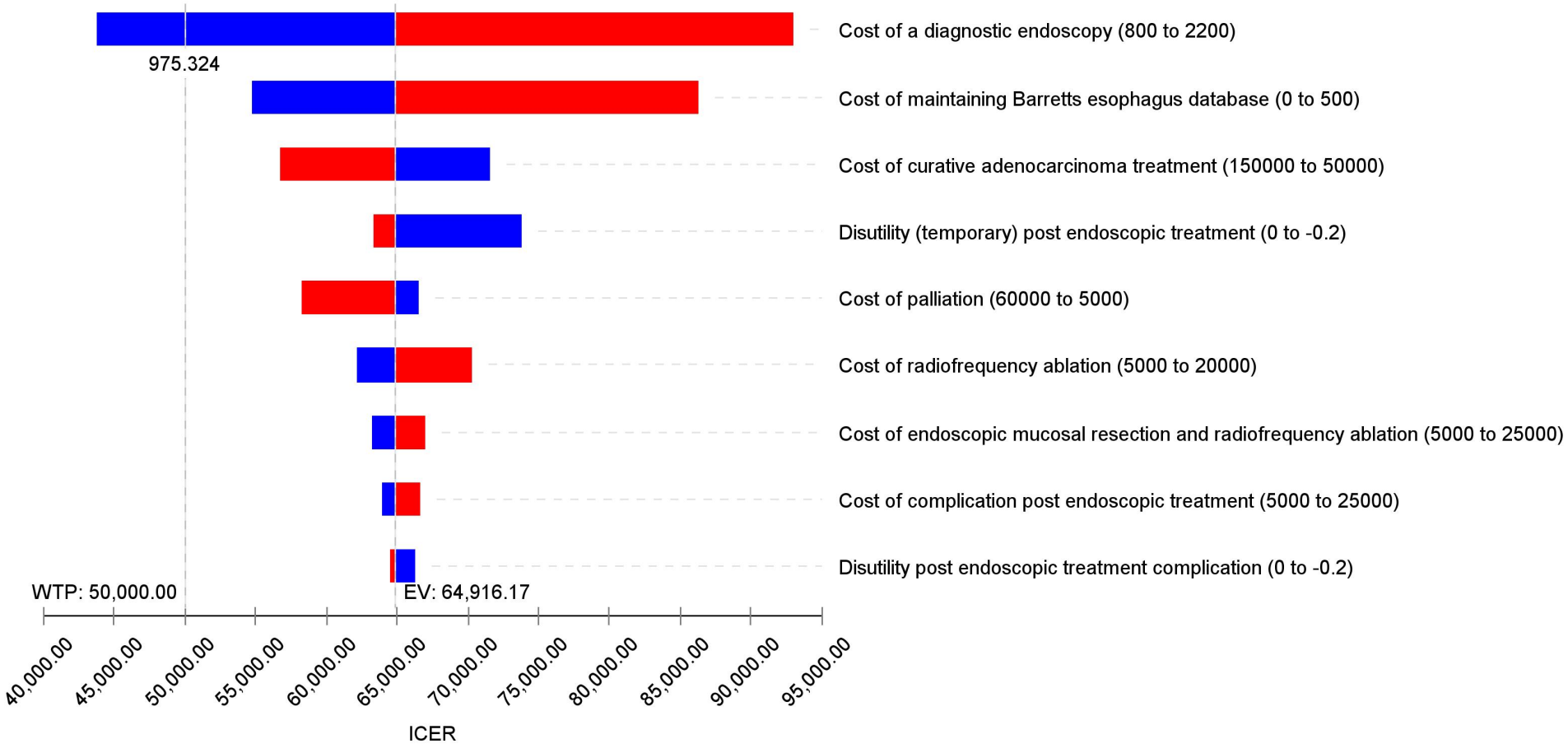
Strategy	EAC	Surv ca	Symp cancers	Cancers avoided	Cancer deaths	% endos reduced	ICER	% ca deaths
Natural history/ No surveillance	11.00%	0.00%	11.00%	0.00%	10.70%	100.00%	$0	97.70%
Female no surv; male 2 yearly; (LGD 12 monthly)	7.50%	4.40%	3.10%	3.50%	5.00%	38.10%	$64,916	66.70%
Female 10 yearly; male 2 yearly; (LGD 12 monthly)	7.00%	4.60%	2.30%	4.00%	4.30%	36.90%	$72,778	61.40%
Female 9 yearly; male 2 yearly; (LGD 12 monthly)	6.90%	4.70%	2.20%	4.10%	4.20%	36.60%	$73,410	60.90%
Female 8 yearly; male 2 yearly; (LGD 12 monthly)	6.80%	4.70%	2.00%	4.20%	4.10%	36.30%	$74,134	60.30%
Female no surv; male 2 yearly (LGD 6 monthly)	7.50%	4.40%	3.10%	3.50%	5.00%	35.30%	$74,340	66.70%
Female 7 yearly; male 2 yearly; (LGD 12 monthly)	6.70%	4.80%	1.90%	4.30%	4.00%	35.90%	$74,963	59.70%
Female 6 yearly; male 2 yearly; (LGD 12 monthly)	6.60%	4.90%	1.70%	4.40%	3.80%	35.40%	$75,914	57.60%
Female 5 yearly; male 2 yearly; (LGD 12 monthly)	6.50%	5.00%	1.50%	4.50%	3.70%	34.70%	$77,034	56.90%
Female 4 yearly; male 2 yearly; (LGD 12 monthly)	6.40%	5.10%	1.30%	4.60%	3.50%	33.80%	$78,443	54.70%
Female 3 yearly; male 2 yearly; (LGD 12 monthly)	6.30%	5.30%	1.00%	4.70%	3.30%	32.30%	$80,504	52.40%
Female 10 yearly; male 2 yearly (LGD 6 monthly)	7.00%	4.60%	2.30%	4.00%	4.30%	34.00%	$82,558	61.40%
Female 9 yearly; male 2 yearly (LGD 6 monthly)	6.90%	4.70%	2.20%	4.10%	4.20%	33.70%	$83,266	60.90%
Female 8 yearly; male 2 yearly (LGD 6 monthly)	6.80%	4.70%	2.00%	4.20%	4.10%	33.30%	$84,081	60.30%
Female 7 yearly; male 2 yearly (LGD 6 monthly)	6.70%	4.80%	1.90%	4.30%	4.00%	32.90%	$85,016	59.70%
Female 6 yearly; male 2 yearly (LGD 6 monthly)	6.60%	4.90%	1.70%	4.40%	3.80%	32.30%	$86,089	57.60%
Female 5 yearly; male 2 yearly (LGD 6 monthly)	6.50%	5.00%	1.50%	4.50%	3.70%	31.50%	$87,344	56.90%
Female 4 yearly; male 2 yearly (LGD 6 monthly)	6.40%	5.10%	1.30%	4.60%	3.50%	30.50%	$88,889	54.70%
Female 3 yearly; male 2 yearly (LGD 6 monthly)	6.30%	5.30%	1.00%	4.70%	3.30%	28.80%	$91,068	52.40%
Female no surv; male 3 yearly; (LGD 12 monthly)	7.90%	2.50%	5.40%	3.10%	6.40%	88.00%	$170,413	81.00%
Female no surv; male 3 yearly (LGD 6 monthly)	7.90%	2.50%	5.40%	3.10%	6.40%	86.60%	$188,487	81.00%
Female 5 yearly; male 3 yearly; (LGD 12 monthly)	6.90%	3.10%	3.80%	4.10%	5.00%	84.60%	$205,549	72.50%
Female 5 yearly; male 3 yearly (LGD 6 monthly)	6.90%	3.10%	3.80%	4.10%	5.00%	82.90%	$226,111	72.50%

*Values as percentage of cohort developing the model outputs (per cohort of 1). **EAC**- Total % of cohort developing Oesophageal adenocarcinoma (surveillance and symptomatic combined); **Surv ca**- Surveillance detected oesophageal adenocarcinoma; **Symp ca**- presenting with symptomatic oesophageal adenocarcinoma; **% endos reduced**- refers to how many fewer endoscopies were performed compared to comparator strategy: every 2 years for non-dysplastic Barrett's oesophagus, 6mo for low grade dysplasia; **ICER**- incremental cost-effectiveness ratio; **% ca deaths**- mortality % in cohort that progressed to oesophageal adenocarcinomas. Displayed in increasing order of ICER value.

6.3.1.2 One way sensitivity analysis

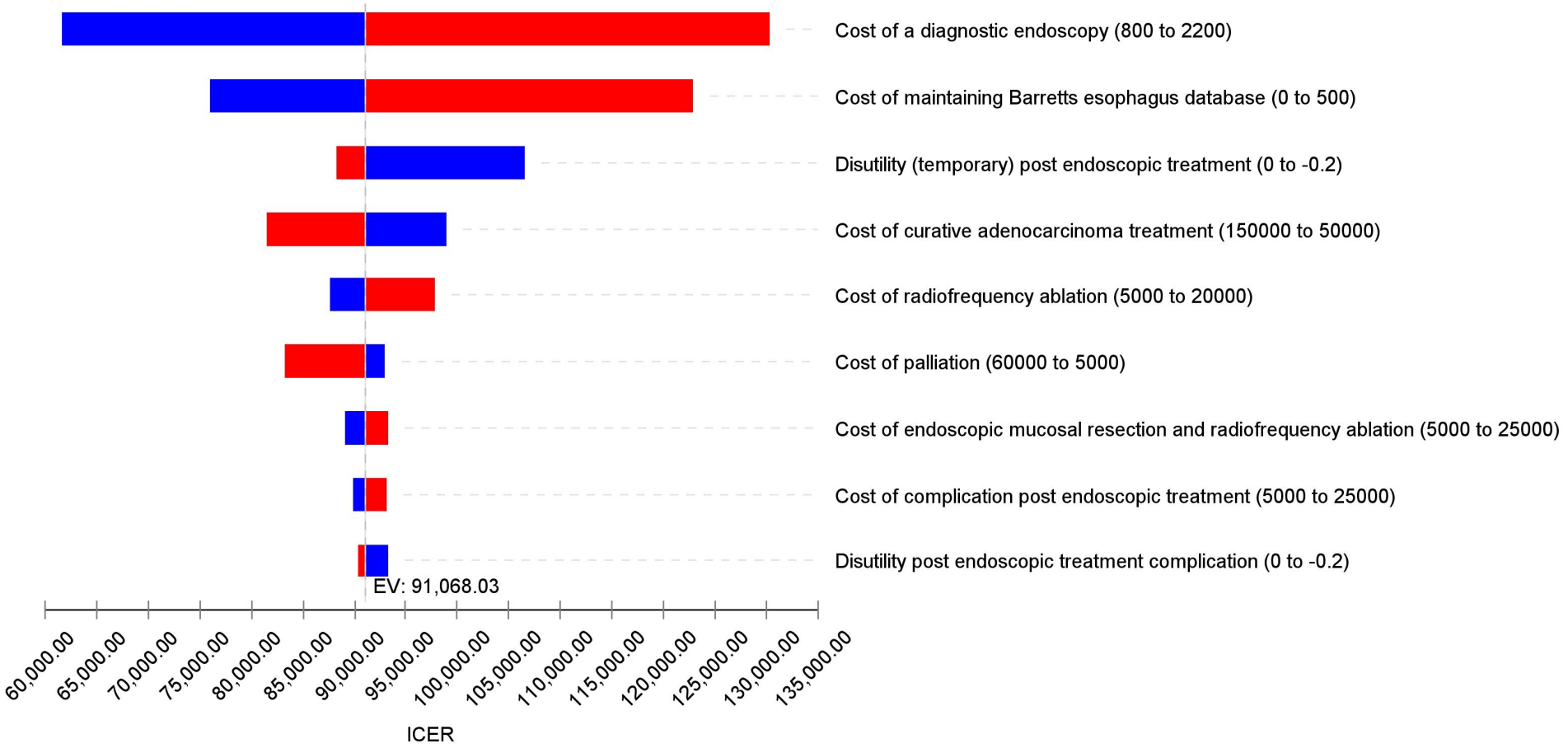
As in previous surveillance strategies discussed in Chapter 5, the key drivers of the model in this group of gender-stratified surveillance options were the costs relating to diagnostic endoscopy and database maintenance. However, varying these variables did not improve cost-effectiveness below the willingness to pay threshold of AU$50,000/QALY except in one instance. In the endoscopic surveillance strategy [Female no surveillance; Male 2 yearly; low grade dysplasia 12 monthly], reducing the cost of diagnostic endoscopy to AU$940 dropped the total cost for the cohort to AU$17,485 (incremental cost AU$11,201) while the QALYs remained the same, resulting in an ICER of AU$48,759/QALY.

Figure 44. One way sensitivity analysis (Tornado diagram) for No surveillance (natural progression) versus exclusion of low risk subgroup (females) from surveillance combined with 2-yearly endoscopies for non-dysplasia in high risk subgroup (male) with 12 monthly surveillance for low grade dysplasia. This is the endoscopic surveillance strategy with the lowest ICER value.



** Values in "red" indicate an increase in the value of the variable. Values in "blue" indicated decrease in variable value. Vertical dashed line indicates willingness to pay threshold (AU$50,000/QALY). ICER- incremental cost-effectiveness ratio; LGD- low grade dysplasia; EV – expected value of ICER; WTP- willingness to pay threshold*

Figure 45. One way sensitivity analysis (Tornado diagram) for No surveillance (natural progression) versus 3-yearly endoscopies for low risk subgroup (females) combined with 2-yearly endoscopies for non-dysplasia in high risk subgroup (male) with 6 monthly surveillance for low grade dysplasia. This is the endoscopic surveillance strategy with the highest frequency of endoscopies.



** Values in "red" indicate an increase in the value of the variable. Values in "blue" indicated decrease in variable value. Vertical dashed line indicates willingness to pay threshold (AU$50,000/QALY). ICER- incremental cost-effectiveness ratio; LGD- low grade dysplasia; EV – expected value of ICER; WTP- willingness to pay threshold*

6.3.1.3 Probabilistic Sensitivity Analysis

Probabilistic sensitivity analysis was performed as methods described in Chapter 5. 1000 simulations were carried out with 22 strategies examining a gender-based risk-stratified approach to reduced endoscopic surveillance. A scatter graph shows the distribution of ICER values for each of these simulations (Figure 44). Only a small percentage of these simulations were cost-effective for several endoscopic surveillance strategies. These can be seen as a bar graph in Figure 45, which presents the percentage of simulations where each endoscopic surveillance strategy was cost-effective below the willingness to pay threshold of AU$50,000/QALY.

19 of the 22 endoscopic surveillance strategies were found to be cost-effective in a fraction of the simulations, but none were found to be cost-effective in more than 50% of the simulations at the willingness to pay threshold. Exclusion of the female subgroup from surveillance, while performing endoscopy 2-yearly for male subgroup was cost-effective in 21% of the simulations, which was the highest percentage among all endoscopic surveillance strategies. The rest of the 18 strategies were cost-effective in ≤12% of the simulations. Of note, the 3 endoscopic surveillance strategies not found to be cost-effective in any of the simulations all had 3-yearly endoscopies for the high risk subgroup (male).

Results of probabilistic analysis are also displayed as a cost-effectiveness acceptability curve in Figure 46. This shows below a willingness to pay threshold of ~AU$30,000/QALY, no surveillance (natural history) is the most cost-effective strategy in 100% of the simulations. At AU$50,000/QALY, no surveillance (natural history) is cost-effective in ~79% of the simulations. For willingness to pay thresholds greater than AU$65,000/QALY, [0 yearly female; 2 yearly male; LGD 12 monthly] is cost-effective in >50% of the simulations.

6.3.1.4 Summary

None of gender-based risk-stratified endoscopic surveillance intervals for Barrett's oesophagus were found to be cost-effective. The female subgroup has a lower risk of developing oesophageal adenocarcinoma, but the risk isn't great enough to warrant reduced endoscopic surveillance.

Figure 46. Probabilistic sensitivity analysis scatter plot on incremental cost-effectiveness plane for gender-based risk-stratified reduction in frequency of endoscopic surveillance

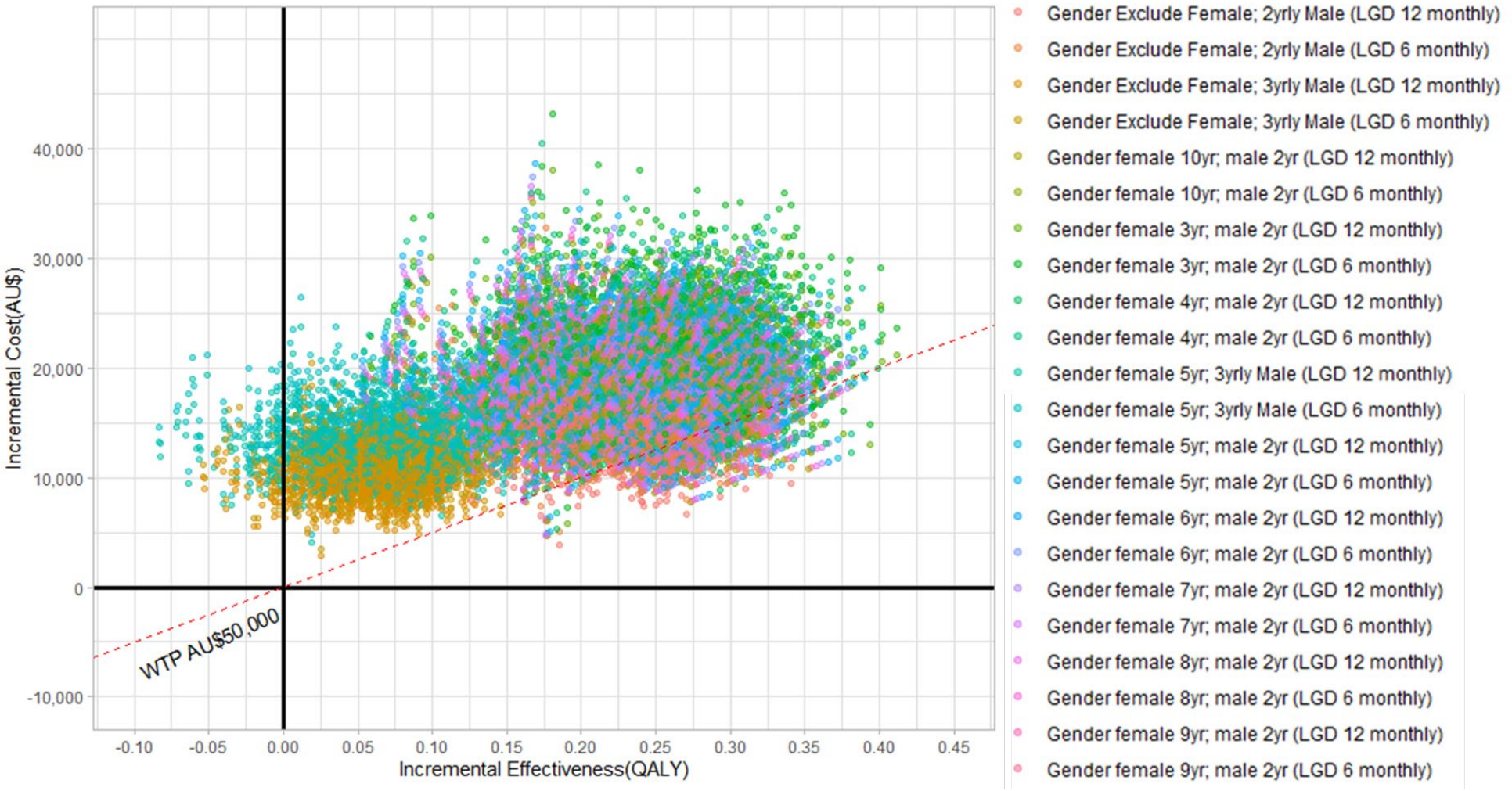
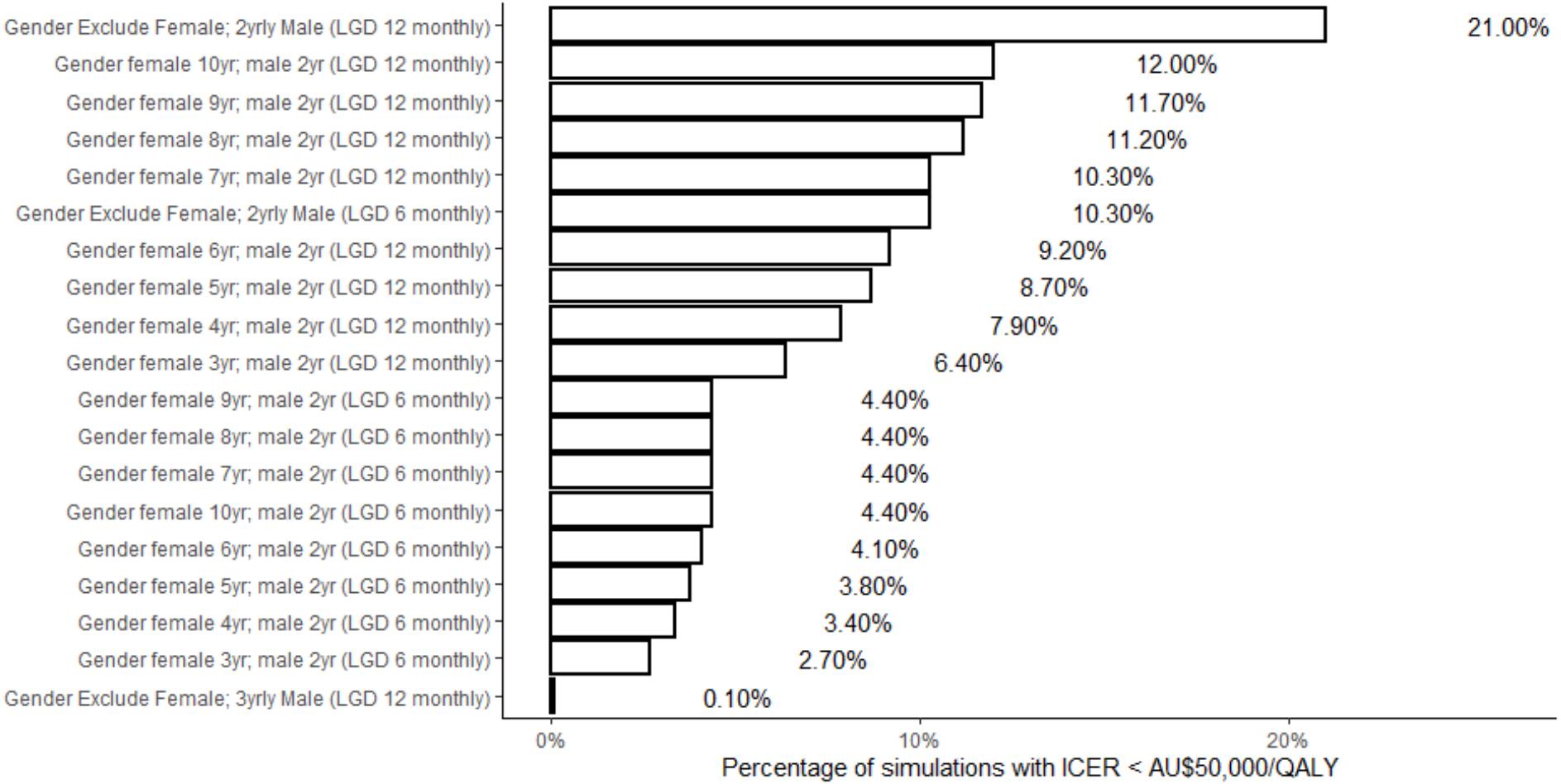
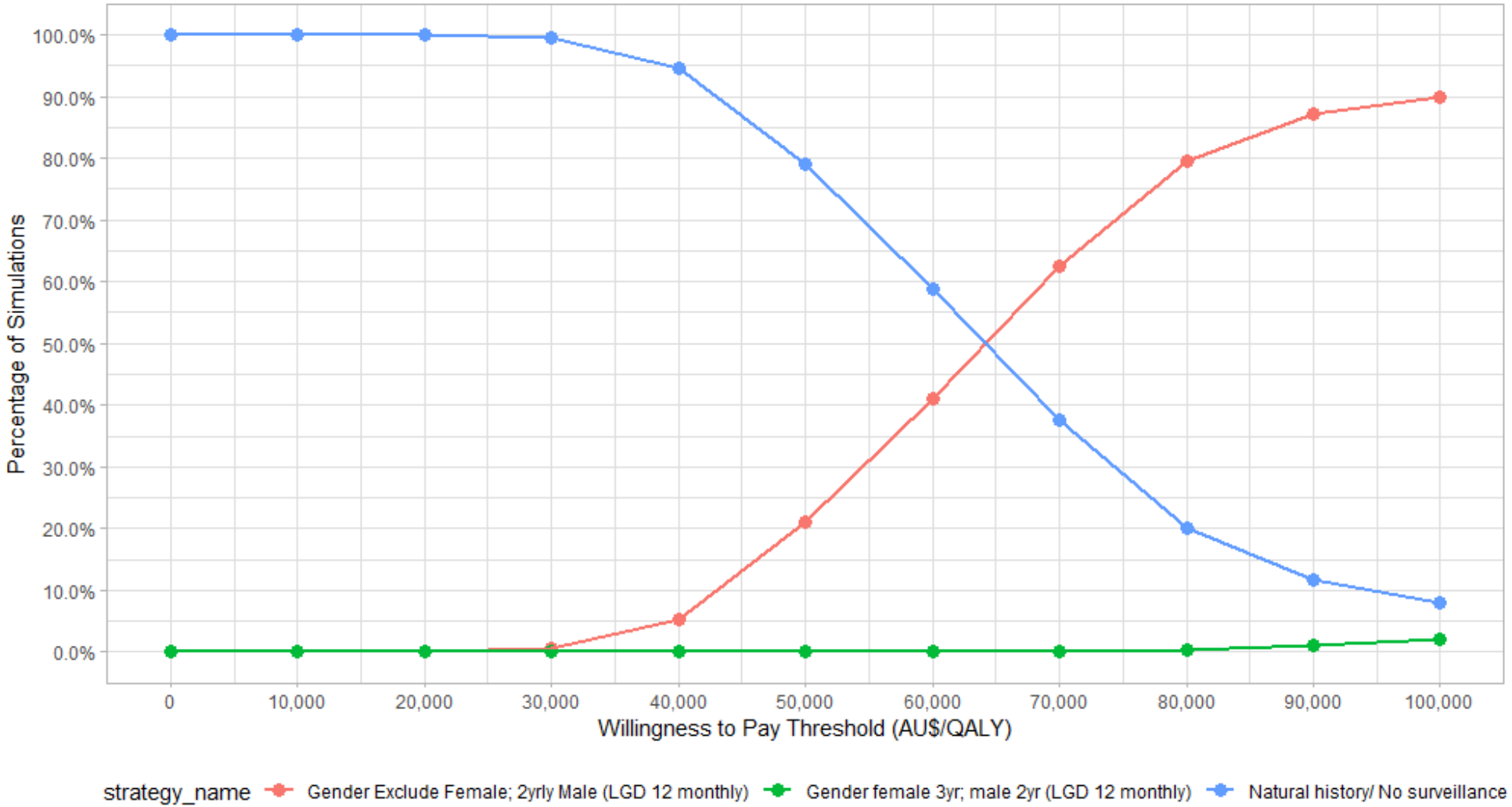


Figure 47. Probabilistic sensitivity analysis showing gender-based endoscopic surveillance strategies with incremental cost-effectiveness ratio (ICER) of less than willingness-to-pay threshold (WTP) of AU$50,000/QALY.



** X-axis shows the percentage of simulations that had ICER < WTP*

Figure 48. Cost-effectiveness acceptability curve of gender-based risk-stratified strategies showing percent of simulations each strategy was cost-effective at willingness to pay thresholds between 0-AU$100,000/WTP



Reduction of surveillance frequency of short segment Barrett's oesophagus (2 cm threshold)

Results of risk stratified endoscopic surveillance using Barrett's oesophagus segment length are presented below. Short segment Barrett's oesophagus was considered the low risk subgroup, while long segment Barrett's oesophagus was the high risk subgroup. This section presents results pertaining to the 2 cm threshold, where short segment Barrett's oesophagus is defined as 2 cm or less. Combinations of clinically plausible surveillance intervals produced 22 strategies.

6.3.1.5 Base parameter conditions

Under base parameter conditions, 9 endoscopic surveillance strategies were found to be cost-effective under the willingness to pay threshold (AU$50,000/QALY). The results of total and incremental costs, QALYs, along with ICER and net monetary benefit values are presented in Table 25. Other model outputs are shown in Table 26.

Exclusion of short segment Barrett's oesophagus with 2 yearly endoscopic surveillance for long segment Barrett's oesophagus [0 yearly SSBE (≤2 cm); 2 yearly LSBE; LGD 12 monthly] was the most cost-effective strategy with a total cost of AU$17,509 per cohort (incremental AU$10,764), 24.545 QALYs (incremental 0.326 QALYs) and an ICER value of AU$33,031/QALY. 7.2% of the cohort progressed to oesophageal adenocarcinoma, with 5.4% being detected through surveillance (74.9% of all cancers), 1.8% presenting with symptomatic oesophageal adenocarcinoma (25.1%), and 4.1% resulting in death at the end of the time horizon (57.5% mortality in cancers). This endoscopic surveillance strategy also managed to reduce 68.9% of the endoscopies performed compared to [2 yearly for all non-dysplastic Barrett's oesophagus; 6 monthly for low-grade dysplasia].

The next most cost-effective endoscopic surveillance strategy was [10 yearly SSBE (≤2 cm); 2 yearly LSBE; LGD 12 monthly] with a total cost of AU$20,462 (incremental AU$13,718) producing 24.544 QALYs (0.324 incremental) and ICER value of AU$42,290/QALY. 6.9% of the total cohort progressed to oesophageal adenocarcinoma, of which 5.5% were detected through surveillance (80.4%) and 1.3% were symptomatic oesophageal adenocarcinomas (19.6%). 3.7% of the total cohort resulted in death due to cancer (54.5% of all cancers). Overall, this strategy reduced 67.4% of endoscopies performed compared to 2-yearly endoscopy for aggregate group.

The endoscopic surveillance strategy that reduced the highest percentage of endoscopies was [0 yearly SSBE (≤2 cm); 3 yearly LSBE; LGD 12 monthly] at 88.8% (compared to 2-yearly endoscopy for aggregate group). Performing the fewest endoscopies resulted in a greater percentage of the cohort progressing to oesophageal adenocarcinoma ~ 7.4%, with the lowest percentage detected within a surveillance program ~ 55.2% (4.1% of total cohort) and conversely

the highest percentage of cancers presenting with symptomatic oesophageal adenocarcinoma (~ 44.8%; 3.3% of total cohort). While the reduced number of endoscopies accrued the lowest cost total ~ AU$15,167 (incremental AU$8,422), the increased progression to symptomatic oesophageal adenocarcinoma resulted in lower QALYs ~ 24.4 (0.194 incremental) with an ICER value AU$43,325/QALY that was able to stay under the willingness to pay threshold to be cost-effective.

On the opposite spectrum, the strategy with highest resultant QALYs was [4 yearly SSBE (≤2 cm); 2 yearly LSBE; LGD 6 months] at ~ 24.548 QALYs (incremental 0.329), while recording the highest percentage of cancers detected through surveillance (~87.2%), the lowest progression to oesophageal adenocarcinoma (~6.6%), and the lowest cancer related mortality (~ 3.3% of total cohort; 50.8% among cancers). This was directly a result of performing the most endoscopies out of this group of strategies using risk-stratification using Barrett's oesophagus segment length at 2 cm threshold. Yet, this strategy managed to reduce ~57.7% of the endoscopies compared to 2-yearly endoscopy for the aggregate group. This came at a literal cost of AU$28,514 (incremental AU$21,769) and an ICER value of AU$66,234/QALY, which was not cost-effective at the set willingness to pay threshold (AU$50,000/QALY).

Table 25. Cost and QALY rankings table: Segment length-based risk-stratified reduction in frequency of endoscopic surveillance (2 cm threshold). Incremental cost-effectiveness ratio values are calculated using costs and utilities from "Natural history."

Strategy	Cost		QALY		ICER	NMB
Natural history/ No surveillance	$6,745	Incr	24.219	incr	$0	$1,204,219
0 yearly SSBE (≤2 cm); 2 yearly LSBE (>2 cm) (LGD 12 monthly)	$17,509	$10,764	24.545	0.326	**$33,031**	$1,209,749
10 yearly SSBE (≤2 cm); 2 yearly LSBE (>2 cm) (LGD 12 monthly)	$20,462	$13,718	24.544	0.324	**$42,290**	$1,206,720
9 yearly SSBE (≤2 cm); 2 yearly LSBE (>2 cm) (LGD 12 monthly)	$20,720	$13,975	24.544	0.324	**$43,080**	$1,206,464
0 yearly SSBE (≤2 cm); 3 yearly LSBE (>2 cm) (LGD 12 monthly)	$15,167	$8,422	24.414	0.194	**$43,325**	$1,205,517
8 yearly SSBE (≤2 cm); 2 yearly LSBE (>2 cm) (LGD 12 monthly)	$21,057	$14,313	24.544	0.325	**$44,099**	$1,206,134
0 yearly SSBE (≤2 cm); 2 yearly LSBE (>2 cm) (LGD 6 monthly)	$21,482	$14,737	24.545	0.326	**$45,223**	$1,205,776
7 yearly SSBE (≤2 cm); 2 yearly LSBE (>2 cm) (LGD 12 monthly)	$21,505	$14,761	24.544	0.325	**$45,432**	$1,205,703
6 yearly SSBE (≤2 cm); 2 yearly LSBE (>2 cm) (LGD 12 monthly)	$22,110	$15,365	24.545	0.326	**$47,196**	$1,205,132
5 yearly SSBE (≤2 cm); 2 yearly LSBE (>2 cm) (LGD 12 monthly)	$22,971	$16,226	24.546	0.327	**$49,666**	$1,204,328
4 yearly SSBE (≤2 cm); 2 yearly LSBE (>2 cm) (LGD 12 monthly)	$24,247	$17,503	24.548	0.329	$53,253	$1,203,150
10 yearly SSBE (≤2 cm); 2 yearly LSBE (>2 cm) (LGD 6 monthly)	$24,496	$17,751	24.544	0.324	$54,725	$1,202,686
9 yearly SSBE (≤2 cm); 2 yearly LSBE (>2 cm) (LGD 6 monthly)	$24,772	$18,027	24.544	0.324	$55,570	$1,202,412
8 yearly SSBE (≤2 cm); 2 yearly LSBE (>2 cm) (LGD 6 monthly)	$25,133	$18,388	24.544	0.325	$56,657	$1,202,058
7 yearly SSBE (≤2 cm); 2 yearly LSBE (>2 cm) (LGD 6 monthly)	$25,612	$18,868	24.544	0.325	$58,072	$1,201,596
0 yearly SSBE (≤2 cm); 3 yearly LSBE (>2 cm) (LGD 6 monthly)	$18,223	$11,479	24.414	0.194	$59,047	$1,202,460
6 yearly SSBE (≤2 cm); 2 yearly LSBE (>2 cm) (LGD 6 monthly)	$26,257	$19,512	24.545	0.326	$59,935	$1,200,985
5 yearly SSBE (≤2 cm); 2 yearly LSBE (>2 cm) (LGD 6 monthly)	$27,170	$20,425	24.546	0.327	$62,519	$1,200,129
4 yearly SSBE (≤2 cm); 2 yearly LSBE (>2 cm) (LGD 6 monthly)	$28,514	$21,769	24.548	0.329	$66,234	$1,198,883
5 yearly SSBE (≤2 cm); 3 yearly LSBE (>2 cm) (LGD 12 monthly)	$20,629	$13,884	24.415	0.195	$71,118	$1,200,096
4 yearly SSBE (≤2 cm); 3 yearly LSBE (>2 cm) (LGD 12 monthly)	$21,906	$15,161	24.416	0.197	$76,883	$1,198,918
5 yearly SSBE (≤2 cm); 3 yearly LSBE (>2 cm) (LGD 6 monthly)	$23,912	$17,167	24.415	0.195	$87,931	$1,196,814
4 yearly SSBE (≤2 cm); 3 yearly LSBE (>2 cm) (LGD 6 monthly)	$25,256	$18,511	24.416	0.197	$93,870	$1,195,568

*Costs are in Australian Dollars (2020 value) per cohort of 1. Incremental cost-effectiveness ratio (**ICER**) units are AU$/QALY. Displayed in descending ICER value. **incr**- incremental; **QALY**- quality adjusted life years; **NMB**- net monetary benefit; SSBE- short segment Barrett's oesophagus; LSBE- long segment Barrett's oesophagus;

Table 26. Model outputs: Segment length-based risk-stratified reduction in frequency of endoscopic surveillance (2 cm threshold). Incremental cost-effectiveness ratio values are calculated using costs and utilities from "Natural history."

Strategy	EAC	Surv ca	Symp cancers	Cancers avoided	Cancer deaths	% endos reduced	ICER	% ca deaths
Natural history/ No surveillance	11.0%	0.0%	11.0%	0.0%	10.7%	100.0%	$0	97.7%
0 yearly SSBE (<=2 cm); 2 yearly LSBE (>2 cm) (LGD 12 monthly)	7.2%	5.4%	1.8%	3.8%	4.1%	68.9%	$33,031	57.5%
10 yearly SSBE (<=2 cm); 2 yearly LSBE (>2 cm) (LGD 12 monthly)	6.9%	5.5%	1.3%	4.1%	3.7%	67.4%	$42,290	54.5%
9 yearly SSBE (<=2 cm); 2 yearly LSBE (>2 cm) (LGD 12 monthly)	6.8%	5.5%	1.3%	4.2%	3.7%	67.1%	$43,080	54.0%
0 yearly SSBE (<=2 cm); 3 yearly LSBE (>2 cm) (LGD 12 monthly)	7.4%	4.1%	3.3%	3.6%	5.0%	88.8%	$43,325	66.9%
8 yearly SSBE (<=2 cm); 2 yearly LSBE (>2 cm) (LGD 12 monthly)	6.8%	5.6%	1.2%	4.2%	3.6%	66.7%	$44,099	53.5%
0 yearly SSBE (<=2 cm); 2 yearly LSBE (>2 cm) (LGD 6 monthly)	7.2%	5.4%	1.8%	3.8%	4.1%	64.3%	$45,223	57.5%
7 yearly SSBE (<=2 cm); 2 yearly LSBE (>2 cm) (LGD 12 monthly)	6.7%	5.6%	1.1%	4.3%	3.6%	66.1%	$45,432	53.0%
6 yearly SSBE (<=2 cm); 2 yearly LSBE (>2 cm) (LGD 12 monthly)	6.7%	5.6%	1.0%	4.3%	3.5%	65.3%	$47,196	52.3%
5 yearly SSBE (<=2 cm); 2 yearly LSBE (>2 cm) (LGD 12 monthly)	6.6%	5.7%	1.0%	4.4%	3.4%	64.3%	$49,666	51.6%
4 yearly SSBE (<=2 cm); 2 yearly LSBE (>2 cm) (LGD 12 monthly)	6.6%	5.7%	0.8%	4.4%	3.3%	62.7%	$53,253	50.8%
10 yearly SSBE (<=2 cm); 2 yearly LSBE (>2 cm) (LGD 6 monthly)	6.9%	5.5%	1.3%	4.1%	3.7%	62.7%	$54,725	54.5%
9 yearly SSBE (<=2 cm); 2 yearly LSBE (>2 cm) (LGD 6 monthly)	6.8%	5.5%	1.3%	4.2%	3.7%	62.4%	$55,570	54.0%
8 yearly SSBE (<=2 cm); 2 yearly LSBE (>2 cm) (LGD 6 monthly)	6.8%	5.6%	1.2%	4.2%	3.6%	61.9%	$56,657	53.5%
7 yearly SSBE (<=2 cm); 2 yearly LSBE (>2 cm) (LGD 6 monthly)	6.7%	5.6%	1.1%	4.3%	3.6%	61.3%	$58,072	53.0%
0 yearly SSBE (<=2 cm); 3 yearly LSBE (>2 cm) (LGD 6 monthly)	7.4%	4.1%	3.3%	3.6%	5.0%	85.2%	$59,047	66.9%
6 yearly SSBE (<=2 cm); 2 yearly LSBE (>2 cm) (LGD 6 monthly)	6.7%	5.6%	1.0%	4.3%	3.5%	60.5%	$59,935	52.3%
5 yearly SSBE (<=2 cm); 2 yearly LSBE (>2 cm) (LGD 6 monthly)	6.6%	5.7%	1.0%	4.4%	3.4%	59.4%	$62,519	51.6%
4 yearly SSBE (<=2 cm); 2 yearly LSBE (>2 cm) (LGD 6 monthly)	6.6%	5.7%	0.8%	4.4%	3.3%	57.7%	$66,234	50.8%
5 yearly SSBE (<=2 cm); 3 yearly LSBE (>2 cm) (LGD 12 monthly)	6.9%	4.4%	2.5%	4.1%	4.3%	84.1%	$71,118	62.0%
4 yearly SSBE (<=2 cm); 3 yearly LSBE (>2 cm) (LGD 12 monthly)	6.8%	4.5%	2.4%	4.2%	4.2%	82.6%	$76,883	61.3%
5 yearly SSBE (<=2 cm); 3 yearly LSBE (>2 cm) (LGD 6 monthly)	6.9%	4.4%	2.5%	4.1%	4.3%	80.3%	$87,931	62.0%
4 yearly SSBE (<=2 cm); 3 yearly LSBE (>2 cm) (LGD 6 monthly)	6.8%	4.5%	2.4%	4.2%	4.2%	78.6%	$93,870	61.3%

*Values as percentage of cohort developing the model outputs (per cohort of 1). **EAC**- Total % of cohort developing Oesophageal adenocarcinoma (surveillance and symptomatic combined); **Surv ca**- Surveillance detected oesophageal adenocarcinoma; **Symp ca**- presenting with symptomatic oesophageal adenocarcinoma; **% endos reduced**- refers to how many fewer endoscopies were performed compared to comparator strategy: every 2 years for non-dysplastic Barrett's oesophagus, 6mo for low grade dysplasia; **ICER**- incremental cost-effectiveness ratio; **% ca deaths**- mortality % in cohort that progressed to oesophageal adenocarcinomas. Displayed in increasing order of ICER values

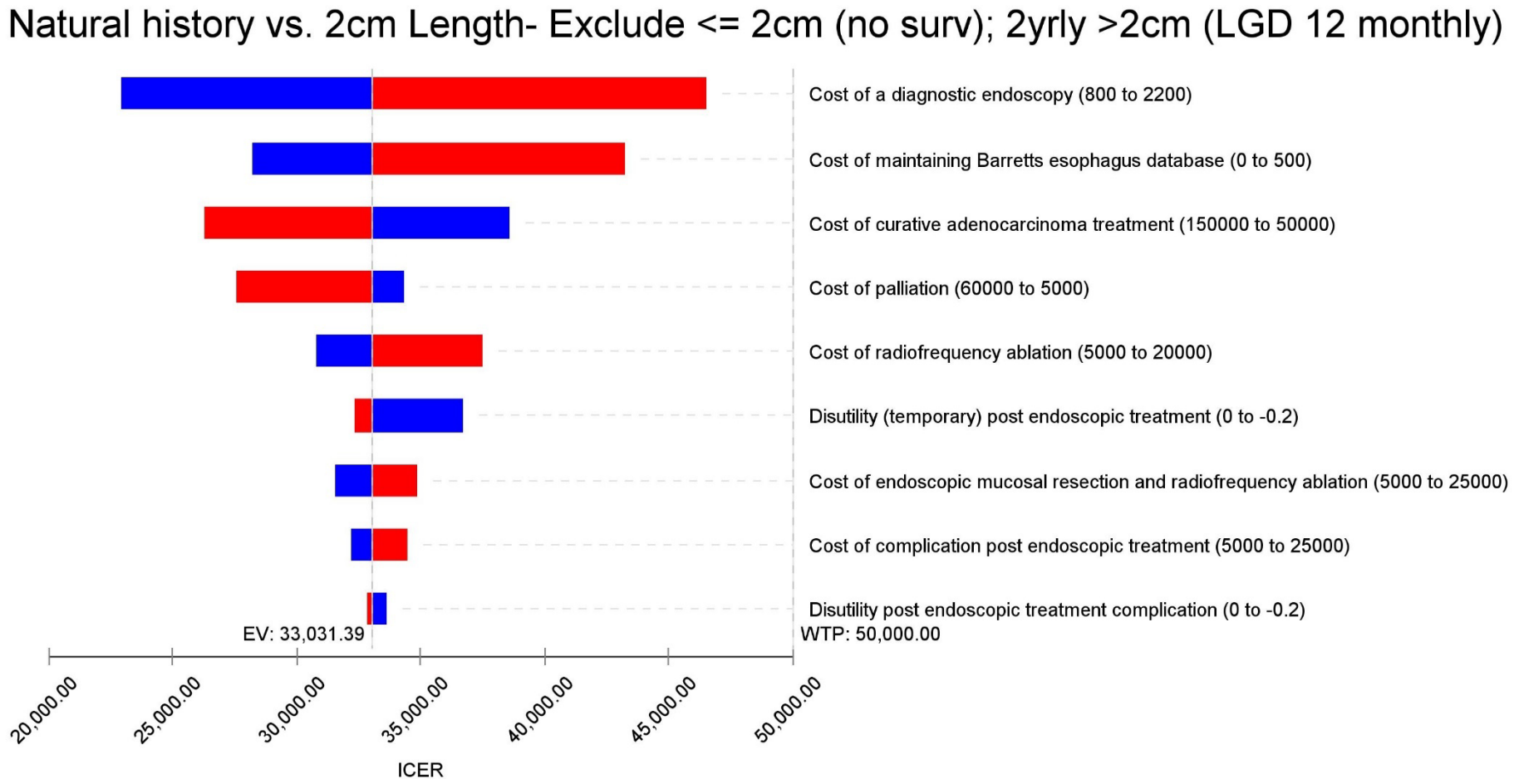
6.3.1.6 One way sensitivity analysis

The two key drivers of the model in the strategies reducing frequency of surveillance were similar to previously discussed endoscopic surveillance strategies: costs of database maintenance and cost of diagnostic endoscopy. Only one endoscopic surveillance strategy [0 yearly SSBE (≤2 cm); 2 yearly LSBE; LGD 12 monthly] remained cost-effective despite changes to variable values. As seen in Table 25, this endoscopic surveillance strategy, uncoincidentally, had the lowest ICER value. The rest of the 8 endoscopic surveillance strategies were seen to cross the AU$50,000/QALY threshold due to changes in one or more variables.

[5 yearly SSBE (≤2 cm); 2 yearly LSBE; LGD 12 monthly] is perhaps the most intriguing endoscopic surveillance strategy from the viewpoint of clinicians as it potentially allows some surveillance to take place while being cost-effective. A deeper look into the one-way sensitivity analysis, however, (Figure 47) showed that even small changes in costs and utilities caused the ICER value to increase above the willingness to pay threshold (AU$50,000/QALY). The base parameter cost of maintaining the Barrett's oesophagus database was AU$163 per annum, but this endoscopic surveillance strategy was not cost-effective at an increase to AU$166 (~1.8% increase). Similarly, the base parameter cost of diagnostic endoscopy was AU$1391, but an increase to AU$1414 (~1.7%) resulted in this endoscopic surveillance strategy resulting in an ICER value above AU$50,000/QALY. This is much of the case for every variable tested in the one-way sensitivity analysis demonstrated in Figure 47.

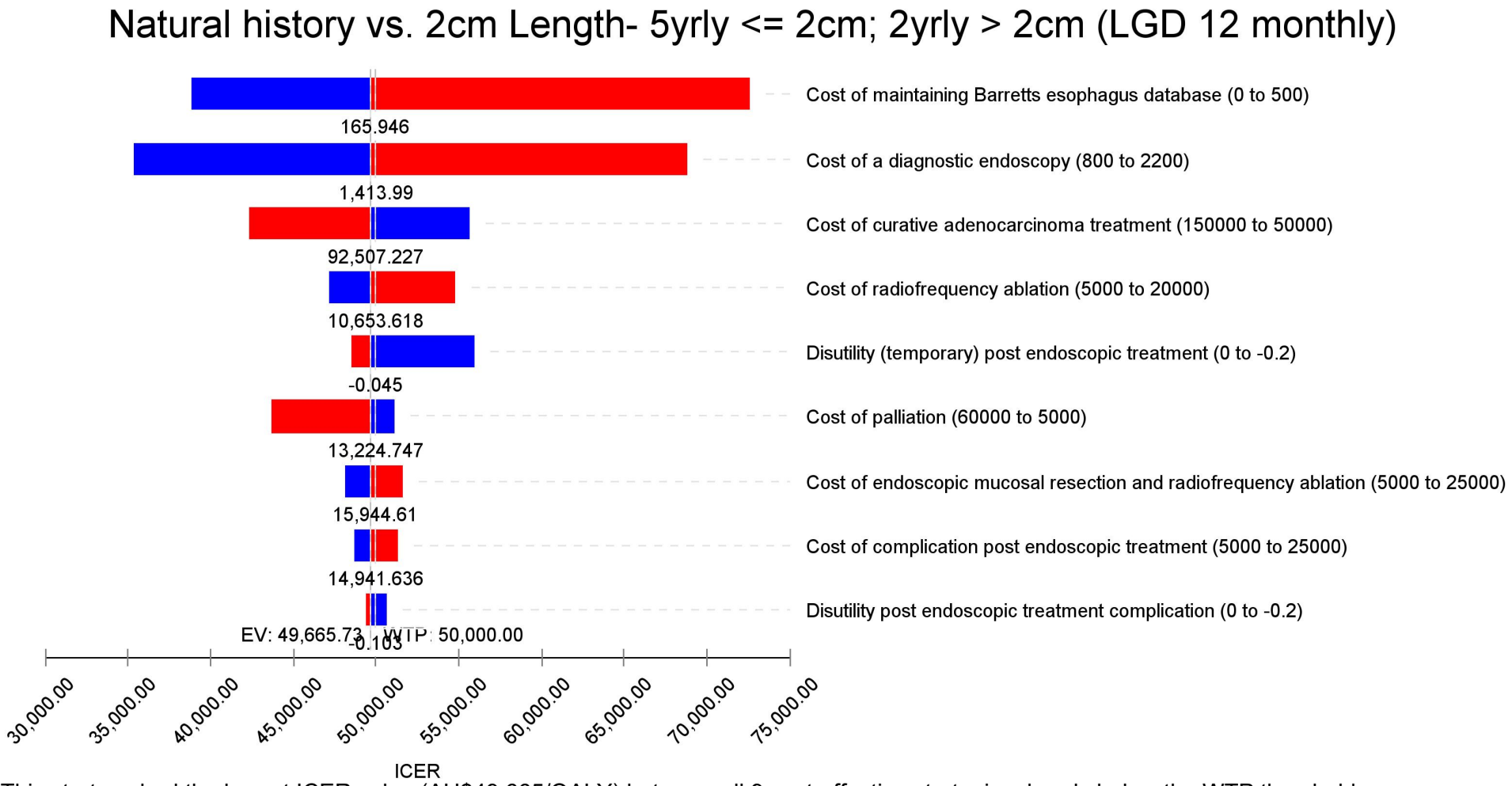
This is in stark contrast to the endoscopic surveillance strategy [0 yearly SSBE (≤2 cm); 2 yearly LSBE; LGD 12 monthly], which was cost-effective despite changes large changes to multiple variables (Figure 46). Exclusion of the low risk subgroup of individuals with short segment Barrett's oesophagus that makes up a large percentage of any surveillance program cohort likely reduces the sensitivity to changes in costs associated with endoscopic surveillance. Performing endoscopy at high cost for the high risk subgroup is thus cost-effective. Even applying a low-frequency of endoscopies such as [10 yearly SSBE (≤2 cm); 2 yearly LSBE; LGD 12 monthly] to this cohort increases the sensitivity to costs related to endoscopic surveillance (Figure 48). Compared the strategy [5 yearly SSBE (≤2 cm); 2 yearly LSBE; LGD 12 monthly], which required less than 2% change in cost variables to push it over the AU$50,000/QALY threshold, a much larger increase in cost for diagnostic endoscopy (>30%) or database maintenance (>68%) was required to make the [10 yearly SSBE (≤2 cm); 2 yearly LSBE; LGD 12 monthly] not cost-effective.

Figure 49. One way sensitivity analysis (Tornado diagram) for natural history (no surveillance) versus exclusion of low risk subgroup (≤2 cm) from surveillance combined with 2-yearly endoscopies for non-dysplasia in high risk subgroup (>2 cm) with 12 monthly surveillance for low grade dysplasia.



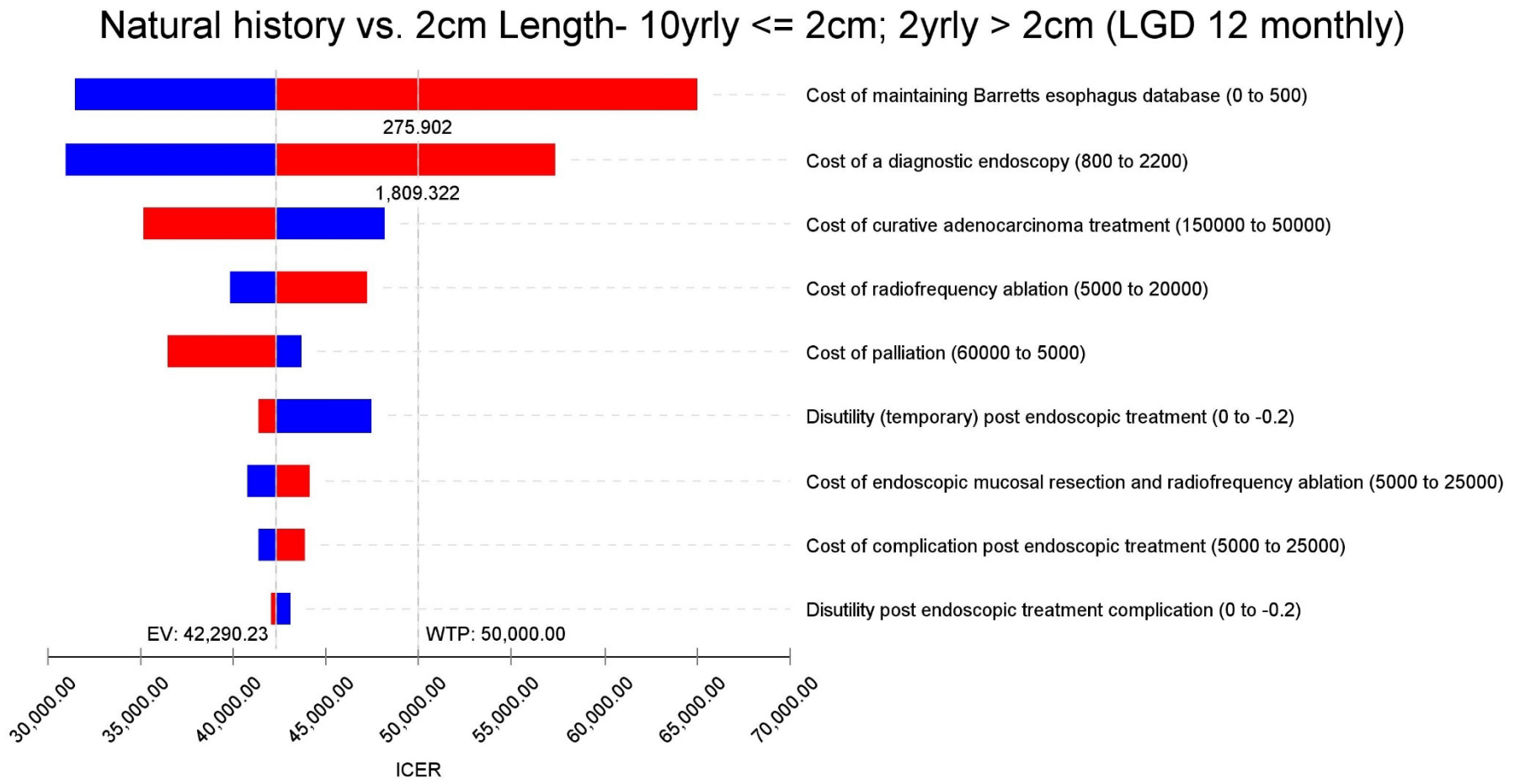
* This is the endoscopic surveillance strategy with the lowest ICER value. Values in “red” indicate an increase in the value of the variable. Values in “blue” indicated decrease in variable value. Vertical dashed line indicates willingness to pay threshold (AU$50,000/QALY). ICER- incremental cost-effectiveness ratio; LGD- low grade dysplasia; EV – expected value of ICER; WTP- willingness to pay threshold

Figure 50. One way sensitivity analysis (Tornado diagram) for natural history (no surveillance) versus 5-yearly endoscopy for non-dysplasia of low risk subgroup (≤2 cm) from surveillance combined with 2-yearly endoscopies for non-dysplasia in high risk subgroup (>2 cm) with 12 monthly surveillance for all low grade dysplasia.



* This strategy had the lowest ICER value (AU$49,665/QALY) between all 9 cost-effective strategies, barely below the WTP threshold (AU$50,000/QALY). Values in “red” indicate an increase in the value of the variable. Values in “blue” indicated decrease in variable value. Vertical dashed line indicates willingness to pay threshold (AU$50,000/QALY). ICER- incremental cost-effectiveness ratio; LGD- low grade dysplasia; EV – expected value of ICER; WTP- willingness to pay threshold

Figure 51. One way sensitivity analysis (Tornado diagram) for natural history (no surveillance) versus 10-yearly endoscopy for non-dysplasia of low risk subgroup (≤2 cm) from surveillance combined with 2-yearly endoscopies for non-dysplasia in high risk subgroup (>2 cm) with 12 monthly surveillance for all low grade dysplasia.



* Values in “red” indicate an increase in the value of the variable. Values in “blue” indicated decrease in variable value. Vertical dashed line indicates willingness to pay threshold (AU$50,000/QALY). ICER- incremental cost-effectiveness ratio; LGD- low grade dysplasia; EV – expected value of ICER; WTP- willingness to pay threshold

6.3.1.7 Probabilistic sensitivity analysis

In contrast to gender-based endoscopic surveillance strategies, using Barrett's oesophagus segment length (2 cm threshold) generated a number of cost-effective strategies. The 9 out 22 endoscopic surveillance strategies that were found to be cost-effective under base parameter conditions were all seen to be cost-effective in > 50% of the simulations in the probabilistic sensitivity analysis. Another 8 strategies were seen to be cost-effective in 25-45% of the simulations. Of the remaining 5 strategies, 3 were cost-effective in 10-20% of the simulations, and the last 2 strategies were cost-effective in less than 4% of the simulations. This is represented by the ICER scatter plot in Figure 52, which shows approximately 40% of the points lying below the willingness to pay threshold line. The numeric value of the percentage of simulations where the ICER value was <AU$50,000/QALY is provided in Figure 53.

The most cost-effective endoscopic surveillance strategy was [0 yearly SSBE (≤2 cm); 2 yearly LSBE; LGD 12 monthly]. The subgroup with short segment Barrett's oesophagus were designated to no surveillance, while the long-segment subgroup received 2-yearly endoscopies for non-dysplasia with 12-monthly endoscopies for low-grade dysplasia. At a willingness to pay threshold of AU$50,000/QALY, it was seen to be cost-effective 95% of the simulations. It was also the only endoscopic surveillance strategy that was undominated (among this specific length-based strategies). All other strategies seen to be cost-effective in the base case analysis were either externally dominated or absolutely dominated in comparison to this strategy. This is represented in the cost-effectiveness acceptability curve (Figure 54), where the no surveillance strategy is seen to be cost-effective in less than 50% of the simulations for willingness to pay thresholds above ~AU$33,031/QALY.

The next most cost-effective strategy was [10 yearly SSBE (≤2 cm); 2 yearly LSBE; LGD 12 monthly], which was cost-effective in nearly 80% of the simulations, followed closely by was [9 yearly SSBE (≤2 cm); 2 yearly LSBE; LGD 12 monthly], cost-effective in 78.1% of the simulations, and then by was [8 yearly SSBE (≤2 cm); 2 yearly LSBE; LGD 12 monthly] which was cost-effective in 74.8% of the simulations (Figure 53). Even reducing the surveillance frequency of the high risk (long segment) group to 3-yearly was seen to be cost-effective when combined with excluding the low-risk (short segment) group from surveillance. The strategy [0 yearly SSBE (≤2 cm); 3 yearly LSBE; LGD 12 monthly] was cost-effective in 74.6% of the simulations

6.3.1.8 Summary

Using Barrett's oesophagus segment length to discriminate between low and high risk subgroups allowed development of several cost-effective strategies in a high percentage of simulations. The trend favoured strategies that employed 12-monthly intervals between endoscopies for low grade dysplasia, with intervals greater than 5 years for non-dysplastic low-risk

(short segment) subgroups, while continuing 2-yearly endoscopies for the high risk (long segment) subgroup. The strategy [5 yearly SSBE (≤2 cm); 2 yearly LSBE; LGD 12 monthly] was seen to be cost-effective under base parameter conditions and in 56% of the simulations in the probabilistic analysis but was dominated by other strategies. One-way sensitivity analysis supported these results, showing even small changes in costs and utilities (attributable to uncertainty) would make this strategy unlikely to be cost-effective.

Figure 52. Scatter plot on incremental cost-effectiveness plane for Barrett's oesophagus segment length-based (2 cm threshold) risk-stratified reduction in frequency of endoscopic surveillance

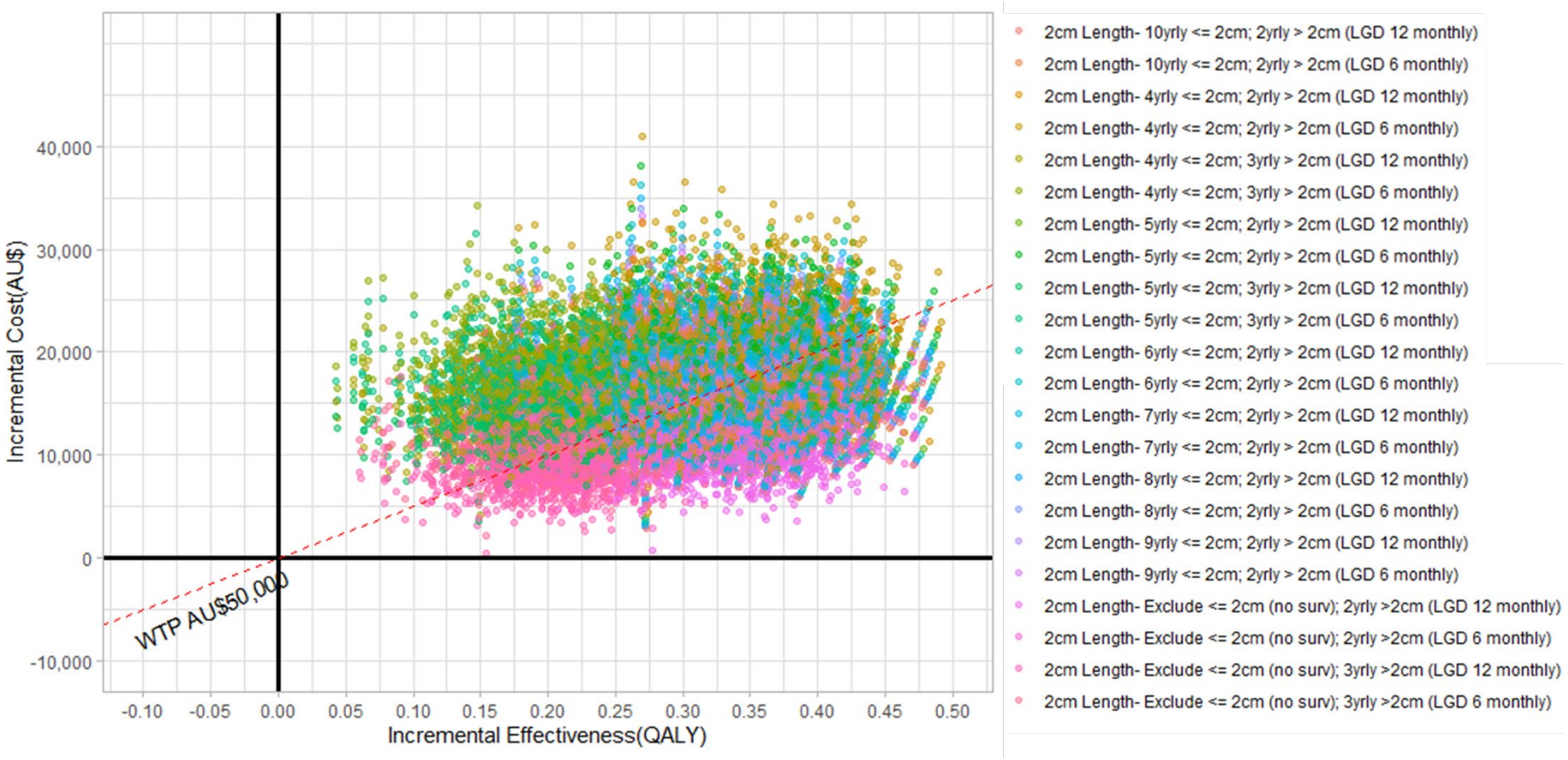
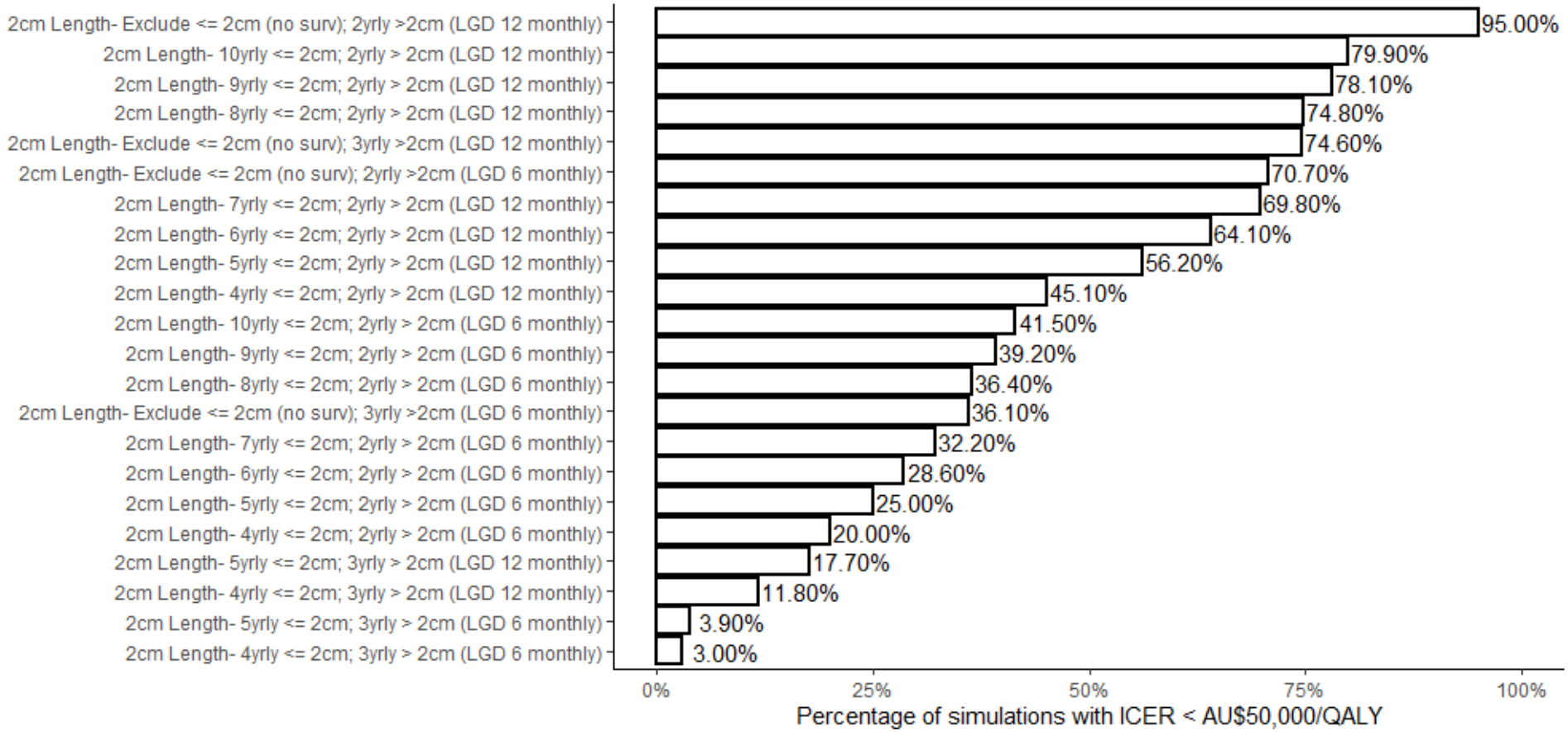
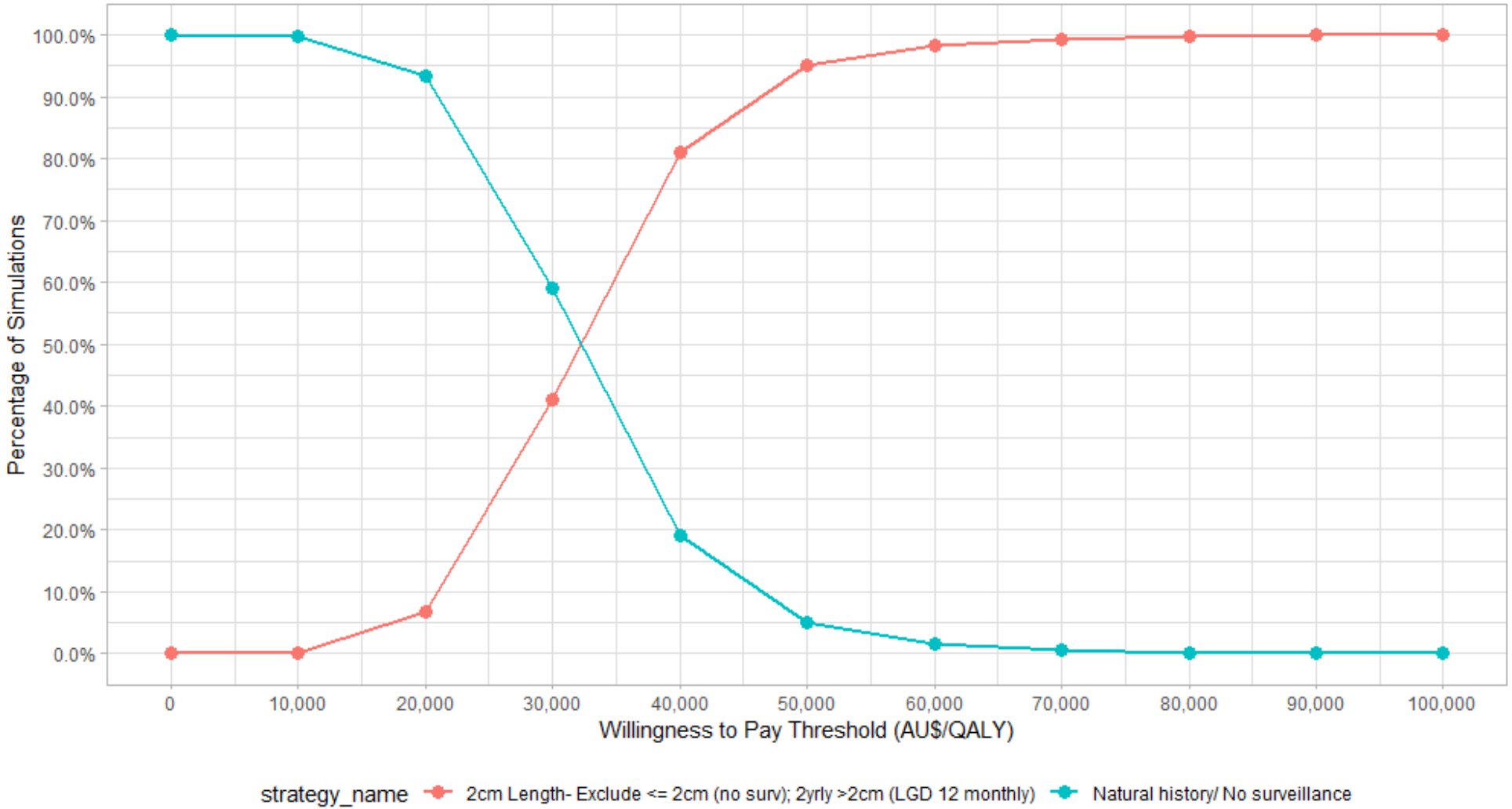


Figure 53. Probabilistic sensitivity analysis results showing Barrett's oesophagus segment length-based (2 cm threshold) endoscopic surveillance strategies with incremental cost-effectiveness ratio (ICER) of less than willingness-to-pay threshold (WTP) of AU$50,000/QALY



*ICER values were calculated using base strategy- Natural history/No surveillance

Figure 54. Cost-effectiveness acceptability curve of Barrett's oesophagus segment length based (2 cm threshold) risk-stratified strategies showing percent of simulations each strategy was cost-effective at willingness to pay thresholds between 0-AU$100,000/WTP



Reduction of surveillance frequency of short segment Barrett's oesophagus (3 cm threshold)

A set of 22 strategies were generated exactly as the previous section but with one variation. The threshold for Barrett's oesophagus segment length was set at 3 cm. This meant a subgroup of patients between 2-3 cm previously assigned to the high-risk group would now be included in the low-risk subgroup.

6.3.1.9 Base parameter conditions

4 out of 22 endoscopic surveillance strategies were found to be cost-effective under the willingness to pay threshold of AU$50,000/QALY (Table 30). The endoscopic surveillance strategy with the lowest ICER value was [0 yearly SSBE (<3 cm); 2 yearly LSBE; LGD 12 monthly], with a total cost AU$13,580 (incremental AU$6,835) and 24.439 QALYs (incremental 0.219 QALYs) resulting in an ICER AU$31,163/QALY. Excluding the low risk (short segment) subgroup from surveillance, while performing 2-yearly endoscopies for non-dysplastic Barrett's oesophagus for the high risk (long segment) subgroup and 12-monthly endoscopies for low grade dysplasia allowed an 79.9% reduction in total number of endoscopies performed (compared to 2 yearly endoscopies for all non-dysplasia and 6-monthly for low-grade dysplasia in aggregate group) (shown in Table 31). 6.9% of the total cohort progressed to oesophageal adenocarcinoma; 4.7% were detected through surveillance and were amenable to endoscopic treatment (68% of all cancers), while 2.2% of the total cohort progressed to symptomatic oesophageal adenocarcinoma (32% of all cancers).

The second lowest ICER value was generated by the endoscopic surveillance strategy [0 yearly SSBE (<3 cm); 2 yearly LSBE; LGD 6 monthly]. This is similar to the strategy discussed above but with 6-monthly endoscopies for a diagnosis of low grade dysplasia. This difference resulted in a total cost per cohort of AU$15,531 (incremental AU$8,787) but had similar QALYs ~ 24.439 (incremental 0.219) resulting in an ICER of AU$40,060/QALY that was considered cost-effective. Increasing surveillance intervals for low grade dysplasia reduced the percentage of endoscopies performed to 77.6%, which is only 2.3% more endoscopies compared to its (12-monthly LGD) counterpart.

The endoscopic surveillance strategy with the highest QALYs was, expectedly, had the highest frequency of endoscopic examinations [4 yearly SSBE (<3 cm); 2 yearly LSBE; LGD 6 monthly] with 24.442 QALYs (incremental 0.223 QALYs). This had the highest total cost of this group of strategies at AU$24,076 (incremental AU$17,332) resulting in an ICER of AU$77,861/QALY, which was not considered to be cost-effective. 6.1% of the total cohort progressed to oesophageal adenocarcinoma, with 85% of them being detected through surveillance (5.2% of total cohort) and 15% progressing to symptomatic cancer (0.9% of total

cohort). This strategy also had the lowest death related to cancers at 54.1% while managing to reduce ~70% of endoscopies performed (compared to 2 yearly endoscopies for all non-dysplasia and 6-monthly for low-grade dysplasia in aggregate group).

Only two strategies accrued lower total costs per cohort compared to [0 yearly SSBE (<3 cm); 2 yearly LSBE; LGD 12 monthly]. These were [0 yearly SSBE (<3 cm); 3 yearly LSBE; LGD 12 monthly] and [0 yearly SSBE (<3 cm); 3 yearly LSBE; LGD 6 monthly] at AU$12,009 (incremental AU$5,264) and AU$13,399/QALY (incremental AU$6,654) respectively. This was primarily attributed to a 91.7% and 90.0% reduction in endoscopic examinations performed, for the above-mentioned strategies respectively. However, this led to 7.2% of the total cohort progressing to oesophageal adenocarcinoma, of which only 43% were detected through surveillance (3.1% of total cohort) and 57% had progressed to symptomatic oesophageal adenocarcinoma (4.1% of total cohort). The endoscopic surveillance strategy [0 yearly SSBE (<3 cm); 3 yearly LSBE; LGD 12 monthly] had an ICER of AU$118,642 while [0 yearly SSBE (<3 cm); 3 yearly LSBE; LGD 6 monthly] had an ICER of AU$149,968, both of which were well above the willingness to pay threshold of AU$50,000/QALY.

Table 27. Cost and QALY rankings table: Segment length-based risk-stratified reduction in frequency of endoscopic surveillance (3 cm threshold). Incremental cost-effectiveness ratio values are calculated using costs and utilities from "Natural history."

Strategy	Cost		QALY		ICER	NMB
Natural history/ No surveillance	$6,745	$0	24.219	0.000	$0	$1,204,219
0 yearly SSBE (<3 cm); 2 yearly LSBE (>=3 cm) (LGD 12 monthly)	$13,580	$6,835	24.439	0.219	**$31,163**	$1,208,351
0 yearly SSBE (<3 cm); 2 yearly LSBE (>=3 cm) (LGD 6 monthly)	$15,531	$8,787	24.439	0.219	**$40,060**	$1,206,399
10 yearly SSBE (<3 cm); 2 yearly LSBE (>=3 cm) (LGD 12 monthly)	$17,150	$10,405	24.437	0.217	**$47,855**	$1,204,685
9 yearly SSBE (<3 cm); 2 yearly LSBE (>=3 cm) (LGD 12 monthly)	$17,463	$10,719	24.437	0.217	**$49,288**	$1,204,374
8 yearly SSBE (<3 cm); 2 yearly LSBE (>=3 cm) (LGD 12 monthly)	$17,873	$11,129	24.437	0.218	$51,131	$1,203,973
7 yearly SSBE (<3 cm); 2 yearly LSBE (>=3 cm) (LGD 12 monthly)	$18,418	$11,673	24.437	0.218	$53,528	$1,203,450
6 yearly SSBE (<3 cm); 2 yearly LSBE (>=3 cm) (LGD 12 monthly)	$19,150	$12,406	24.438	0.219	$56,681	$1,202,757
10 yearly SSBE (<3 cm); 2 yearly LSBE (>=3 cm) (LGD 6 monthly)	$19,183	$12,438	24.437	0.217	$57,205	$1,202,652
9 yearly SSBE (<3 cm); 2 yearly LSBE (>=3 cm) (LGD 6 monthly)	$19,521	$12,776	24.437	0.217	$58,750	$1,202,316
8 yearly SSBE (<3 cm); 2 yearly LSBE (>=3 cm) (LGD 6 monthly)	$19,963	$13,218	24.437	0.218	$60,731	$1,201,883
5 yearly SSBE (<3 cm); 2 yearly LSBE (>=3 cm) (LGD 12 monthly)	$20,193	$13,448	24.440	0.220	$61,057	$1,201,784
7 yearly SSBE (<3 cm); 2 yearly LSBE (>=3 cm) (LGD 6 monthly)	$20,548	$13,804	24.437	0.218	$63,299	$1,201,319
6 yearly SSBE (<3 cm); 2 yearly LSBE (>=3 cm) (LGD 6 monthly)	$21,334	$14,590	24.438	0.219	$66,660	$1,200,573
4 yearly SSBE (<3 cm); 2 yearly LSBE (>=3 cm) (LGD 12 monthly)	$21,735	$14,991	24.442	0.223	$67,344	$1,200,358
5 yearly SSBE (<3 cm); 2 yearly LSBE (>=3 cm) (LGD 6 monthly)	$22,445	$15,701	24.440	0.220	$71,284	$1,199,531
4 yearly SSBE (<3 cm); 2 yearly LSBE (>=3 cm) (LGD 6 monthly)	$24,076	$17,332	24.442	0.223	$77,861	$1,198,017
0 yearly SSBE (<3 cm); 3 yearly LSBE (>=3 cm) (LGD 12 monthly)	$12,009	$5,264	24.264	0.044	$118,642	$1,201,173
0 yearly SSBE (<3 cm); 3 yearly LSBE (>=3 cm) (LGD 6 monthly)	$13,399	$6,654	24.264	0.044	$149,968	$1,199,783
5 yearly SSBE (<3 cm); 3 yearly LSBE (>=3 cm) (LGD 12 monthly)	$18,622	$11,877	24.265	0.045	$262,239	$1,194,606
4 yearly SSBE (<3 cm); 3 yearly LSBE (>=3 cm) (LGD 12 monthly)	$20,164	$13,420	24.267	0.048	$281,716	$1,193,181
5 yearly SSBE (<3 cm); 3 yearly LSBE (>=3 cm) (LGD 6 monthly)	$20,313	$13,568	24.265	0.045	$299,580	$1,192,915
4 yearly SSBE (<3 cm); 3 yearly LSBE (>=3 cm) (LGD 6 monthly)	$21,944	$15,200	24.267	0.048	$319,078	$1,191,401

*Costs are in Australian Dollars (2020 value) per cohort of 1. Incremental cost-effectiveness ratio (**ICER**) units are AU$/QALY. Displayed in descending ICER value. **incr**- incremental; **QALY**- quality adjusted life years; **NMB**- net monetary benefit; SSBE- short segment Barrett's oesophagus; LSBE- long segment Barrett's oesophagus;

Table 28. Model outputs: Segment length-based risk-stratified reduction in frequency of endoscopic surveillance (3 cm threshold). Incremental cost-effectiveness ratio values are calculated using costs and utilities from "Natural history."

Strategy	EAC	Surv ca	Symp cancers	Cancers avoided	Cancer deaths	% endos reduced	ICER	% ca deaths
Natural history/ No surveillance	11.0%	0.0%	11.0%	0.0%	10.7%	100.0%	$0	97.7%
0 yearly SSBE (<3 cm); 2 yearly LSBE (>=3 cm) (LGD 12 monthly)	6.9%	4.7%	2.2%	4.1%	4.3%	79.9%	$31,163	62.6%
0 yearly SSBE (<3 cm); 2 yearly LSBE (>=3 cm) (LGD 6 monthly)	6.9%	4.7%	2.2%	4.1%	4.3%	77.6%	$40,060	62.6%
10 yearly SSBE (<3 cm); 2 yearly LSBE (>=3 cm) (LGD 12 monthly)	6.5%	4.9%	1.6%	4.5%	3.8%	78.1%	$47,855	58.8%
9 yearly SSBE (<3 cm); 2 yearly LSBE (>=3 cm) (LGD 12 monthly)	6.5%	5.0%	1.5%	4.5%	3.8%	77.7%	$49,288	58.2%
8 yearly SSBE (<3 cm); 2 yearly LSBE (>=3 cm) (LGD 12 monthly)	6.4%	5.0%	1.4%	4.6%	3.7%	77.1%	$51,131	57.6%
7 yearly SSBE (<3 cm); 2 yearly LSBE (>=3 cm) (LGD 12 monthly)	6.3%	5.0%	1.3%	4.7%	3.6%	76.4%	$53,528	56.9%
6 yearly SSBE (<3 cm); 2 yearly LSBE (>=3 cm) (LGD 12 monthly)	6.3%	5.1%	1.2%	4.7%	3.5%	75.5%	$56,681	56.1%
10 yearly SSBE (<3 cm); 2 yearly LSBE (>=3 cm) (LGD 6 monthly)	6.5%	4.9%	1.6%	4.5%	3.8%	75.7%	$57,205	58.8%
9 yearly SSBE (<3 cm); 2 yearly LSBE (>=3 cm) (LGD 6 monthly)	6.5%	5.0%	1.5%	4.5%	3.8%	75.2%	$58,750	58.2%
8 yearly SSBE (<3 cm); 2 yearly LSBE (>=3 cm) (LGD 6 monthly)	6.4%	5.0%	1.4%	4.6%	3.7%	74.7%	$60,731	57.6%
5 yearly SSBE (<3 cm); 2 yearly LSBE (>=3 cm) (LGD 12 monthly)	6.2%	5.1%	1.1%	4.8%	3.4%	74.2%	$61,057	55.1%
7 yearly SSBE (<3 cm); 2 yearly LSBE (>=3 cm) (LGD 6 monthly)	6.3%	5.0%	1.3%	4.7%	3.6%	73.9%	$63,299	56.9%
6 yearly SSBE (<3 cm); 2 yearly LSBE (>=3 cm) (LGD 6 monthly)	6.3%	5.1%	1.2%	4.7%	3.5%	72.9%	$66,660	56.1%
4 yearly SSBE (<3 cm); 2 yearly LSBE (>=3 cm) (LGD 12 monthly)	6.1%	5.2%	0.9%	4.9%	3.3%	72.3%	$67,344	54.1%
5 yearly SSBE (<3 cm); 2 yearly LSBE (>=3 cm) (LGD 6 monthly)	6.2%	5.1%	1.1%	4.8%	3.4%	71.5%	$71,284	55.1%
4 yearly SSBE (<3 cm); 2 yearly LSBE (>=3 cm) (LGD 6 monthly)	6.1%	5.2%	0.9%	4.9%	3.3%	69.5%	$77,861	54.1%
0 yearly SSBE (<3 cm); 3 yearly LSBE (>=3 cm) (LGD 12 monthly)	7.2%	3.1%	4.1%	3.8%	5.4%	91.7%	$118,642	74.6%
0 yearly SSBE (<3 cm); 3 yearly LSBE (>=3 cm) (LGD 6 monthly)	7.2%	3.1%	4.1%	3.8%	5.4%	90.0%	$149,968	74.6%
5 yearly SSBE (<3 cm); 3 yearly LSBE (>=3 cm) (LGD 12 monthly)	6.5%	3.5%	3.0%	4.5%	4.5%	86.1%	$262,239	68.8%
4 yearly SSBE (<3 cm); 3 yearly LSBE (>=3 cm) (LGD 12 monthly)	6.5%	3.6%	2.9%	4.5%	4.4%	84.2%	$281,716	68.0%
5 yearly SSBE (<3 cm); 3 yearly LSBE (>=3 cm) (LGD 6 monthly)	6.5%	3.5%	3.0%	4.5%	4.5%	84.0%	$299,580	68.8%
4 yearly SSBE (<3 cm); 3 yearly LSBE (>=3 cm) (LGD 6 monthly)	6.5%	3.6%	2.9%	4.5%	4.4%	82.0%	$319,078	68.0%

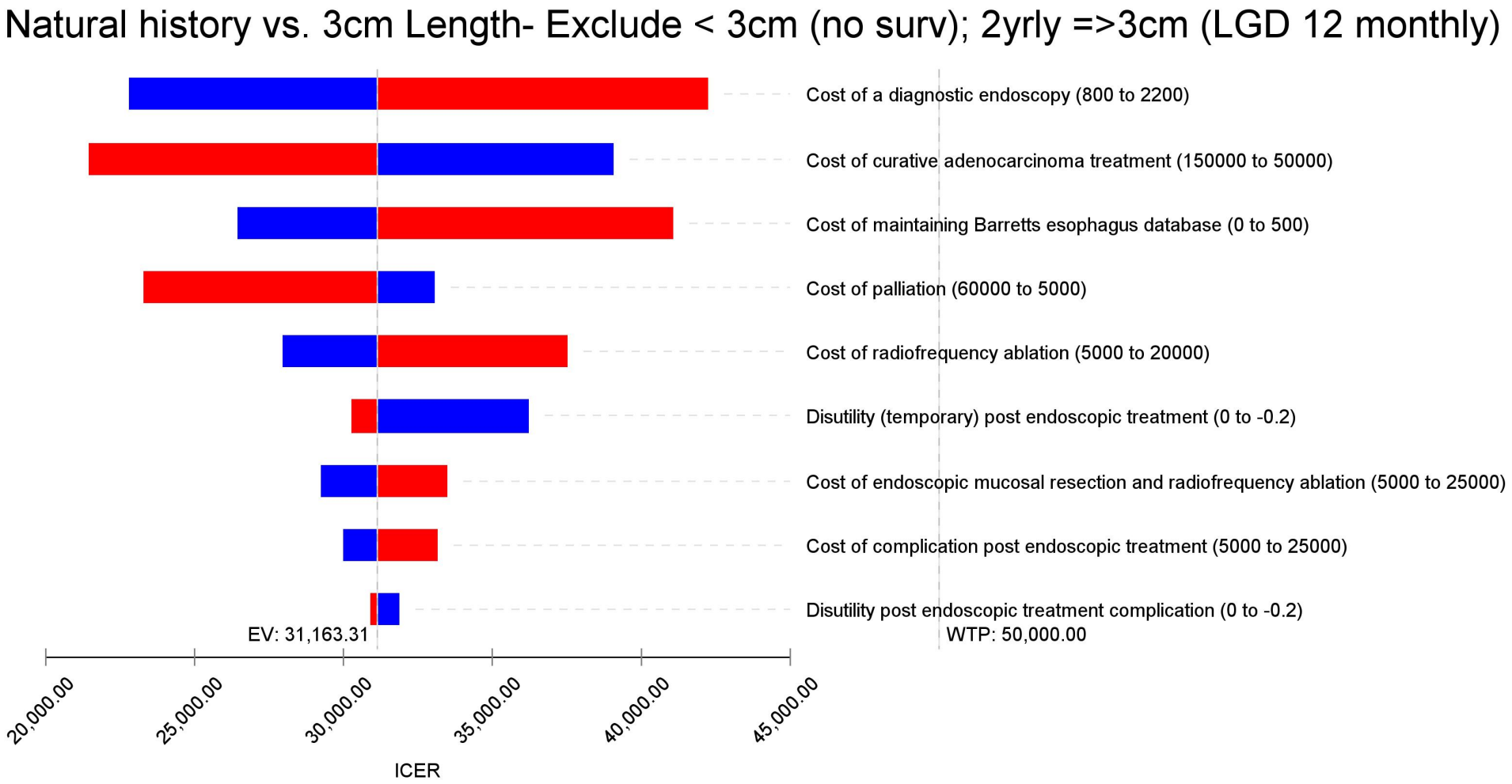
*Values as percentage of cohort developing the model outputs (per cohort of 1). **EAC**- Total % of cohort developing Oesophageal adenocarcinoma (surveillance and symptomatic combined); **Surv ca**- Surveillance detected oesophageal adenocarcinoma; **Symp ca**- presenting with symptomatic oesophageal adenocarcinoma; **% endos reduced**- refers to how many fewer endoscopies were performed compared to comparator strategy: every 2 years for non-dysplastic Barrett's oesophagus, 6mo for low grade dysplasia; **ICER**- incremental cost-effectiveness ratio; **% ca deaths**- mortality % in cohort that progressed to oesophageal adenocarcinomas. Displayed in increasing order of ICER values

6.3.1.10 One way sensitivity analysis

Results of the one way sensitivity analysis for the 4 strategies that were cost-effective under base parameters are shown below in Figure 55, Figure 56, Figure 57, and Figure 58. Similar to other strategies discussed in this chapter and previously, the key drivers identified in the one-way sensitivity analysis included costs related to endoscopic examination, treatment of oesophageal adenocarcinoma, and maintaining the database of Barrett's oesophagus patients. Even though these variables were key drivers, varying their values impacted some strategies more than others.

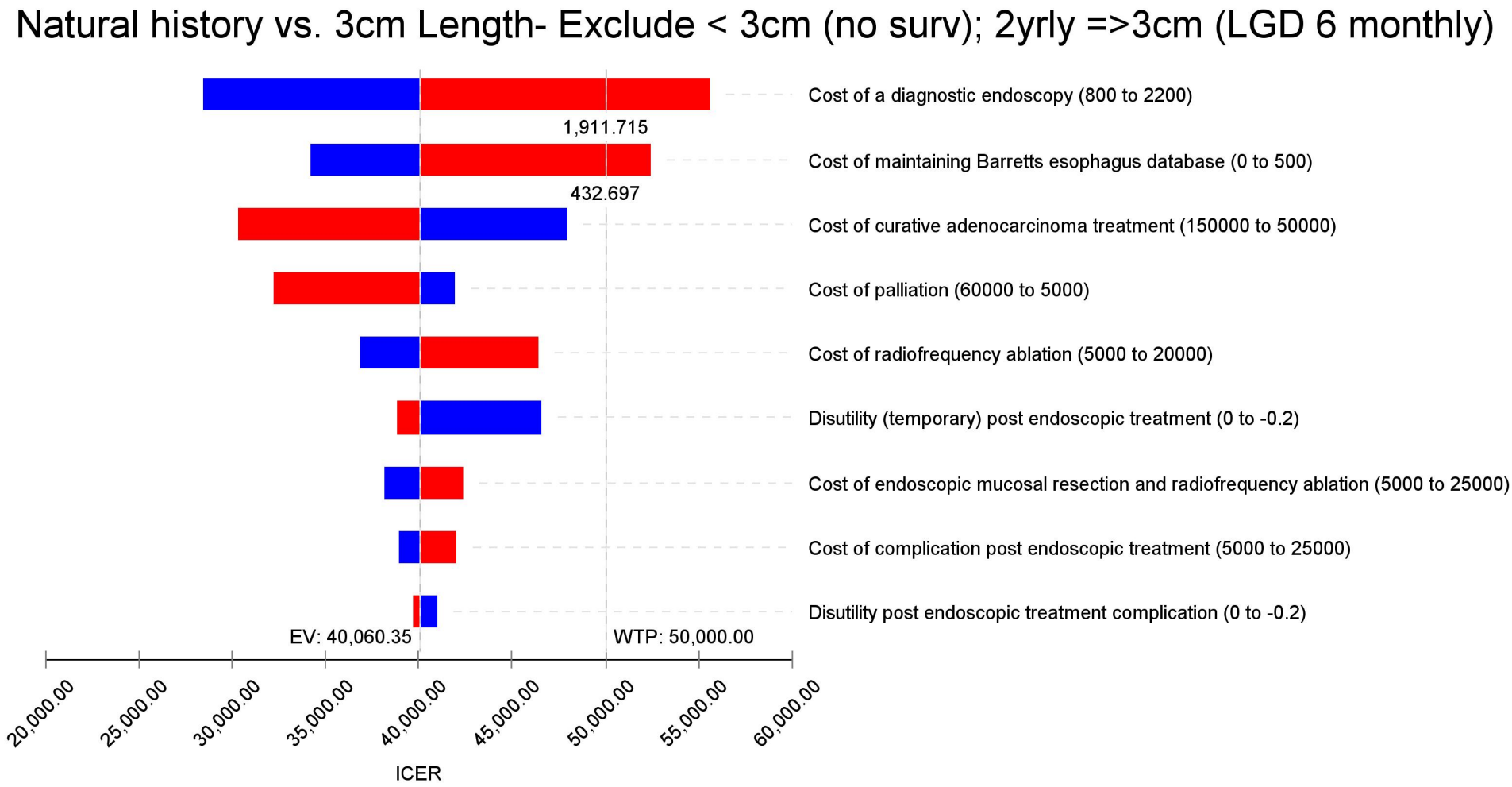
Only one endoscopic surveillance strategy [0 yearly SSBE (<3 cm); 2 yearly LSBE; LGD 12 monthly] remained cost-effective at a willingness to pay threshold of AU$50,000/QALY with variations in cost and utility values (Figure 55). Whereas a 3-4% variation in any cost and utility values increased the ICER value of the endoscopic surveillance strategy [9 yearly SSBE (<3 cm); 2 yearly LSBE; LGD 12 monthly] above the same willingness to pay threshold (Figure 58). For example, an increase of the cost of a diagnostic endoscopy from AU$1,391 to AU$1,438.8 was sufficient to result in an ICER value above AU$50,000/QALY. This was a similar trend seen in the endoscopic surveillance strategy [10 yearly SSBE (<3 cm); 2 yearly LSBE; LGD 12 monthly], but the required variation in costs and utilities was higher ~ 12-14% (Figure 57).

Figure 55. One way sensitivity analysis (Tornado diagram) for natural history (no surveillance) versus exclusion of low risk subgroup (<3 cm) from surveillance combined with 2-yearly endoscopies for non-dysplasia in high risk subgroup with 12 monthly surveillance for low grade dysplasia.



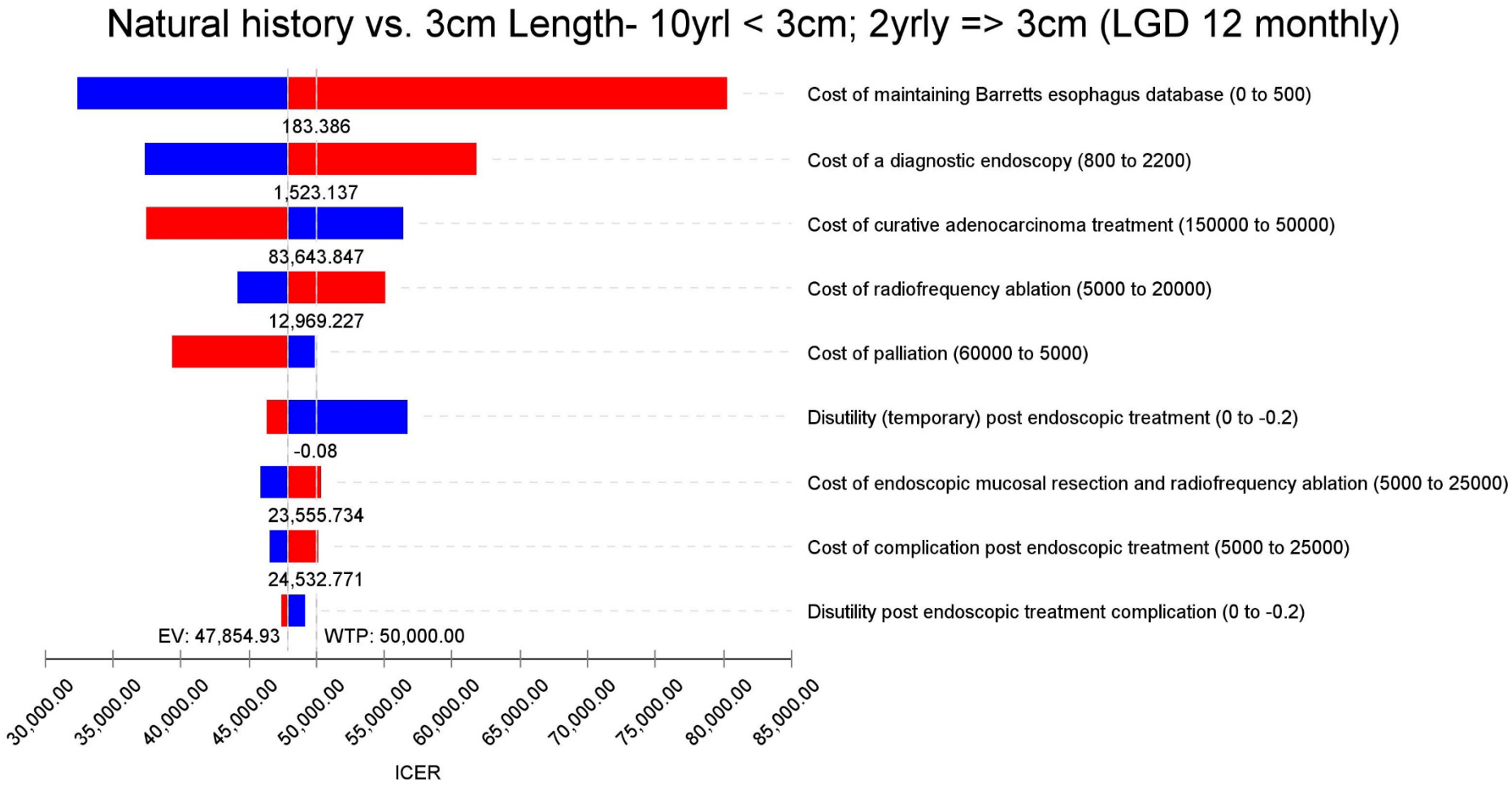
*Values in “red” indicate an increase in the value of the variable. Values in “blue” indicated decrease in variable value. Vertical dashed line indicates willingness to pay threshold (AU$50,000/QALY). ICER- incremental cost-effectiveness ratio; LGD- low grade dysplasia; EV – expected value of ICER; WTP- willingness to pay threshold.

Figure 56. One way sensitivity analysis (Tornado diagram) for natural history (no surveillance) versus exclusion of low risk subgroup (<3 cm) from surveillance combined with 2-yearly endoscopies for non-dysplasia in high risk subgroup with 6 monthly surveillance for low grade dysplasia.



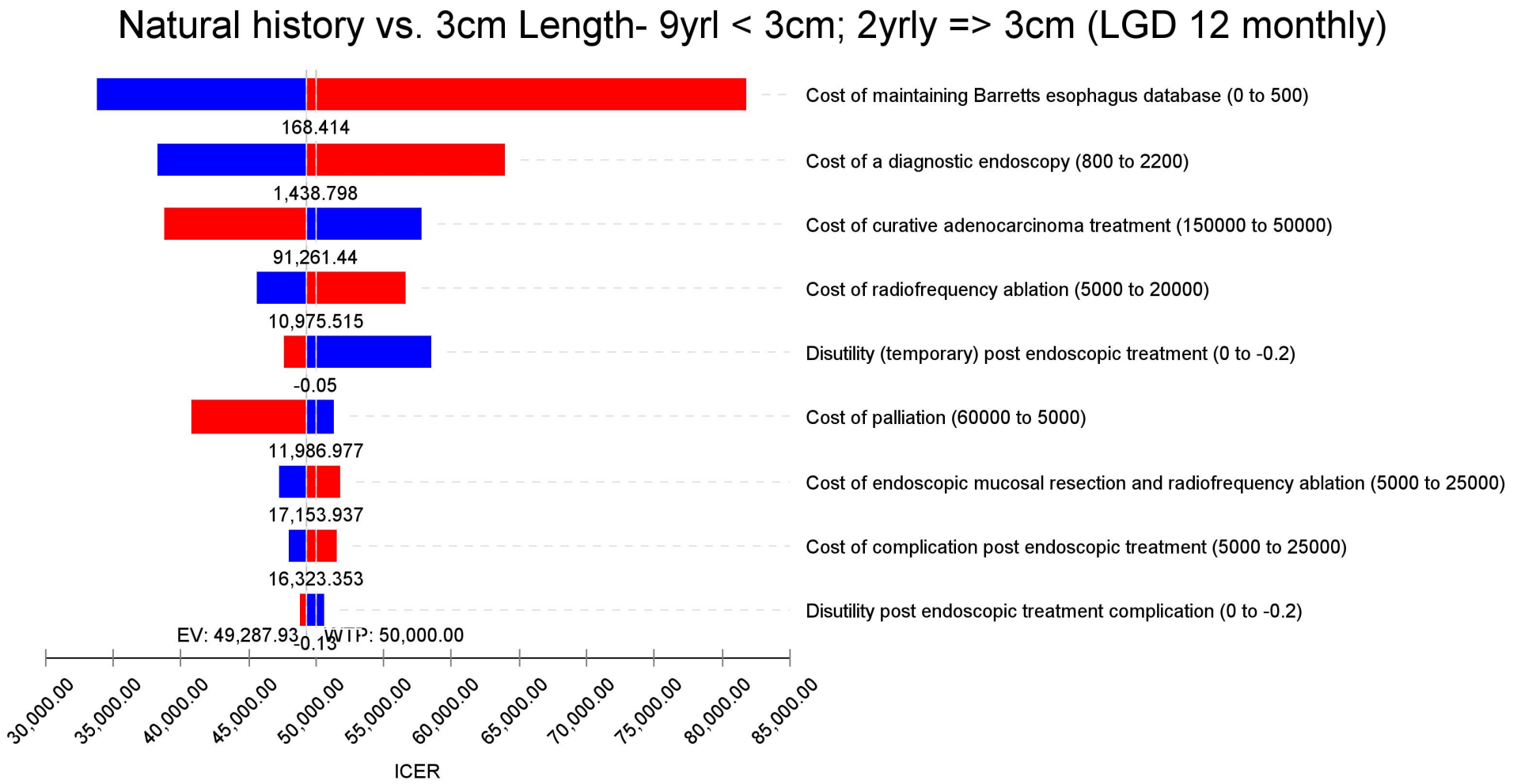
*Values in “red” indicate an increase in the value of the variable. Values in “blue” indicated decrease in variable value. Vertical dashed line indicates willingness to pay threshold (AU$50,000/QALY). ICER- incremental cost-effectiveness ratio; LGD- low grade dysplasia; EV – expected value of ICER; WTP- willingness to pay threshold.

Figure 57. One way sensitivity analysis (Tornado diagram) for natural history (no surveillance) versus 10-yearly endoscopies of low risk subgroup (<3 cm) from surveillance combined with 2-yearly endoscopies for non-dysplasia in high risk subgroup with 12 monthly surveillance for low grade dysplasia.



*Values in “red” indicate an increase in the value of the variable. Values in “blue” indicated decrease in variable value. Vertical dashed line indicates willingness to pay threshold (AU$50,000/QALY). ICER- incremental cost-effectiveness ratio; LGD- low grade dysplasia; EV – expected value of ICER; WTP- willingness to pay threshold.

Figure 58. One way sensitivity analysis (Tornado diagram) for natural history (no surveillance) versus 10-yearly endoscopies of low risk subgroup (<3 cm) from surveillance combined with 2-yearly endoscopies for non-dysplasia in high risk subgroup with 12 monthly surveillance for low grade dysplasia.



*Values in “red” indicate an increase in the value of the variable. Values in “blue” indicated decrease in variable value. Vertical dashed line indicates willingness to pay threshold (AU$50,000/QALY). ICER- incremental cost-effectiveness ratio; LGD- low grade dysplasia; EV – expected value of ICER; WTP- willingness to pay threshold.

6.3.1.11 Probabilistic sensitivity analysis

Probabilistic sensitivity analysis performed for the 22 strategies examining Barrett's oesophagus segment length (3 cm threshold) demonstrated the 4 endoscopic surveillance strategies that were cost-effective under base parameters were had ICER values above AU$50,000/QALY in more than 50% of the simulations. This is seen as an ICER scatter plot in Figure 59 with the numeric values of the percentage of the simulations provided in Figure 60.

The endoscopic surveillance strategy [0 yearly SSBE (<3 cm); 2 yearly LSBE; LGD 12 monthly] was cost-effective in nearly 90% of the simulations (Figure 60) and was undominated among this group of strategies. Cost-effectiveness acceptability curve (Figure 61) shows this endoscopic surveillance strategy was cost-effective in more than 50% of the simulations after a willingness to pay threshold of ~AU$33,000/QALY. The strategy [0 yearly SSBE (<3 cm); 2 yearly LSBE; LGD 6 monthly] was seen to be cost-effective in ~75% of the simulations at a willingness to pay threshold of AU$50,000/QALY. Strategies with surveillance more frequent than every 9 years were cost-effective in less than 50% of the simulations Figure 60.

6.3.1.12 Summary

Among the group of strategies risk-stratifying using Barrett's oesophagus segment length (3 cm threshold), it was cost-effective to exclude the low risk (short segment) subgroup from surveillance, while maintaining 2-yearly endoscopies for the high risk (long segment) subgroup. This was true for both the 6 and 12-monthly endoscopic intervals for low grade dysplasia. Performing 10-yearly or 9-yearly endoscopies for the low risk subgroup could be cost-effective under some conditions and was only seen to be cost-effective in 52-56% of the simulations.

6.4 Combined summary of 85 strategies

Results of probabilistic sensitivity analysis and Monte-Carlo simulations combining all endoscopic surveillance strategies aimed at reducing the frequency through a risk-stratified or non-risk stratified approach are shown as a cost-effectiveness acceptability curve in Figure 62. This included 85 endoscopic surveillance strategies discussed in this chapter and Chapter 5. Excluding any absolutely dominated or extendedly dominated strategies (as defined in Chapter 1.3.6), only three strategies were seen to be cost-effective namely: No surveillance for aggregate group, [0 yearly SSBE (≤2 cm); 2 yearly LSBE; LGD 12 monthly], and [0 yearly SSBE (<3 cm); 2 yearly LSBE; LGD 12 monthly]. At a willingness to pay threshold of AU$50,000/QALY, [0 yearly SSBE (≤2 cm); 2 yearly LSBE; LGD 12 monthly] was the most cost-effective strategy in 93.7% of the simulations.

Figure 59. Scatter plot on incremental cost-effectiveness plane for Barrett's oesophagus segment length-based (3 cm threshold) risk-stratified reduction in frequency of endoscopic surveillance

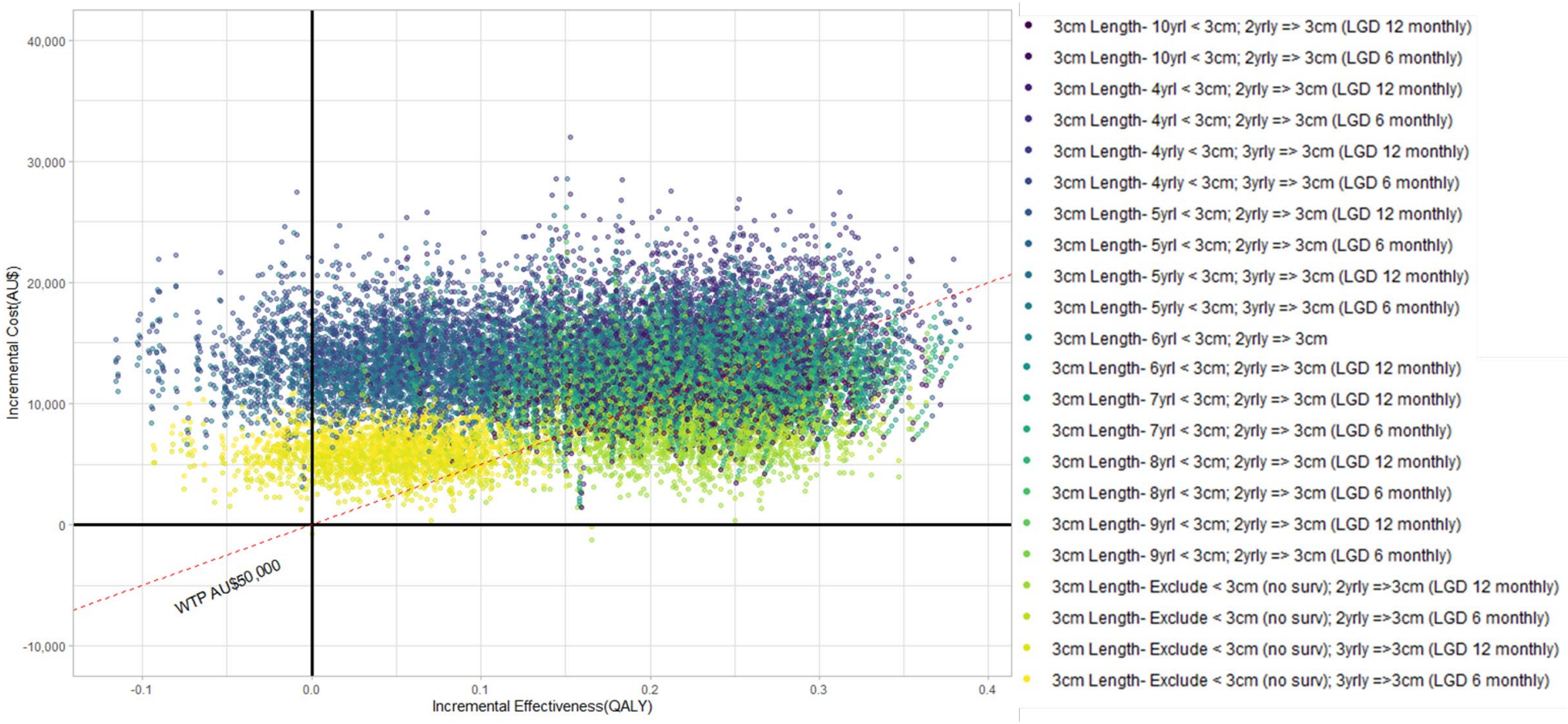
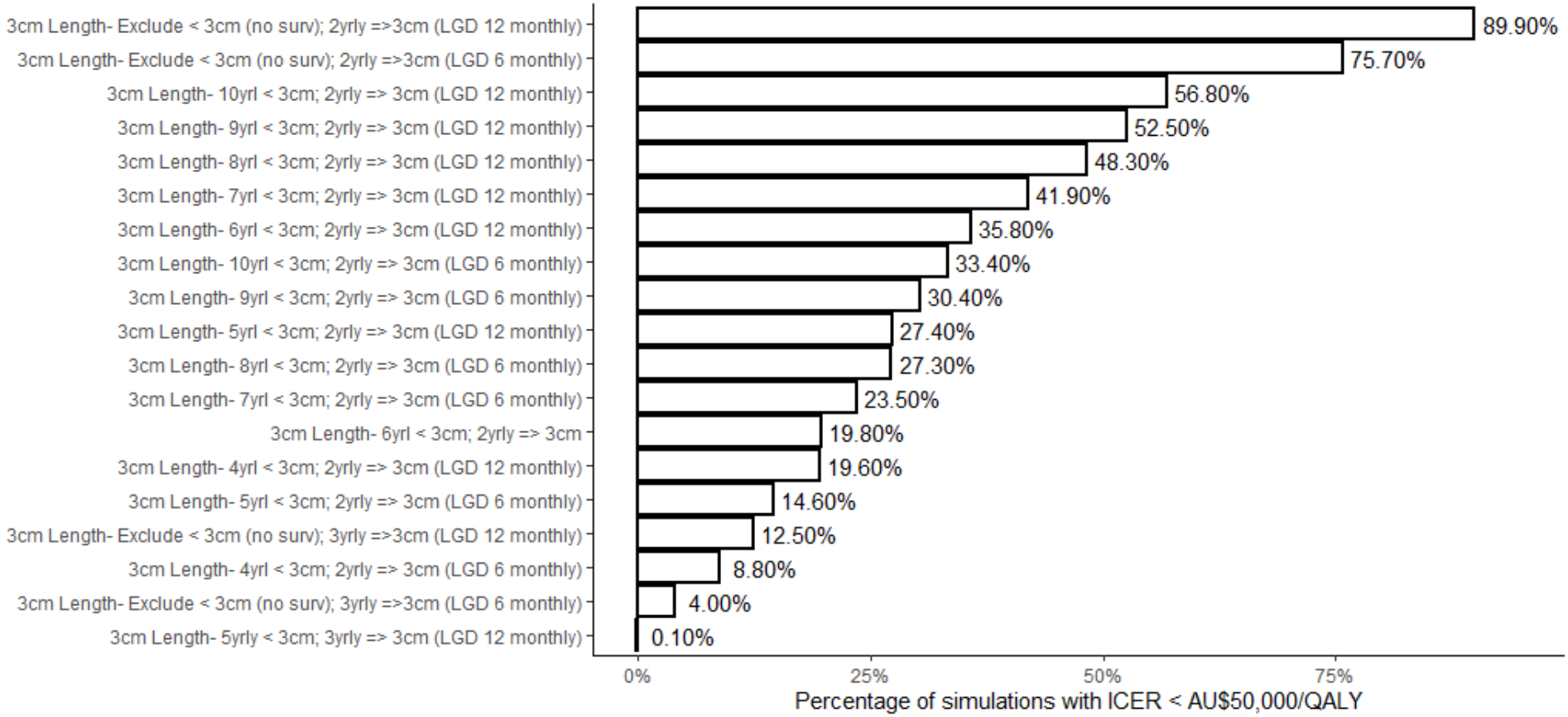


Figure 60. Probabilistic sensitivity analysis results showing Barrett's oesophagus segment length-based (3 cm threshold) endoscopic surveillance strategies with incremental cost-effectiveness ratio (ICER) of less than willingness-to-pay threshold (WTP) of AU$50,000/QALY



*ICER values were calculated using base strategy- Natural history/No surveillance

Figure 61. Cost-effectiveness acceptability curve of Barrett's oesophagus segment length based (3 cm threshold) risk-stratified strategies showing percent of simulations each strategy was cost-effective at willingness to pay thresholds between 0-AU$100,000/WTP

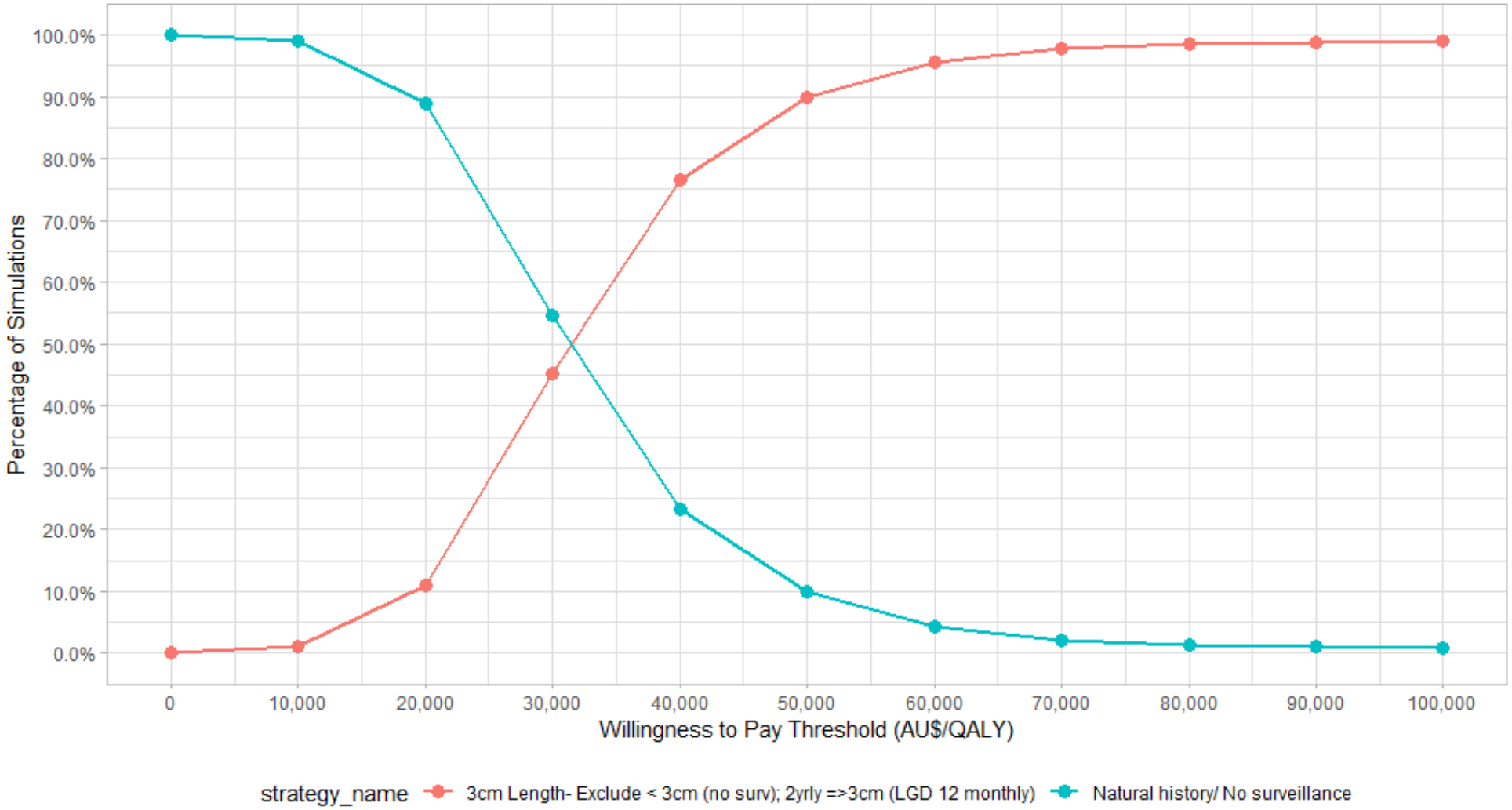


Figure 62. Cost-effectiveness acceptability curve of all risk-stratified and non-risk stratified strategies showing percent of simulations each strategy was cost-effective at willingness to pay thresholds between 0-AU$100,000/WTP

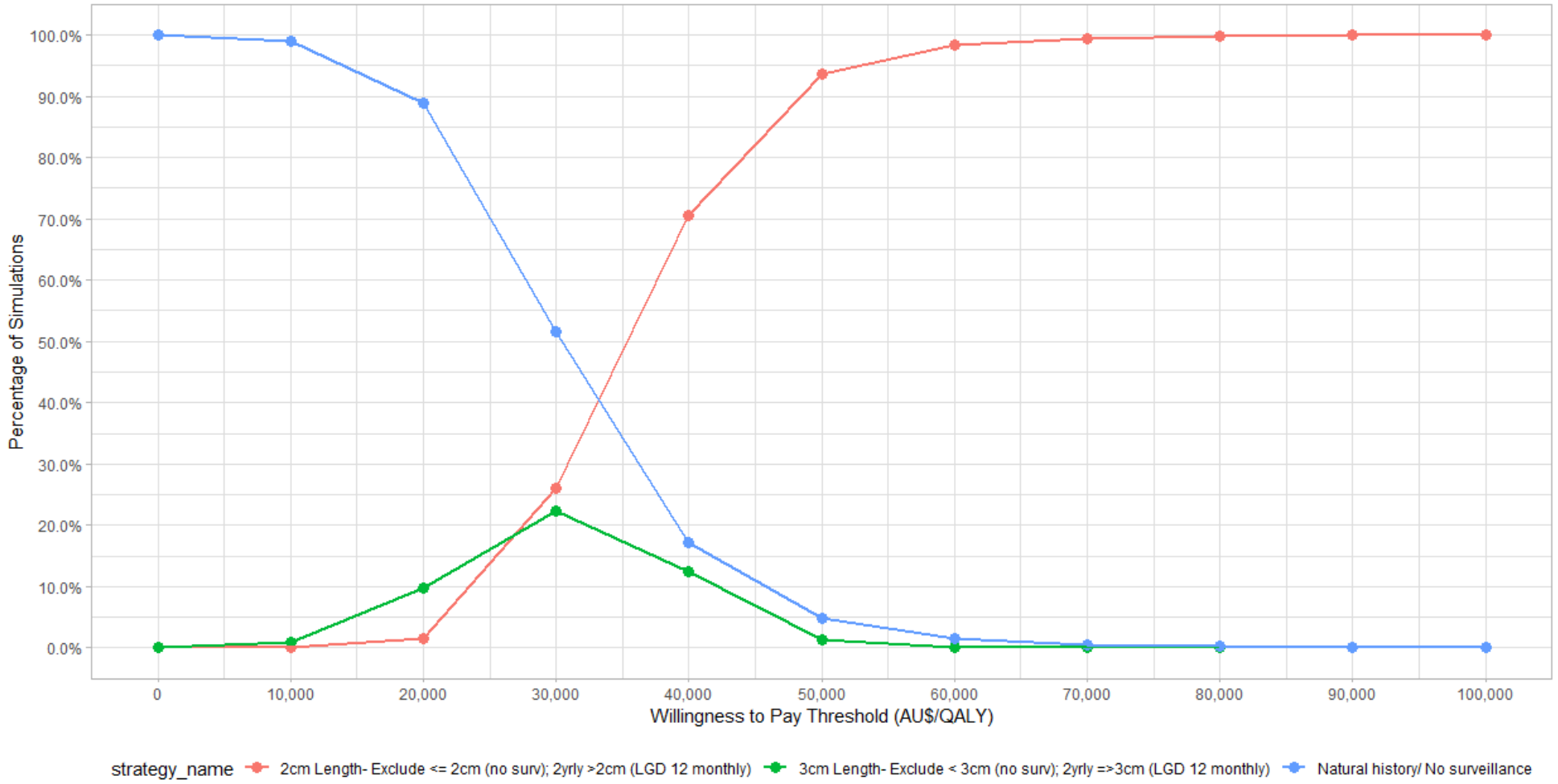
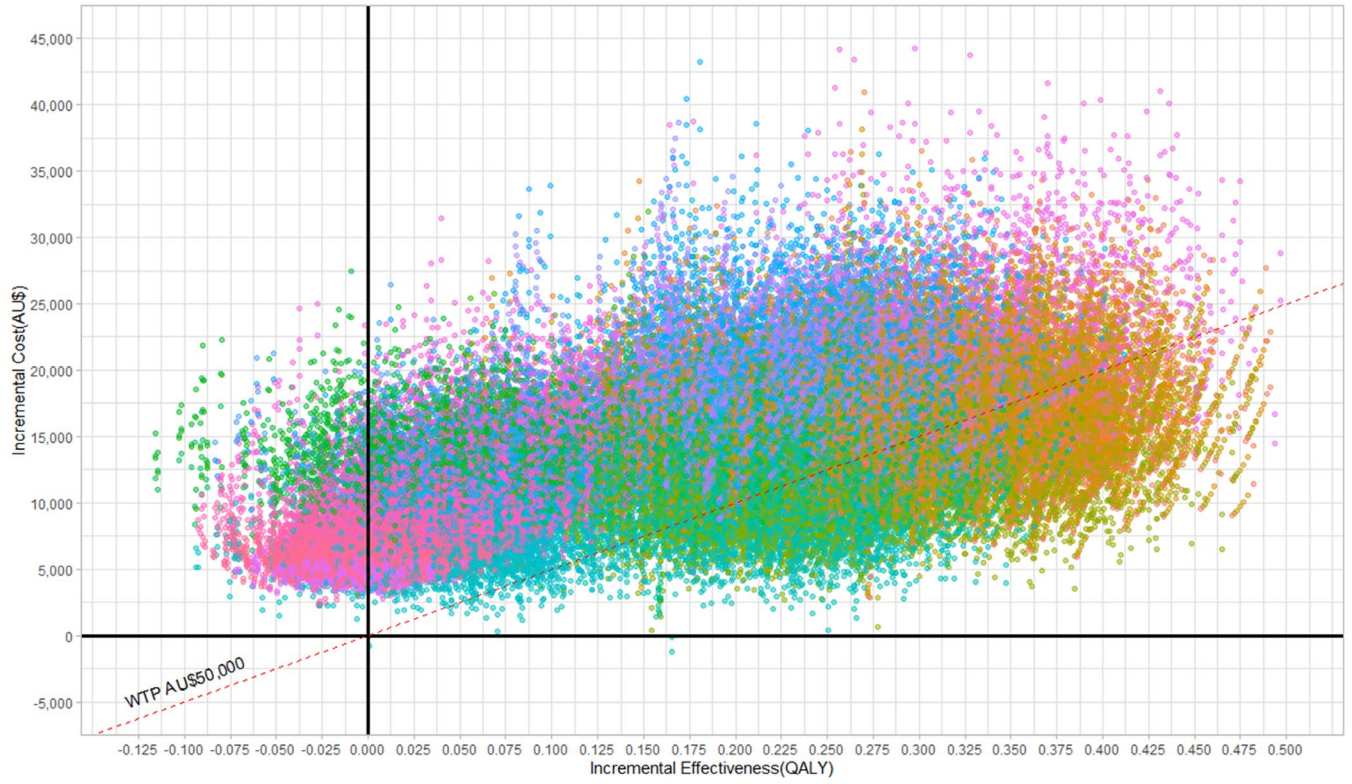


Figure 63. Scatter plot on incremental cost-effectiveness plane for 85 strategies aimed at reducing frequency of endoscopic surveillance



6.5 Discussion

In this chapter, two risk factors, namely gender and two thresholds of Barrett's oesophagus segment length (2 cm and 3 cm) were used to define low and high risk individuals. Endoscopic surveillance strategies for Barrett's oesophagus were altered systematically for low and high risk subgroups to find the optimal cost-effective method of surveillance. Segment length was a more sensitive determinant of risk of progression from non-dysplastic Barrett's oesophagus to oesophageal adenocarcinoma, as none of the gender-based surveillance strategies were seen to be cost-effective. Between the two length-based thresholds, there were more cost-effective surveillance strategies utilising the 2 cm threshold (9 out of 22 strategies) than the 3 cm threshold (4 out of 22 strategies).

Combining 85 strategies reducing the frequency of endoscopic surveillance, either using a risk-stratified or non-risk stratified approach, the endoscopic surveillance strategy with the highest probability of being cost-effective is one that excluded the short segment Barrett's oesophagus ≤ 2 cm (low risk) subgroup from all endoscopic surveillance, while performing 2-yearly endoscopies for long segment non-dysplastic Barrett's oesophagus >2 cm with 12-monthly endoscopies for low-grade dysplasia.

The scatter plot shown in Figure 63 demonstrates what each strategy achieved with each simulation in comparison to no surveillance (natural history). If the 2-yearly endoscopic surveillance for non-dysplastic Barrett's oesophagus is considered as the standard of care, the two ways of improving cost-effectiveness of surveillance are 1) reduction of costs and/or 2) improving outcomes (QALYs). Both these options are difficult to achieve, as health care related costs are likely to rise rather than fall. And health utility values improve with fewer invasive procedures and less complications, both scenarios which require earlier detection and treatment of high grade dysplasia or cancer.

Another way to look at what contributes to reduced health utility values is to imagine a scenario where the probability of progression to any cancer or disease is 0%, and the starting population is comprised of healthy 50-year old mixed gender individuals for a time-horizon of 35 years. Assuming all-cause mortality, the maximum utility value accrued would be 25.389 QALYs. What diminishes this QALY value in the presented model is disease progression to oesophageal adenocarcinoma, early mortality, disutility associated with treatments and complications of treatments. Progression to surveillance detected oesophageal adenocarcinoma generated a higher utility value than symptomatic oesophageal adenocarcinoma. This is firstly because of low mortality in cancer amenable to endoscopic resection (minimal risk of nodal spread and lower risk of post-operative mortality) and secondly lower morbidity associated with endoscopic treatments.

Somewhat diametrically, whereas utility values were predominantly influenced by the small fraction of the cohort that progressed to oesophageal adenocarcinoma costs were primarily driven by the larger group of individuals with non-dysplastic Barrett's esophagus. This was evidenced by the results of the one-way analysis, where many of the surveillance strategies revealed the two key drivers of the model were costs related to diagnostic endoscopy and biopsy and maintenance of a database of individuals (for follow up). It was unsurprising that minimizing the total costs of a strategy was directly correlated with the frequency of endoscopic surveillance and the percentage of cohort constituting each risk subgroup.

For instance, a strategy that excluded the low-risk subgroup of short-segment Barrett's esophagus (3 cm threshold), which accounted for 75% of the cohort, resulted in one of the lowest total costs - AU$13,850- [0 yearly SSBE (<3 cm); 2 yearly LSBE; LGD 12 monthly]. A similar strategy excluding the gender-based low risk subgroup, which accounted for 35% of the starting cohort [Female no surveillance; male 2 yearly; LGD 12 monthly] resulted in a total cost of AU$21,657. This further supports the notion that endoscopic examinations contribute significantly to costs, as the reduction in endoscopic examinations was 79.9% when excluding the short-segment subgroup compared to 38.1% in the strategy excluding the female subgroup.

Reducing the frequency of endoscopic examinations in an extremely low-risk subgroup led to a decrease in the number of procedures performed. Although only a small percentage of the cohort eventually developed symptomatic esophageal adenocarcinoma, this was still a much smaller percentage compared to the absence of risk stratification. On the other hand, increasing the frequency of endoscopic surveillance in the same low-risk subgroup would always result in improved utility values (QALYs) because even a smaller percentage of the cohort would progress to esophageal adenocarcinoma, and surveillance would likely detect those who do progress. The magnitude of the difference in utility values between various surveillance frequencies depended on the discriminative power of the risk factor or risk stratifier used.

In an ideal situation, the risk-stratification would distinguish with 100% accuracy the entire fraction of cohort that will develop oesophageal adenocarcinoma and allocate them to the high risk group, while the low risk subgroup could be excluded from surveillance entirely. No such tools exist to identify these individuals with 100% accuracy, but male gender and long segments of Barrett’s oesophagus have been linked to greater progression. In the second instance, endoscopic measurement of Barrett’s oesophagus segment length was used to define short segment (low risk) and long segment (high risk) subgroups. Measuring the length of Barrett's segment poses challenges for proceduralists and is often estimated based on notches on the scope, which are

spaced 5 cm apart. Therefore, in our study, we utilized two commonly used thresholds (2 cm and 3 cm) to create subgroups within the overall population of individuals with non-dysplastic Barrett's esophagus. These thresholds are most commonly reported in the literature.

We developed 22 surveillance strategies for each group by varying the frequency of endoscopic surveillance for non-dysplastic Barrett's esophagus (ranging from 4 to 10 years or no surveillance) in the short segment subgroup, maintaining 2-3 year intervals in the long segment subgroup, and 6-12 month intervals for low-grade dysplasia. While we identified several cost-effective surveillance strategies for both thresholds, it became clear that using the 2 cm threshold was more advantageous. This was initially puzzling because we expected the high-risk subgroup with long segment Barrett's esophagus (≥ 3 cm) to perform better at improving cost-effectiveness since they were at a higher risk of progressing to esophageal adenocarcinoma. However, upon closer examination, two reasons emerged. First, the long-segment subgroup defined by the 2 cm threshold included a higher number of individuals who would progress to cancer compared to the 3 cm threshold. Second, the short-segment subgroup defined by the 2 cm threshold had fewer individuals who would progress, meaning that reducing endoscopic surveillance did not result in as many cases of symptomatic esophageal adenocarcinoma. To elaborate further, the short segment subgroup (3 cm threshold) constituted 75% of the starting cohort, while the remaining 25% had long segment Barrett's esophagus. Reducing endoscopic examinations in the 75% subgroup increased the number and percentage of individuals presenting with symptomatic esophageal adenocarcinoma. Conversely, the short segment subgroup defined as ≤ 2 cm constituted 62.5% of the cohort, so reducing endoscopic examinations in this subgroup resulted in fewer cases of oesophageal adenocarcinoma presenting with symptoms. Additionally, the risk of progression to esophageal adenocarcinoma was lower in individuals with less than 2 cm of visible Barrett's esophagus compared to those with less than 3 cm. Thus, reducing the frequency of surveillance in the lower-risk subgroups was more cost-effective.

On the other hand, gender-based risk-stratified strategies were not seen to be cost-effective for the same syllogism. Even though the female subgroup had lower risk of progression from Barrett’s oesophagus to oesophageal adenocarcinoma, it only constituted ~35% of the cohort (compared to 62.5% or 75% in 2cm or 3cm threshold subgroups). The male subgroup made up the rest of the 65% of the cohort. Reduction in frequency of surveillance in the female subgroup, thus, had a diminished effect on reduction of costs and was further marred by attrition of utility due to progression of Barrett’s oesophagus to symptomatic oesophageal adenocarcinoma.

Within the group of strategies that reduced frequency of endoscopic surveillance in short segment Barrett’s oesophagus (2 cm), several strategies were seen to be cost-effective. It was important to comprehensively test as many clinically relevant permutations of intervals to ensure

the optimally cost-effective endoscopic surveillance strategy can be designed for each risk subgroup. From a purely numeric point of view, the strategy marked as [0 yearly SSBE (≤2 cm); 2 yearly LSBE; LGD 12 monthly] was the most cost-effective with the lowest ICER value, highest net monetary benefit, and highest percentage of cost-effective simulations among 85 strategies. However, it still resulted in 1.8% of the cohort progressing to symptomatic oesophageal adenocarcinoma. Other cost-effective strategies such as [5 yearly SSBE (≤2 cm); 2 yearly LSBE; LGD 12 monthly] were also cost-effective under the willingness to pay threshold but resulted in 1% of the cohort progressing to symptomatic oesophageal adenocarcinoma, with the caveat that it was uncertainty analysis (probabilistic) showed it was cost-effective in just over 50% of the simulations. The questions to be answered are, what percentage of progression to symptomatic oesophageal adenocarcinoma is acceptable, and what are the factors surrounding the acceptability of that risk.

6.6 Conclusion

Several surveillance strategies were identified, which reduced the frequency of endoscopic surveillance in low and/or high risk subgroups, which led to decreased costs but also diminished utility values. The degree to which determinants of costs and utility values were affected depended on the risk of progression from Barrett's oesophagus to oesophageal adenocarcinoma in the subgroup and the number of endoscopies performed in that subgroup. The strategy [0 yearly SSBE (≤2 cm); 2 yearly LSBE; LGD 12 monthly] was the undominated strategy which achieved cost-effectiveness in 93.7% of the simulations, when compared to 84 other strategies. The next chapter will explore whether a Barrett's oesophagus segment length-based approach can be applied in conjunction with endoscopic treatment of low grade dysplasia with radiofrequency ablation.

7 CHAPTER 7- COST EFFECTIVENESS OF RADIOFREQUENCY ABLATION OF LOW-GRADE DYSPLASIA COMBINED WITH PREFERENTIAL SURVEILLANCE OF LONG SEGMENT BARRETT'S OESOPHAGUS

7.1 Background

Results of the previous chapter (Chapter 6) indicated that maximum length of the endoscopically visible salmon coloured mucosa is a useful variable for discriminating between Barrett's individuals with low (short segment) and high risk (long segment) of progression to oesophageal adenocarcinoma. Various intervals of endoscopic surveillance with reduced frequency were cost-effective for short segment Barrett's oesophagus could afford to undergo fewer endoscopic examinations. This was primarily due to two factors: 1) the low probability of progression to oesophageal adenocarcinoma in short segment Barrett's oesophagus and 2) high prevalence of individuals with short segment in a cohort of Barrett's oesophagus in the surveillance programs. This was complemented by a high probability of progression to oesophageal adenocarcinoma in long segment Barrett's oesophagus who make up a smaller percentage of individuals in surveillance programs. Thus, it was cost-effective to reduce endoscopic surveillance in the large low-risk subgroup while maintaining a 2-yearly endoscopic surveillance frequency in the smaller high risk cohort.

Contrastingly reduction in frequency of surveillance in the female subgroup did not prove to be cost-effective because 1) the difference in risk of progression from Barrett's oesophagus to oesophageal adenocarcinoma was not high enough to warrant reduced endoscopic surveillance and 2) female subgroup constituted a small percentage of surveillance programs, which did not reduce the overall number of endoscopies compared to risk-stratified surveillance frequency reduction with segment length.

Endoscopic treatment with radiofrequency ablation of low grade dysplasia has been controversial for a number of reasons(217). Features relating to low grade dysplasia on histopathological analysis can be present during episodes of oesophagitis. Not all centres performing endoscopic surveillance have expert gastrointestinal pathologists on staff, leading to inconsistent overdiagnosis or underdiagnosis of low grade dysplasia. Even when present, there is considerable interobserver variability between expert pathologists when diagnosing low grade dysplasia in Barrett's oesophagus. Current recommendations from medical societies are to repeat the endoscopy after 3-6 months to confirmation of low grade dysplasia, but these are recent and may not have been adopted globally. Two aspects are definite: 1) presence of low grade dysplasia in Barrett's oesophagus is an independent risk factor for increased progression to oesophageal adenocarcinoma and 2) endoscopic treatment with radiofrequency ablation of low grade dysplasia is highly effective in reducing progression to oesophageal adenocarcinoma(203, 206).

Results of treating low grade dysplasia with endoscopic radiofrequency ablation for the aggregate group were discussed in Chapter 5. Surprisingly, reduced frequency of surveillance for the aggregate group combined with endoscopic treatment of low grade dysplasia was not cost

effective, but somewhat counterintuitively 2-yearly endoscopic surveillance combined with endoscopic ablation was seen to be cost-effective. It was postulated that non-discriminant reduction of endoscopic surveillance allowed individuals with Barrett's oesophagus to progress undetected to symptomatic oesophageal adenocarcinoma, therefore diminishing the effectiveness (QALYs) of this management strategy. Ablation of low grade dysplasia in all Barrett's oesophagus individuals ensured improved overall outcomes at the proposed costs.

It is conceivable then that treatment of low grade dysplasia would also be cost-effective for a high risk subgroup such as long segment Barrett's oesophagus. However, knowing that low grade dysplasia in an independent risk factor of progression to adenocarcinoma, it would be unethical to offer treatment only to a subgroup of individuals, even if they encompass high risk features. Surveillance strategies presented in this chapter combine results from the previous chapter (Chapter 6) to devise new surveillance management strategies by 1) reducing endoscopic surveillance frequency in short segment Barrett's oesophagus, 2) maintaining 2-3 yearly endoscopic surveillance in long segment Barrett's oesophagus, 3) and incorporating treatment of low grade dysplasia when detected through endoscopy. The aim was to find the optimal combination of endoscopic surveillance frequency between short and long segment Barrett's oesophagus when treating low grade dysplasia with endoscopic ablation.

7.2 Results

Ablate Length 2 cm threshold

7.2.1.1 Base parameter conditions

14 strategies testing cost-effectiveness of low grade dysplasia ablation with risk-stratified endoscopic surveillance based on endoscopically visible length of Barrett's oesophagus were developed. Endoscopic surveillance for non-dysplastic short segment Barrett's oesophagus was varied from 5-10 years (and including no surveillance), and 2-3 years for long segment Barrett's oesophagus. Under base parameter conditions, all 14 surveillance strategies were found to be cost-effective under the willingness to pay threshold (AU$50,000/QALY). The results of total and incremental costs, QALYs, along with ICER and net monetary benefit values are presented in Table 29. Other model outputs are shown in Table 30.

The most cost-effective endoscopic surveillance strategy was [0 yearly SSBE (≤2 cm); 2 yearly LSBE; LGD ablation], which excluded all short segment Barrett's oesophagus (low risk subgroup) from surveillance, while performing 2 yearly endoscopies for long segment Barrett's oesophagus and treated with endoscopic radiofrequency ablation when low grade dysplasia was detected. This produced a total cost of AU$19,650 (incremental AU$12,906), effectiveness of 24.910 QALYs (incremental 0.691 QALYs) and an ICER value of AU$18,688/QALY. This strategy was one of

three undominated surveillance strategies among all 123 strategies tested in this study with the highest net monetary benefit at ~AU$1,225,842. 24% of the cohort had endoscopic ablation by the end of the time horizon. 3.1% of the cohort progressed to oesophageal adenocarcinoma, of which 42% were detected through the surveillance program (1.3% of total cohort), and 58% presented with symptomatic cancer (1.8% of total cohort). 2.3% of the total cohort ended in mortality related to cancer (75% of oesophageal adenocarcinomas).

The second most cost-effective endoscopic surveillance strategy also had the lowest costs associated with it, namely [0 yearly SSBE (≤2 cm); 2 yearly LSBE; LGD ablation]. This also involved exclusion of the short segment Barrett's oesophagus (low risk) subgroup from endoscopic surveillance, but instead of 2-yearly endoscopies non-dysplastic long segment Barrett's oesophagus (high risk) subgroup as the previous strategy, it involved endoscopy every 3 years. This resulted in AU$16,527 (incremental AU$9,782) producing 24.671 QALYs (incremental 0.452 QALYs), and an ICER value of AU$21,661/QALY. 20.1% of the total cohort under endoscopic ablation. 4.1% of the total cohort progressed to oesophageal adenocarcinoma, of which only 20% was detected through surveillance (0.8%) and the rest 80% presented with symptomatic cancer (3.3%). 3.6% of the total cohort had cancer-related mortality (86% of all cancers).

The endoscopic surveillance strategy that generated the highest utility value was [5 yearly SSBE (≤2 cm); 2 yearly LSBE; LGD ablation] with ~24.911 QALYs (incremental 0.691 QALYs) for a total cost of AU$26,188 (incremental AU$19,443) giving an ICER of AU$28,120 that was considered cost-effective (but externally dominated). At the end of the time horizon, 28.1% of the total cohort under ablation when low grade dysplasia was detected. 2.5% of total cohort progressed to oesophageal adenocarcinoma, 62.4% of which was detected through surveillance program (1.5% of total cohort) and 37.6% presenting with symptomatic cancer (0.9% of total cohort), 64.1% had cancer-related deaths (1.6% of total cohort).

Table 29. Cost and QALY rankings table: Segment length-based risk-stratified reduction in frequency of endoscopic surveillance (3 cm threshold). Incremental cost-effectiveness ratio values are calculated using costs and utilities from "Natural history."

Strategy	Cost		QALY		ICER	NMB
Natural history/ No surveillance	$6,745	incr	24.219	incr	$0	$1,204,219
0 yearly SSBE (2 cm); 2 yearly LSBE (LGD ablation)	$19,650	$12,906	24.910	0.691	$18,688	$1,225,842
0 yearly SSBE (2 cm); 3 yearly LSBE (LGD ablation)	$16,527	$9,782	24.671	0.452	$21,661	$1,217,017
10 yearly SSBE (2 cm); 2 yearly LSBE (LGD ablation)	$22,887	$16,143	24.908	0.689	$23,427	$1,222,529
9 yearly SSBE (2 cm); 2 yearly LSBE (LGD ablation)	$23,235	$16,490	24.908	0.689	$23,930	$1,222,184
8 yearly SSBE (2 cm); 2 yearly LSBE (LGD ablation)	$23,689	$16,944	24.909	0.689	$24,583	$1,221,738
7 yearly SSBE (2 cm); 2 yearly LSBE (LGD ablation)	$24,288	$17,544	24.909	0.690	$25,439	$1,221,157
6 yearly SSBE (2 cm); 2 yearly LSBE (LGD ablation)	$25,085	$18,340	24.910	0.690	$26,569	$1,220,394
5 yearly SSBE (2 cm); 2 yearly LSBE (LGD ablation)	$26,188	$19,443	24.911	0.691	$28,120	$1,219,348
10 yearly SSBE (2 cm); 3 yearly LSBE (LGD ablation)	$19,764	$13,020	24.669	0.450	$28,926	$1,213,705
9 yearly SSBE (2 cm); 3 yearly LSBE (LGD ablation)	$20,112	$13,367	24.669	0.450	$29,695	$1,213,359
8 yearly SSBE (2 cm); 3 yearly LSBE (LGD ablation)	$20,566	$13,821	24.670	0.450	$30,692	$1,212,914
7 yearly SSBE (2 cm); 3 yearly LSBE (LGD ablation)	$21,165	$14,420	24.670	0.451	$31,997	$1,212,333
6 yearly SSBE (2 cm); 3 yearly LSBE (LGD ablation)	$21,962	$15,217	24.671	0.451	$33,715	$1,211,569
5 yearly SSBE (2 cm); 3 yearly LSBE (LGD ablation)	$23,065	$16,320	24.672	0.452	$36,067	$1,210,523

*Costs are in Australian Dollars (2020 value) per cohort of 1. Incremental cost-effectiveness ratio (**ICER**) units are AU$/QALY. Displayed in descending ICER value. **incr**- incremental; **QALY**- quality adjusted life years; **NMB**- net monetary benefit; SSBE- short segment Barrett's oesophagus; LSBE- long segment Barrett's oesophagus;

Table 30. Model outputs: Segment length-based risk-stratified reduction in frequency of endoscopic surveillance (3 cm threshold). Incremental cost-effectiveness ratio values are calculated using costs and utilities from "Natural history."

Strategy	EAC	Surv ca	Symp cancers	Cancers avoided	Cancer deaths	% ablated	ICER	% ca deaths
Natural history	11.0%	0.0%	11.0%	0.0%	10.7%	0.0%	$0	97.7%
0 yearly SSBE (2 cm); 2 yearly LSBE (LGD ablation)	3.1%	1.3%	1.8%	7.9%	2.3%	24.0%	$18,688	75.5%
0 yearly SSBE (2 cm); 3 yearly LSBE (LGD ablation)	4.1%	0.8%	3.3%	6.9%	3.6%	20.1%	$21,661	86.3%
10 yearly SSBE (2 cm); 2 yearly LSBE (LGD ablation)	2.8%	1.4%	1.3%	8.2%	1.9%	25.2%	$23,427	70.1%
9 yearly SSBE (2 cm); 2 yearly LSBE (LGD ablation)	2.7%	1.4%	1.3%	8.3%	1.9%	25.5%	$23,930	69.2%
8 yearly SSBE (2 cm); 2 yearly LSBE (LGD ablation)	2.7%	1.5%	1.2%	8.3%	1.8%	25.9%	$24,583	68.2%
7 yearly SSBE (2 cm); 2 yearly LSBE (LGD ablation)	2.6%	1.5%	1.1%	8.4%	1.7%	26.5%	$25,439	67.1%
6 yearly SSBE (2 cm); 2 yearly LSBE (LGD ablation)	2.5%	1.5%	1.0%	8.5%	1.7%	27.2%	$26,569	65.7%
5 yearly SSBE (2 cm); 2 yearly LSBE (LGD ablation)	2.5%	1.5%	0.9%	8.5%	1.6%	28.1%	$28,120	64.1%
10 yearly SSBE (2 cm); 3 yearly LSBE (LGD ablation)	3.8%	1.0%	2.8%	7.2%	3.2%	21.3%	$28,926	83.2%
9 yearly SSBE (2 cm); 3 yearly LSBE (LGD ablation)	3.8%	1.0%	2.8%	7.2%	3.1%	21.6%	$29,695	82.8%
8 yearly SSBE (2 cm); 3 yearly LSBE (LGD ablation)	3.7%	1.0%	2.7%	7.3%	3.1%	22.1%	$30,692	82.3%
7 yearly SSBE (2 cm); 3 yearly LSBE (LGD ablation)	3.7%	1.0%	2.6%	7.3%	3.0%	22.6%	$31,997	81.7%
6 yearly SSBE (2 cm); 3 yearly LSBE (LGD ablation)	3.6%	1.1%	2.5%	7.4%	2.9%	23.3%	$33,715	81.0%
5 yearly SSBE (2 cm); 3 yearly LSBE (LGD ablation)	3.5%	1.1%	2.4%	7.5%	2.8%	24.2%	$36,067	80.1%

*Values as percentage of cohort developing the model outputs (per cohort of 1). **EAC**- Total % of cohort developing Oesophageal adenocarcinoma (surveillance and symptomatic combined); **Surv ca**- Surveillance detected oesophageal adenocarcinoma; **Symp ca**- presenting with symptomatic oesophageal adenocarcinoma; **% ablated**- refers to what percentage of the cohort received endoscopic ablation; **ICER**- incremental cost-effectiveness ratio; **% ca deaths**- mortality % in cohort that progressed to oesophageal adenocarcinomas. Displayed in increasing order of ICER values

7.2.1.2 One-way sensitivity analysis

All surveillance strategies using length based (2 cm threshold) risk-stratification with endoscopic ablation (for low grade dysplasia) were seen to be cost effective under base parameter conditions and mostly remained cost-effective despite varying all costs and utility values in one-way sensitivity analysis. Only the strategy [5 yearly SSBE (≤2 cm); 2 yearly LSBE; LGD ablation] crossed the willingness to pay threshold when the cost of database maintenance was increased to AU$461 (183% change). The ICER values for the rest of the surveillance strategies tested were below AU$50,000/QALY in one way sensitivity analysis for multiple variables. The key drivers were similar to previously discussed surveillance strategies: costs of database maintenance and cost of diagnostic endoscopy. Expectedly, for this group of strategies, cost of radiofrequency ablation was also a key driver seen in one-way sensitivity analyses. Tornado diagrams for the two most-cost effective surveillance strategies is shown in Figure 64 and Figure 65. The endoscopic surveillance strategy with the highest effectiveness is shown in Figure 66.

Figure 64. One way sensitivity analysis (Tornado diagram) for natural history (no surveillance) versus ablation of low grade dysplasia with exclusion of low risk subgroup (≤2 cm) from surveillance combined with 2-yearly endoscopies for non-dysplasia in high risk subgroup

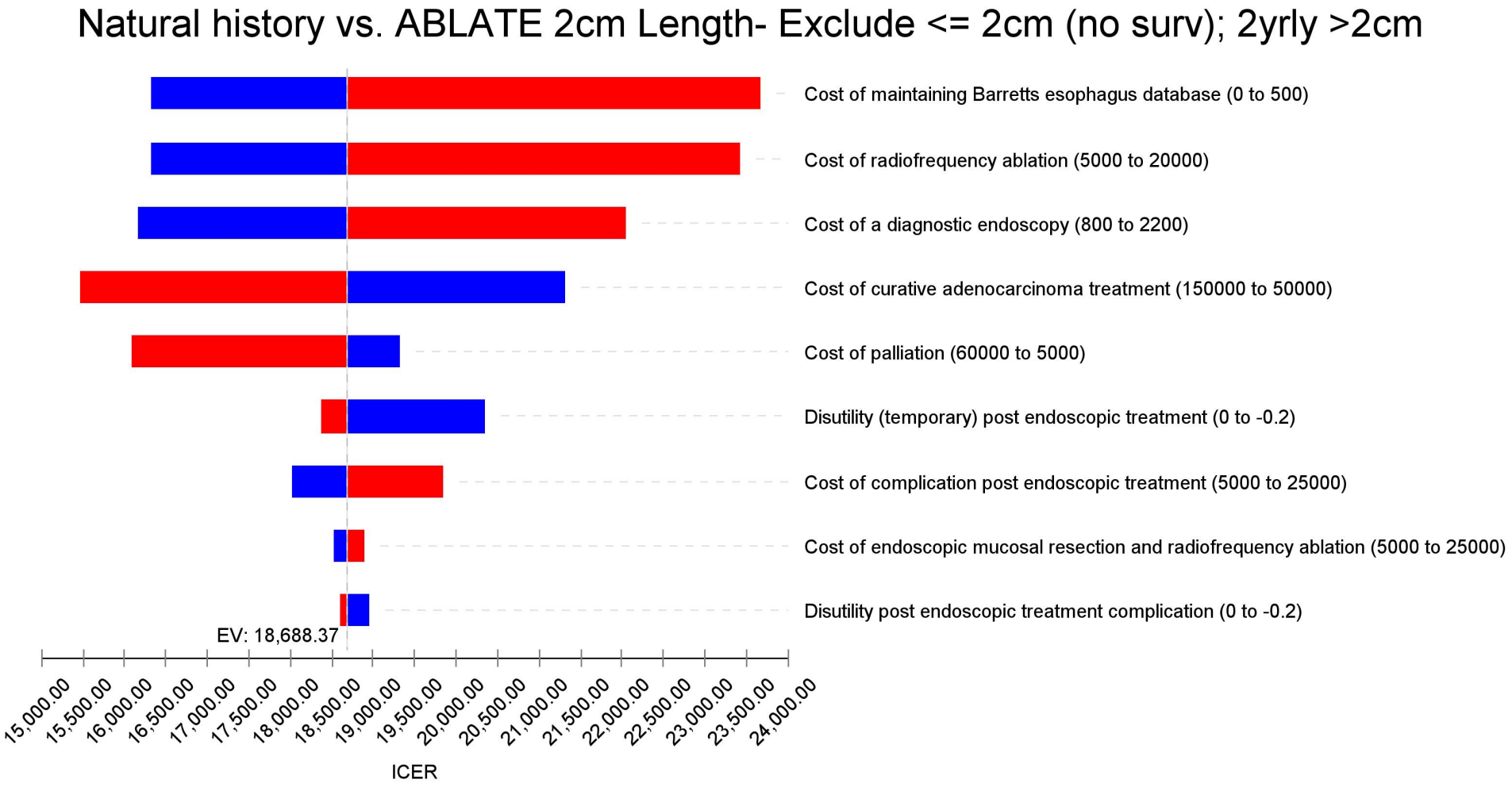


Figure 65. One way sensitivity analysis (Tornado diagram) for natural history (no surveillance) versus ablation of low grade dysplasia with exclusion of low risk subgroup (≤2 cm) from surveillance combined with 3-yearly endoscopies for non-dysplasia in high risk subgroup.

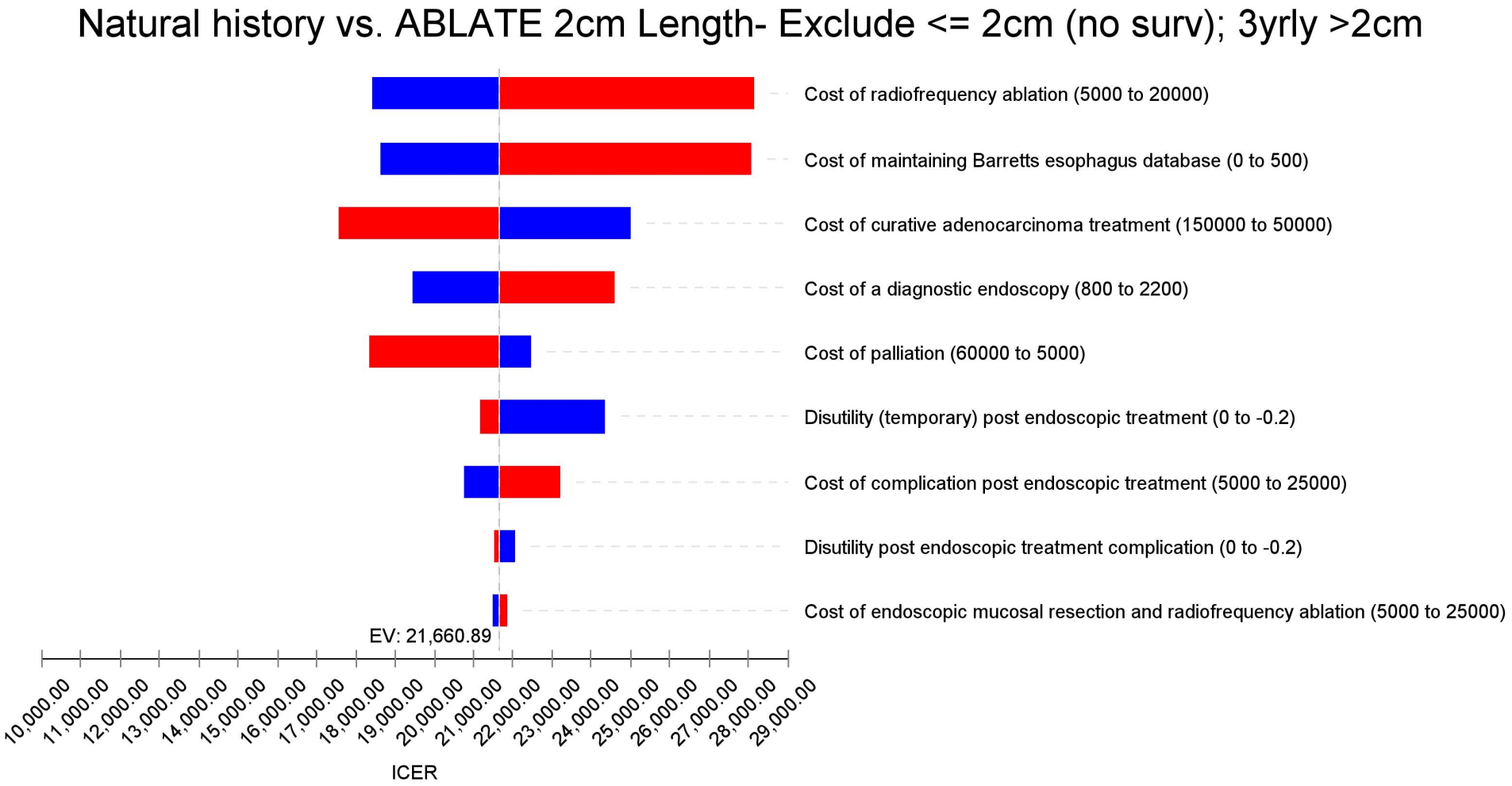
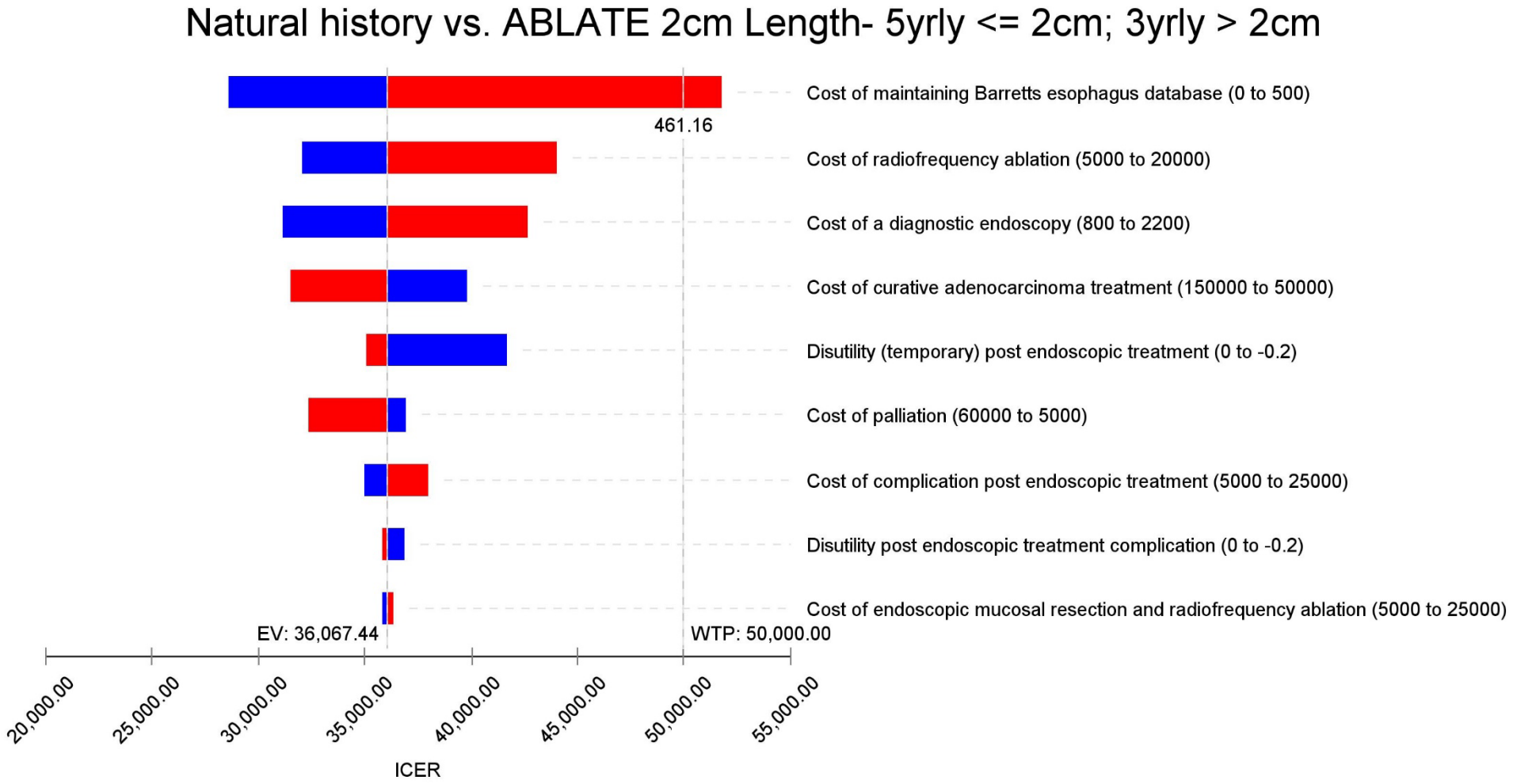


Figure 66. One way sensitivity analysis (Tornado diagram) for natural history (no surveillance) versus ablation of low grade dysplasia with 5-yearly endoscopies for low risk subgroup (≤2 cm) from surveillance combined with 3-yearly endoscopies for non-dysplasia in high risk subgroup.



7.2.1.3 Probabilistic sensitivity analysis

Probabilistic sensitivity analysis confirmed results of the base case analysis. All surveillance strategies were cost-effective in > 99% of the simulations (Figure 68) for a willingness to pay threshold of AU$50,000/QALY. An ICER scatter graph shows most of the simulations lying below this willingness to pay line, seen in Figure 67. There were two notable clusters of points, which correlate with the surveillance interval for the long segment (high risk) subgroup. The first cluster ranges from ~ 0.3 – 0.55 incremental QALYs (x-axis), while the second cluster ranges ~ 0.6 – 0.8 incremental QALYs. The second cluster with higher QALYs correlates to the higher frequency of endoscopic surveillance which was 2-yearly endoscopies for non-dysplastic long segment Barrett's oesophagus, and the first cluster correlates with the lower frequency of surveillance which was 3-yearly endoscopies for non-dysplastic long segment Barrett's oesophagus.

Cost-effectiveness acceptability curve (Figure 69) surveillance strategies that were most cost-effective in at least one simulation across various willingness to pay thresholds. Between AU$5,000 – AU$15,000/QALY, [0 yearly SSBE (≤2 cm); 3 yearly LSBE; LGD ablation] was cost-effective in more than 50% of the simulations. Between AU$15,000 – AU$20,000/QALY [0 yearly SSBE (≤2 cm); 2 yearly LSBE; LGD ablation] was cost-effective in at least 50% of the simulations. This probability reached 100% > AU$20,000/QALY.

7.2.1.4 Summary

Exclusion of short segment Barrett's oesophagus from endoscopic surveillance with 2-yearly endoscopic surveillance of non-dysplasia and endoscopic ablation of low grade dysplasia in long segment Barrett's oesophagus (>2 cm) was the most cost-effective and undominated endoscopic surveillance strategy in 100% of the simulations at a willingness to pay threshold of AU$50,000/QALY. Other low-frequency endoscopic surveillance intervals for short segment Barrett's oesophagus were also cost-effective, but to a lesser extent. Focusing high frequency endoscopic surveillance and treatment for a high risk subgroup such as long-segment Barrett's oesophagus allows detection of a high percentage of oesophageal adenocarcinoma, while restricting the number of unnecessary endoscopies and ablative treatments.

Figure 67. Scatter plot on incremental cost-effectiveness plane for Barrett's oesophagus segment length-based (2 cm threshold) risk-stratified reduction in frequency of endoscopic surveillance combined with ablation of low grade dysplasia

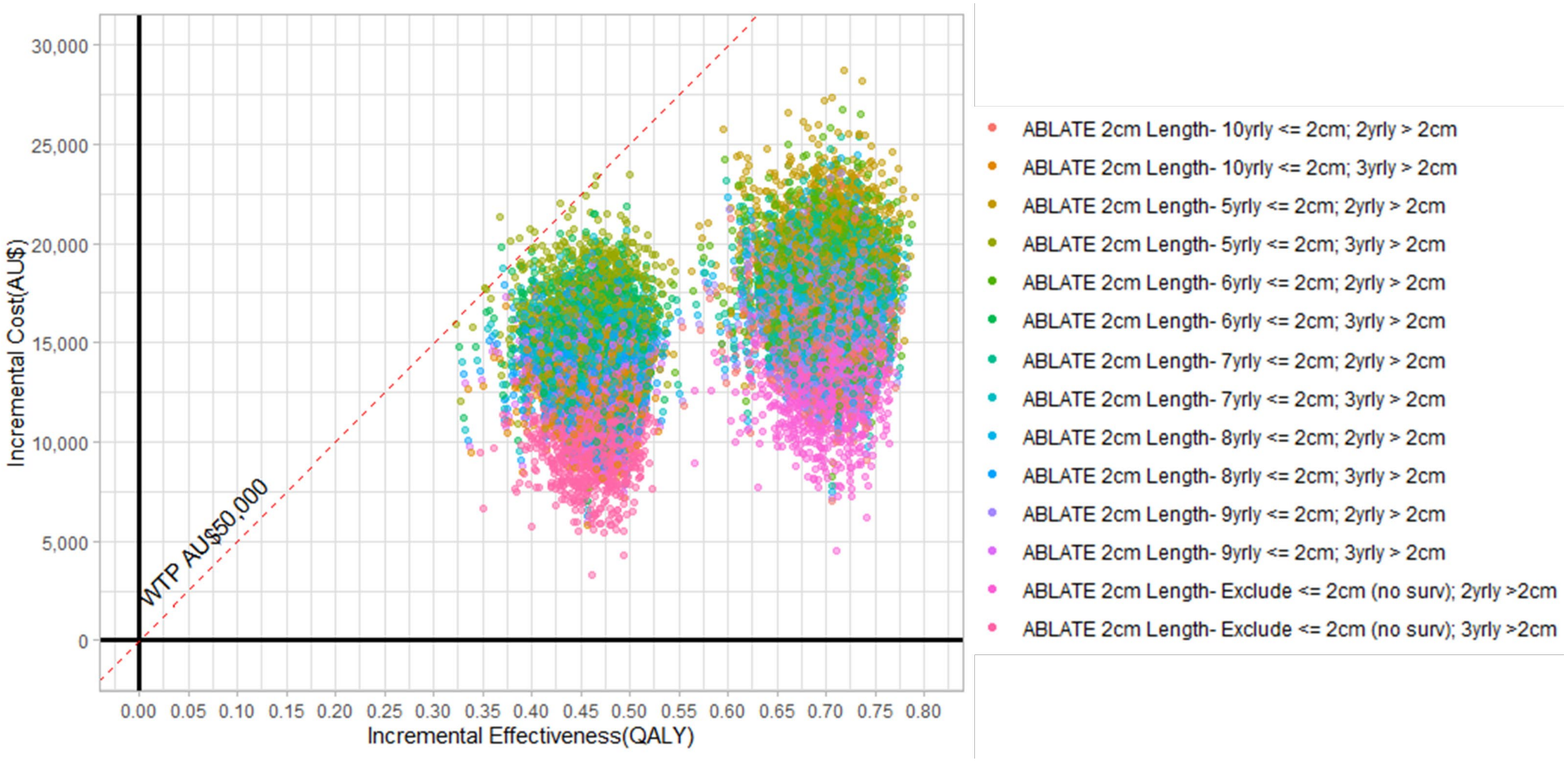


Figure 68. Probabilistic sensitivity analysis results showing Barrett's oesophagus segment length-based (2scm threshold) surveillance strategies with incremental cost-effectiveness ratio (ICER) of less than willingness-to-pay threshold (WTP) of AU$50,000/QALY

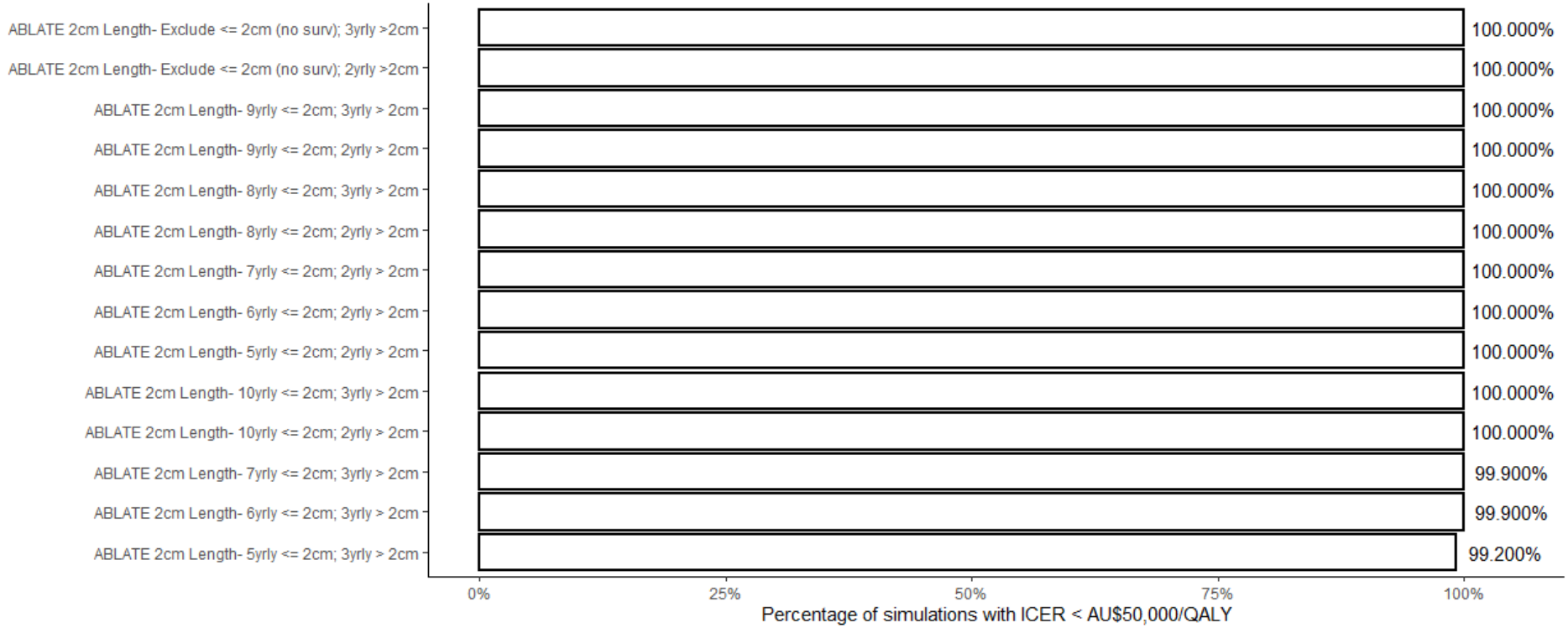
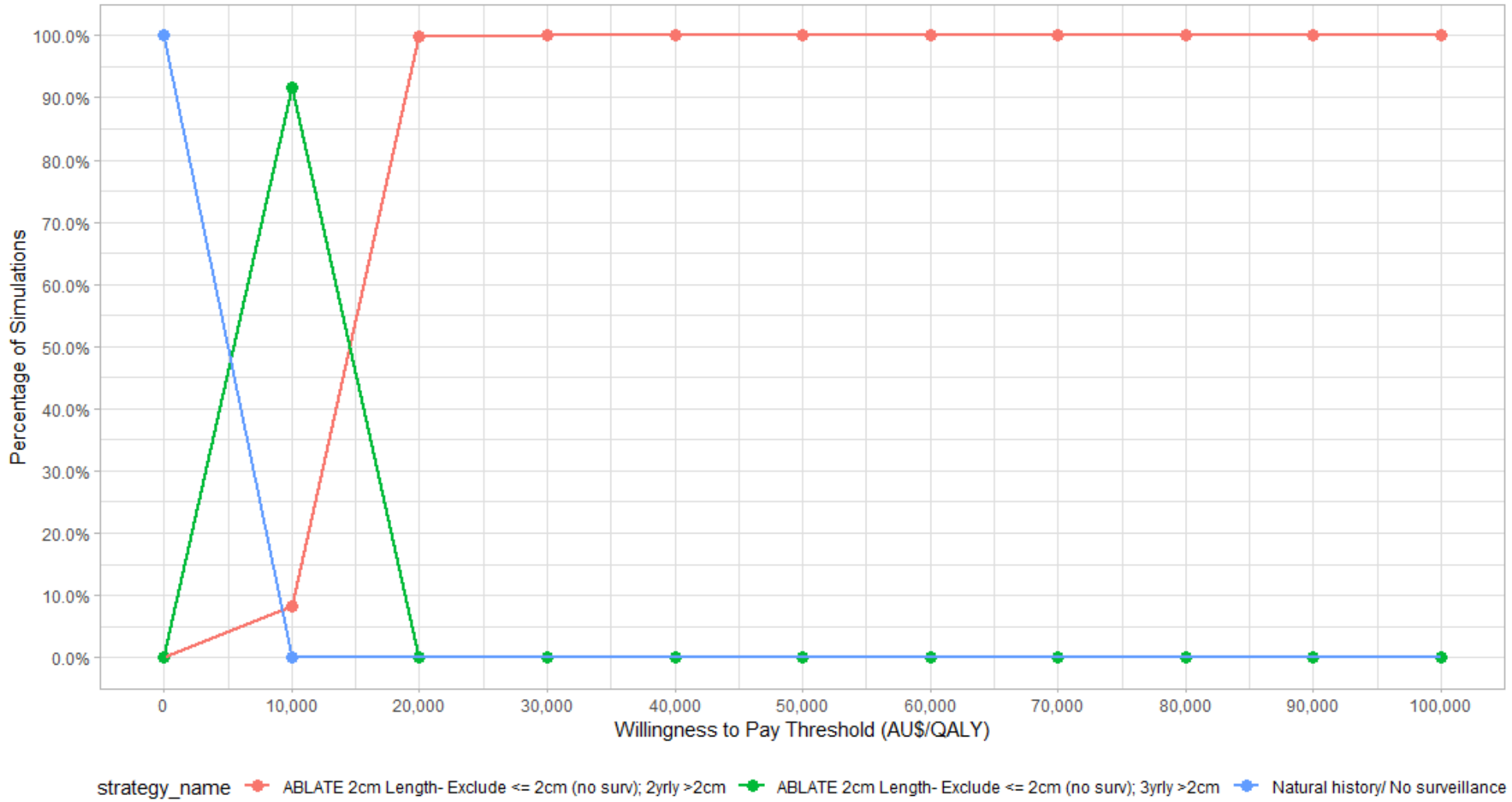


Figure 69. Cost-effectiveness acceptability curve of Barrett's oesophagus segment length based (2 cm threshold) risk-stratified strategies showing percent of simulations each strategy was cost-effective at willingness to pay thresholds between 0-AU$100,000/WTP



Ablate Length 3 cm threshold

7.2.1.5 Base parameter conditions

Similar to the previous length-based risk-stratification, an additional 14 surveillance strategies testing cost-effectiveness of low grade dysplasia ablation with risk-stratified endoscopic surveillance based on endoscopically visible length of Barrett's oesophagus were developed (3 cm threshold). 7 strategies examined surveillance intervals ~ 5-10 years (and including no surveillance) for short segment with 2-yearly intervals for long segment Barrett's oesophagus, and the other 7 strategies included 3-yearly surveillance for long segment Barrett's oesophagus with same intervals for short segment (5-10 years and no surveillance). Again all 14 surveillance strategies testing risk-stratified endoscopic surveillance with ablation when low grade dysplasia was detected were cost-effective under the willingness to pay threshold of AU$50,000/QALY. The results of total and incremental costs, QALYs, along with ICER and net monetary benefit values are presented in Table 31. Other model outputs are shown in Table 32.

The most cost-effective endoscopic surveillance strategy was [0 yearly SSBE (<3 cm); 2 yearly LSBE; LGD ablation] with total cost of AU$14,666 (incremental AU$7,921), 24.801 QALYs (incremental 0.582 QALYs) with an ICER value of AU$13,605. This was the lowest ICER value among 123 strategies and was one of 3 strategies that was undominated. 15.2% of the total cohort underwent ablation when detected with low grade dysplasia. At the end of the time horizon, 4% of the total cohort progressed to oesophageal adenocarcinoma, 46.1% of whom were detected through the surveillance program (1.8% of total cohort), 53.9% presenting with symptomatic adenocarcinoma (2.2% of total cohort), and 3% of the total cohort had cancer related mortality (75% of all cancers).

The next most cost-effective endoscopic surveillance strategy also had the lowest costs associated with it, namely [0 yearly SSBE (<3 cm); 2 yearly LSBE; LGD ablation]. This resulted in AU$12,565 (incremental AU$5,820) producing 24.502 QALYs (incremental 0.283 QALYs), and an ICER value of AU$20,561/QALY. 11.8% of the total cohort under endoscopic ablation. 5% of the total cohort progressed to oesophageal adenocarcinoma, of which only 18.7% was detected through surveillance (0.9%) and the rest 81.3% presented with symptomatic cancer (4.1%). 4.4% of the total cohort had cancer-related mortality (87.7% of all cancers).

The endoscopic surveillance strategy that associated the highest total QALYs was [5 yearly SSBE (<3 cm); 2 yearly LSBE; LGD ablation] with ~24.803 QALYs (incremental 0.584 QALYs) for a total cost of AU$22,672 (incremental AU$15,928) giving an ICER of AU$27,282 that was considered cost-effective (but externally dominated). At the end of the time horizon, 20.6% of the total cohort under ablation when low grade dysplasia was detected. 3.2% of total cohort progressed to oesophageal adenocarcinoma, two-thirds were detected through surveillance

program (2.1% of total cohort) and one-third presenting with symptomatic cancer (1.1% of total cohort). 63.8% of cancers had ended in mortality (2% of total cohort).

Table 31. Cost and QALY rankings table: Segment length-based risk-stratified reduction in frequency of endoscopic surveillance (3 cm threshold). Incremental cost-effectiveness ratio values are calculated using costs and utilities from "Natural history."

Strategy	Cost		QALY		ICER	NMB
Natural history/ No surveillance	$6,745	incr	24.219	incr	$0	$1,204,219
0 yearly SSBE (3 cm); 2 yearly LSBE (LGD ablation)	$14,666	$7,921	24.801	0.582	$13,605	$1,225,408
0 yearly SSBE (3 cm); 3 yearly LSBE (LGD ablation)	$12,565	$5,820	24.502	0.283	$20,561	$1,212,552
5 yearly SSBE (3 cm); 2 yearly LSBE (LGD ablation)	$22,672	$15,928	24.803	0.584	$27,282	$1,217,482
6 yearly SSBE (3 cm); 2 yearly LSBE (LGD ablation)	$22,672	$15,928	24.802	0.582	$27,355	$1,217,482
7 yearly SSBE (3 cm); 2 yearly LSBE (LGD ablation)	$22,672	$15,928	24.801	0.581	$27,399	$1,217,482
8 yearly SSBE (3 cm); 2 yearly LSBE (LGD ablation)	$22,672	$15,928	24.800	0.581	$27,424	$1,217,482
9 yearly SSBE (3 cm); 2 yearly LSBE (LGD ablation)	$22,672	$15,928	24.800	0.581	$27,437	$1,217,482
10 yearly SSBE (3 cm); 2 yearly LSBE (LGD ablation)	$22,672	$15,928	24.800	0.580	$27,443	$1,217,482
10 yearly SSBE (3 cm); 3 yearly LSBE (LGD ablation)	$16,508	$9,763	24.501	0.281	$34,711	$1,208,519
9 yearly SSBE (3 cm); 3 yearly LSBE (LGD ablation)	$16,938	$10,193	24.501	0.281	$36,228	$1,208,094
8 yearly SSBE (3 cm); 3 yearly LSBE (LGD ablation)	$17,500	$10,755	24.501	0.282	$38,187	$1,207,546
7 yearly SSBE (3 cm); 3 yearly LSBE (LGD ablation)	$18,239	$11,494	24.501	0.282	$40,733	$1,206,834
6 yearly SSBE (3 cm); 3 yearly LSBE (LGD ablation)	$19,219	$12,475	24.502	0.283	$44,061	$1,205,901
5 yearly SSBE (3 cm); 3 yearly LSBE (LGD ablation)	$20,571	$13,827	24.504	0.285	$48,570	$1,204,626

*Costs are in Australian Dollars (2020 value) per cohort of 1. Incremental cost-effectiveness ratio (**ICER**) units are AU$/QALY. Displayed in descending ICER value. **incr**- incremental; **QALY**- quality adjusted life years; **NMB**- net monetary benefit; SSBE- short segment Barrett's oesophagus; LSBE- long segment Barrett's oesophagus;

Table 32. Model outputs: Segment length-based risk-stratified reduction in frequency of endoscopic surveillance (3 cm threshold). Incremental cost-effectiveness ratio values are calculated using costs and utilities from "Natural history."

Strategy	EAC	Surv ca	Symp cancers	Cancers avoided	Cancer deaths	% ablated	ICER	% ca deaths
Natural history/ No surveillance	11.0%	0.0%	11.0%	0.0%	10.7%	0.0%	**$0**	97.7%
0 yearly SSBE (3 cm); 2 yearly LSBE (LGD ablation)	4.0%	1.8%	2.2%	7.0%	3.0%	15.2%	**$13,605**	75.0%
0 yearly SSBE (3 cm); 3 yearly LSBE (LGD ablation)	5.0%	0.9%	4.1%	6.0%	4.4%	11.8%	**$20,561**	87.7%
5 yearly SSBE (3 cm); 2 yearly LSBE (LGD ablation)	3.2%	2.1%	1.1%	7.8%	2.0%	20.6%	**$27,282**	63.8%
6 yearly SSBE (3 cm); 2 yearly LSBE (LGD ablation)	3.3%	2.1%	1.2%	7.7%	2.1%	19.4%	**$27,355**	65.3%
7 yearly SSBE (3 cm); 2 yearly LSBE (LGD ablation)	3.4%	2.1%	1.3%	7.6%	2.2%	18.5%	**$27,399**	66.6%
8 yearly SSBE (3 cm); 2 yearly LSBE (LGD ablation)	3.4%	2.0%	1.4%	7.6%	2.3%	17.8%	**$27,424**	67.8%
9 yearly SSBE (3 cm); 2 yearly LSBE (LGD ablation)	3.5%	2.0%	1.5%	7.5%	2.4%	17.2%	**$27,437**	68.8%
10 yearly SSBE (3 cm); 2 yearly LSBE (LGD ablation)	3.6%	2.0%	1.6%	7.4%	2.5%	16.7%	**$27,443**	69.6%
10 yearly SSBE (3 cm); 3 yearly LSBE (LGD ablation)	4.6%	1.1%	3.5%	6.4%	3.9%	13.4%	**$34,711**	84.8%
9 yearly SSBE (3 cm); 3 yearly LSBE (LGD ablation)	4.6%	1.1%	3.4%	6.4%	3.9%	13.8%	**$36,228**	84.3%
8 yearly SSBE (3 cm); 3 yearly LSBE (LGD ablation)	4.5%	1.2%	3.4%	6.5%	3.8%	14.4%	**$38,187**	83.8%
7 yearly SSBE (3 cm); 3 yearly LSBE (LGD ablation)	4.4%	1.2%	3.2%	6.6%	3.7%	15.1%	**$40,733**	83.2%
6 yearly SSBE (3 cm); 3 yearly LSBE (LGD ablation)	4.3%	1.2%	3.1%	6.7%	3.6%	16.0%	**$44,061**	82.5%
5 yearly SSBE (3 cm); 3 yearly LSBE (LGD ablation)	4.3%	1.2%	3.0%	6.7%	3.5%	17.2%	**$48,570**	81.7%

*Values as percentage of cohort developing the model outputs (per cohort of 1). **EAC**- Total % of cohort developing Oesophageal adenocarcinoma (surveillance and symptomatic combined); **Surv ca**- Surveillance detected oesophageal adenocarcinoma; **Symp ca**- presenting with symptomatic oesophageal adenocarcinoma; **% ablated**- refers to what percentage of the cohort received endoscopic ablation; **ICER**- incremental cost-effectiveness ratio; **% ca deaths**- mortality % in cohort that progressed to oesophageal adenocarcinomas. Displayed in increasing order of ICER values

7.2.1.6 One way sensitivity analysis

Similar to the surveillance strategies detailed earlier in this chapter, most surveillance strategies remained cost-effective despite variation in cost and utility values in the one-way sensitivity analysis. The only strategy that was susceptible to worse ICER values was [5 yearly SSBE (<3 cm); 3 yearly LSBE; LGD ablation] (seen in Figure 73). This was the strategy with the highest ICER value under base conditions (AU$48,570/QALY). A 10% increase in cost of database maintenance increased the ICER value above the willingness to pay threshold of AU$50,000/QALY, making it not cost-effective. An increase of 9% in the cost of endoscopic examination resulted similarly in this endoscopic surveillance strategy not being cost-effective. Changes in nearly all key variables, with the exception cost of treatment for surveillance detected cancer (endoscopic mucosal resection and radiofrequency ablation) resulted in ICER values above the willingness to pay threshold.

For the most part, the key drivers similar to previously discussed surveillance strategies: costs of database maintenance and cost of diagnostic endoscopy. For strategies excluding short-segment Barrett's oesophagus (low risk) subgroup, the two key drivers were cost of radiofrequency ablation and cost of treatment of oesophageal adenocarcinoma. The ICER values remained well below WTP threshold of AU$50,000/QALY even with large variations within these two key drivers (Figure 70 and Figure 71).

Figure 70. One way sensitivity analysis (Tornado diagram) for natural history (no surveillance) versus ablation of low grade dysplasia with exclusion of low risk subgroup (<3 cm) from surveillance combined with 2-yearly endoscopies for non-dysplasia in high risk subgroup.

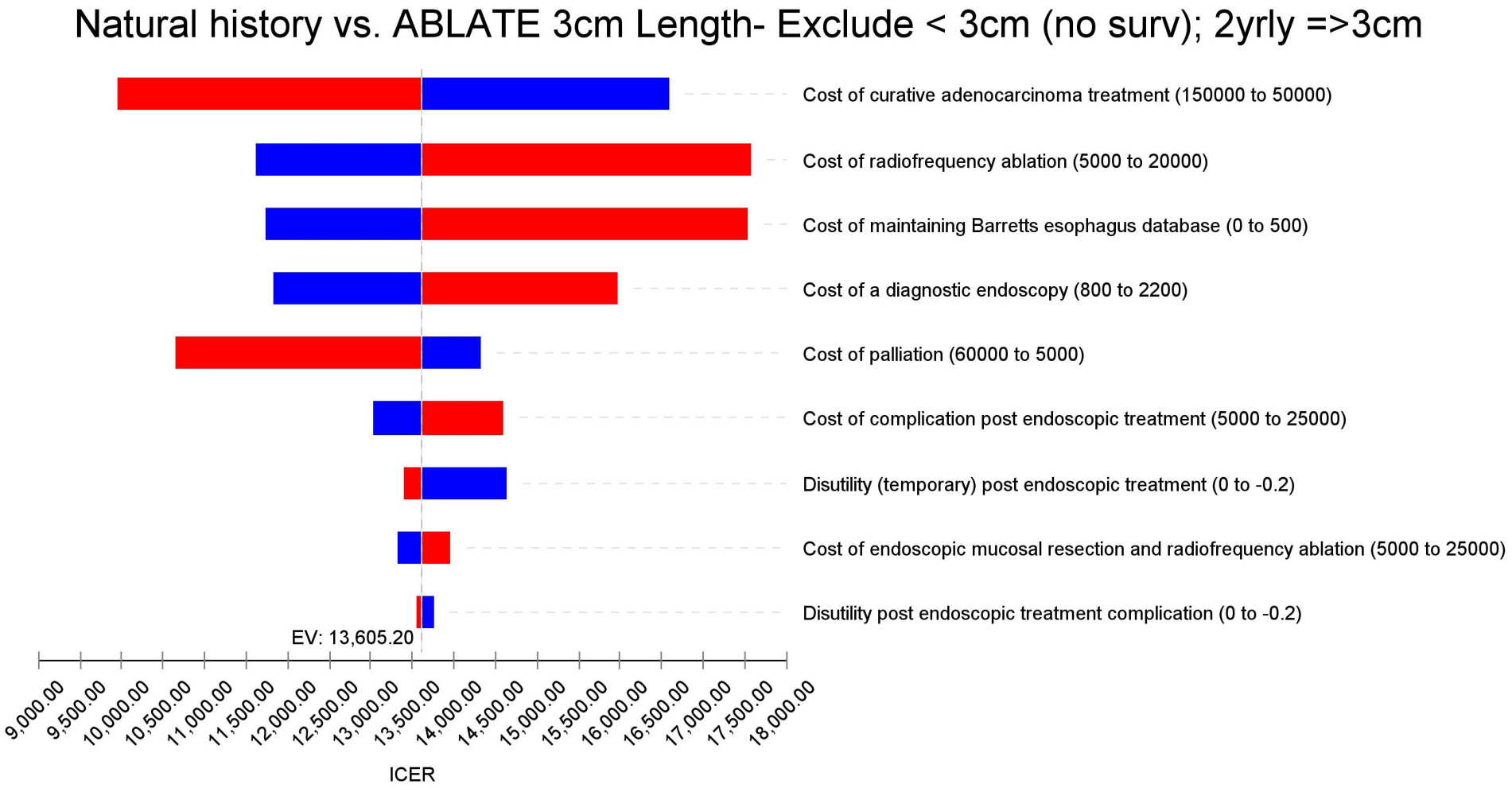


Figure 71. One way sensitivity analysis (Tornado diagram) for natural history (no surveillance) versus ablation of low grade dysplasia with exclusion of low risk subgroup (<3 cm) from surveillance combined with 3-yearly endoscopies for non-dysplasia in high risk subgroup.

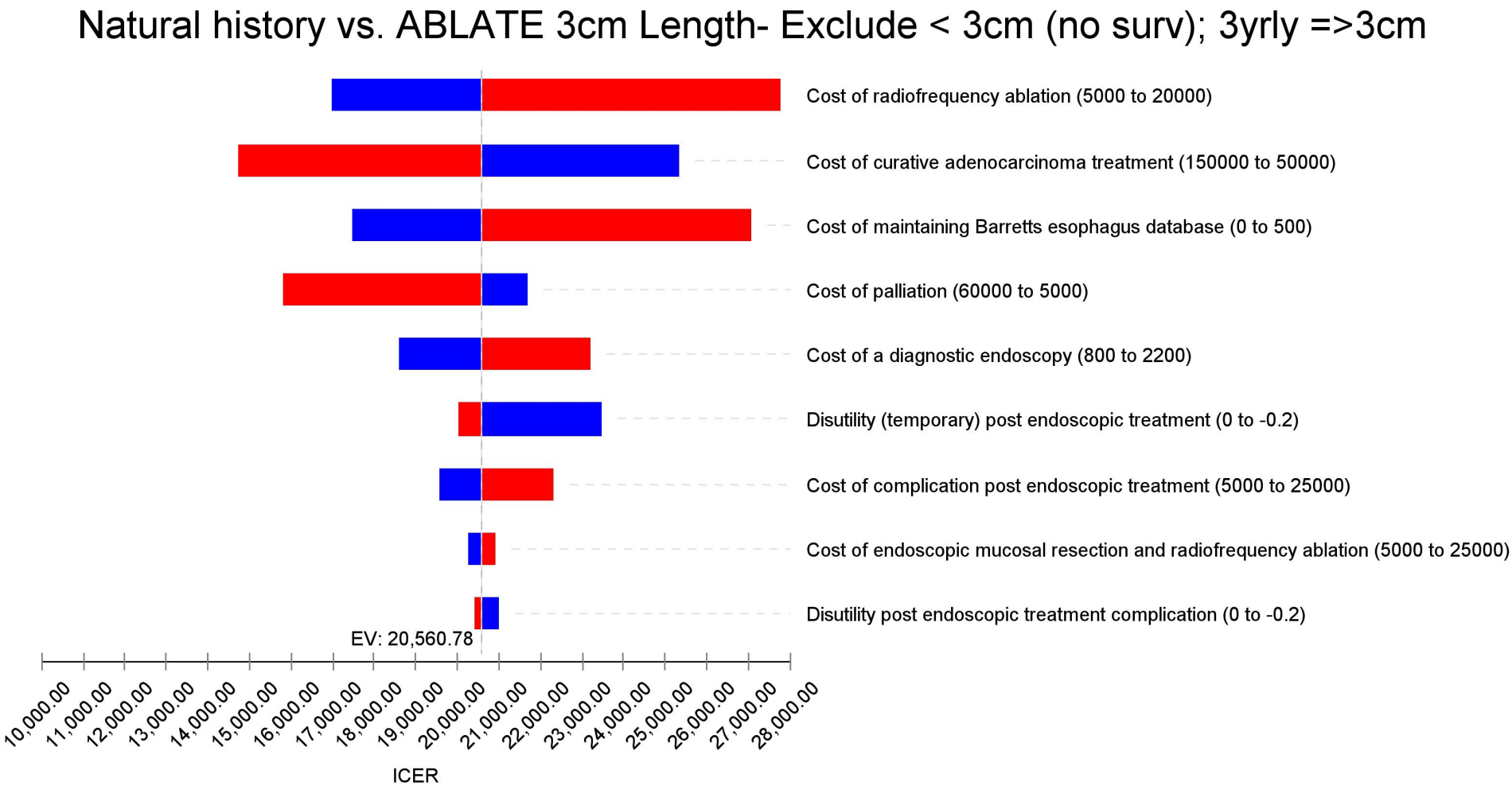
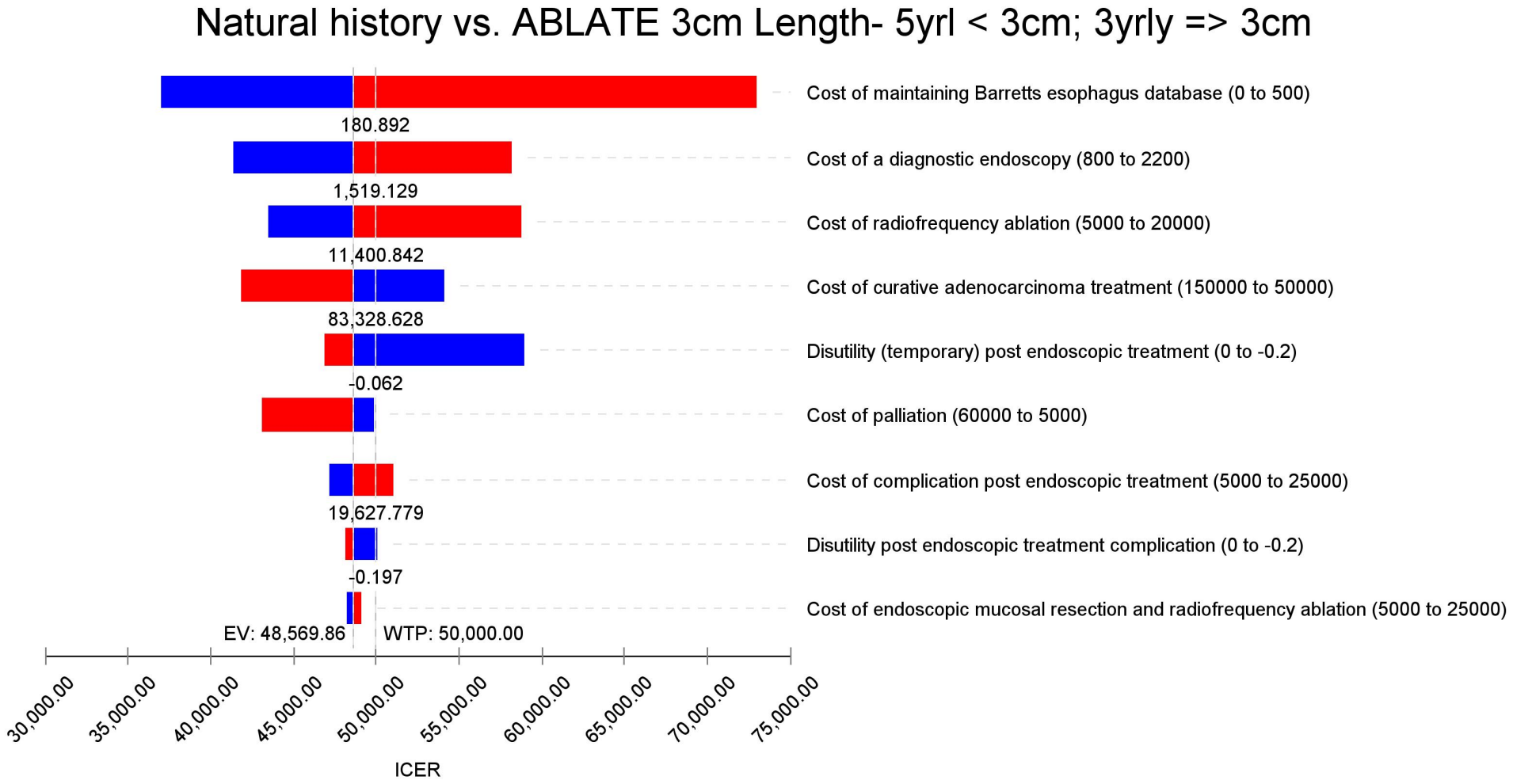


Figure 72. One way sensitivity analysis (Tornado diagram) for natural history (no surveillance) versus ablation of low grade dysplasia with 5-yearly endoscopies for low risk subgroup (<3 cm) from surveillance combined with 3-yearly endoscopies for non-dysplasia in high risk subgroup.



7.2.1.7 Probabilistic sensitivity analysis

Probabilistic sensitivity analysis confirmed results of the base case analysis. 8 of 14 surveillance strategies were cost-effective in > 99% of the simulations (Figure 68) for a willingness to pay threshold of AU$50,000/QALY. The rest, 6 out of 14, surveillance strategies were cost-effective in at least 50% of the simulations. An ICER scatter graph shows most of the simulations lying below this willingness to pay line, seen in Figure 74. As seen with the previous set of surveillance strategies, there were two notable clusters of points, which correlate with the surveillance interval for the long segment. The first cluster ranges from ~ 0.2 – 0.35 QALYs (x-axis), while the second cluster ranges ~ 0.5 – 0.65 QALYs. The second cluster with higher QALYs correlates to the higher frequency of endoscopic surveillance which was 2-yearly endoscopies for non-dysplastic long segment Barrett's oesophagus, and the first cluster correlates with the lower frequency of surveillance which was 3-yearly endoscopies for non-dysplastic long segment Barrett's oesophagus.

Cost-effectiveness acceptability curve (Figure 76) the two strategies that were most cost-effective in any simulations across various willingness to pay thresholds. Although the endoscopic surveillance strategy [0 yearly SSBE (<3 cm); 3 yearly LSBE; LGD ablation] was cost-effective in some simulations, it was largely negligible. The undominated strategy was [0 yearly SSBE (≤2 cm); 2 yearly LSBE; LGD ablation], seen to be cost-effective in 100% of the simulations with a willingness to pay threshold above AU$20,000/QALY.

7.2.1.8 Summary

As with the previous section, surveillance strategies based on excluding short segment Barrett's oesophagus (<3 cm) with 2-yearly endoscopies for long segment non-dysplastic Barrett's oesophagus and endoscopic ablation treatment when low grade dysplasia is detected was clearly the undominated strategy, proving to be cost-effective under base conditions as well as probabilistic analysis.

Figure 73. Scatter plot on incremental cost-effectiveness plane for Barrett's oesophagus segment length-based (3 cm threshold) risk-stratified reduction in frequency of endoscopic surveillance combined with ablation of low grade dysplasia

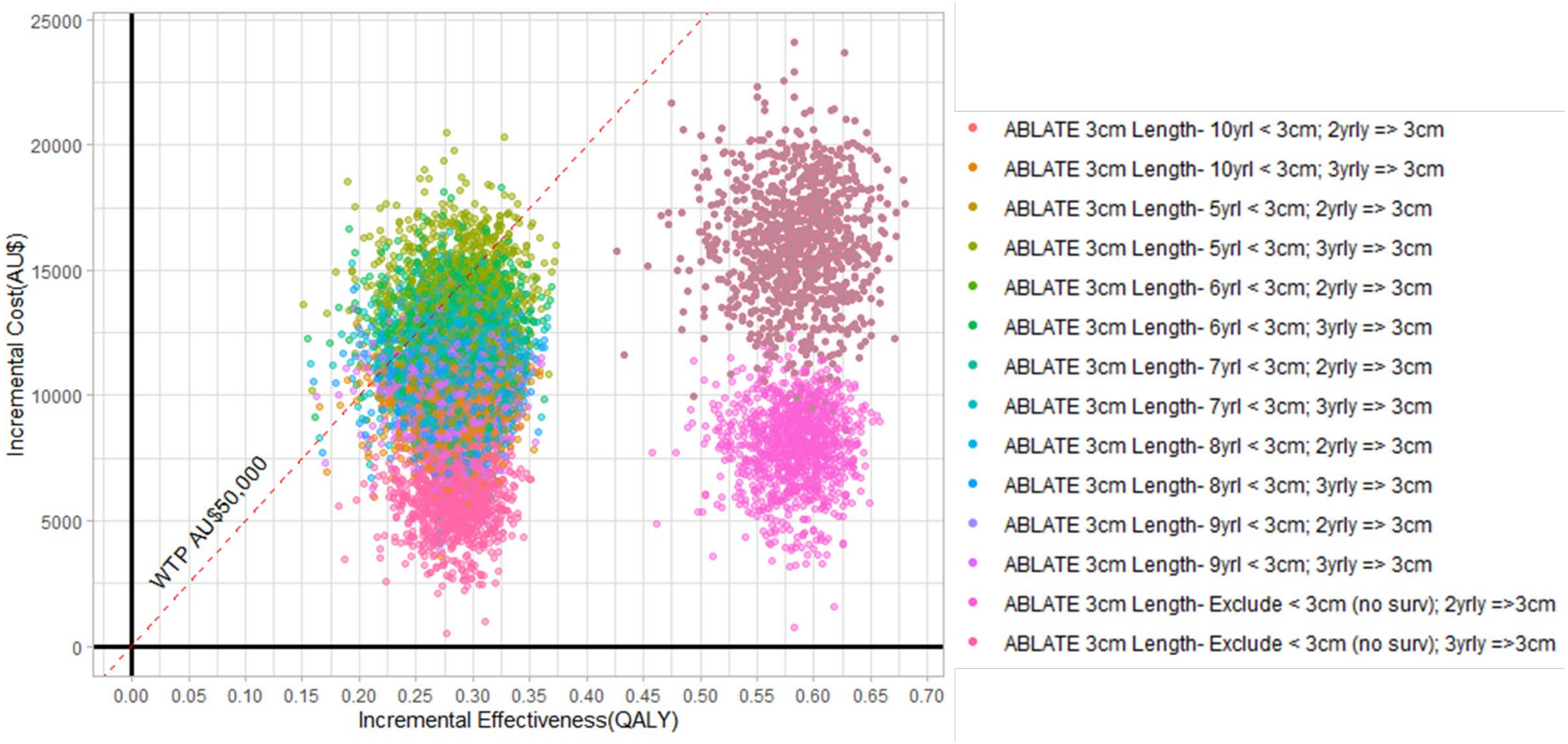


Figure 74. Probabilistic sensitivity analysis results showing Barrett's oesophagus segment length-based (3 cm threshold) surveillance strategies with incremental cost-effectiveness ratio (ICER) of less than willingness-to-pay threshold (WTP) of AU$50,000/QALY

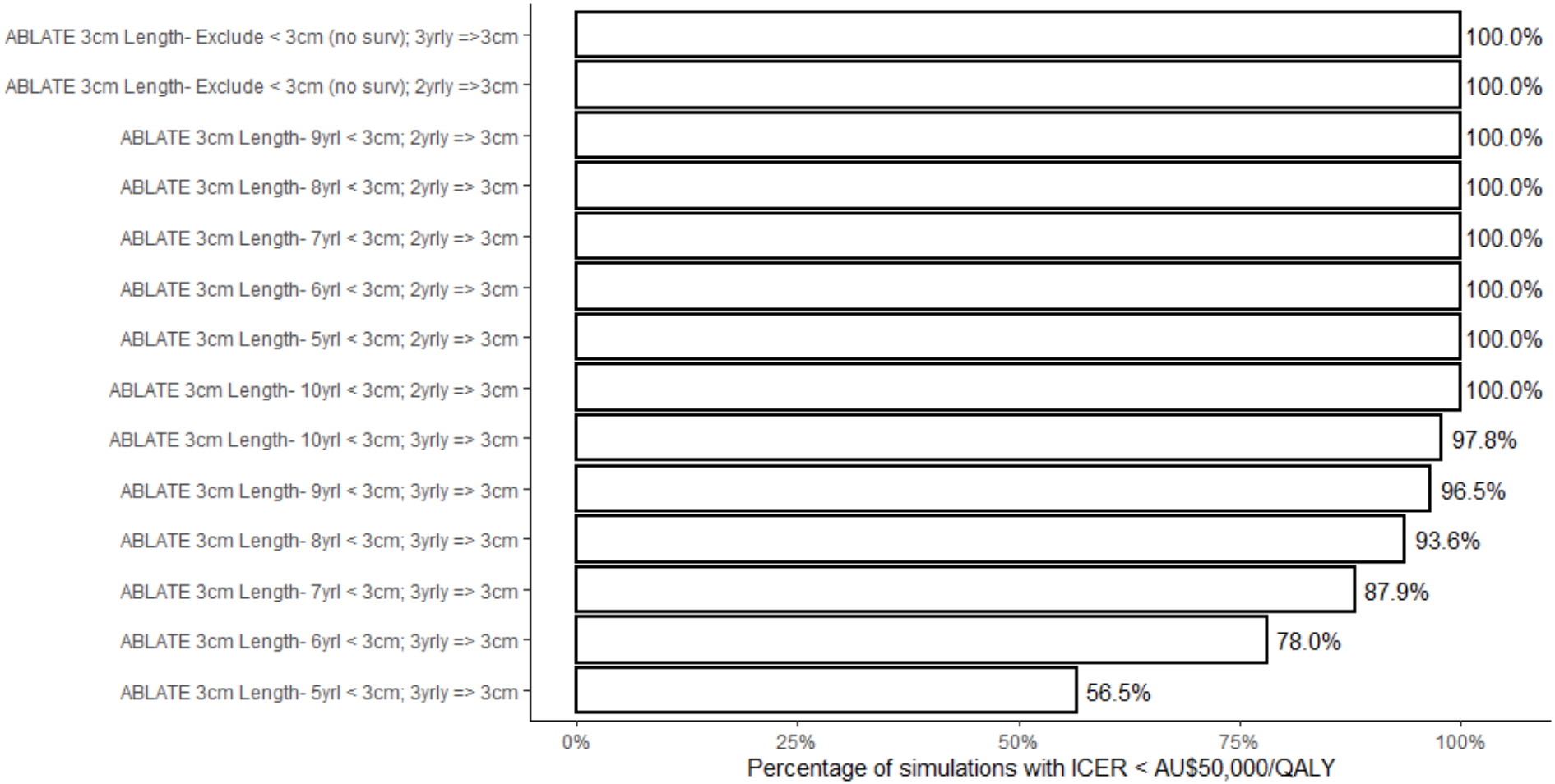


Figure 75. Cost-effectiveness acceptability curve of Barrett's oesophagus segment length based (3 cm threshold) risk-stratified strategies showing percent of simulations each strategy was cost-effective at willingness to pay thresholds between 0-AU$100,000/WTP

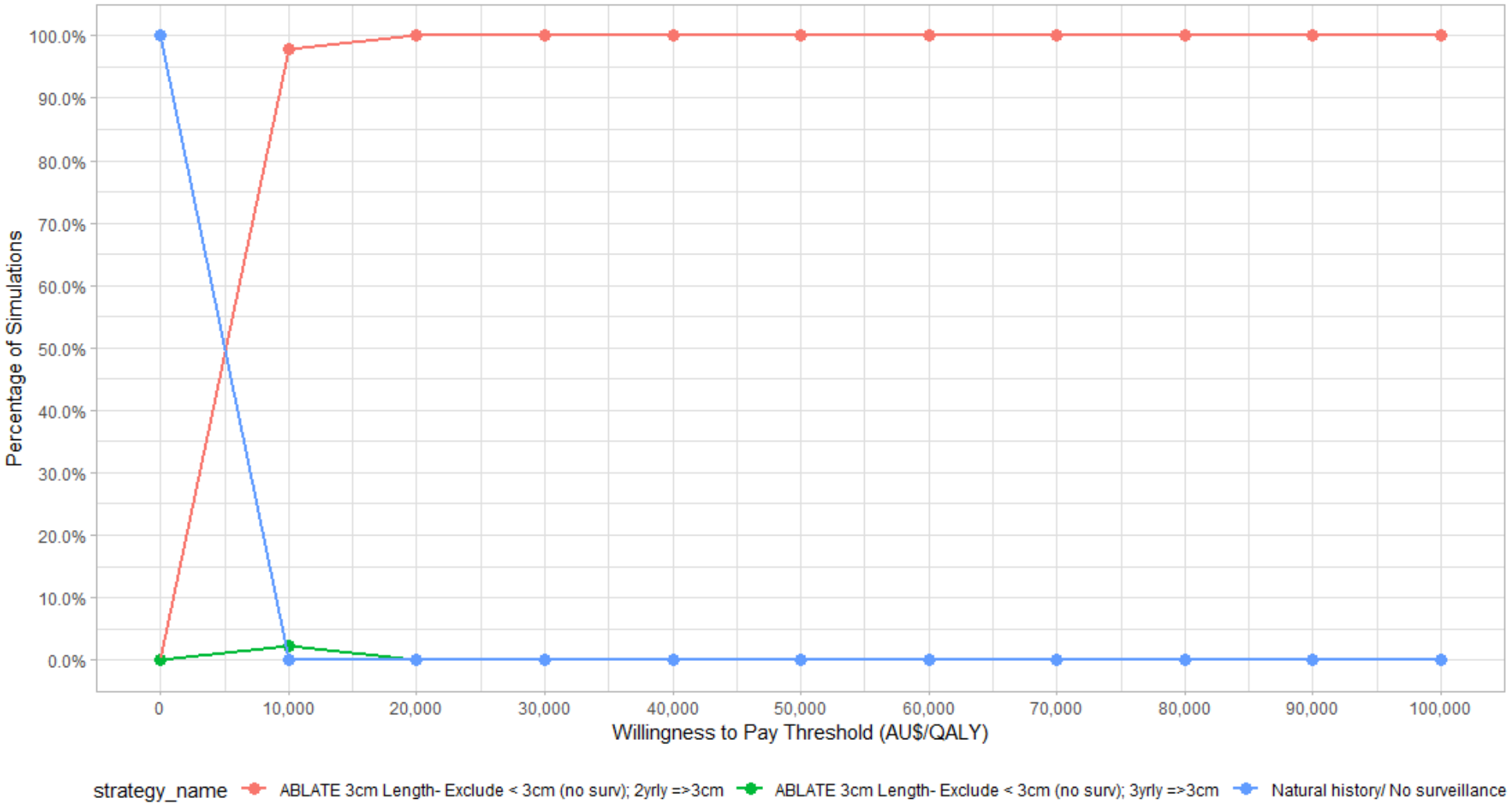


Figure 76. Scatter plot on incremental cost-effectiveness plane for Barrett's oesophagus segment length-based risk-stratified reduction in frequency of endoscopic surveillance combined with ablation of low grade dysplasia in both 2 cm and 3 cm thresholds

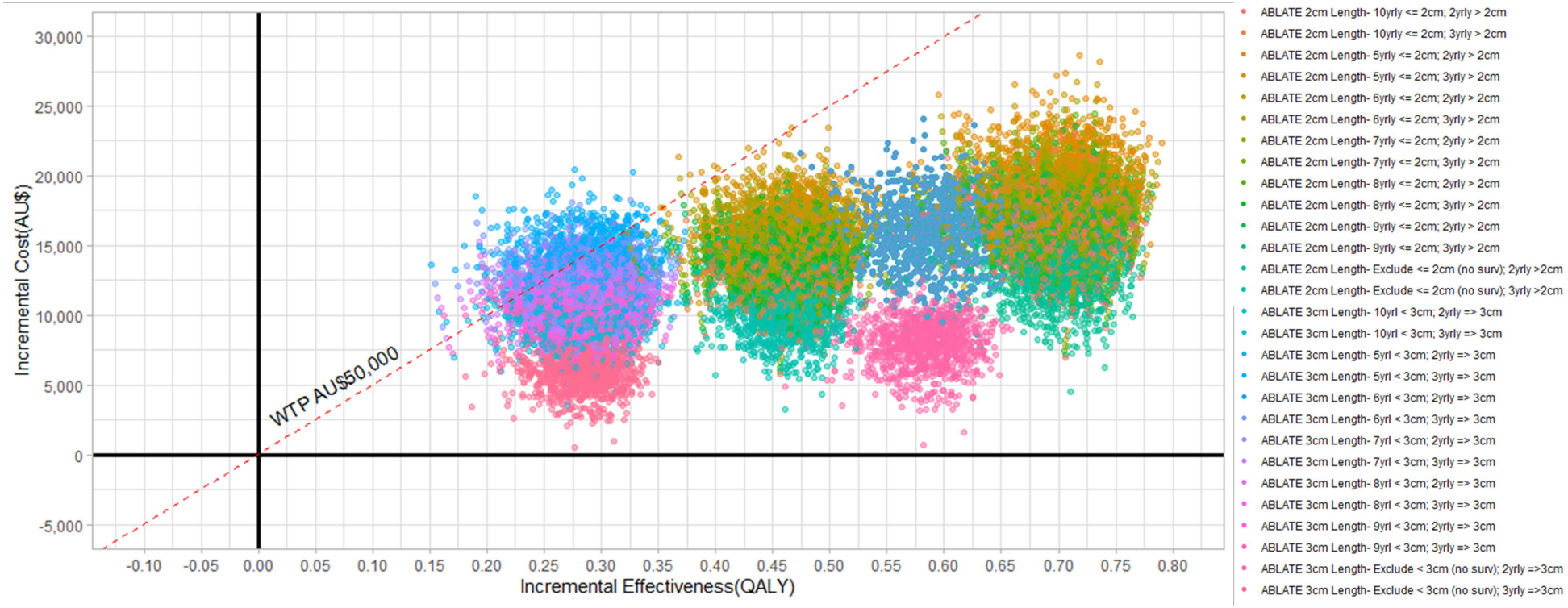
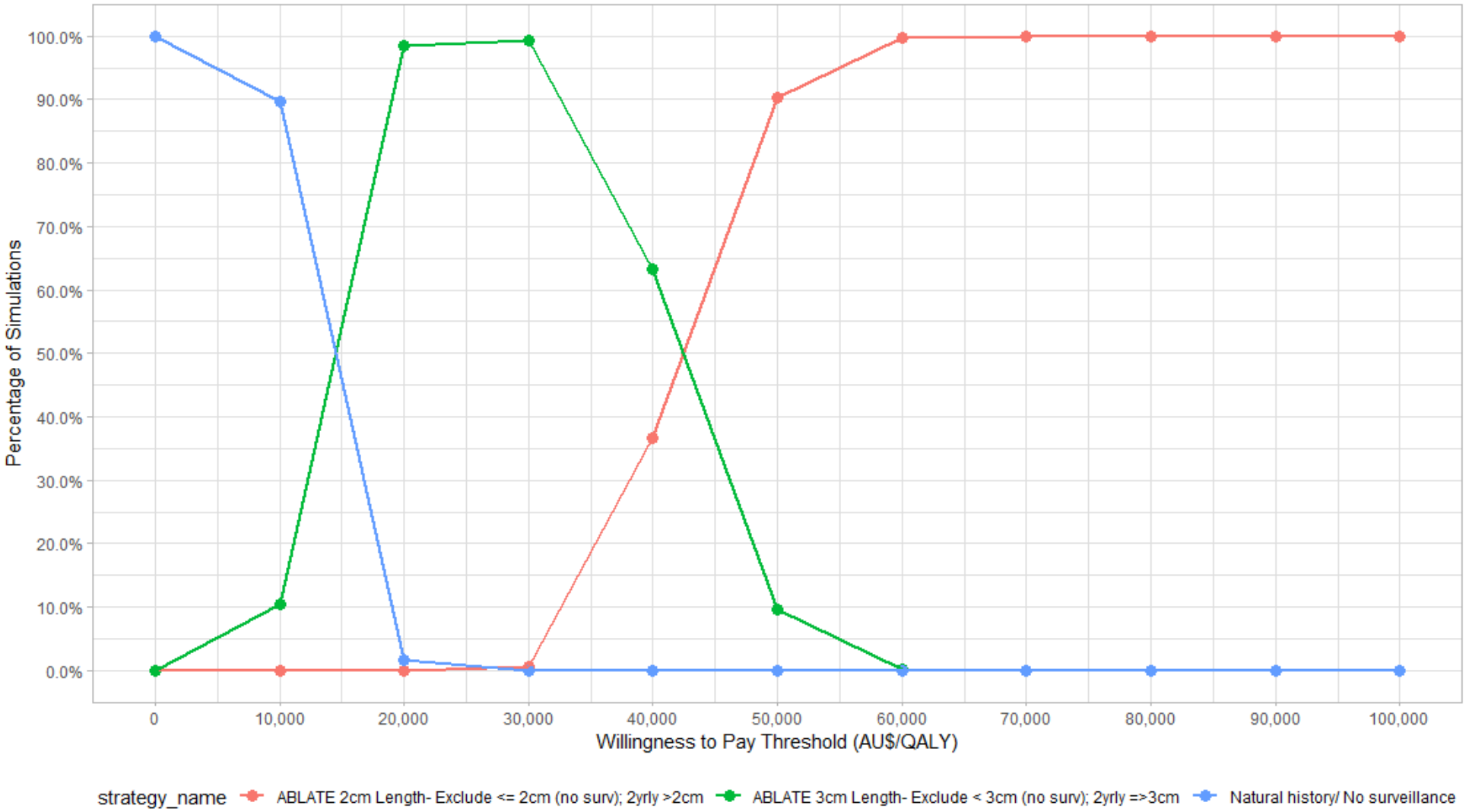


Figure 77. Cost-effectiveness acceptability curve of Barrett's oesophagus segment length based (2 cm threshold) risk-stratified strategies showing percent of simulations each strategy was cost-effective at willingness to pay thresholds between 0-AU$100,000/WTP



7.3 Discussion

Individuals with long-segment Barrett’s oesophagus are a greater risk of progression to oesophageal adenocarcinoma and thus require adequate endoscopic surveillance for detection and treatment at early stages of dysplasia. Low grade dysplasia is an independent risk factor for progression in Barrett’s oesophagus. A subgroup analysis of 11 studies conducted by Krishnamoorthi et al. revealed an odds ratio of 4.25 (95% CI 2.58-7.00) for progression from low-grade dysplasia to oesophageal adenocarcinoma. .Radiofrequency ablation has shown effectiveness in reducing the likelihood of progression in low-grade dysplasia, as demonstrated in a meta-analysis by Qumseya et al., where the relative risk of progression was found to be 0.14% (95% CI 0.04-0.45%) compared to endoscopic surveillance alone.

(206).

Further supporting evidence comes from a systematic review and meta-analysis by Pandey et al., which indicated that radiofrequency ablation had a 96.7% higher chance of eradicating dysplastic Barrett's esophagus compared to surveillance alone. Despite these findings, the treatment of low-grade dysplasia has not been uniformly adopted in all guidelines. The concern lies not in the effectiveness of ablation but rather in factors related to patient selection, accurate diagnosis, and appropriate follow-up.

The accuracy of diagnosing low-grade dysplasia has been a topic of discussion, as it is crucial to identify the subgroup of patients who would benefit from early endoscopic intervention. Variability among expert pathologists in diagnosing low-grade dysplasia complicates the recommendation of invasive treatment options in national and international guidelines. Inflammatory changes in the esophageal mucosa can mimic dysplastic features, and often, treatment with acid suppression therapy followed by repeat endoscopic examinations can help reduce false positives. However, there is likely a subgroup of Barrett's esophagus individuals with persistent dysplasia who can benefit from endoscopic treatments.

However, medical societies have chosen to equivocate, letting clinicians decide between regular 6-monthly endoscopic surveillance or ablation treatments for low-grade dysplasia. This is to primarily reduce the potential for unnecessary invasive procedures, which can lead to complications. Minor adverse events such as strictures are reported to be usually around 5.6% but can be higher up to 37.4% (95% CI 24.4% - 52.6%), with overall adverse rates around 8.8% (95% CI 6.5% - 11.9%) (199, 218). whereas major complications such as oesophageal perforation is lower around 0.6%

(95% CI 0.4% - 0.9%) but reported as high as 2.3% (95% CI 1.3% - 4.1%) (199, 218). Lastly, there are no recommendations for post-endoscopic treatment follow up. Lastly, there are currently no recommendations for post-endoscopic treatment follow-up, as this is an area that is still evolving, awaiting long-term prospective data on the risk of progression and other outcomes.

The results presented in this chapter indicate that ablative treatments in a high risk population with routine 2 yearly endoscopic surveillance is cost-effective. Offering ablation to all individuals who progress to low-grade dysplasia was still seen to be cost-effective in a previous chapter (Chapter 5.3.3) but was dominated by a risk-stratified approach based on Barrett's oesophagus segment length. Although this was always suspected, it had not been fully elucidated, which was one of the major drivers to adding endoscopic treatment of low grade dysplasia into the model.

The results of endoscopically treating low grade dysplasia were surprising at first. Due to the extra costs and disutility associated with endoscopic ablation, I did not expect all length based strategies to be cost-effective. A closer look made it clear that the reduction in oesophageal adenocarcinoma in the high risk group was the key to improved overall outcomes for the cohort in the form of QALYs. The high risk group of individuals with long segment Barrett's oesophagus contributed to a large percentage of the cohort that would have progressed to oesophageal adenocarcinoma without intervention. And yet, it only represented a small fraction of the starting population of non-dysplastic Barrett's oesophagus, and so surveillance and treatment in this group was going to be undeniably cost-effective.

Conversely, the subgroup with short-segment Barrett's esophagus formed a large percentage of the starting population but contributed a disproportionately smaller percentage to the progression of oesophageal adenocarcinoma. As a result, reducing or ceasing surveillance in this subgroup was deemed cost-effective across various surveillance intervals.

Additional evidence to this is provided through the utility values, which depended on surveillance interval prescribed for long segment rather than short segment Barrett's oesophagus. 7 strategies testing surveillance intervals between 5-10 years (and including no surveillance) for short segment and 2-yearly for long segment Barrett's oesophagus generated a narrow range of QALYs between 24.908 – 24.911 (incremental 0.689 – 0.691 QALYs). The other 7 surveillance strategies utilising the same intervals 5-10 years (and including no surveillance) for short segment and 3-year interval for long segment Barrett's oesophagus had utility values between 24.669 – 24.672 QALYs (incremental 0.450 – 0.425 QALYs).

Within both thresholds (2 cm and 3 cm) defining short and long segment Barrett's oesophagus, exclusion of short segment individuals was the most cost-effective endoscopic surveillance strategy when combined with 2-yearly surveillance for non-dysplastic Barrett's oesophagus with endoscopic ablation treatment when detected with low grade dysplasia. When comparing all 28 strategies, at lower willingness to pay thresholds, between ~AU$15,000/QALY to ~AU$43,000/QALY, [0 yearly SSBE (<3 cm); 2 yearly LSBE; LGD ablation] was the most cost-effective endoscopic surveillance strategy. But [0 yearly SSBE (≤2 cm); 2 yearly LSBE; LGD ablation] was the most cost-effective strategy at a willingness to pay threshold of AU$50,000/QALY or higher (shown in Figure 78). This strategy yielded significantly higher QALYs at an acceptable cost.

There are many similarities between these strategies and a few differences. They are both excluding a low risk subgroup of short segment Barrett's oesophagus, performing 2-yearly endoscopies on non-dysplastic long segment Barrett's oesophagus and treating low grade dysplasia with radiofrequency ablation. The first difference is that the low risk subgroup constitutes a smaller percentage of the starting population for the 2 cm threshold (62.5%) than at the 3 cm threshold (75%). Conversely, the high risk subgroup of long segment Barrett's oesophagus is larger at the 2 cm threshold (37.5%) than in the 3 cm threshold group of strategies (25%). The second is the difference in progression rate between the low and high risk groups. The interplay between these two differences was not fully apparent until the model results were analysed, which is why my initial hypothesis that the 3 cm threshold would be the more dominant strategy was only partially correct (dominant at lower willingness to pay threshold).

Individuals with a longer segment of Barrett's esophagus (>3 cm) are likely to be at even higher risk of progression than those with a segment length greater than 2 cm. However, the short segment subgroup of the 3 cm threshold, accounting for 75% of the starting population, is expected to have a higher overall progression rate to oesophageal adenocarcinoma compared to the 62.5% of the 2 cm threshold subgroup.Excluding the former short segment subgroup (3 cm threshold) from surveillance means greatly reduced costs related to endoscopic surveillance but also means more advanced oesophageal cancers presenting with symptoms leading to poorer outcomes (lower QALYs generated). This extends to the high risk subgroup i.e., long segment Barrett's oesophagus at the 2 cm threshold (37.5% of starting population), where the costs for high frequency endoscopic surveillance for non-dysplasia and endoscopic treatments for low grade dysplasia increases the overall costs but delivers better outcomes because of a smaller percentage of the cohort progressing to advanced oesophageal adenocarcinoma.

The long segment subgroup at the 3 cm threshold represents a smaller percentage of the starting population (25%), but there is a higher rate of progression to oesophageal

adenocarcinoma. This results in fewer endoscopies and ablative treatments performed, and since the risk of progression to cancer is high, ablative treatments are greatly helpful in reducing the morbidity and mortality of oesophageal adenocarcinoma. This roughly translates to a lower cost per QALY and is the reason why [0 yearly SSBE (<3 cm); 2 yearly LSBE; LGD ablation] is cost-effective at lower willingness to pay thresholds. Above a certain willingness to pay threshold, the cost involved in generating a higher effectiveness/utility is acceptable, which is why [0 yearly SSBE (≤2 cm); 2 yearly LSBE; LGD ablation] is the dominant strategy at higher willingness to pay thresholds.

Several economic evaluations have tested the cost-effectiveness of endoscopic treatment of low grade dysplasia. Phoa et al. performed a cost-effectiveness analysis alongside the SURF trial, but effectiveness was not measured through QALYs but in terms of “prevented events” and found it to be cost-effective (219). Omidvari et al. also reported that treatment of low grade dysplasia in men was cost-effective at US$53,044/QALY. This would not be cost-effective as per Australian the willingness to pay threshold of AU$50,000/QALY but also is not considering the differences in costs between Australian and American health care services. Of note, gender based approaches were not adopted for endoscopic ablative treatments in this thesis study because reduced surveillance based on gender stratification was not seen to be cost-effective in the previous chapter. The idea was to present an endoscopic surveillance strategy that could be cost-effective with or without ablation of low grade dysplasia.

7.4 Conclusion

The results of the cost-utility analysis indicate that ceasing surveillance short segment Barrett’s oesophagus combined with endoscopic ablation of low grade dysplasia is cost-effective, particularly for the sub-cohort with less than 2 cm of endoscopy visible maximal length. The low costs and favourable outcomes for this type of endoscopic surveillance strategy warrants serious consideration of introducing endoscopic ablation into national and international guidelines.

8 CHAPTER 8- DISCUSSION AND CONCLUSION

8.1 Thesis inception

The overarching aim of the thesis study was to understand and improve the cost-effectiveness of endoscopic surveillance in Barrett's oesophagus. This was done in several smaller steps, starting with an establishing the clinical aspects of Barrett's oesophagus and oesophageal adenocarcinoma that have evolved over the last decade. Oesophageal adenocarcinoma is found mainly in developed nations, where gastroesophageal reflux disease is prevalent. Previously a diagnosis of oesophageal adenocarcinoma would have meant a highly invasive and morbid surgical procedure, but novel treatment options such as endoscopic mucosal resections are now available for cancer restricted to the mucosal layers (or even submucosal layers in some cases). This requires detection at the earliest stages of cancer, which cannot be left to chance. For this reason, endoscopic surveillance is recommended for precursor conditions such as Barrett's oesophagus.

8.2 Lessons from Systematic Review of Economic Evaluations

Individuals with Barrett's oesophagus are considered to be 30-120x risk of developing oesophageal adenocarcinoma. It would seem reasonable to continue endoscopic surveillance for these individuals, but this includes an overwhelming number of endoscopies. Endoscopic surveillance for non-dysplastic Barrett's oesophagus has always been suspected to not be cost-effective, but two previous systematic review of economic evaluations were vague in their conclusions regarding non-dysplastic (metaplastic) Barrett's oesophagus (104, 220). Strong recommendations were provided for endoscopic surveillance of dysplastic Barrett's oesophagus and endoscopic treatment of high-grade dysplasia. Inadequate evidence was available for commenting on cost-effectiveness of endoscopic treatment of low grade dysplasia. This was the starting point for the work presented in this thesis, which is to improve upon the existing literature in providing conclusive evidence for or against 1) endoscopic surveillance in non-dysplastic Barrett's oesophagus and 2) endoscopic treatment of low-grade dysplasia.

There were several reasons behind conducting my own systematic review of economic evaluations regarding cost-effectiveness of endoscopic surveillance. Initially, it was to update the literature with newly published studies, but more importantly, it was also to take an in-depth look into why a conclusion could not be drawn regarding cost-effectiveness of endoscopic surveillance in non-dysplastic Barrett's oesophagus. As presented in Chapter 2, routine endoscopic surveillance did not demonstrate cost-effectiveness in all but one study. As an added benefit, I was also able to extract key features of studies that contributed positively or negatively towards answer the questions regarding cost-effectiveness of endoscopic surveillance in Barrett's oesophagus. The findings from this review were incorporated into the structure of the model with the purpose to maximise the number of strategies to be tested for the surveillance/management of Barrett's

oesophagus as well as be exhaustive in the search for cost-effective alternatives. The findings were:

1) **Improving cost-effectiveness means *reducing or eliminating* endoscopic examinations in low-risk subgroups:** Several publications improved cost-effectiveness by discriminately restricting endoscopic surveillance to a subgroup of Barrett's oesophagus individuals defined by higher risk features. A deeper look (Table 5) into the specifics of these studies revealed that in order to achieve cost-effectiveness, the number of endoscopies must be reduced by 40-80% (compared to a 2-yearly frequency for all). *NB: The endoscopies were variably reduced in the low-risk subgroups, which contributed to the cost-effectiveness of these studies.* Risk stratification was through clinical features such as male gender (123), long-segment Barrett's oesophagus (70) as well as biochemical features such as mutational load/genomic instability (127) or epithelial/stromal abnormalities (118). This concept was incorporated into my state transition model, seen by formation of risk subgroups running in parallel and utilising different strategies such as endoscopic surveillance intervals or ablation at low or high-grade dysplastic Barrett's oesophagus stages.
2) **Endoscopic treatment is cost-effective in high-grade dysplasia:** The review of economic evaluations also confirmed findings from an older systematic review (104). Specifically, endoscopic ablation of high-grade dysplasia was seen to be cost-effective in multiple studies (128, 191, 213, 221-223). This was expected due to the superior outcomes offered by endoscopic treatments (55), reduction in costs as well as improved quality of life compared to oesophagectomy (224). Clinical guidelines across most countries have changed to include high-grade dysplasia as a clinical indication for endoscopic ablation therapy. For this reason, all strategies in my modelling included endoscopic treatment of high-grade dysplasia.
3) **Low-grade dysplasia diagnostic controversy:** All studies commented on the variability in diagnosing low grade dysplasia as major factor affecting cost-effectiveness (123, 219, 221). A low threshold for diagnosing low-grade dysplasia meant less selective endoscopic ablation, which increases costs without the benefit of reducing progression to adenocarcinoma. A tighter definition for low-grade dysplasia helps select individuals with higher potential for conversion to oesophageal adenocarcinoma. Another way of stating this is that cost-effectiveness of endoscopic ablation in dysplastic Barrett's oesophagus depends on the number needed to treat. A strategy that resulted in a lower number needed to treat is preferred to reduce costs while avoiding progression to symptomatic oesophageal adenocarcinoma. The designed strategies in this thesis attempted to correlate the cost-effectiveness with this number needed to treat. In order to determine the number needed to treat, special "payoffs" were designed to be able to calculate the percentage of the cohort that received endoscopic ablation and the percentage that progressed to adenocarcinoma.

4) **Testing all strategies within the same cohort allows better comparison:** A common theme among studies evaluating cost-effectiveness of endoscopic treatment for dysplastic Barrett's oesophagus was to model it in a starting population made entirely of individuals with either low-grade or high-grade dysplasia. From a theoretical perspective, if "endoscopic ablation" is cost-effective compared to "endoscopic surveillance only" strategy, in a cohort of dysplastic Barrett's oesophagus, then it is reasonable to assume it would be cost-effective in the larger/realistic cohort where a percentage of non-dysplastic Barrett's oesophagus slowly progress to dysplasia. In clinical practice, there are some crucial differences that must be considered. In a cohort made of non-dysplastic Barrett's oesophagus that progress to dysplasia as per a given transition probability, only a small percentage of individuals will be treated with endoscopic ablation every cycle. An example is seen in Chapter 5. We see in a cohort made of non-dysplastic Barrett's oesophagus patients only, depending on the surveillance interval, as few as 5% or as high as 46% of the cohort may undergo endoscopic treatment (Table 22). In a clinical setting, the number of dysplastic Barrett's oesophagus seen is low, so results from a cohort of purely dysplastic Barrett's individuals may be highly exaggerated. There is also an element of "lead time" because progression to dysplasia (high or low-grade) in some individuals may occur immediately whereas others may not be detected until years from the index endoscopy. Both these distinctions are not made clear in a model simulating a starting population purely made of dysplastic Barrett's oesophagus. Depending on the model inputs, discount rate, and time horizon of these models, this could either underestimate or overestimate the costs and outcomes. Factors such as conversion of dysplasia to adenocarcinoma come into play because if the conversion rate is low, then endoscopic treatment is likely to be less cost-effective, because the ratio of "treated to cancers avoided" is high and *vice versa*. Additionally, this approach of adapting a new starting population to test different strategies also makes it difficult to compare ICER values between strategies. For example, Hur et al (191) tested the cost-effectiveness of radiofrequency ablation versus endoscopic surveillance for the three stages of Barrett's oesophagus: non-dysplasia, low-grade dysplasia, and high-grade dysplasia. The authors used three different starting populations corresponding to each of the Barrett's oesophagus stages, which yielded different costs and utilities that are only comparable within each starting population. A starting population of non-dysplastic Barrett's oesophagus will have a lower conversion to cancer, whereas a population of dysplastic individuals will have a higher conversion to cancer. The outcomes of these populations are not comparable, and neither are the ICER values. In contrast, Omidvari et al. used a population model, in which they tested 78 different endoscopic surveillance and treatment strategies, concluding that surveillance every 3 years for non-dysplasia with endoscopic ablation of low-grade dysplasia was the most cost-effective strategy for a cohort of males. For the female cohort, the most cost-effective strategy was endoscopic surveillance every 5 years for non-dysplasia and low-grade dysplasia with

endoscopic ablation for high grade dysplasia. Using a previously developed and calibrated population model allowed testing a large number of intervals and interventions, answering the question, “What is the optimal cost-effective strategy?” In other studies, such as Hur et al. (191, 213, 221, 225), where an initial model was not calibrated to run varying intervals of endoscopic surveillance, the research questions had to be more specific. Instead, they posed a different question i.e., what is the comparative cost-effectiveness between [Strategy A (base)] versus [Strategy B]? My aim was to build a model that could keep testing new strategies as we advance our clinical knowledge. To ensure every strategy can be compared on a level playing field, the model developed for this thesis study included undetected states. This allowed realistic simulation of natural progression of Barrett’s oesophagus in the background such that any endoscopic surveillance interval between 6 months and 30+ years could be tested.

5) **Genders are unequally represented in a Barrett’s oesophagus cohort:** Omidvari et al. (123) worked with a population model to test a plethora of strategies, the models developed were specific to male and female populations, and thus the study was limited to testing strategies separately for these cohorts. Males and females represent different proportion of the starting population as well as proportion of those progressing from Barrett’s oesophagus to dysplasia and oesophageal adenocarcinoma. While the conclusions made by Omidvari et al. would probably apply to a mixed-gender population, the interplay of varying the strategy for male versus female subgroups is difficult to predict over a 35-year time horizon. So, it was decided that the model being developed for this thesis would feature a starting population of mixed-gender individuals diagnosed with non-dysplastic Barrett’s oesophagus, which is the exact scenario for any centre involved in the care of patients with this disease.

8.3 Understanding the natural history (undetected progression) of Barrett’s oesophagus

A common aphorism in the world of statistical modelling is, “All models are wrong, but some are useful.” Statistician, Dr. George Box, was referring to the inability of a model to perfectly replicate real world events. This applies to health economic models, which in this study was a Markov model, based on mathematical principles introduced initially by Dr. Andrey Markov. Our group had previously created a cohort model approximately 10 years ago, so building another model from scratch was debated. Ultimately, there were three main reasons the previous model was passed over for a new one: 1) to include updated recommendations for surveillance and treatment of both low-grade dysplasia and high-grade dysplasia, 2) to improve accuracy of model outputs with aid of recently published literature, and 3) to build a model capable of incorporating new and future interventions (including customizability in risk-modified surveillance/treatment).

The first task was to decide whether the model should simulate the general population or a specific cohort diagnosed with Barrett's oesophagus. A literature review was conducted to gain a better understanding of the progression of oesophageal adenocarcinoma from several starting points, i.e. male versus female in general population or male/female with Barrett's oesophagus. Some of the findings from the literature were unsurprising. We knew that the risk of natural progression from non-dysplastic Barrett's oesophagus to oesophageal adenocarcinoma was quite low, approximately 9-13% over 30-40 years. We also knew that the risk of someone in the community, i.e., general population would be low, but calculating the exact risk percentage required more work. Several other insights were gained through this work.

1) Oesophageal adenocarcinoma as an entity is not well subtyped in cancer registries around the world. Although both squamous cell carcinoma and adenocarcinoma of the oesophagus are found within the same anatomical organ, risk factors, treatment, and general localisation are different between these two cancers. Adenocarcinoma is more likely to be found at or near the junction and sometimes is subtyped under gastric adenocarcinoma. Accurately subtype these cancers can help define the natural history of Barrett's oesophagus better.
2) Natural progression of non-dysplastic Barrett's oesophagus has to be assumed from long term prospective studies from Barrett's oesophagus surveillance programs. This certainly cannot be proven, albeit it was mitigated by selecting data from pre-ablation era. For most patients, surveillance was the mainstay,but certain high risk individuals would have been selected for oesophagectomy at the high grade dysplasia stage. Under a surveillance program, compliance to medication and reduction in modifiable risk factors, which may affect disease progression. Additionally, there may well be a sampling bias, as the population in the surveillance programs has been selected due to known or unknown risk factors, which may translate to a higher risk of progression to oesophageal adenocarcinoma. However, no better way of studying natural progression of this disease currently exists.
3) Because Barrett's oesophagus is a silent/asymptomatic disease, it is practically impossible to calculate the prevalence. Several assumptions must be made in order to calculate the prevalence with the existing data. We assumed that all person that developed oesophageal adenocarcinoma would be identified by the cancer registry. This is certainly flawed, as there will be a small number of individuals that would have developed oesophageal adenocarcinoma without seeking medical attention. We assumed this number would be small, however, and without this assumption, it is difficult to calibrate the model. We also assumed that all oesophageal adenocarcinoma comes from Barrett's oesophagus. Currently, the pathophysiology of oesophageal adenocarcinoma hypothesizes a metaplasia → dysplasia → adenocarcinoma model. Whether the macroscopic changes in the oesophagus seen on endoscopy defined as Barrett's oesophagus are the only possible gateway to the cascade of

metaplasia-dysplasia-adenocarcinoma is not yet studied. Several studies have marked that Barrett's oesophagus has not been identified in histopathological analysis of resected oesophageal adenocarcinoma. This may be due to malignant transformation of all metaplastic tissue or inflammatory changes over, but it is still a lingering question within the umbrella of "natural history of Barrett's oesophagus and oesophageal adenocarcinoma."

8.4 Summary of results

Base case results

The main aim of this thesis project was to improve the cost-effectiveness of endoscopic surveillance in Barrett's oesophagus. This was achieved through reducing the frequency of endoscopies in a low risk subgroup, particularly individuals with short segment Barrett's oesophagus. Addition of endoscopic treatment for low-grade dysplasia improved the cost-effectiveness further. An exhaustive 123 strategies were tested, 85 of which varied the interval between endoscopic examinations and another 38 that investigated reduced intervals as well as endoscopic ablation for low-grade dysplastic Barrett's oesophagus. In the base case scenario, 43 out 123 strategies were found to have an ICER value less than the pre-determined willingness to pay threshold of AU$50,000/QALY. A breakdown of these strategies is provided in Figure 78.

Figure 78. Summary of results. Numbers in black indicate total strategies in each group, and numbers in green indicate the strategies with incremental cost-effectiveness ratio less than the willingness to pay threshold of AU$50,000/QALY.

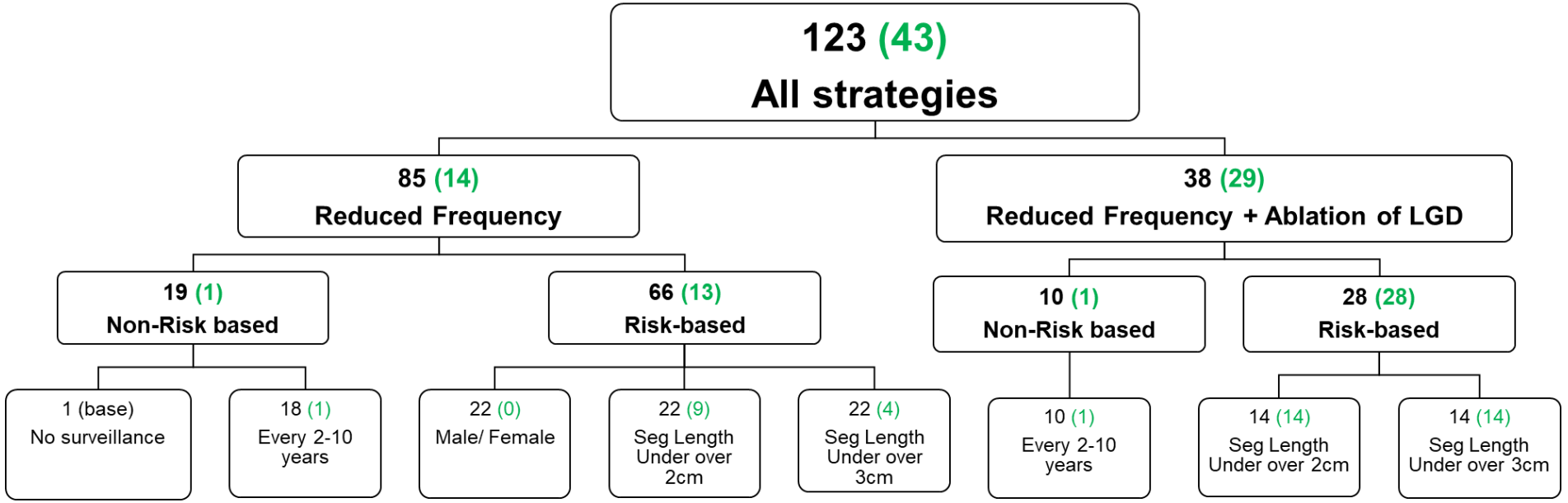


Table 33. Summary of total and incremental costs and health utility values of undominated strategies

	Total Cost	Total QALY	Incr Cost	Incr QALY	ICER (vs. base strategy)	ICER (vs. previous best strategy)
Natural History/No surveillance	AU$6,745	24.219				
Risk subgrouping = Segment Length (3cm threshold) Short segment NDBE = No surveillance Long segment NDBE = every 2 years LGD= Endoscopic ablation after confirmation (@2nd endoscopy)	AU$14,666	24.801	AU$7,921	0.582	AU$13,605 /QALY	AU$13,605 /QALY
Risk subgrouping = Segment Length (2cm threshold) Short segment Barrett's oesophagus = No surveillance Long segment Barrett's oesophagus= every 2 years LGD= Endoscopic ablation after confirmation (@2nd endoscopy)	AU$19,650	24.910	AU$4,985	0.108	AU$18,688 /QALY	AU$45,998 /QALY
Risk subgrouping = None NDBE= every 2 years LGD= Endoscopic ablation after confirmation (@2nd endoscopy)	AU$38,743	24.917	AU$19,093	0.007	AU$45,863 /QALY	AU$2,679,221 /QALY

* QALY= quality adjusted life years; Inc = Incremental; NDBE = Non-dysplastic Barrett's Oesophagus; LGD = Low-grade dysplastic Barrett's Oesophagus

Although 43 of the strategies had ICER values less than the WTP of AU$50,000/QALY, most of the strategies were considered to be “dominated.” This meant that another strategy resulted in either equal or improved health utility value (QALY) while costing less. Only 3 strategies were considered to be “undominated” and are listed in Table 33. Of these 3 strategies, 2 of them were risk-modified strategies for Barrett’s oesophagus segment length. All three strategies implemented endoscopic ablation of low-grade dysplasia. To decide between the 3 strategies, an incremental approach to calculating the ICER value is employed, which is also shown in Table 33 (last column). The strategies are listed in increasing order of effectiveness (QALY). The least effective strategy was “No surveillance (natural history)” with a total QALY of 24.219. Compared to this, the strategy [0 yearly SSBE (<3 cm); 2 yearly LSBE; LGD Ablation] or “*exclusion of short segment Barrett’s oesophagus (3cm threshold) with 2 yearly endoscopy for long segment Barrett’s oesophagus and endoscopic ablation of low grade dysplasia (after confirmation at 2nd endoscopy with expert gastrointestinal pathologist)*” was cost-effective at AU$13,605/QALY. This is below the WTP threshold of AU$50,000/QALY, so is considered cost-effective and the running winner. Then the next most effective strategy is compared to the running winner. This was [0 yearly SSBE (≤2 cm); 2 yearly LSBE; LGD Ablation]. Now a new ICER is calculated with these two strategies, as shown below:

$$AU\$45{,}998/QALY = \frac{(AU\$19{,}650 - AU\$14{,}666)}{(24.910\ \text{QALYs} - 24.801\ \text{QALYs})}$$

This is lower than the WTP threshold and makes the strategy [0 yearly SSBE (≤2 cm); 2 yearly LSBE; LGD Ablation] the new running winner. The next most effective strategy is a non-risk modified strategy, where the whole cohort undergoes 2 yearly endoscopies but receives ablation when low-grade dysplasia is confirmed. Again, the ICER is calculated as shown below:

$$AU\$2{,}679{,}221/QALY = \frac{(AU\$38{,}743 - AU\$19{,}650)}{(24.917\ \text{QALYs} - 24.910\ \text{QALYs})}$$

This new ICER value of AU$2,679,221/QALY is higher than the set WTP threshold, and thus, we stop the exercise and declare the most cost-effective strategy to be [0 yearly SSBE (≤2 cm); 2 yearly LSBE; LGD Ablation].

Probabilistic sensitivity analysis

Deciding between these three strategies is made more accurate with a probabilistic analysis. Results of the probabilistic analysis (Figure 77) indicated that at WTP threshold < AU$15,000/QALY any type of endoscopic surveillance of Barrett’s oesophagus is not cost-effective. To put this into perspective low ICER values are typically associated with interventions that have only marginally higher costs but result in much higher outcomes (QALYs). If a national

funding agency were set at WTP under AU$15,000/QALY, endoscopic surveillance would not be considered a valid program to fund. This does not imply an individual with Barrett's oesophagus would not receive endoscopic surveillance, but simply that a nationwide program would not be the best use of resources.

A relevant side note: WTP thresholds vary with funding agencies, as alluded to in Chapter 1 (sub-section 1.3.6). Several debates exist over how these thresholds should be calculated. In the developed nations, a tacit consensus exists over the approximate WTP threshold. In developing nations, this is not always the case. The World Health Organization suggests in low- and middle-income countries WTP thresholds can be estimated by multiplying their gross domestic product per capita by a factor of 1x-3x (226). The reasoning is that in an economic evaluation, the cost and health-utility values estimate the opportunity cost of one intervention versus another. Cost is self-explanatory, but the health utility value (QALY) estimates the loss or gain of human quality of life, which may be indirectly understood to be loss or gain in economic productivity. This would mean countries like Burundi and South Sudan would have WTP thresholds between AU$400/QALY – AU$1,200/QALY whereas countries like Luxembourg and Ireland would be estimated to have thresholds between AU$200,000/QALY – AU$500,000/QALY. As it is clear, this approach of estimating WTP thresholds using gross domestic product is fraught with issues. This is perhaps a little out of the scope of this thesis but nonetheless raises the question of which undominated strategy would be most cost-effective.

At WTP thresholds < AU$13,000/QALY, the only cost-effective option is "No surveillance (natural history)." This likely applies to low-income nations, who would much rather fund other programs that are less resource intensive and result in much better outcomes, for example, HIV screening (227, 228) or malaria control(229). Between the WTP threshold of ~AU$15,000/QALY – ~AU$43,000/QALY, the strategy [0 yearly SSBE (<3 cm); 2 yearly LSBE; LGD Ablation] was cost-effective in the majority of the simulations. This may apply to several middle-income nations, who would prefer to exclude the majority of (~75%) of Barrett's oesophagus and focus the resources on individuals with long segment Barrett's oesophagus, who have a much higher hazard ratio of progression.

At WTP thresholds > AU$50,000/QALY, the strategy that was cost-effective in 90+% of the simulations was [0 yearly SSBE (≤2 cm); 2 yearly LSBE; LGD Ablation]. For purposes of this thesis, this was the most cost-effective option of all 123 strategies. This ensures that the surveillance program for Barrett's oesophagus:

- Conducts the fewest number of endoscopies on a low-risk subgroup of individuals such as those with short segment non-dysplastic Barrett's oesophagus (reduction of cohort by 62.5%)
- Treats high risk individuals earlier when confirmed with low-grade dysplastic Barrett's oesophagus, which dramatically lowers the conversion to oesophageal adenocarcinoma
- Misses very few cancers compared to a surveillance program that undergoes two-yearly endoscopies for all patients
- Ensures the resources saved by excluding low-risk individuals can be better used towards detecting and treating high-risk individuals

Clinical Implications

From a health economic perspective, the results indicate exclusion of short segment non-dysplastic Barrett's oesophagus is the optimal cost-effective option. However compelling the results are, it is still a modelling experiment, and understandably from a patient representative point of view, it may be difficult to palate. Patients diagnosed with Barrett's oesophagus already enrolled in an endoscopic surveillance program have been told their risk of conversion to oesophageal adenocarcinoma are high. If >60% of that cohort is then told they no longer will be receiving surveillance, it can be confronting. Even if the risks are explained as being miniscule, the perception of the patient is that they have a disease that requires monitoring or treatment, and without conducting either, it is a disservice. Patients who have already undergone endoscopic surveillance prefer an unnecessary and invasive medical test such as endoscopy if it provides them with a guarantee at regular intervals that they are cancer free. We know this from our own group's discrete choice experiment (230), in which patients had a strong aversion to reducing endoscopy frequency from every 5 years compared to every 3 years, if it meant a slightly increased chance of missing cancer. In order to bridge the gap between exclusion of the short segment subgroup, a new analysis was performed. The probabilistic sensitivity analysis for strategies that had increased intervals between endoscopies for short segment Barrett's oesophagus are shown in Figure 79 and Figure 80. These results do not contain strategies that excluded individuals from endoscopic surveillance but instead increased the interval between endoscopies.

Figure 79. Probabilistic sensitivity analysis re-drawn after removing strategies that excluded low-risk subgroups (non ablative strategies for low-grade dysplasia), displayed as a cost-effectiveness acceptability curve

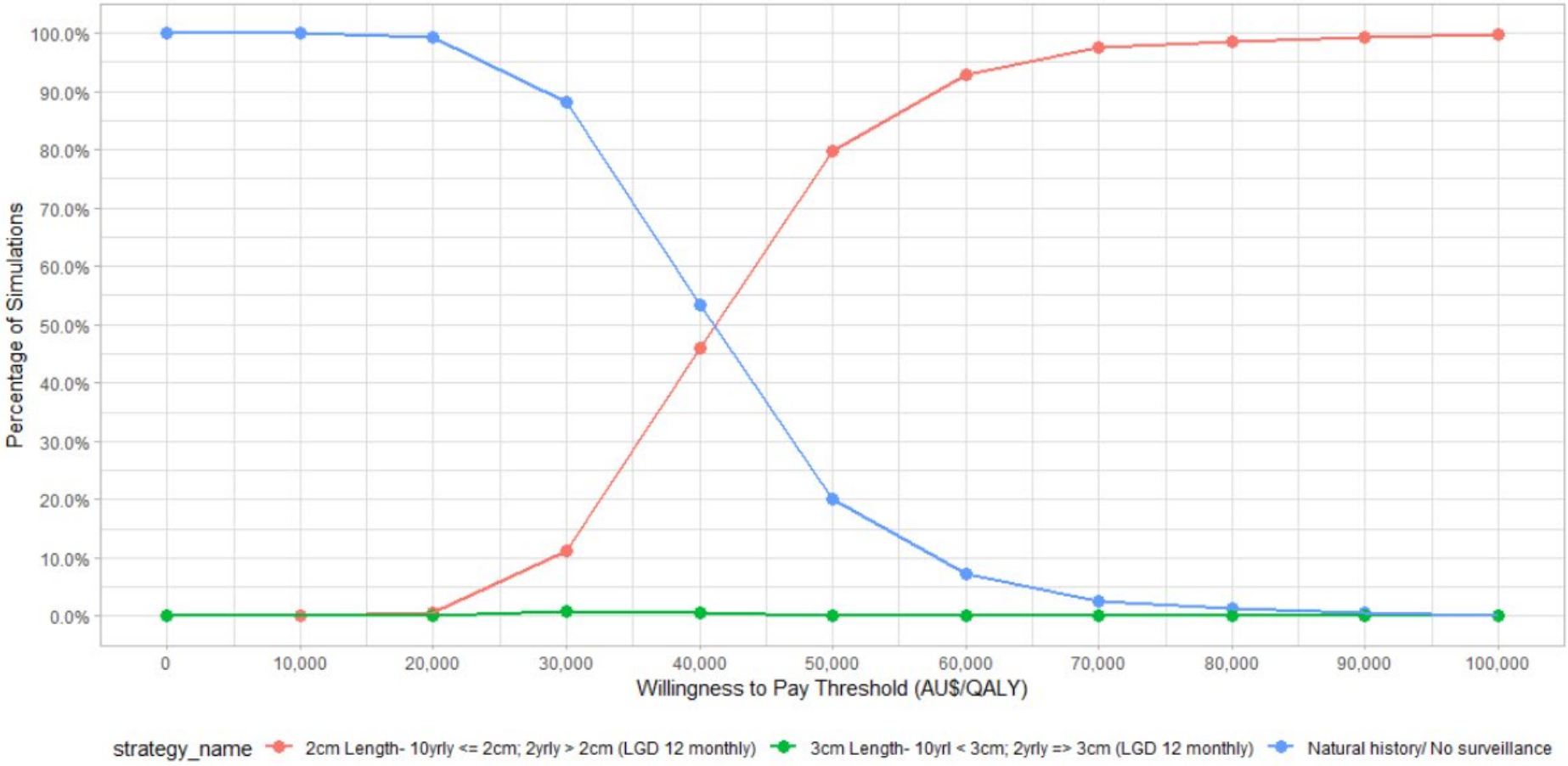
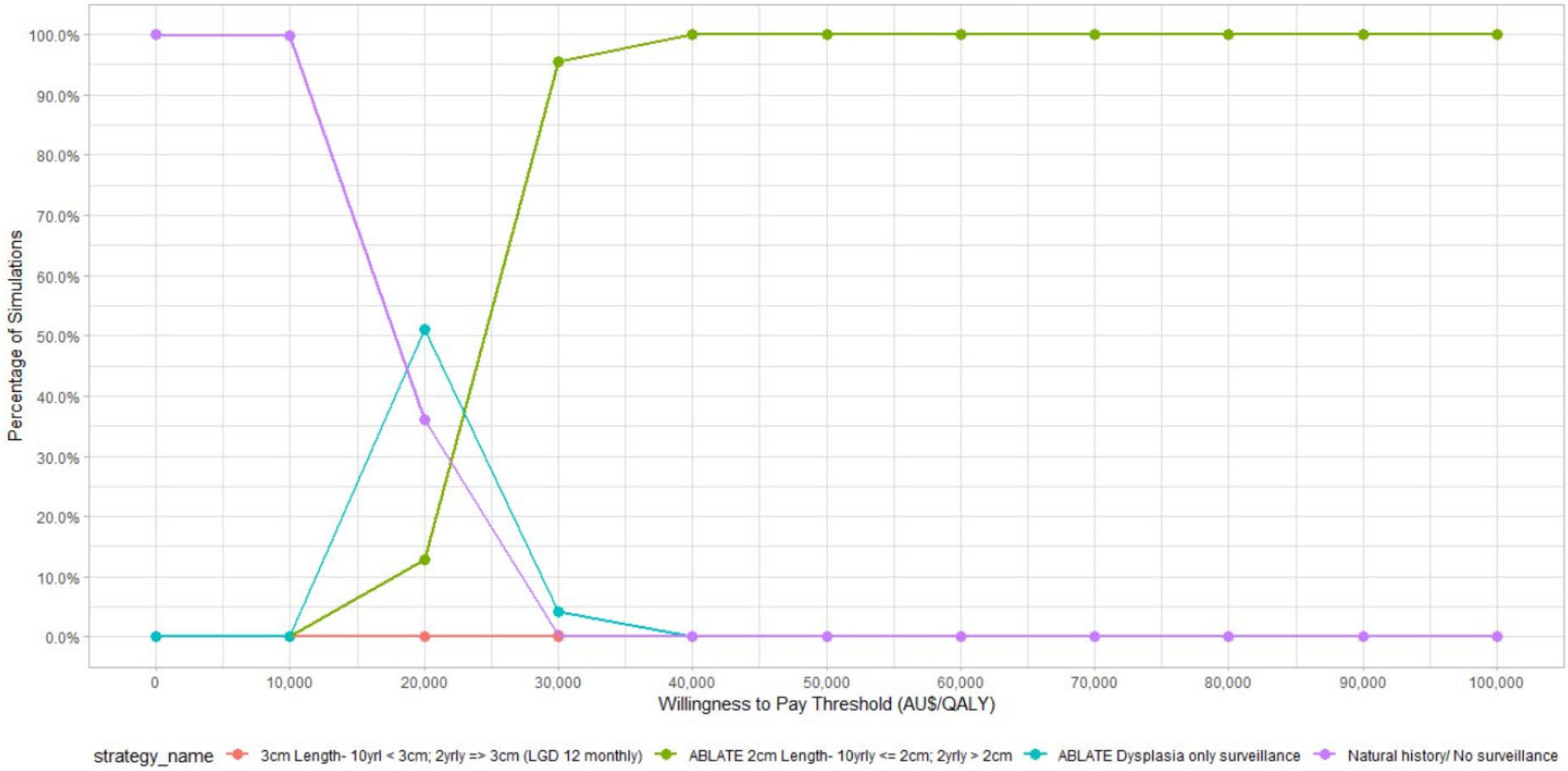


Figure 80. Probabilistic sensitivity analysis after removing strategies that excluded low risk subgroup from endoscopic surveillance (including ablative strategies for low-grade dysplasia), displayed as a cost-effectiveness acceptability curve



As seen in the figures above, the best non-excluding alternative was [10 yearly SSBE (≤2 cm); 2 yearly LSBE; LGD Ablation] (Figure 80). When not performing endoscopic ablation for low grade dysplasia, the most cost-effective strategy was [10 yearly SSBE (≤2 cm); 2 yearly LSBE; LGD 12 months] (Figure 79). This suggests 1) the 2cm threshold is superior to 3cm threshold in classifying short versus long segment Barrett's oesophagus, 2) in the absence of the option to exclude patients from surveillance program, such as those with short segment non-dysplastic Barrett's oesophagus, the best alternative is to increase the interval between endoscopies of that subgroup, and 3) endoscopic ablation of low-grade dysplasia is cost-effective regardless of risk profile. It is likely that if intervals greater 10-yearly were to be tested, they would likely prove to be cost-effective as well. This trend presents a particular opportunity, discussed in the next section (section 8.5- Future directions). These results prove it is not cost-effective to perform routine surveillance on short segment Barrett's oesophagus compared to long segment Barrett's oesophagus. While it would be most cost-effective to exclude all short-segment individuals, ***any amount of reduction in surveillance for this group increases cost-effectiveness***.

One of the strengths of this thesis study is that the results are applicable readily to clinical practice. Length-based risk stratification of Barrett's oesophagus patients was found to be cost-effective under a set of surveillance intervals. Furthermore, ablation of low-grade dysplasia has been proven to be cost-effective in a number of publications (Chapter 7.3, page 250). Evidence collected to populate the presented health economic model was derived from high quality publications. Additionally, a high-fidelity stepwise calibration approach ensured model outputs simulated a cohort of Barrett's oesophagus patients. Developing risk subgroups allowed testing different risk factors without changing the characteristics of the whole cohort, permitting comparison between risk-modified and non-risk-modified set of strategies. Factors impeding uptake of these results include scepticism of results provided by the constructed health economic model, lack of awareness by clinicians about adopting cost-effective treatments, stigma associated with missing cancer diagnoses, and patient perception of culling low risk individuals from a surveillance program.

8.5 Future directions

The future directions of this project are aimed to address the above-mentioned points to improve uptake of results from this project from a clinician and patient perspective.

Clinician and consumer involvement

The particular opportunity presented through these results is a clinician and patient preference study. This thesis has modelled over 100 strategies that combine reduced surveillance intervals with risk-stratification and earlier treatment with endoscopic ablation. Each strategy

detects a number of cancers through the surveillance but also misses some. This percentage of missed cancers eventuates to symptomatic/advanced cancers. A preferences-based study such as a discrete choice experiment can help quantify how patients feel about the trade-off between the percentage of missed cancers and reduction in endoscopic surveillance. It should be explained that 90% of patients diagnosed with oesophageal adenocarcinoma have never been in a surveillance program. Only 10% of the diagnosed oesophageal adenocarcinomas are detected from surveillance programs for Barrett's oesophagus. This means for every cancer detected through the endoscopic surveillance program, 9 are being missed from the community currently. The reduced endoscopic examinations from the low-risk subgroup can be used to identify more cancers in the community. Hence, the "missed cancers" from Barrett's oesophagus will be more than well recompensed by finding high risk individuals in the community that are more likely to develop oesophageal adenocarcinoma. The research question would thus aim to understand, "What number or percentage of cancers are acceptable to miss in low-risk individuals from an endoscopic surveillance program in order to allow more high-risk individuals to be placed under surveillance?" From our model, in a cohort made entirely of long-segment Barrett's oesophagus individuals (2cm threshold), approximately 36.1% would develop high-grade dysplasia and 24.8% would go on to develop oesophageal adenocarcinoma. Conversely, in a cohort of short segment Barrett's oesophagus individuals (2cm threshold), only 3.9% of the cohort would develop high grade dysplasia with 2.7% developing oesophageal adenocarcinoma. This means if 100 short-segmented Barrett's oesophagus patients were excluded from endoscopic surveillance programs, 4 patients would develop oesophageal adenocarcinoma classified as "missed cancers" (over 30+ years). However, this would allow 36 cancers to be detected in 100 long-segment Barrett's oesophagus individuals, resulting in a net gain of 32 oesophageal adenocarcinoma diagnosed through the surveillance program. The question to answer thus is which number is most important to patients/clinicians:

A) The number of cancers missed by removing patients from surveillance termed "missed cancers"

B) Number of potential cancers in the community that are not receiving surveillance

C) The net number of cancers diagnosed through surveillance

A discrete choice experiment would be able to establish the preferences of either clinicians or patients for each of these scenarios as well as quantify how many "missed cancers" are acceptable knowing it would mean 8x more would be diagnosed in the community. Results generated from this type of experiment could be highly supportive of the ultimate decision to reduce endoscopic surveillance in low risk individuals.

Extending the model

The last point leads to the next natural phase of this project, which is creating a model for screening for oesophageal adenocarcinoma in the community to identify more high risk individuals who would benefit from endoscopic surveillance. Cancer survival overall has improved significantly over the last few decades from approximately 30% in 1970 to ~55% in 2010 (231). The improvement was most significant in cancers related to breast, prostate, melanoma, and testis with moderate improvement of survival in cancers of colon/rectum, bladder, cervix, and larynx. Cancers of the brain, stomach, oesophagus, and pancreas have seen some improvement but continue to have the lowest five-year survival rates. A key difference between the cancers with significant improvement versus minimal improvement in survival is introduction of population screening. There are no approved means of screening cancers of the oesophagus, stomach, pancreas, and brain. The simplest way to improve survival for a disease with high morbidity and mortality such as oesophageal cancer is earlier detection, preferably prior to requiring oesophagectomy. The base strategy will likely continue to be “No surveillance/screening – Natural history.” The model will be expanded to include progression to Barrett’s oesophagus from general population. This will aid in discovering cost-effective approaches to screening.

The model was initially created to be able to include new risk factors or discriminators. Factors such as Trefoil factor 3 (TFF3) may be able to identify Barrett’s oesophagus using non-endoscopic examination(34). New diagnostic modalities such as Cytosponge, EsophaCap(35, 232), and biomarkers can easily be added into the model.

8.6 Concluding remarks

As health care costs rise, the services being provided by governmental bodies will start to shrink. It is important for clinicians and funding agencies to identify ways to make health care more cost-effective. Although reducing endoscopic surveillance in a subgroup of individuals seems discriminatory and Machiavellian, the unfortunate reality is that every endoscopy performed on a low-risk individual is an endoscopy that could be detecting someone with a higher risk of developing oesophageal adenocarcinoma. Results of my thesis project advocate excluding short segment Barrett’s oesophagus from endoscopic surveillance programs with ablation of low-grade dysplasia in long-segment Barrett’s oesophagus individuals (classified by the 2cm threshold). This was seen to be cost-effective in >90% of the simulations. Implementing these results requires participation from clinical and consumer community, which starts with dissemination of these results in appropriate fora. Secondly, stated preference studies must be conducted to understand the trade-off between missing cancers in short segment Barrett’s oesophagus individuals and improving cost-effectiveness of the program.

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APPENDIX

Consolidated Health Economic Evaluation Reporting Standards

CHEERS checklist—Items to include when reporting economic evaluations of health interventions.

Section/item	Item no.	Recommendation	Reported on page no./line no.
Title and abstract			
Title	1	Identify the study as an economic evaluation, or use more specific terms such as ''cost-effectiveness analysis'' and describe the interventions compared.	
Abstract	2	Provide a structured summary of objectives, perspective, setting, methods (including study design and inputs), results (including base-case and uncertainty analyses), and conclusions.	
Introduction			
Background and objectives	3	Provide an explicit statement of the broader context for the study. Present the study question and its relevance for health policy or practice decisions.	
Methods			
Target population and subgroups	4	Describe characteristics of the base-case population and subgroups analyzed including why they were chosen.	
Setting and location	5	State relevant aspects of the system(s) in which the decision(s) need(s) to be made.	
Study perspective	6	Describe the perspective of the study and relate this to the costs being evaluated.	
Comparators	7	Describe the interventions or strategies being compared and state why they were chosen.	
Time horizon	8	State the time horizon(s) over which costs and consequences are being evaluated and say why appropriate.	
Discount rate	9	Report the choice of discount rate(s) used for costs and outcomes and say why appropriate.	
Choice of health outcomes	10	Describe what outcomes were used as the measure(s) of benefit in the evaluation and their relevance for the type of analysis performed.	
Measurement of effectiveness	11a	Single study–based estimates: Describe fully the design features of the single effectiveness study and why the single study was a sufficient source of clinical effectiveness data.	
	11b	Synthesis-based estimates: Describe fully the methods used for the identification of included studies and synthesis of clinical effectiveness data.	
Measurement and valuation of preference-based outcomes	12	If applicable, describe the population and methods used to elicit preferences for outcomes.	
Estimating resources and costs	13a	Single study–based economic evaluation: Describe approaches used to estimate resource use associated with the alternative interventions. Describe primary or secondary research methods for valuing each resource item in terms of its unit cost. Describe any adjustments made to approximate to opportunity costs.	
	13b	Model-based economic evaluation: Describe approaches and data sources used to estimate resource use associated with model health states. Describe primary or secondary research methods for valuing each resource item in terms of its unit cost. Describe any adjustments made to approximate to opportunity costs.	
Currency, price date, and conversion	14	Report the dates of the estimated resource quantities and unit costs. Describe methods for adjusting estimated unit costs to the year of reported costs if necessary. Describe methods for converting costs into a common currency base and the exchange rate.	
Choice of model	15	Describe and give reasons for the specific type of decision-analytic model used. Providing a figure to show model structure is strongly recommended.	
Assumptions Analytic	16	Describe all structural or other assumptions underpinning the decision-analytic model.	
methods	17	Describe all analytic methods supporting the evaluation. This could include methods for dealing with skewed, missing, or censored data; extrapolation methods; methods for pooling data; approaches to validate or make adjustments (e.g., half-cycle corrections) to a model; and methods for handling population heterogeneity and uncertainty.	

Table 2 – continued

Section/item	Item no.	Recommendation	Reported on page no./line no.
Results			
Study parameters	18	Report the values, ranges, references, and if used, probability distributions for all parameters. Report reasons or sources for distributions used to represent uncertainty where appropriate. Providing a table to show the input values is strongly recommended.	
Incremental costs and outcomes	19	For each intervention, report mean values for the main categories of estimated costs and outcomes of interest, as well as mean differences between the comparator groups. If applicable, report incremental cost-effectiveness ratios.	
Characterizing uncertainty	20a	Single study–based economic evaluation: Describe the effects of sampling uncertainty for estimated incremental cost, incremental effectiveness, and incremental cost-effectiveness, together with the impact of methodological assumptions (such as discount rate, study perspective).	
	20b	Model-based economic evaluation: Describe the effects on the results of uncertainty for all input parameters, and uncertainty related to the structure of the model and assumptions.	
Characterizing heterogeneity	21	If applicable, report differences in costs, outcomes, or cost-effectiveness that can be explained by variations between subgroups of patients with different baseline characteristics or other observed variability in effects that are not reducible by more information.	
Discussion			
Study findings, limitations, generalizability, and currentknowledge	22	Summarize key study findings and describe how they support the conclusions reached. Discuss limitations and the generalizability of the findings and how the findings fit with current knowledge.	
Other			
Source of funding	23	Describe how the study was funded and the role of the funder in the identification, design, conduct, and reporting of the analysis. Describe other nonmonetary sources of support.	
Conflicts of interest	24	Describe any potential for conflict of interest among study contributors in accordance with journal policy. In the absence of a journal policy, we recommend authors comply with International Committee of Medical Journal Editors' recommendations.	

Note. For consistency, the CHEERS statement checklist format is based on the format of the CONSORT statement checklist.

The Consolidated Health Economic Evaluation Reporting Standards (CHEERS) checklist is a published statement by International Society for Pharmacoeconomics and Outcomes Research (ISPOR), now currently known as The Professional Society for Health Economics and Outcomes Research. This was used to perform the risk of bias analysis for the systematic review in Figure 5. Risk of Bias using Consolidated Health Economic Evaluations Reporting Standards Tool (page 46).

South Australian Barrett's oesophagus surveillance database analysis

Table 34. Characteristics of South Australian Barrett's Esophagus Surveillance Study. EAC: Oesophageal adenocarcinoma; PIB- Progression in Barrett's risk factor; M-length- Maximal length of endoscopically visible Barrett's oesophagus

Variable	**Non-Progressors**, N = 1,041[1]	**Progressors**, N = 28[1]	**p-value**[2]
EAC Reached			
Did not progress	1,041 (100%)	0 (0%)	
HGD	0 (0%)	**15** (54%)	
OAC	0 (0%)	**13** (46%)	
Gender			0.2
Female	364 (35%)	6 (21%)	
Male	671 (65%)	22 (79%)	
Unknown	6	0	
PIB score*			<0.001
High	117 (11%)	21 (75%)	
Intermediate	416 (40%)	7 (25%)	
Low	508 (49%)	0 (0%)	
Time to event	1,179 (448, 2,598)	1,004 (508, 1,864)	0.6
Age at Progression			<0.001
35-49	0 (0%)	3 (11%)	
50-64	0 (0%)	6 (21%)	
65+	0 (0%)	19 (68%)	
Did not progress	1,041 (100%)	0 (0%)	
M Length (Prague)	2.00 (1.00, 4.00)	6.00 (3.75, 8.50)	<0.001
Unknown	5	0	
Short (<= 3cm)			<0.001
Long	267 (25%)	21 (75%)	
Short	769 (75%)	7 (25%)	
Unknown	5	0	

Additional methodology used

This local database contained 18 years of prospectively collected data from 1,089 patients diagnosed with Barrett's esophagus at initial endoscopy and enrolled into a routine surveillance program. Patients are removed from the program if more than two consecutive endoscopic examinations show absence of Barrett's esophagus (no metaplasia and dysplasia on histology).

Ethical approval for the use of the Barrett's oesophagus surveillance database was obtained from Southern Adelaide Human Research Ethics Committee (AUD/20/SAC/138). Several risk factors

were tested, but ultimately only gender and Barrett's oesophagus segment length were used for modelling.

This was a retrospective cohort study, and data were collected from March 2003 - March 2021 including demographics, diagnosis by Barrett's esophagus stage, and circumferential and maximum length of Barrett's segment. Descriptive and statistical analysis was carried out with Rstudio (R version 3.6.3 2020-02-29). Specifically, survival analysis and Cox-proportional hazard models were performed for estimating risk of progressing to HGD or esophageal adenocarcinoma (using "survival" and "survminer" packages). The following parameters were used:

- Time to event analysis
- Event = progression to HGD or OAC
- Time = days
- Cox proportional hazard model
- Variables tested: Age, Sex, PIB risk score, Length (3cm and 2cm cut off)

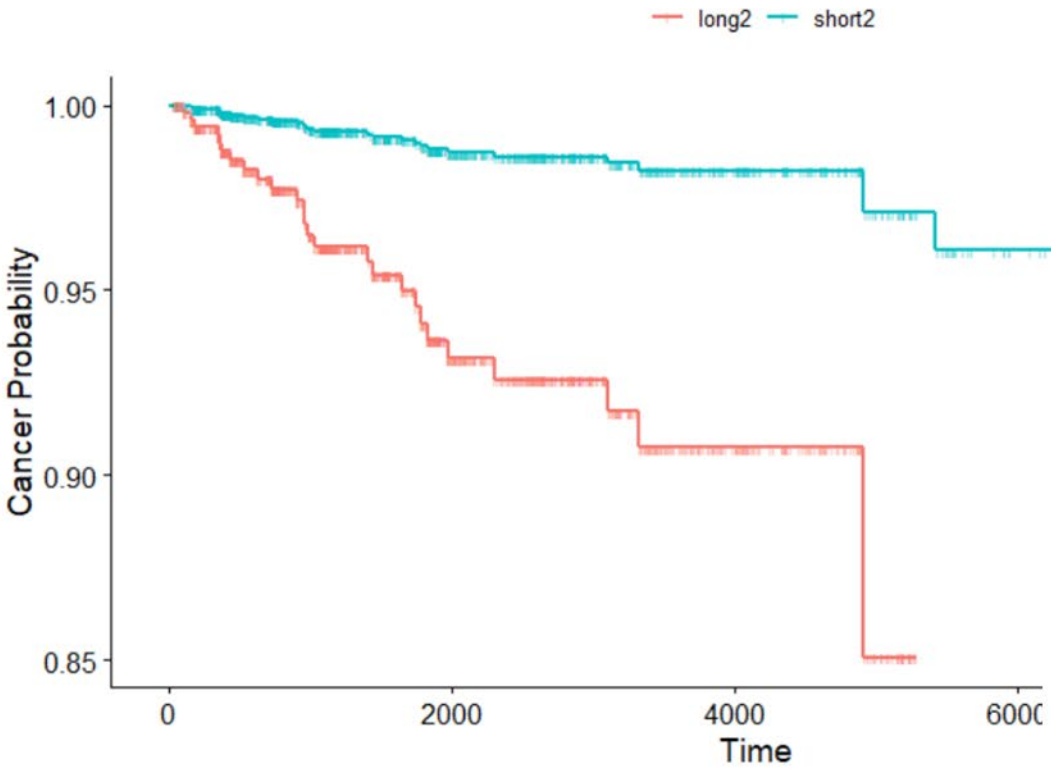
Results

Descriptive results

- Full results in Table 34
- 1069 patients
- 5081 patient years
- 28 progressors (HGD or OAC)
    - 5.51 per 1000 person years incidence
- Compared to other cohort studies
    - Peters 2019 Dutch study = 6.76 per 1000 person years (95% CI = 6.1 – 7.4)
    - De Jonge 2010 (Dutch)
        - Largest study to date
        - 666 HGD/OAC in 78131 person years → 8.5 per 1000 person years (prior to HGD treatment)

s

Figure 81. Time to high-grade dysplasia or oesophageal adenocarcinoma of short segment Barrett's oesophagus (short2) versus long segment Barrett's oesophagus (long2) defined by 2cm threshold. HR = Hazard Ratio



Characteristic	HR[1]	95% CI[1]	p-value
short2			
short2	—	—	
long2	5.46	2.21, 13.5	<0.001

[1] HR = Hazard Ratio, CI = Confidence Interval

Figure 82. Time to high-grade dysplasia or oesophageal adenocarcinoma of short segment Barrett's oesophagus (short) versus long segment Barrett's oesophagus (long) defined by 3cm threshold. HR = Hazard Ratio

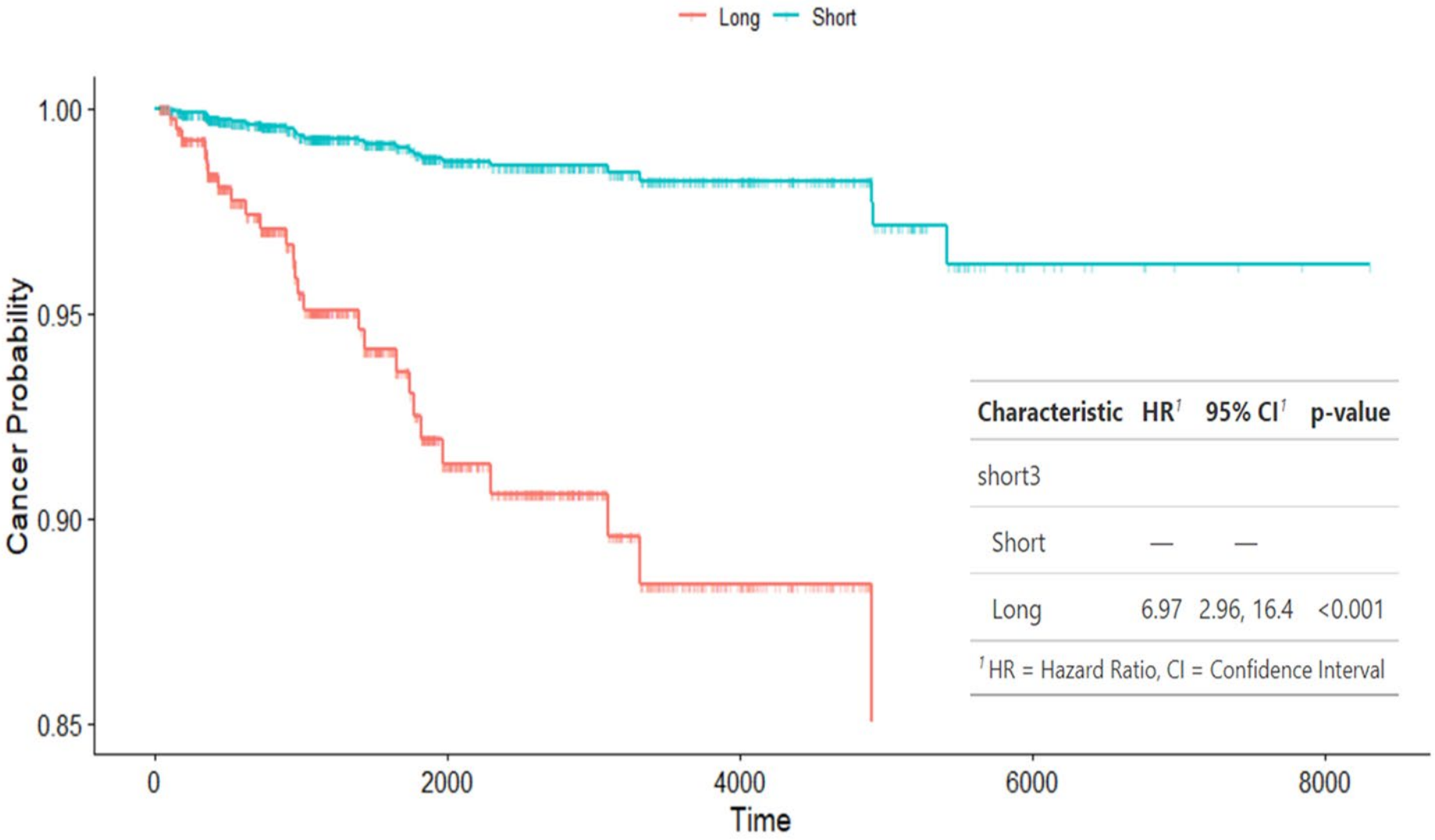


Table 35. Profiles based on permutations of risk factors and the percentage they represent in total cohort. Largest proportion of surveillance program is made of non-progressors.

Sex	Age	PIB Score	Length (<= 3cm)	Progression	n	% total cohort
Female	**over 50**	**Low**	**Short**	**Non-Progressors**	**203**	**19.19%**
Male	**over 50**	**Intermediate**	**Short**	**Non-Progressors**	**169**	**15.97%**
Male	**over 50**	**Low**	**Short**	**Non-Progressors**	**129**	**12.19%**
Male	over 50	Intermediate	Long	Non-Progressors	93	8.79**%**
Male	**less than 50**	**Intermediate**	**Short**	**Non-Progressors**	**76**	**7.18%**
Male	over 50	High	Long	Non-Progressors	59	5.58%
Male	**less than 50**	**Low**	**Short**	**Non-Progressors**	**56**	**5.29%**
Female	**less than 50**	**Low**	**Short**	**Non-Progressors**	**54**	**5.10%**
Female	over 50	Low	Long	Non-Progressors	48	4.54%
Male	over 50	High	Short	Non-Progressors	37	3.50%
Male	less than 50	Intermediate	Long	Non-Progressors	27	2.55%
Female	over 50	Intermediate	Short	Non-Progressors	23	2.17%
Female	over 50	Intermediate	Long	Non-Progressors	17	1.61%
Male	less than 50	High	Short	Non-Progressors	11	1.04%
Female	less than 50	Intermediate	Short	Non-Progressors	7	0.66%
Male	less than 50	High	Long	Non-Progressors	6	0.57%
Female	less than 50	Intermediate	Long	Non-Progressors	4	0.38%
Female	over 50	High	Long	Non-Progressors	4	0.38%
Male	over 50	Low	Long	Non-Progressors	4	0.38%
Female	less than 50	Low	Long	Non-Progressors	2	0.19%
Male	less than 50	Low	Long	Non-Progressors	1	0.09%
Male	**over 50**	**High**	**Long**	**Progressors**	**14**	**1.32%**
Male	**over 50**	**High**	**Short**	**Progressors**	**4**	**0.38%**
Female	**over 50**	**Intermediate**	**Short**	**Progressors**	**3**	**0.28%**
Female	**over 50**	**Intermediate**	**Long**	**Progressors**	**2**	**0.19%**
Male	**less than 50**	**High**	**Long**	**Progressors**	**2**	**0.19%**
Female	**over 50**	**High**	**Long**	**Progressors**	**1**	**0.09%**
Male	**less than 50**	**Intermediate**	**Long**	**Progressors**	**1**	**0.09%**
Male	**over 50**	**Intermediate**	**Long**	**Progressors**	**1**	**0.09%**

Table 35 and Table 36: Results

The Barrett's oesophagus surveillance study database was analysed for patterns, specifically which risk factors were at the lowest risk of progression from metaplasia to high grade dysplasia or adenocarcinoma. This was to aid in reducing surveillance in the low-risk groups. The first step was to draw from our own cohort the characteristics of non-progressors. The following risk factors were identified in our cohort: Sex, Age, Progression in Barrett's Score (PIB), and Length of Barrett's (<=3cm threshold, short vs. long). In the non-progressor pool, 29 permutations of these risk factors were identified. The most prevalent (least likely to progress) was Female + Over 50 + Low PIB score + Short segment, which comprised of roughly one-fifth of the entire non-progressor pool. This was an indicator of where the reduction in surveillance should be aimed at, which formed the hypothesis of the health economic modelling.

Table 36. Risk profiles of non-progressors and percentage they represent in the total number of non-progressors.

Sex	Age	PIB score	Length (<= 3cm)	%
Female	over 50	Low	Short	33.10%
Male	over 50	Intermediate	Short	21.50%
Male	over 50	Low	Short	17.80%
Male	less than 50	Intermediate	Short	9.20%
Female	less than 50	Low	Short	6.13%
Male	less than 50	Low	Short	6.13%

* Females with short segment Barrett's oesophagus make up the largest percentage of non-progressors.

Model and model characteristics

List of abbreviations/terms in model

Term	Explanation
Clone	Decision analytic tree is a cloned copy of indicated
NH	Natural history/ No surveillance
endo_surv	Designated to endoscopic surveillance
NH_	Designated to no surveillance (natural history)
sympx_OAC	Detected and treated when oesophageal adenocarcinoma symptoms present
endosurg	Endoscopic treatment with Radiofrequency ablation
NDBE	Non-dysplastic Barrett's oesophagus
Bfree	No metaplasia (regression from NDBE)
LGD	Low grade dysplasia
HGD	High grade dysplasia
OAC	Oesophageal adenocarcinoma
Risk1	Belongs to risk stratified group 1
Risk2	Belongs to risk stratified group 2
Risk3	Belongs to risk stratified group 3
Localised	Cancer with local extension
Regional	Cancer with nodal spread
Unstaged	Patients not fully staged at diagnosis
Metastatic	Cancer spread to distant organs
allcause_mort	All-cause mortality (non-cancer)
c_endo	Cost of endoscopy
c_ndbe	Cost of database upkeep
freq_KNDBE	Interval between endoscopies
undNDBE	Non-dysplastic Barrett's oesophagus
undBfree	No metaplasia (regression from non-dysplastic Barrett's oesophagus)
undLGD	Low grade dysplasia
undHGD	High grade dysplasia
symp OAC	Patients presenting with cancer due to symptoms (not through surveillance)
Regress und	Regress undetected
LGD_reg	Regression from low grade dysplasia to non-dysplastic Barrett's oesophagus
p_S_dysp	Probability of endoscopic surveillance in dysplastic Barrett's oesophagus
p_NS_dysp	Probability of no surveillance in dysplastic Barrett's oesophagus
2ndscope	Confirmation of Low-grade dysplasia with second endoscopy within 6 months
non-confirmed	No confirmation of low-grade dysplasia performed within 6 months
EET	Endoscopic treatment with Radiofrequency ablation
RFA	Radiofrequency ablation
Needs redo	Requires re-endoscopic treatment with radiofrequency ablation
_tunnel	Treeage Pro function which allows counting number of cycles spent in the loop
#	Complement of all probabilities in a given set of branches from a node

Using Clones

Clones are copies of a set of nodes and branches that can be assigned as required. This offers a specific advantage when developing a model because altering the original ensures all cloned copies are changed accordingly, eliminating the need to comb through the model over again each time. The use of identical/parallel health states for each risk factors required cloned nodes. 29 clones listed below were employed in this model.

Table 37. List of Clones

Index	Clone Name	Node Label
1	NH_ndbe_risk1	No surveillance
2	endo_surv_ndbe_risk1	Endo surveillance
3	NH_no_IM_risk1	No surveillance
4	endosurv_no_IM_risk1	Endo surveillance
5	NH_lgd_risk1	No surveillance
6	endosurv_lgd_risk1	Endo surveillance
7	nh_hgd_risk1	No surveillance
8	endosurv_hgd_RFA_risk1	Radiofrequency ablation
9	sympx_OAC_risk1	Progress symp OAC
10	whole thing	Natural history
11	NH_ndbe_risk2	No surveillance
12	endo_surv_NDBE_risk2	Endo surveillance
13	NH_no_IM_risk2	No surveillance
14	endosurv_no_IM_risk2	Endo surveillance
15	NH_lgd_risk2	No surveillance
16	endosurv_lgd_risk2	Endo surveillance
17	nh_hgd_risk2	No surveillance
18	endosurv_hgd_RFA_risk2	Radiofrequency ablation
19	sympx_OAC_risk2	Progress symp OAC
20	empty one	Stay/cured
21	NH_ndbe_risk3	No surveillance
22	endosurv_ndbe_risk3	Endo surveillance
23	NH_no_IM_risk3	No surveillance
24	endosurv_no_IM_risk3	Endo surveillance
25	NH_lgd_risk3	No surveillance
26	endosurv_LGD_risk3	Endo surveillance
27	nh_HGD_risk3	No surveillance
28	endosurg_HGD_RFA_risk3	Radiofrequency ablation
29	sympx_OAC_risk3	Progress symp OAC

Decision analytic structure

Full structure of model is provided below (in sections).

Figure 83. Model starts with a cohort of individuals with non-dysplastic Barrett's oesophagus

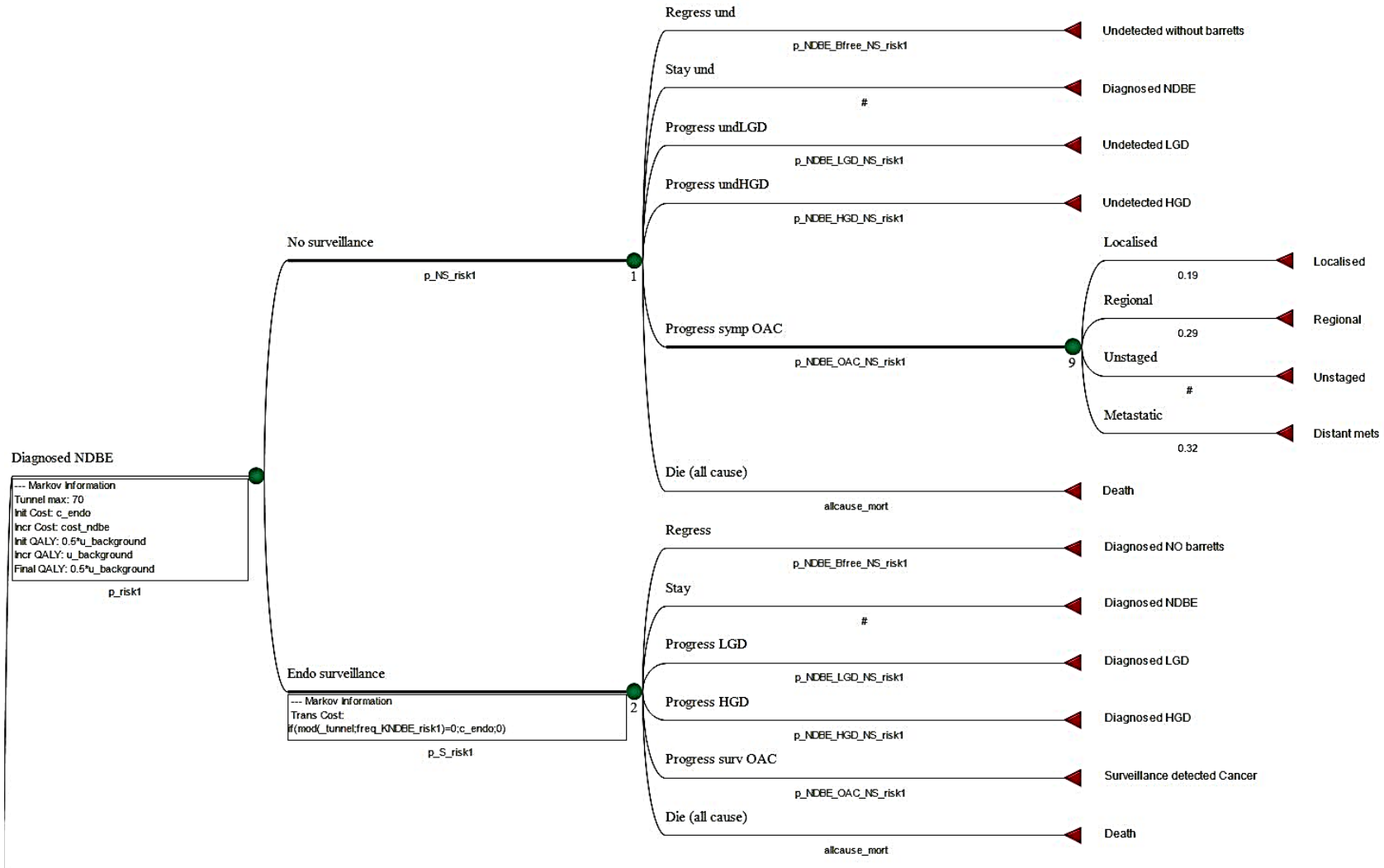


Figure 84. Regression state “No Barrett’s” which is synonymous to No intestinal metaplasia

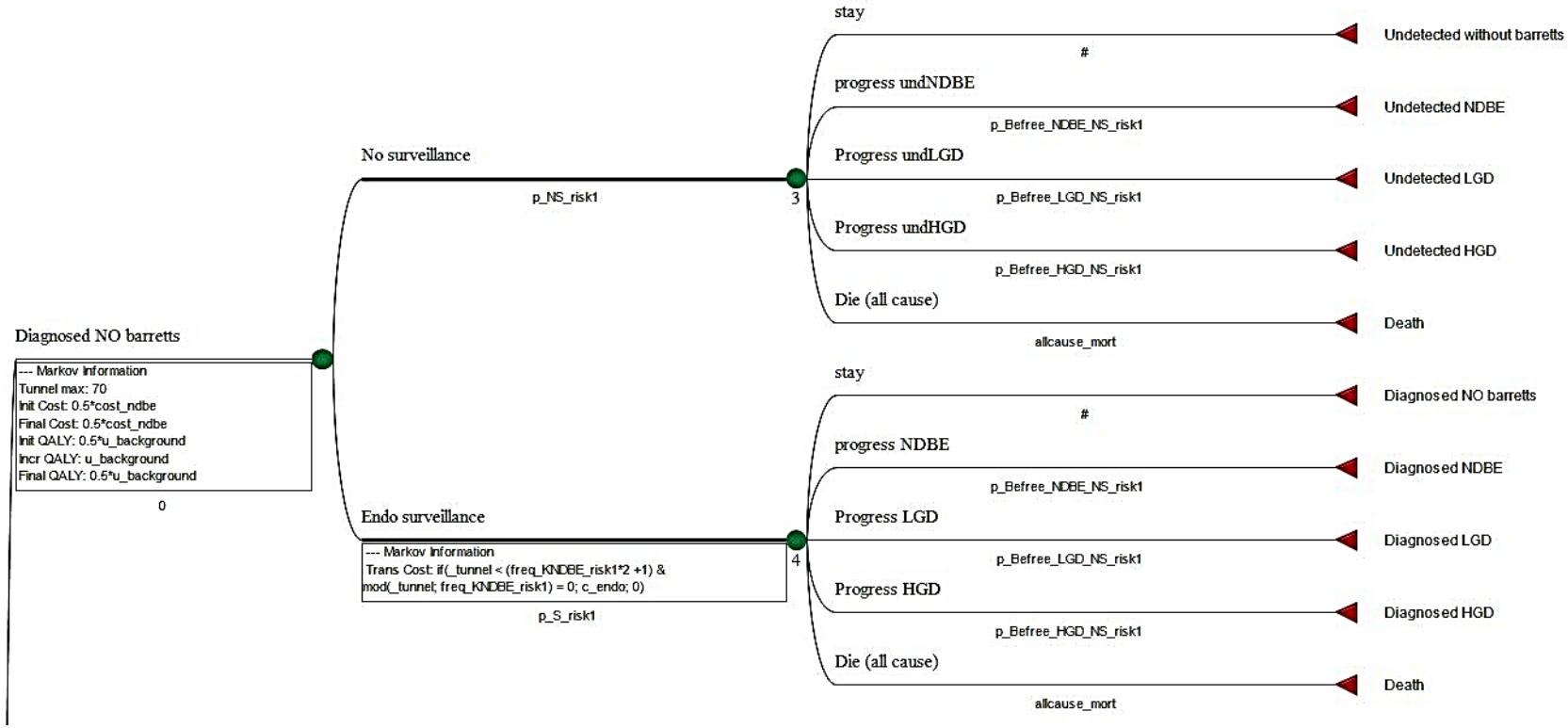


Figure 85. Low grade dysplasia: can undergo no surveillance or endoscopic surveillance. Within endoscopic surveillance, cohort can undergo "confirmatory 2nd endoscopy" or "no confirmatory 2nd endoscopy." Can also undergo ablative treatment or not

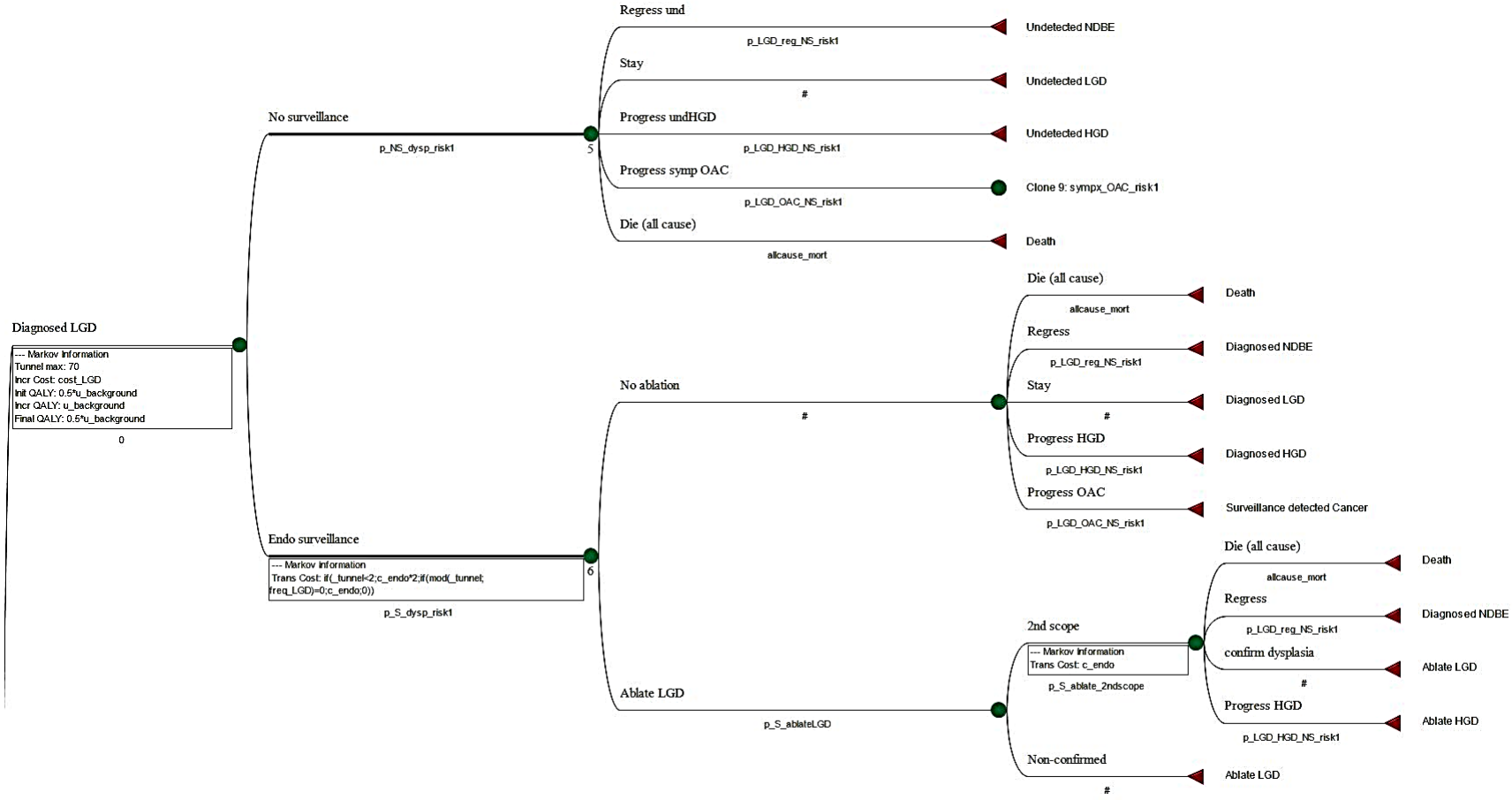


Figure 86. High grade dysplasia. Undergoes no surveillance or endoscopic treatment (after confirmation)

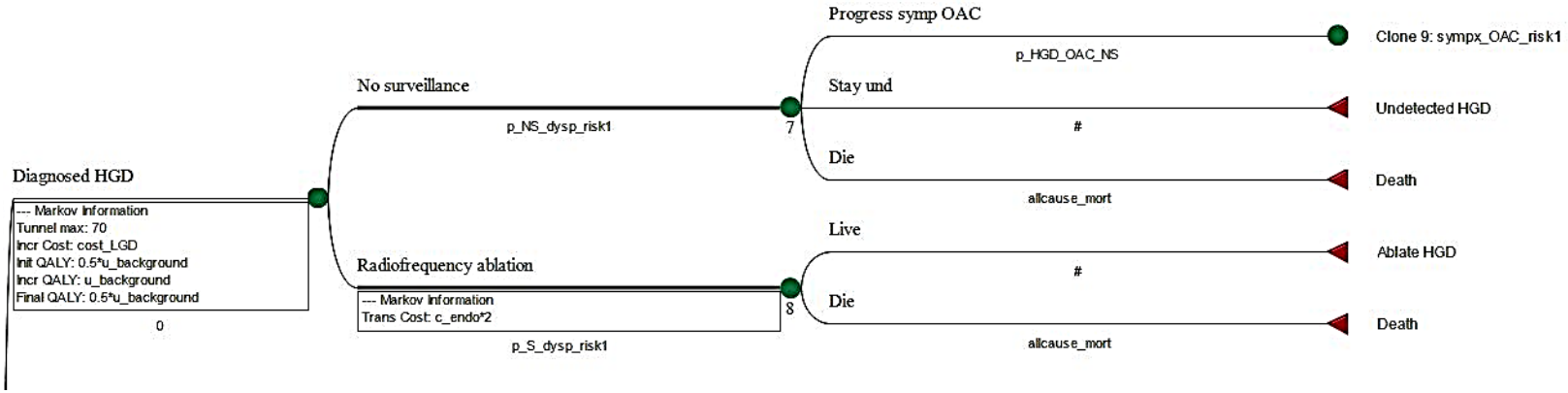


Figure 87. Undetected states can switch to endoscopic surveillance as seen here using tunnel function.

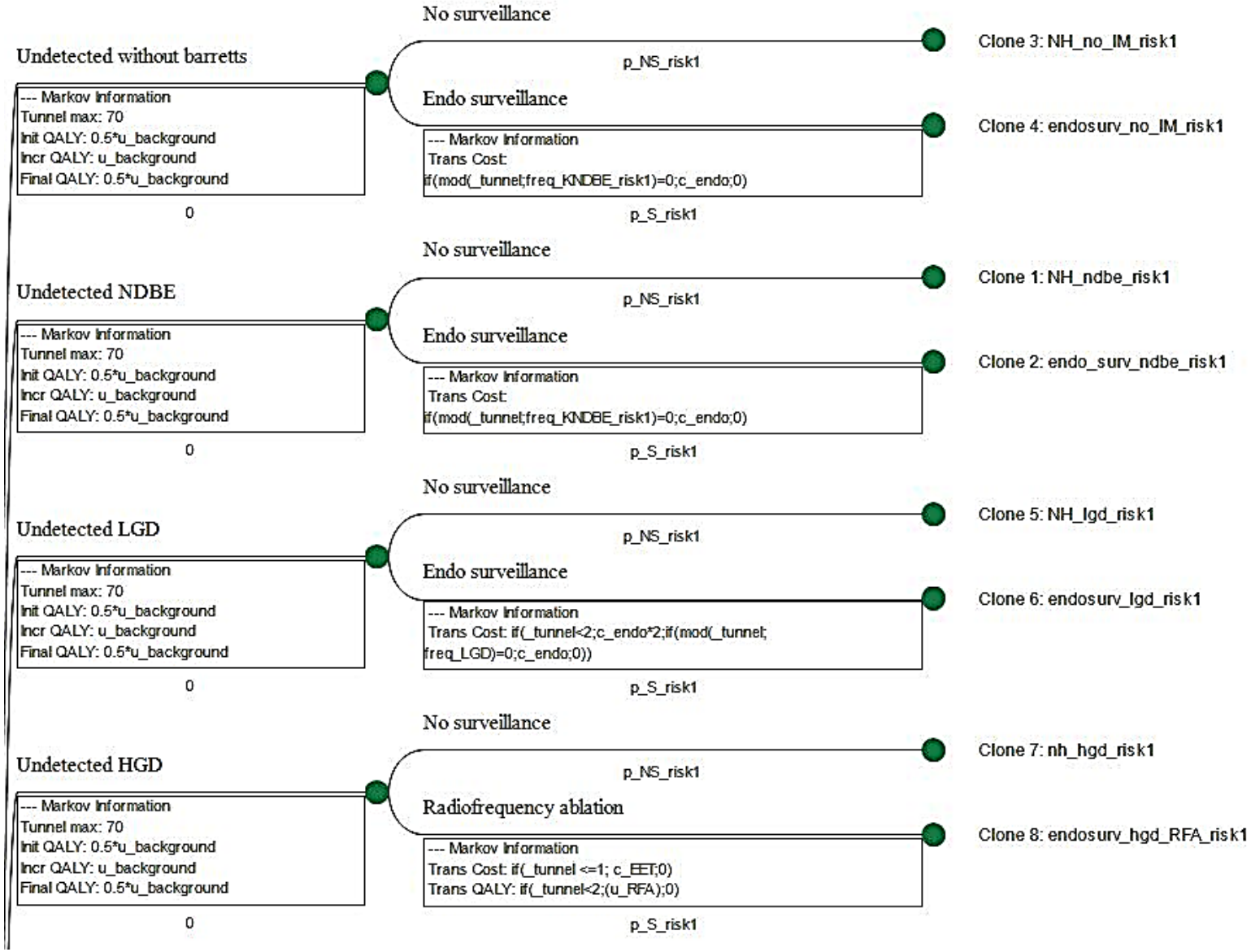


Figure 88. Ablation of low-grade dysplasia

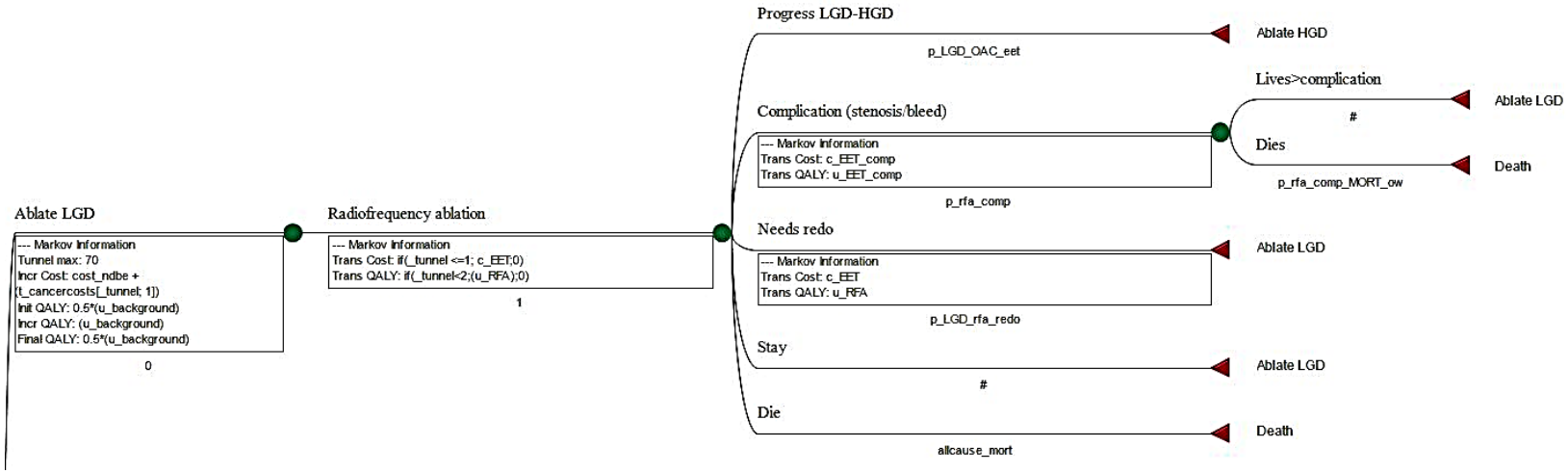


Figure 89. Ablation of high-grade dysplasia

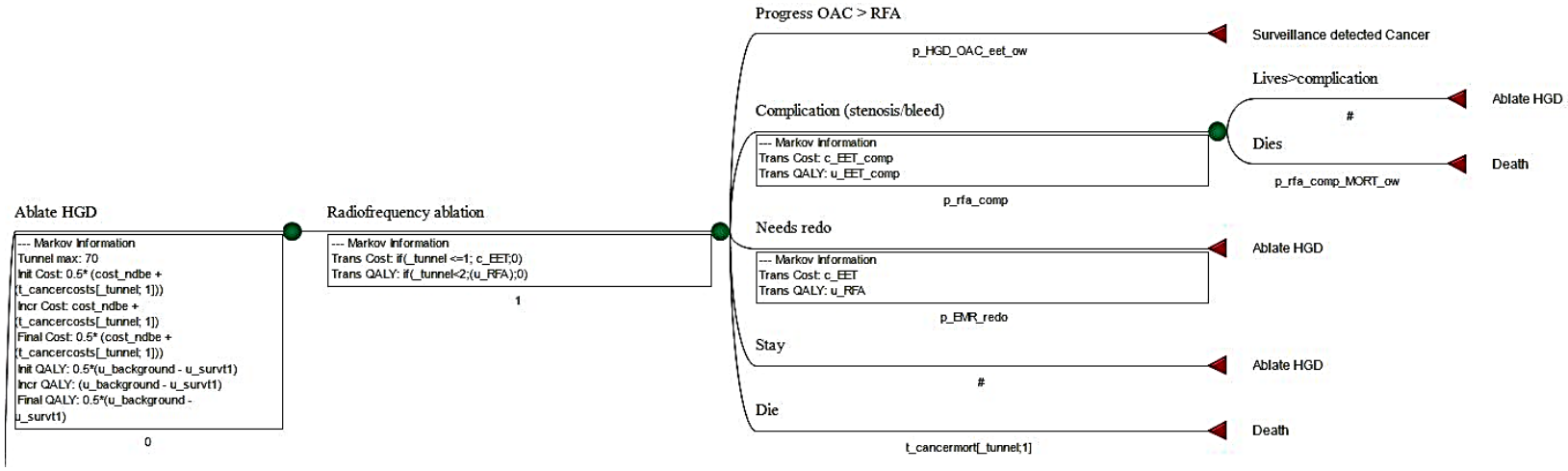


Figure 90. Endoscopic treatment of early-stage oesophageal adenocarcinoma

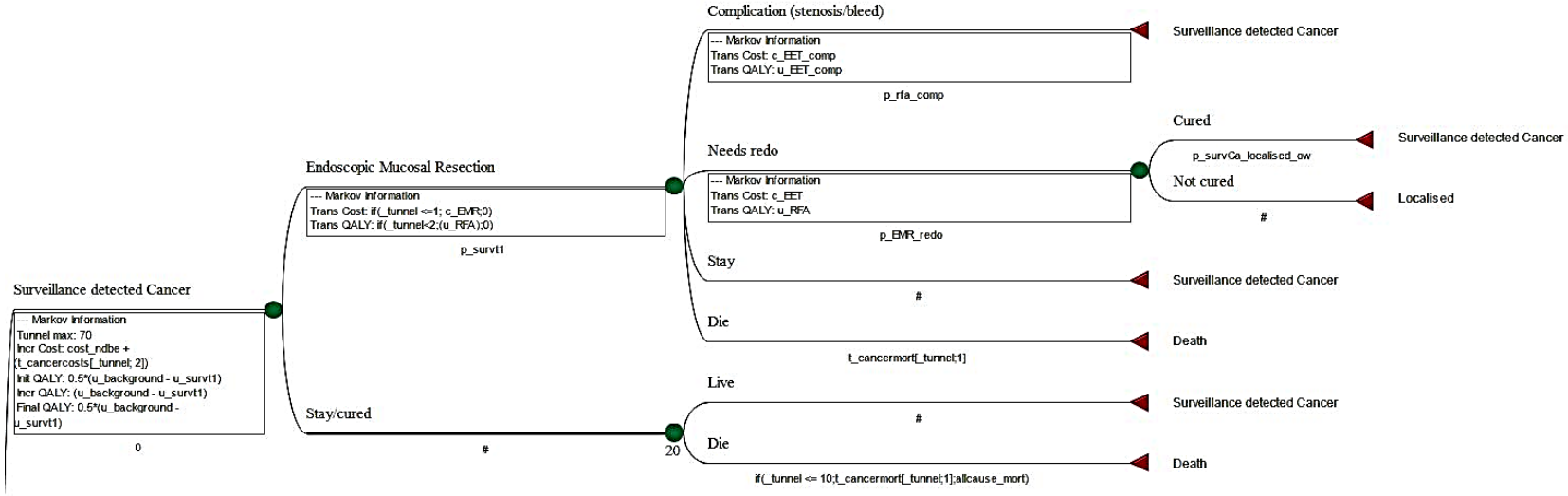


Figure 91. Symptomatic oesophageal adenocarcinoma states.

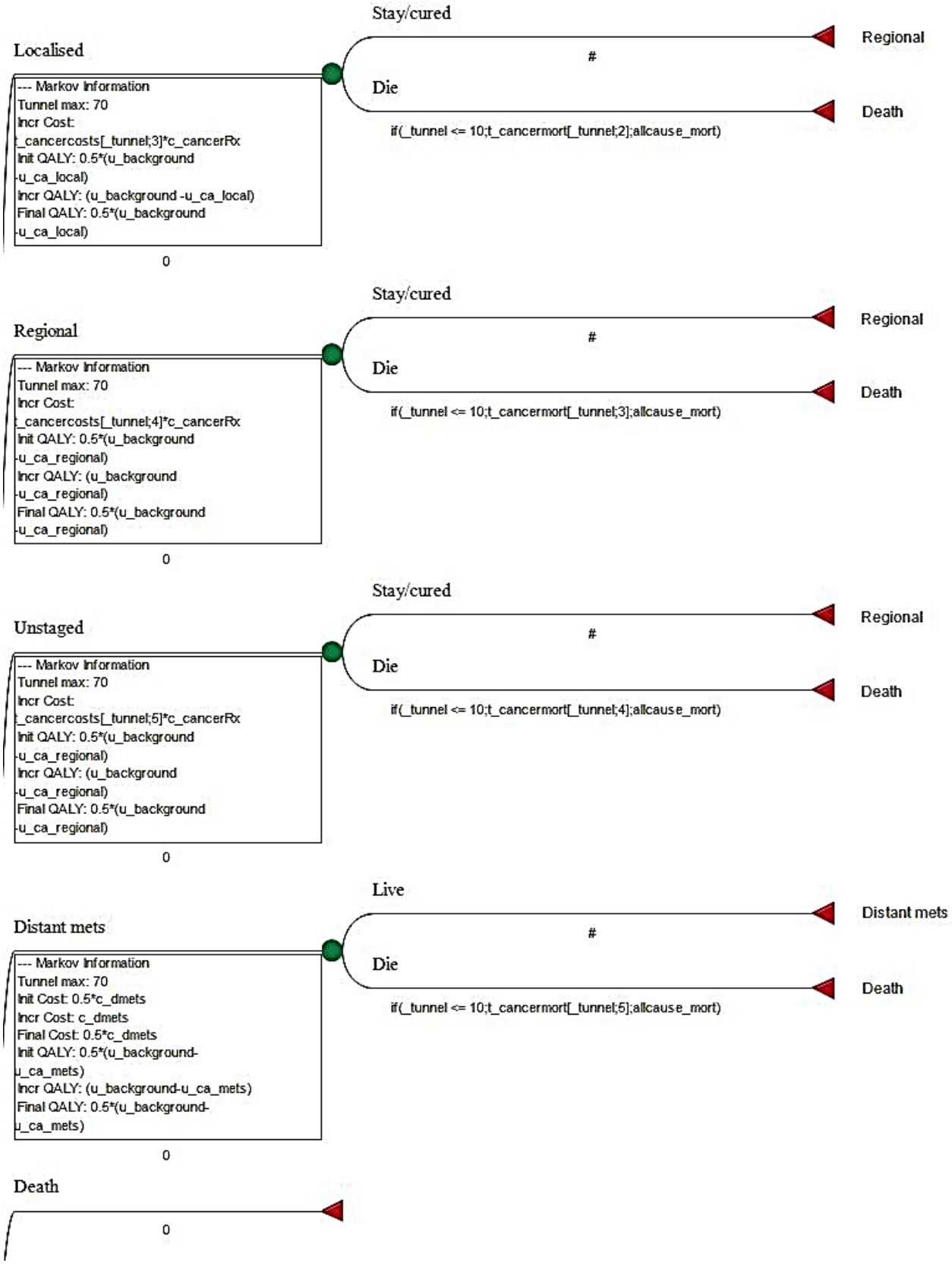


Figure 92. Risk 2 health states.

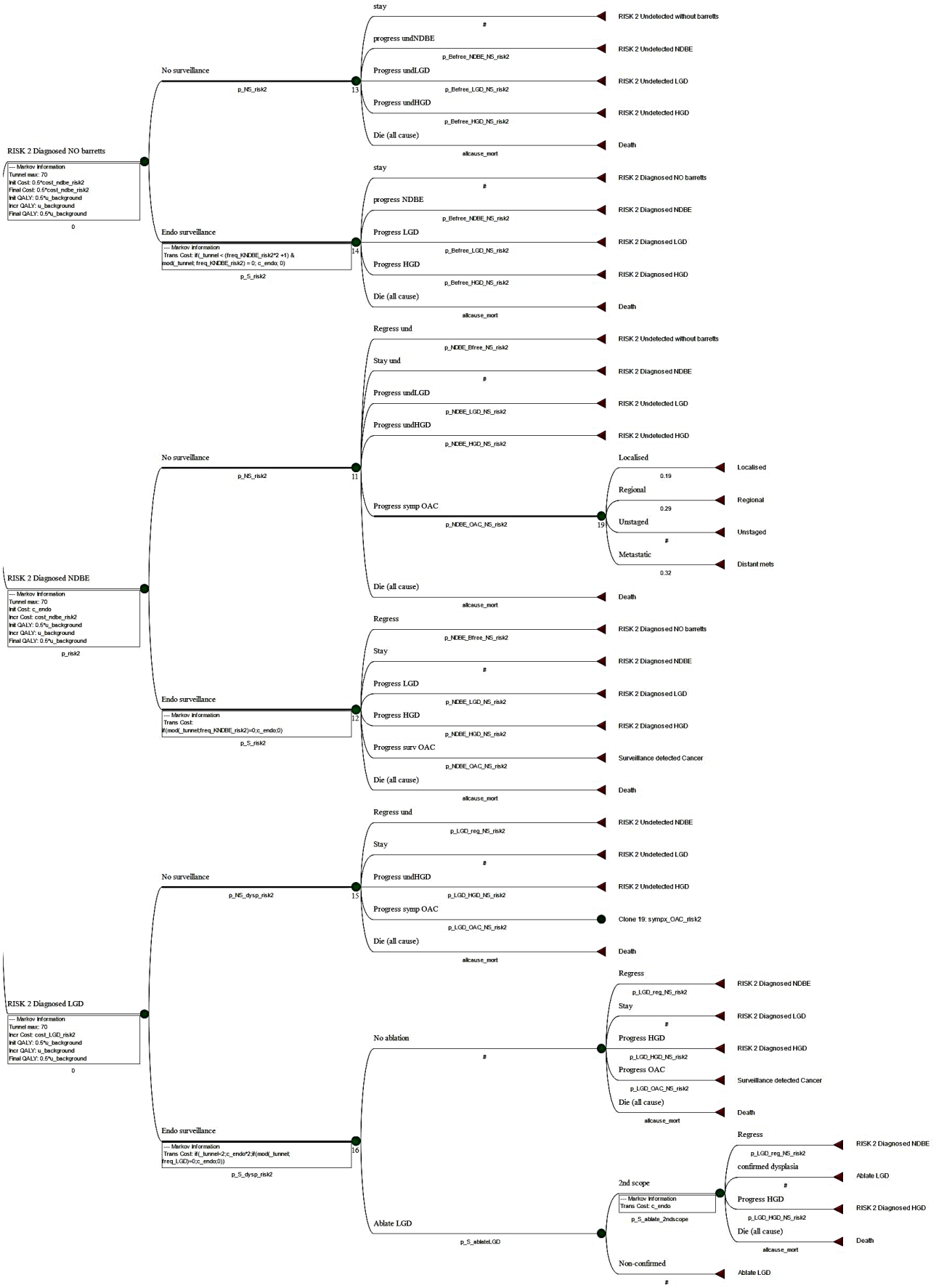


Figure 93. Risk 2 health states continued

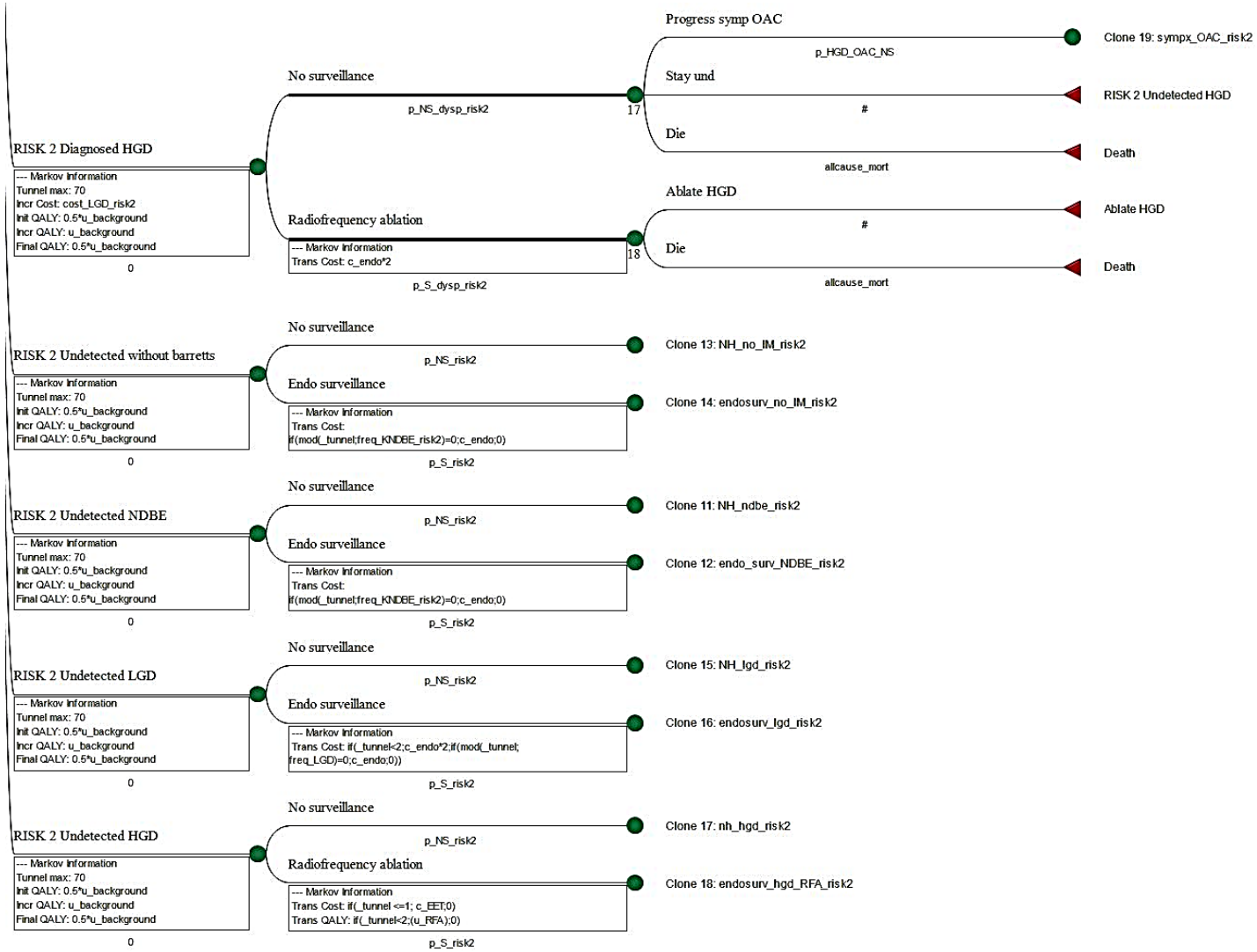


Figure 94. Risk 3 health states

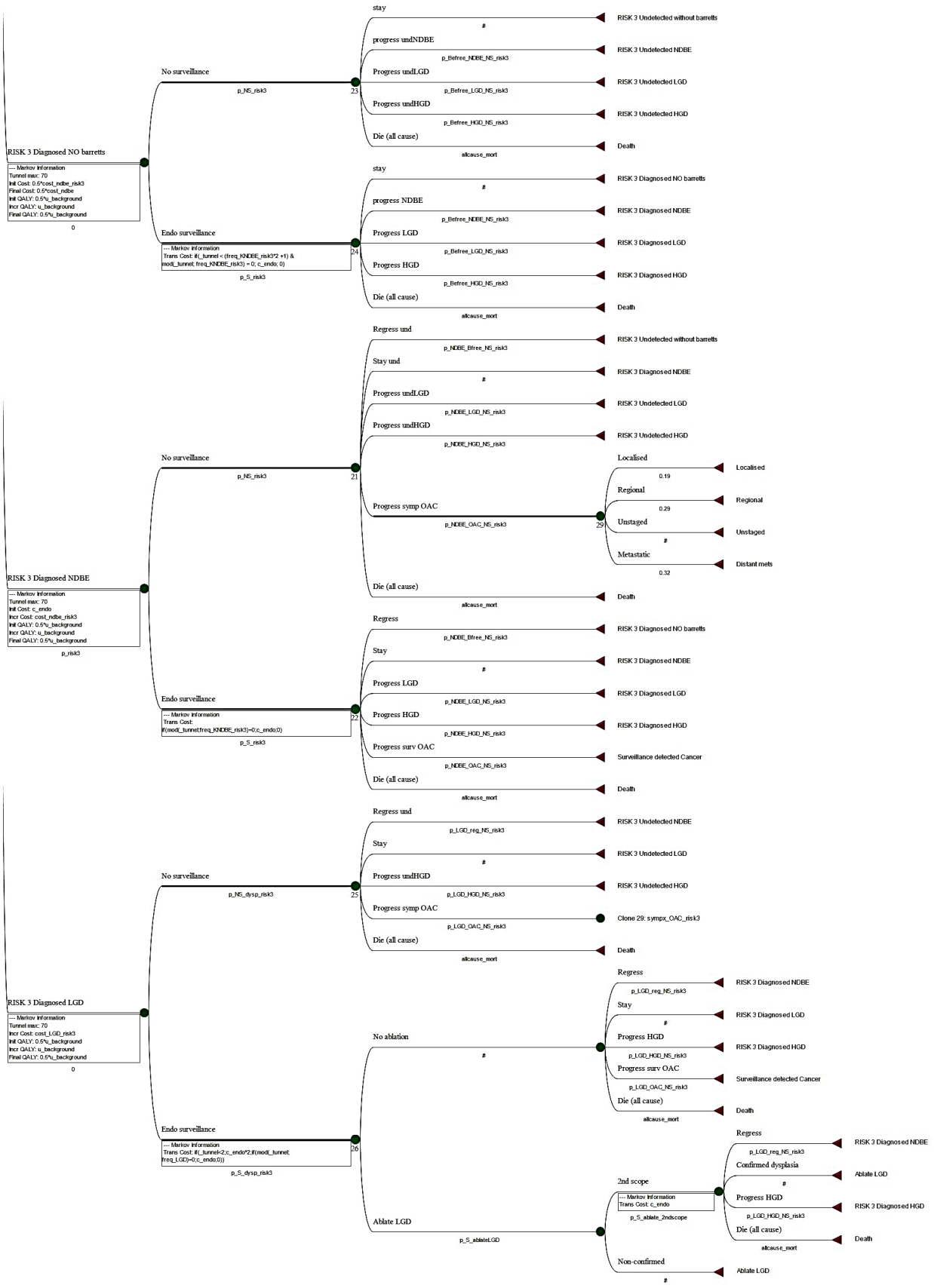
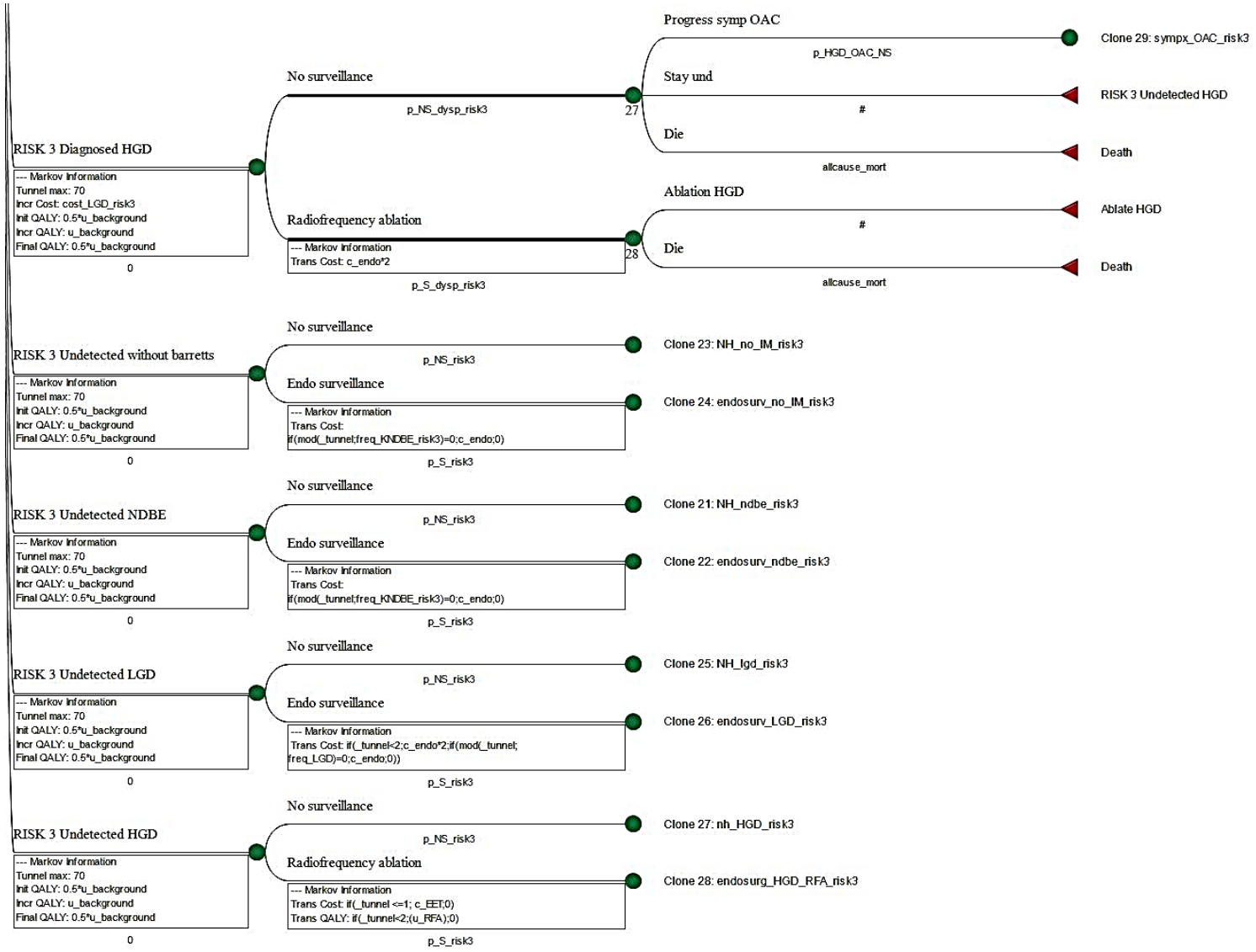


Figure 95. Risk 3 health states continued



The End