

Original Article

Factors influencing the cost-effectiveness of radiofrequency ablation for Barrett's esophagus with low-grade dysplasia in Australia

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SUMMARY. Endoscopic eradication therapy using radiofrequency ablation (RFA) is considered an acceptable alternative to surveillance monitoring for Barrett's esophagus with low-grade dysplasia (LGD). This study aimed to estimate whether RFA for LGD is cost-effective and to determine which factors influence cost-effectiveness. A Markov model was developed to estimate the incremental cost per quality-adjusted life year (QALY) gained for RFA compared with endoscopic surveillance. An Australian longitudinal cohort study (PROBE-NET) provides the basis of the model. Replacing surveillance with RFA yields 10 fewer cases of HGD and 9 fewer esophageal adenocarcinoma (EAC)-related deaths per 1000 patients' treatment, giving an average 0.192 QALYs at an additional cost of AU\$9211 (€5689; US\$6262) per patient (incremental cost-effectiveness ratio AU\$47,815 per QALY). The model is sensitive to the rate of EAC from LGD health state, the utility values, and the number of RFA sessions. Hence, the incremental benefit ranges from 0.080 QALYs to 0.198 QALYs leading to uncertainty in the cost-effectiveness estimates. When the cancerous progression rate of LGD falls <0.47% per annum, the cost-effectiveness of RFA becomes questionable. RFA treatment of LGD provides significantly better clinical outcomes than surveillance. The additional cost of RFA is acceptable if the LGD to EAC rate is >0.47% per annum and no more than three RFA treatment sessions are provided. Accurate estimates of the risk of developing EAC in patients with LGD are needed to validate the analyses.

KEY WORDS: Barrett's esophagus, cost-effectiveness, economic evaluation, esophageal adenocarcinoma, radiofrequency ablation.

INTRODUCTION

The presence and severity of dysplasia is the main factor influencing the risk of progression from Barrett's esophagus (BE) to esophageal adenocarcinoma (EAC) and guides the management of patients with this disease.¹ Endoscopic eradication therapy (EET) by resection and often radiofrequency ablation (RFA) is the standard of care treatment for BE with high-grade dysplasia (HGD).^{2–6}

For patients diagnosed with BE with low-grade dysplasia (LGD), EET using RFA is considered an acceptable alternative to surveillance monitoring, but there is uncertainty regarding the role of RFA versus surveillance for LGD due to the wide variation in the reported rate of progression from LGD to HGD/EAC

in different studies, from <1.0% per year to >10% per year.^{7–9} This wide range reflects pathologists' difficulty and variability in diagnosing LGD. This variability in pathological diagnosis could account for the outlying high progression rates if some of the LGD diagnoses would be classified as HGD by others.⁹ Overdiagnosis of LGD in cases that would be classified as non-dysplastic elsewhere may be a concern in other studies. Other complicating factors are that the progression rates for unifocal and multifocal LGD may differ, and that a diagnosis of LGD can be transient.

Previous studies have found RFA to be cost-effective^{10–15} for LGD treatment. Our study extends knowledge on this topic by incorporating pooled RFA effectiveness results from three randomized controlled

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Conflicts of interest: The authors declare that they have no conflicts of interest.

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trials (RCTs), using progression rates from a rigorous Australian longitudinal cohort study,¹⁶ incorporating realistic utility values, and estimating parameter uncertainty by probabilistic sensitivity analysis. We also investigated which parameters influenced the cost-effectiveness of RFA for BE with LGD. Unlike most previous studies on this subject,^{10,13–15} we did not receive financial support from the RFA manufacturer.

METHODS

Model structure and disease prevalence

A decision analytic model was developed to capture the progression of an Australian cohort of BE patients with LGD. A Markov model was constructed to model the natural history of the cohort and examine the costs and benefits associated with the treatment of patients with LGD with RFA compared to surveillance (TreeAge Software Inc, Williamstown, MA). A cohort of 1000 patients, 61 years of age,¹⁶ entered the model in the LGD health state and transitioned between six different health states (viz. complete eradication of intestinal metaplasia [CE-IM], non-dysplastic BE [NDBE], HGD, EAC, and death) by following a multiple event decision tree (see [supplementary material, Fig. S1](#)). Costs and outcomes were incorporated into the model as a mean value per dysplastic state per cycle. The cycle length was 1 year, and all costs (2022 Australian dollars) and outcomes were discounted at 5% per annum. A within-cycle correction was used in the model to account for patients who transition to other health states at different time points throughout the cycle. As there is no publicly stated willingness-to-pay threshold for a quality-adjusted life year (QALY) in Australia, a threshold of \$50,000 per QALY is used as this is an acceptable threshold for pharmaceutical reimbursement.¹⁷

The perspective of the study was the Australian health care system. The time horizon was a lifetime model run until death or 100 years of age. The rationale of the model is that RFA will lead to fewer patients progressing to HGD or EAC which in turn reduces the number of hospitalizations and leads to measurable impacts on both mortality and morbidity. To capture these benefits, the results are presented in terms of gains in quality-adjusted life years. The incremental cost-effectiveness ratio (ICER) was calculated for RFA relative to surveillance. The ICER is defined as the ratio of the change in costs relative to the change in effectiveness of RFA compared to surveillance.

Transition probabilities and effectiveness

The model utilized data from an Australian multi-center collaboration (PROBE_NET) that reported

rates of NDBE and LGD progressing to HGD and EAC.¹⁶ RFA efficacy in causing CE-IM in LGD patients was derived using an inverse variance weighting method of three RCTs, showing a pooled estimate of 78.5% (72.6%–84.5%), contrasting a natural regression rate from LGD to NDBE of 26.4% (18.9%–33.9%).^{7,18,19} Transition probabilities between dysplastic states were uniform across surveillance and treatment arms, except for the LGD to CE-IM transition rate reflecting RFA efficacy compared to a natural LGD to NDBE regression rate. Other yearly transition probabilities were estimated from the literature (see [supplementary material, Table S1](#) for further details).

Cost and utilities

Intervention costs were based on the Medicare Benefits Schedule fee, sourced from the Australian Department of Health Medical Costs Finder.²⁰ In the RFA treatment group, it was assumed that on average each patient would receive three RFA procedures in the first year of treatment.²¹ The cost incurred for the procedure included the RFA ablation catheter, the RFA procedure cost, the cost of anesthesia, and hospital theater and facility costs (see [supplementary material](#)). The estimated annual cost of the treatment arm for three RFA procedures was AU\$13,983. In the surveillance arm, it was assumed that individuals would receive two endoscopies in the first year at a total cost of AU\$4596, and one endoscopy per annum thereafter, incurring an annual surveillance cost of AU\$2298.^{2,3,22,23} The model assumes that all patients with HGD will be treated with RFA; treatment with endoscopic resection (endoscopic mucosal resection or submucosal dissection) is not included in the model for clarity around RFA cost-effectiveness (see [supplementary material, Table S2](#) for further details). Patients who remained in a state of persistent HGD despite 1 year of RFA treatment or who re-entered the HGD state received esophagectomy, incurring a one-off cost of AU\$57,250.²⁴ These patients either progressed into a state of remission with a lower quality of life (QoL) or death. The mean annual healthcare cost of AU\$29,290²⁵ (inflated using the health price index) was applied per year per patient in the EAC state. See [supplementary material](#) for further rationale regarding intervention costs and surveillance intervals.

Utility values, reflecting health status on a scale from 0 to 1, were derived from Gerson *et al.*,²⁶ indicating dysplastic grade-dependent QoL in BE patients. Base case values for NDBE, LGD, HGD, and EAC were 0.91, 0.85, 0.77, and 0.67, respectively, with a 0.1 disutility for post-esophagectomy patients.²⁷

Scenario analysis

Eight sensitivity analyses were conducted to identify the effect different scenarios had on the result-

ing ICER. Scenario 1 tested a standardized utility value of 0.8125 for BE, LGD, and HGD health states (derived from standard gamble elicitation methods in) as opposed to the base case where utility lowered with higher dysplastic states.²⁸ Scenario 2 used an RFA efficacy rate of 91.9% (86.2%–96.0%), generated using an inverse variance weighting of the two SURF trials,^{7,18} in comparison to the base case which additionally included Barrett *et al.*¹⁹ Scenario 3 used an RFA efficacy rate of 37.5%,¹⁹ markedly lower than the reported rate in the industry trial papers. Scenarios 4 and 5 employed an RFA treatment regimen of four and five sessions, respectively, for LGD and HGD, as opposed to the three sessions employed in our base case. Scenario 6 assumed that patients who transition from HGD to NDBE have a higher future transition rate to EAC (0.006) compared to those who started in the NDBE group (0.004) rather than both transitioning at the same rate (0.004).²⁹ Scenario 7 tested the effect that a higher progression rate (28.6%)⁹ had in comparison to the base case (2.4%), largely due to the variation in the literature of HGD to EAC progression rates. Lastly, scenario 8 strictly applied the Australian surveillance guidelines² for BE (see supplementary material, [Table S4](#) for scenario value inputs).

Sensitivity analysis

The study employed univariate and probabilistic sensitivity analyses to test parameter uncertainty and model robustness. Distributions for model parameters were estimated from confidence intervals, standard errors, or an appropriate range of estimates around the mean. Monte Carlo simulation, with 10,000 iterations, captured joint parameter uncertainty (see supplementary material, [Tables S1](#) and [S3](#) for distributions and ranges around mean estimates).

RESULTS

Base case

Based on a hypothetical cohort of 1000 patients with LGD, an estimated 193 patients in the surveillance group would develop HGD in their lifetime and 38 patients would progress to EAC. If treated with RFA, there would be 10 fewer cases of HGD and 9 fewer EAC-related deaths. These estimates are based on an annual LGD to EAC rate of 0.5%¹⁶ and LGD to HGD rate of 2.2% per year.¹⁶ These estimates are consistent with previously published data, which estimates the lifetime risk of adenocarcinoma in patients with BE as between 0.071 and 0.124.³⁰

In the base case model, a 61-year-old patient with BE and LGD who received endoscopic surveillance would accrue on average 11.909 QALYs at a cost of AU\$23,704. When treated with RFA, the average incremental benefit is 0.192 QALYs at an additional

cost of AU\$9211. This yields an ICER of AU\$47,815 per QALY gained ([Table 1](#)).

Scenario analysis

Applying a constant utility across dysplastic states (scenario 1) significantly diminished the cost-effectiveness of RFA compared to the surveillance of LGD patients, resulting in an ICER of AU\$115,815 per QALY gained. Increasing the number of RFA sessions to four and five (scenarios 4 and 5) increases the ICER to AU\$71,795 and AU\$95,774, respectively, suggesting that more than three RFA sessions may not be considered cost-effective. Lowering the RFA efficacy rate to 37.5%¹⁹ (scenario 3) dramatically decreased cost-effectiveness, incurring an ICER of AU\$130,476. Conversely, increasing the RFA efficacy rate to 91.9%^{7,18} (scenario 2) shows no significant effect on the ICER, marginally lowering it to AU\$47,640. Higher transition rates from NDBE to EAC after a previous HGD diagnosis (scenario 6) showed no significant effect on the ICER. A higher HGD to EAC transition rate (scenario 7) slightly lowered the ICER to AU\$46,503; however, this also is unlikely to impact the cost-effectiveness of RFA ([Table 1](#)).

Sensitivity analysis

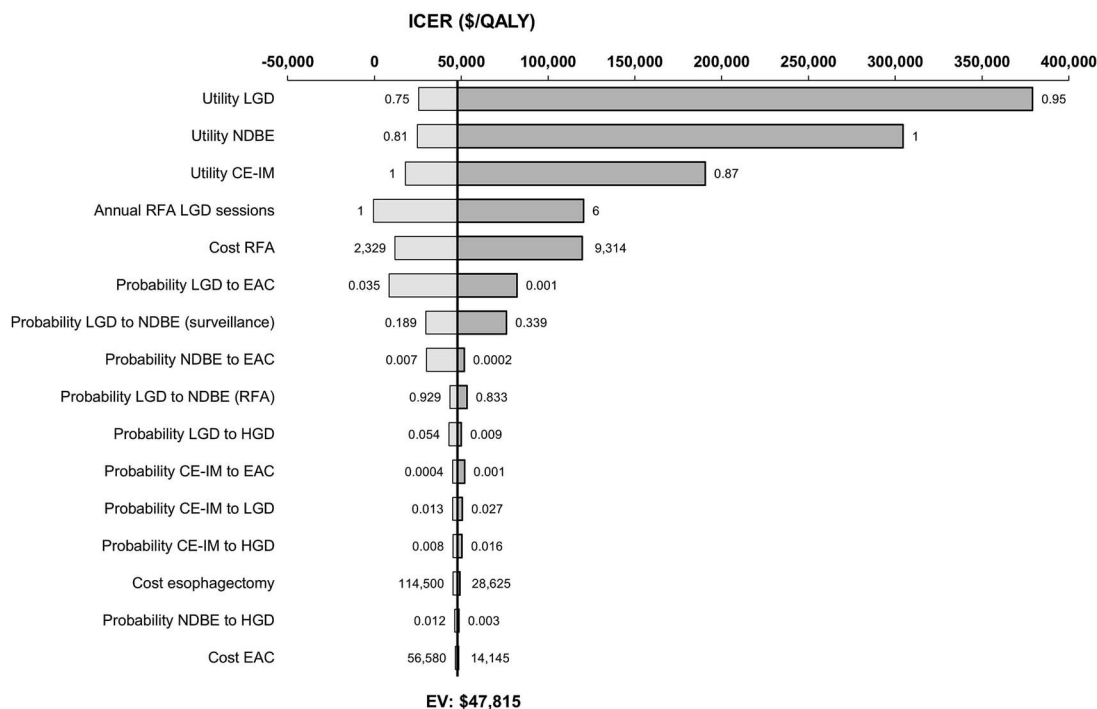
The results of the one-way sensitivity analysis are presented as a tornado diagram in [Fig. 1](#). The utility values for CE-IM, NDBE, and LGD, the cost of RFA, the number of RFA sessions, and progression of LGD to EAC had the largest impact on the ICER. The model was robust to spontaneous regression of LGD to NDBE, NDBE to EAC progression, RFA efficacy, progression from LGD to HGD, progression of CE-IM to LGD, HGD, and EAC, and the cost of esophagectomy. The model predicted that the annual progression rate of LGD to EAC <0.0047 would not be considered cost-effective ([Fig. 2](#)). The probabilistic sensitivity analysis results for 10,000 Monte Carlo simulations are presented in [Fig. S2](#) in the supplementary material. Overall, 52.5% of the simulations considered RFA cost-effective compared to surveillance and 24.9% of simulations considered RFA was more costly and less effective.

DISCUSSION

This study found that treating LGD with RFA may be cost-effective. Most (52.5%) of 10,000 simulations using our modeling found that RFA was cost-effective compared to surveillance for patients with LGD. RFA was less likely or unlikely to be cost-effective if more than three treatment sessions were provided, or if the annual progression rate from LGD to EAC was lower than 0.47%. In view of the uncertainty regarding this

Table 1 Results from the cost-utility analysis

Procedure	Total cost (AUD)	Total QALYs	Incremental cost	Incremental QALYs	ICER (AUD/QALY)
Base case (Utility values differ by dysplastic state)					
Surveillance	\$23,704	11.909			
RFA	\$32,915	12.102	\$9211	0.192	\$47,815
Scenario 1 (Utility values constant over dysplastic state)					
Surveillance	\$23,704	10.817			
RFA	\$32,915	10.897	\$9211	0.080	\$115,815
Scenario 2 (RFA efficacy using Shaheen and Phoa only)					
Surveillance	\$23,534	11.918			
RFA	\$32,889	12.115	\$9355	0.196	\$47,640
Scenario 3 (RFA efficacy using Barrett only)					
Surveillance	\$23,585	11.915			
RFA	\$33,996	11.995	\$10,412	0.080	\$130,476
Scenario 4 (4 RFA sessions)					
Surveillance	\$24,238	11.909			
RFA	\$38,069	12.102	\$13,831	0.193	\$71,795
Scenario 5 (5 RFA sessions)					
Surveillance	\$24,773	11.909			
RFA	\$43,223	12.102	\$18,450	0.193	\$95,774
Scenario 6 (Probability of NDBE to EAC higher from previous HGD)					
Surveillance	\$23,771	11.901			
RFA	\$32,975	12.095	\$9204	0.194	\$47,498
Scenario 7 (HGD to EAC progression rates)					
Surveillance	\$23,962	11.866			
RFA	\$33,146	12.064	\$9184	0.198	\$46,503
Scenario 8 (Australian Surveillance Guidelines)					
Surveillance	\$29,281	11.909			
RFA	\$55,499	12.102	\$26,218	0.193	\$136,099

**Fig. 1** Univariate sensitivity analysis. The vertical line represents the base case ICER (\$47,815/QALY). Bars to the right of the line represent values that increased the ICER, and bars to the left represent values that decreased the ICER relative to the expected value (EV).

progression rate, which is a key variable influencing cost-effectiveness, whether RFA is cost-effective is also uncertain.

Previous studies support RFA as a cost-effective treatment for LGD but have some limitations. An

early study¹⁰ found RFA treatment might be cost-effective for BE with LGD (and even NDBE), but this was contingent on post-ablation surveillance discontinuation, which is now not recommended due to the risk of BE recurrence.⁶ The LGD to EAC

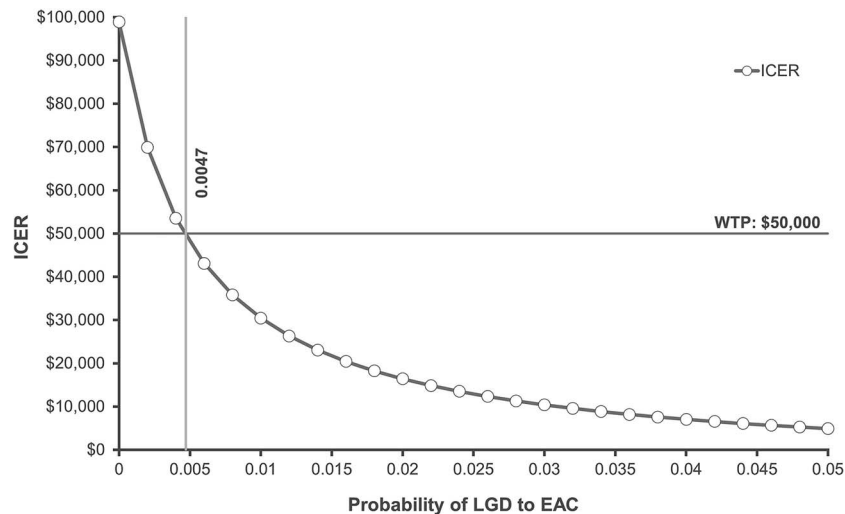


Fig. 2 LGD to EAC willingness-to-pay threshold. With a willingness-to-pay threshold of AU\$50,000 per QALY, RFA would be considered cost-effective compared to surveillance with an annual LGD to EAC progression rate $>0.47\%$.

progression rate used was 2.5% per patient-year, with no sensitivity analysis, which is higher than in our study or large population-based studies.^{1,31} Phoa *et al.*¹³ also supported cost-effectiveness for LGD treatment, but, unlike our study, did not consider QoL or out-of-pocket costs. Pollit *et al.*¹⁴ found that endoscopic eradication therapy (RFA + endoscopic mucosal resection + post-eradication endoscopic surveillance) was cost-effective for LGD in the UK population. However, their utility values were significantly lower than previously reported data (NDBE 0.71, LGD 0.65, HGD 0.57, and EAC 0.48), which may favor a result of cost-effectiveness. Hur *et al.*¹¹ concluded that RFA followed by surveillance was cost-effective for LGD when the annual progression rate of LGD to EAC is 0.5%, a finding supported by this study, but we are unable to directly compare our results as the rate of NDBE to EAC used in their study was not apparent from the methods. These studies did not include recurrence of BE after ablative therapy and hence are less relevant now, as recurrence has been reported as occurring at an annual incidence of 8.6% to 10.5%, with dysplastic BE recurrence at 2% and HGD/EAC recurrence at 1.2%.³² BE recurrence can be persistent, as shown in studies with up to 5 years of follow-up.^{33–35}

Our economic model was sensitive to five main parameters. In order of significance, these were utility values, number of RFA sessions, cost of RFA, LGD to EAC progression rate, and RFA efficacy. It is not unexpected that the LGD to EAC progression rate is a key driver of the model as EAC prevention, including through preventing HGD, is the aim of treatment. We used a 0.50% per annum¹⁶ progression rate, but this value is uncertain. When the cancer progression rate of LGD falls $<0.47\%$ per annum, the cost-effectiveness of RFA becomes questionable.

If the 'real' rate of progression is closer to 0.44% per annum (as estimated by the cohort study by Wani *et al.*³⁶), the resulting ICER increases to AU\$51,112 per QALY, making RFA for LGD unlikely to be considered cost-effective.

This illustrates the importance of identifying the true progression rate from LGD to EAC. Problems for doing this include variability in the histopathological diagnosis of LGD, which causes uncertainty about whether LGD cases are the same in varying studies. Moole *et al.*⁹ highlight the importance of accurately defining the dysplasia state, estimating that the progression of LGD to EAC is estimated at 3 to 20 times higher in LGD that was diagnosed by a consensus agreement of two or more expert pathologists compared to other estimates. Even expert pathologists can disagree however. In the SURF study, for example, the pathology diagnosis of LGD at participating centers was changed to non-dysplastic after central pathology re-review in 239 of 511 (46.8%) cases.⁷ This is despite the original LGD diagnoses being from expert BE centers such as the one in Nottingham, UK, where overdiagnosis of LGD is avoided. The often-transient nature of LGD diagnosis also influences cost-effectiveness. Spontaneous LGD regression rates in the three RCTs used for modeling were 31%,¹⁹ 27.9%,⁷ and 22.7%,¹⁸ with regression contributing to an outcome of nil statistical significance for RFA preventing progression from LGD to EAC in the study with the 31% regression rate study.¹⁹

Our economic model was sensitive to the number of RFA treatment sessions, finding that up to three sessions was more likely to be cost-effective. It is therefore reassuring that studies suggest that a mean of three RFA sessions is sufficient for CE-IM.^{6,21,35,37} Contrary data have also been reported however: the RCT by Barrett *et al.*, for example, found that the CE-

IM rate in the RFA arm, which involved three RFA sessions for most patients, was only 37.5% at 1 year after treatment and 35% at 3 years.¹⁹

The model was also sensitive to utility values, which are a measure of quality-adjusted life years, with a utility value of 1.0 representing full health and 0.0 representing death. The utility values employed in various RFA cost evaluation publications seem unrealistic, with instances of using utility values of 1.0 or 0.99 to represent NDBE, LGD, or HGD health states.^{10,38–40} These values are higher than relevant population normal values; the mean utility value for Australians aged 51–60 years, for comparison, is 0.749.⁴¹ Using utility values that differ by dysplastic and cancer states yields a more robust cost-effectiveness estimate. Testing the hypothesis that QoL does not reduce with disease progression (scenario 1), assuming HGD or LGD patients have the same utility as NDBE, suggests that RFA is unlikely to be cost-effective under such conditions.

Our study improved on previous cost-effectiveness models by including BE recurrence rates, incorporating a pooled RFA effectiveness result from three RCTs and estimating parameter uncertainty by probabilistic sensitivity analysis. A strength of our study was incorporating realistic utility values, hence offering a social perspective on cost-effectiveness. We also used progression rates from a rigorous prospective longitudinal cohort study (PROBE-NET) that involved experienced clinicians and pathologists and included only patients with at least two endoscopic examinations.¹⁶

A limitation of the study pertains to the variability and thus uncertainty in RFA efficacy rates, which were higher in two trials (Shaheen and Phoa)^{7,18} than in the third (non-industry supported) RCT.¹⁹ Number of RFA treatment sessions (up to five^{7,18} vs. up to four¹⁹) may be relevant. In one modeling scenario (scenario 8), RFA efficacy had a marked negative effect on cost-effectiveness. We used a hypothetical 12-month treatment cycle for modeling with estimated results at the conclusion of treatment but used results for up to five treatments^{7,18} even though treatment duration for this would probably have exceeded 12 months. As with the other assumptions made for the base case model, this favored cost-effectiveness for RFA. Data from follow-up reports that demonstrated durability of BE and LGD eradication after RFA were not included because the annual progression rates were not available from one of these studies⁴² and most patients in the surveillance arm received RFA during the follow-up in the other study²⁹ and thus also did not include information for our model.

Wang *et al.*'s⁴³ systematic review confirmed that RFA effectively decreased overall LGD progression to HGD or EAC by up to 75% compared to surveillance. However, their sub-group analysis revealed a lack of statistical significance in preventing LGD to EAC progression compared to LGD to HGD

progression.⁴³ Their review and our study indicate that further research into efficacy rates and long-term results is needed.

CONCLUSION

RFA may be cost-effective for the treatment of patients with BE with any dysplasia, even if moderate surveillance is continued, but this is dependent on the rate of progression from LGD to EAC and the effectiveness of RFA. The cost-effectiveness of RFA becomes unlikely when providing more than three treatment sessions. Comparing the results of dysplastic BE studies is fraught with a high risk of bias due to the wide variation in pathology diagnosis. A classification according to the risk of cancerous progression is needed to replace the current situation so that resources such as RFA can be allocated more rationally.

SUPPLEMENTARY DATA

Supplementary data mentioned in the text are available to subscribers in *DOTESO* online.

AUTHOR CONTRIBUTIONS

Lauren Caush (Conceptualization, Data Curation, Formal Analysis, Investigation, Methodology, Project Administration), Jody Church (Conceptualization, Data Curation, Formal Analysis, Investigation, Methodology, Project Administration), Stephen Goodall (Conceptualization, Data Curation, Methodology, Project Administration, Supervision, Validation), and Reginald V. Lord (Conceptualization, Project Administration, Supervision)

ETHICS APPROVAL

Ethics approval for this study was granted by the University of Technology Sydney Human Research Ethics Committee (HREC Reference No. ETH18-2507).

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