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Radiofrequency ablation for treatment of Barrett's esophagus: A systematic review and cost analysis

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of the McGill University Health Centre (MUHC)

by

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Approved by the Committee of the TAU on **December 1, 2009**

Invitation.

This document was developed to assist decision-making in the McGill University Health Centre. All are welcome to make use of it. However, to help us estimate its impact, it would be deeply appreciated if potential users could inform us whether it has influenced policy decisions in any way.

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ABBREVIATIONS AND ACRONYMS

BE	Barrett's Esophagus
EAC	Equivalent Annual Cost
EMR	Endoscopic Mucosal Resection
ICU	Intensive Care Unit
IMC	Intramucosal Cancer
MUHC	McGill University Health Centre
PDT	Photodynamic Therapy
RCT	Randomized Controlled Trial
RFA	Radiofrequency Ablation

SOMMAIRE

Contexte:

Les patients présentant un œsophage de Barrett avec une dysplasie de haut grade ont un risque important de développer un cancer de l'œsophage (59% à l'intérieur de 5 ans). Le traitement classique pour les dysplasies de haut grade est l'oesophagectomie qui présente des risques de mortalité chirurgicale de 3 à 5% et des taux de complications importantes variant entre 30 et 50%. Par conséquent, il y eut un vif intérêt à trouver des thérapies alternatives et une technologie d'ablation par radiofréquences (ARF), récemment développée par BÂRRX Medical Inc., semble prometteuse. Environ 7 patients par année présentant une dysplasie de haut grade seraient éligibles à une ARF au CUSM.

Objectifs :

Les objectifs de ce rapport sont de faire une revue systématique de la littérature portant sur l'efficacité clinique de l'ARF chez les patients ayant un œsophage de Barrett avec une dysplasie de haut grade, et aussi de comparer les coûts de l'ARF et de l'oesophagectomie selon la perspective du CUSM.

Méthodologie :

Revue systématique de la littérature : Une revue systématique de la littérature fut faite à partir de bases de données en ligne dédiées à des articles médicaux et à des rapports d'évaluation rédigés en anglais et en français. Une méta-analyse fut complétée à partir d'études d'observation pour évaluer les taux d'éradication complète de la dysplasie, de l'éradication complète des métaplasies intestinales ainsi que la progression du cancer suite à une ARF.

Analyse des coûts : Pour calculer les coûts de l'ARF et de l'oesophagectomie selon la perspective du CUSM, nous avons obtenu de la Direction des finances et de services connexes au CUSM, des informations relatives aux coûts et à l'utilisation des ressources. Des analyses de sensibilité monovariables furent utilisées pour étudier l'importance relative de chaque composante budgétaire.

Résultats :

Efficacité clinique : Nous avons identifié une étude randomisée ainsi que 6 études de cohorte d'une branche. L'étude randomisée de Shaheen et al. démontra une éradication complète de la dysplasie chez 81% (34/42) des patients traités par ARF comparée à 19% (4/21) chez les patients ayant reçu une thérapie fictive (P<0.001), une éradication complète des métaplasies intestinales chez 74% (31/42) des patients suite à une ARF comparée à 0% (0/21) suite à une thérapie fictive (P<0.001), et une progression du cancer chez 2% (1/42) des patients traités par ARF comparée à 19% (4/21) chez les patients traités par thérapie fictive. La valeur moyenne des résultats lors du suivi (variant entre 12 et 24 mois) parmi les 6 études de cohorte montrèrent une éradication complète de la dysplasie chez 95,8% des patients (95% CI : 83,8% à 100%), une éradication complète des métaplasies intestinales chez 84,5% des patients (95% CI : 67,3% à 100%) et une progression du cancer chez seulement 2,7% des patients (95% CI : 0,8% à 5,4%). Ces études montrèrent peu d'effets secondaires importants et ceux-ci se résumaient surtout à des douleurs thoraciques, des sténoses œsophagiennes, des hémorragies, etc. Aucun décès relié à cette intervention n'a été rapporté.

Analyse des coûts : Le coût d'acquisition d'un générateur ARF est de 82 041 $ et si, en moyenne, un patient requiert 3 sessions d'éradication par traitement (2 ARF circonférentielles et une ARF focale), le coût d'intervention par patient sera environ 11 208 $. Par comparaison, le coût estimé d'une oesophagectomie est de 13 788 $. Ainsi, si 7 patients par année sont traités par ARF et non par oesophagectomie, il en coûterait environ 18 060 $ de moins par année au CUSM pour traiter ces patients. Ceci ne se traduirait pas par des économies budgétaires mais plutôt par une augmentation d'efficacité de l'établissement. Le coût des cathéters à usage unique représente plus de 80% du coût total d'un traitement par ARF et les paramètres ayant un impact budgétaire important sont le nombre de patients par année ainsi que le nombre de sessions requises par traitement.

Conclusion :

- Malgré le peu de données des suivis à long terme, les évidences présentes sont suffisantes pour conclure que l'ablation par radiofréquences est un traitement très efficace pour les dysplasies œsophagiennes de haut grade (pour au moins deux ans) et beaucoup plus sûr que l'oesophagectomie.

- L'ARF est une thérapie en développement et devrait être utilisée dans un centre hospitalier de soins tertiaires doué d'une clinique spécialisée dans les maladies œsophagiennes, tel le CUSM.
- Si l'on compare à l'oesophagectomie, l'ARF est un traitement moins dispendieux.

Recommandations :

- Le comité du TAU recommande fortement que le traitement ARF pour les dysplasies œsophagiennes de haut grade soit supporté financièrement par le CUSM.
- En l'absence d'un financement gouvernemental additionnel pour ces traitements, un nombre maximal de 10 traitements par année devra être respecté et tout dépassement devra faire l'objet d'une revue de cette décision.
- En raison de la carence des données de suivi, ce rapport devra faire l'objet d'une révision d'ici 2 ans.

EXECUTIVE SUMMARY

Background:

Barrett's esophagus (BE) patients with high-grade dysplasia have a high risk of esophageal cancer (59% in five years). The standard treatment for high-grade dysplasia is esophagectomy. However, it is associated with an operative mortality of 3-5%, and a rate of serious operative complications of 30 to 50%. Therefore there has been a keen interest in alternative therapies. A radiofrequency ablation (RFA) technology recently developed by BÂRRX Medical Inc., has shown promise. Roughly 7 high-grade dysplasia patients would be eligible for RFA treatment each year at the McGill University Health Centre (MUHC).

Objective:

The aims of this report are to systematically review the literature on the effectiveness of RFA for BE patients with high-grade dysplasia, and to compare the cost of RFA and esophagectomy from the point of view of the MUHC.

Methods:

Systematic literature review: A systematic literature search of articles in English and French was performed using online databases of medical articles and health technology assessment reports. A meta-analysis of observational studies was carried out to estimate rates of complete eradication of dysplasia, complete eradication of intestinal metaplasia and progression to cancer following RFA treatment.

Cost analysis: To estimate the cost of RFA and esophagectomy treatments from the perspective of the MUHC, we obtained information on costs and resource use from the Department of Finance and relevant service departments at MUHC. Univariate sensitivity analyses were used to study the relative importance of each component cost.

Results:

Clinical effectiveness: We identified 1 RCT, 6 single-arm cohort studies. The RCT by Shaheen et al. demonstrated complete eradication of dysplasia in 81% (34/42) of RFA treated patients compared to 19% (4/21) following sham therapy (P<0.001); complete eradication of intestinal metaplasia in 74%(31/42) following RFA , compared to 0% (0/21) following sham therapy (P<0.001); and progression to cancer in 2%(1/42) following RFA , compared to 19%(4/21) following sham therapy. The pooled average outcomes at follow-up (which ranged from 12 to 24 months) in the 6 one-arm cohort studies indicated complete eradication of dysplasia in 95.8% patients (95% CI: 83.8% to 100%), complete eradication of intestinal metaplasia in 84.5%(95% CI: 67.3% to 100%) and progression to cancer in only 2.7%(95%CI: 0.8%, 5.4%). Serious adverse events were rare. The common adverse events included chest pain, esophageal stricture, hemorrhage etc. No procedure related mortality was found.

Cost analysis: The capital cost of the RFA generator is $82,041. We expect that on average patients will have 3 ablation sessions (2 circumferential RFA and 1 focal RFA) resulting in a cost per patient of about $11,208. The estimated cost of esophagectomy is $13,788 per patient. Therefore, if 7 cases per year were treated by RFA instead of esophagectomy, there would be a reduction in the cost of treating these patients of approximately $18,060 yearly at the MUHC. (It would not result in budget saving, but in increased efficiency of the institution). The cost of disposable catheters accounts for more than 80% of the overall cost of RFA therapy. The key parameters impacting the budget impact of RFA are the number of patients undergoing RFA therapy, and the average -number of sessions of RFA treatment.

Conclusions:

- In spite of lack of long-term follow-up data there is sufficient evidence to conclude that RFA is a highly effective treatment for extensive high-grade oesophageal dysplasia (for at least two years), and considerably safer than oesophagectomy.
- It is a developing therapy and it is appropriate that it should be administered in a clinic specializing in oesophageal disorders based in a tertiary care institution such as the MUHC.
- Compared to oesophagectomy, RFA treatment is less costly.

Recommendations:

- The TAU committee strongly recommends that RFA treatment for high grade oesophageal dysplasia be funded by the MUHC.
- In the absence of increased funding for this procedure from government, an annual turnover above 10 procedures per year should not be permitted without review of this decision.
- Because of the paucity of follow-up data, this report should be the considered for update within approximately 2 years.

1 INTRODUCTION

1.1 Barrett's esophagus:

Barrett's esophagus (BE) is characterized by replacement of the squamous epithelium that normally lines the distal esophagus by columnar epithelium. This metaplastic change predisposes patients to adenocarcinoma, which develops in approximately 0.5% of patients with Barrett's esophagus per year[1]. In the sub-group of BE patients in whom biopsy specimens show high-grade dysplasia, studies find that the risk of cancer is significantly higher (59 % in five years[2]). The prevalence of Barrett's esophagus in the adult population is 0.4% to 1.6%[3]. By the time Barrett's esophagus is diagnosed, one third of patients may already have an invasive cancer [1].

1.2 Treatment options for Barrett's esophagus:

The standard treatment for high-grade dysplasia is esophagectomy[4]. Although this is an effective cure it is associated with an operative mortality of 3-5%[5, 6], a rate of serious operative complications of 30 to 50%[7], and a rate of permanent morbidity of around 40% [5, 6, 8]. Therefore there has been a keen interest in alternative therapies[9].

When the area of high-grade dysplasia is small, it can be removed by endoscopic mucosal resection (EMR), but when larger areas are involved ablation treatments such as photodynamic therapy (PDT) and radiofrequency ablation (RFA)[9] have been used. PDT has recently been discontinued by the manufacturer due to the associated high morbidity [5, 10]. However, RFA has been reviewed favourably in comparison to PDT in terms of both cost-effectiveness and safety[5, 10].

The RFA treatment may involve one or more sessions of circumferential or focal ablation. Circumferential ablation is used for cases where the metaplasia covers a large area, while focal ablation is for cases where the affected area is small. Details of RFA treatment using the HALO system developed by BÂRRX Medical Inc. is briefly described in Appendix 1.

This report was produced in response to an application by the Division of Gastroenterology to introduce RFA as a treatment for Barrett's esophagus at the MUHC. It consists of a literature based evaluation of the effectiveness of the radiofrequency ablation treatment developed by BÂRRX

Medical Inc., an estimation of the cost and the budget impact to the MUHC, and recommendations of the TAU Steering Committee based on this evidence.

2 METHODS

We carried out a systematic literature review of studies on the effectiveness of RFA for treatment of high-grade dysplasia. Details appear in Appendix 2. Details of patient volume and resource use associated with treatment of high-grade dysplasia at the MUHC were obtained in consultation with Drs. Mayrand and Ferri. We estimated the cost of RFA and esophagectomy from the perspective of the MUHC. Details are given in Appendix 3.

3 RESULTS OF SYSTEMATIC REVIEW

3.1 Literature search

In total, we identified 1 RCT and 6 single-arm cohort studies meeting our inclusion criteria[11-17], and one economic study[10] of RFA for treatment of high-grade dysplasia in BE patients, all published in 2008 or 2009. A Health Technology Assessment (HTA) published in 2007 by HAYES Inc. was not tracked because more relevant evidence has appeared since that time. Patient and study characteristics of the RCT and cohort studies are summarized in Table 1.

3.2 Effectiveness

Clinical outcomes reported by each study are summarized in Table 2. The RCT by Shaheen et al.[11] demonstrated complete eradication of dysplasia in 81% (34/42) of RFA treated patients compared to 19% (4/21) following sham therapy (P<0.001); complete eradication of intestinal metaplasia in 74%(31/42) following RFA , compared to 0% (0/21) following sham therapy (P<0.001); and progression to cancer in 2%(1/42) following RFA , compared to 19%(4/21) following sham therapy. (The apparent occurrence of eradication of dysplasia following sham therapy is almost certainly due to sampling error).

The pooled average outcomes at follow-up (which ranged from 12 to 24 months) in the 6 one-arm cohort studies[12-17] were excellent. There was complete eradication of dysplasia in 95.8% patients (95% CI: 83.8% to 100%), complete eradication of intestinal metaplasia in 84.5%(95% CI: 67.3% to 100%) and progression to cancer in 2.7%(95%CI: 0.8%, 5.4%), respectively.

3.3 Safety

No procedure related mortality was reported in the studies we reviewed [11-17] (Table 2). Serious adverse events were rare[11-17]. The common adverse events included chest pain[11], hemorrhage[11, 12], difficulty swallowing[16], nausea and vomiting[12]. Five studies reported that cases suffered esophageal stricture (narrowing of the esophagus) requiring dilation, from 6% to 8% patients in four studies[11-13, 17] and 1% in the other[15]. Some ablation methods reportedly result in the finding of buried glandular mucosa in the post procedural biopsy [15]. This was not observed in any of the follow-up biopsies examined in the 7 studies of RFA treatments [11-17]. **In summary**, RFA using the BÂRRX system is a safe procedure that can be performed on an outpatient basis[11]. However, long-term prognosis must be reserved because of the short follow-up times (1-2 years) of the studies published so far.

3.4 Cost-effectiveness

In an economic study by Inadomi et al.[10], esophagectomy was found to cost more than RFA (US$: 58,973 vs. 20,776) and was less effective (15.02 vs. 15.67 QALYs). Compared with no intervention, ablation strategies were associated with an incremental cost effectiveness ratio (ICER) of less than 6,000 US$ per QALY gained. This study is described in greater detail in Appendix 4.

4 TREATMENT OF BARRETT'S ESOPHAGUS AT THE MUHC

Patients with Barrett's esophagus are identified at the Esophageal Diseases Clinic at the Montreal General Hospital. Roughly 10 patients with high-grade dysplasia are treated each year, and about 7 of the 10 have metaplasia over a large section of the esophagus. These patients are drawn from across Quebec from areas falling under all 4 RUIS (Réseau universitaire intégré de santé). Till recently these patients were treated by photodynamic therapy (PDT), esophagectomy, or endoscopic mucosal resection (EMR). But as mentioned previously, PDT has now been discontinued. So far 4 patients have been treated by RFA at the MUHC. These treatments have been carried out on a compassionate basis using equipment loaned from the manufacturer. Some patients have also been referred to a centre in Toronto where the procedure is being carried out in a research setting.

4.1 Radiofrequency ablation procedure:

The radiofrequency ablation (RFA) procedure has been performed at the MUHC using the HALO system (BÂRRX Medical, Inc., Sunnyvale, United States)[18]. The HALO system is comprised of two distinct ablation systems, HALO360 for circumferential ablation and HALO90 for focal ablation (Appendix 1). Radiofrequency ablation is an outpatient procedures, carried out under sedation[3].

5 COST ANALYSIS

The details of the methods of cost analysis are presented in Appendix 3. The purchasing cost for the HALO 360/90 generator is $82,041. The equivalent annual cost (EAC) is $16,164 assuming a service lifespan of 6 years and annual interest rate of 5%. It is assumed that 21 sessions of RFA would be performed at MUHC per year (7 patients with an average of 2 circumferential RFA and 1 focal RFA). Therefore, the fraction of EAC attributable to each session is $770 ($16,164 divided by 21). The major costs of the RFA procedure are listed in Table 3. The total cost per patient for 3 sessions is about $11,208. The recurring budget impact would be about $78,456, with 80% of the cost being due to the cost of the disposable catheters.

The resource use and unit cost of esophagectomy are presented in Table 4a, and complication rates following the procedure are presented in Table 4b. The estimated cost of esophagectomy is $13,788 per case, and the budget impact is about $96,516 (7 cases) per year. Therefore, if seven cases per year were treated by RFA instead of esophagectomy, there would be a reduction of approximately $18,060 annually in the cost of treating BE patients with high-grade dysplasia.

Note. In practice this would not result in any budget saving. Instead, freeing the surgical service of seven potential esophagectomies would result in additional surgical procedures for other patients. Thus the net outcome would be an increase in efficiency (more patients at the same cost).

5.1 Sensitivity analysis

We conducted sensitivity analyses to examine the important parameters impacting the budget (See Table 5). The costs of the disposable catheters account for nearly 80% of the overall cost of RFA therapy. The key parameters impacting annual budget of RFA are the number of patients undergoing RFA therapy, and the average -number of sessions of RFA treatment. If 10 or 15 patients underwent RFA therapy instead of esophagectomy each year, the annual budget impact of RFA would be $105,140 and $149,640, respectively, but the costs saving would grow to $32,740 and $57,180. If patients need 2 to 4 RFA sessions on average, the annual budget impact of adoption of RFA would be $57,687 and $92,904, respectively.

6 DISCUSSION

The long-term outcomes of RFA are still insufficiently documented. RFA is an emerging technology. Not surprisingly, the maximal mean/median follow-up did not exceed two years in all 7 studies[11-17]. Since the prevalence of high-grade BE is relatively low, the sample sizes in most studies were small. In four out of 6 cohort studies[12, 13, 16, 17], the sample sizes were less than 12. Three studies had poor follow-up rates of around 60% [12, 13, 15].

Furthermore, the only RCT compared RFA with sham treatment (equivalent to intensive surveillance rather than active treatment), rather than other common interventions in practice, such as esophagectomy or PDT. However, current evidence suggests that RFA is highly efficacious in terms of eradication of dysplasia, intestinal metaplasia and progression to cancer, and has very acceptable safety in term of serious adverse events for high-grade BE patients. By contrast, esophagectomy and PDT are associated with a very high risk of adverse events. The APC treatment is generally not used in high-grade BE patients because of the difficulty in selecting an appropriate energy level that is effective but not harmful. The EMR treatment is only suitable for patients with a small area of BE.

Therefore, RFA appears to be a suitable treatment for BE patients with extensive high-grade dysplasia of the esophagus, although there is no direct evidence of its superiority to esophagectomy. Even if RFA treatment does not show satisfactory effects for an individual, surgery remains an option.
RFA is an outpatient procedure, whereas esophagectomy lasts 6-7 hours in the operating room, 1-2 days in ICU and 12-13 days of hospitalization on average. Furthermore, esophagectomy is associated with higher mortality and morbidity. We did not include medication costs in our analysis as consumption of medication is difficult to estimate. If these were included the cost saving resulting from the use of RFA would be higher than our current estimates. The sensitivity analysis shows these findings to be fairly robust.

Some uncertainties in budget estimates must be noted. The budget estimate is based on 7 candidates (21 sessions) per year at MUHC in this report. But, if surgeons widen their indications for RFA, or if many patients experience more than 3 sessions for recurrences in long-term follow-up etc., the annual budget impact would be higher. It is also possible that the MUHC might attract additional patients from other RUIS for this treatment,

7 CONCLUSIONS

- In spite of lack of long-term follow-up data there is sufficient evidence to conclude that RFA is a highly effective treatment for extensive high-grade esophageal dysplasia (for at least two years), and considerably safer than esophagectomy.
- It is a developing therapy and it is appropriate that it should be administered in a clinic specializing in esophageal disorders based in a tertiary care institutions such as the MUHC.
- Compared to esophagectomy RFA treatment is less costly. (It would not result in budget saving, back in increased efficiency of the institution).

8 RECOMMENDATIONS

- The TAU committee strongly recommends that RFA treatment for high grade oesophageal dysplasia be funded by the MUHC.

- In the absence of increased funding for this procedure from government, an annual turnover above 10 procedures per year should not be permitted without review of this decision.
- Because of the paucity of follow-up data, this report should be the considered for update within approximately 2 years.

Figure 1: HALO360 system for circumferential ablation[18]

a: HALO360 Energy generator

b: Sizing balloon (diameter of balloon: 33.7 mm; balloon length: 4 cm.)

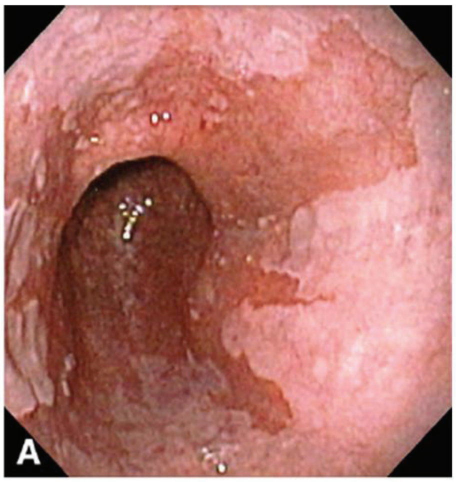
c: Balloon-based ablation catheter (balloon length: 4 cm ; electrode length: 3 cm; diameter size: 22, 25, 28, 31and 34mm)

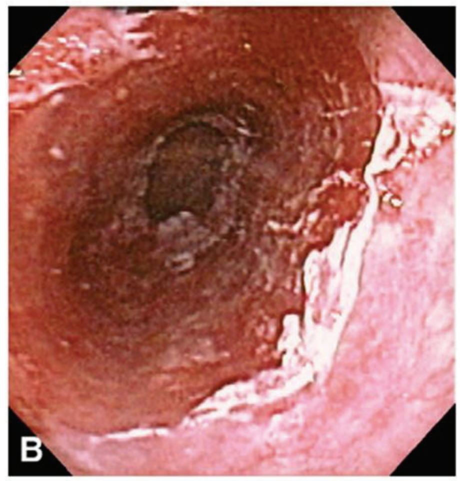
Figure 2: HALO90 system for focal ablation[18]

a: HALO90 Energy generator

b: Focal ablation catheter (Active electrode dimensions: 20 mm length x 13 mm width)

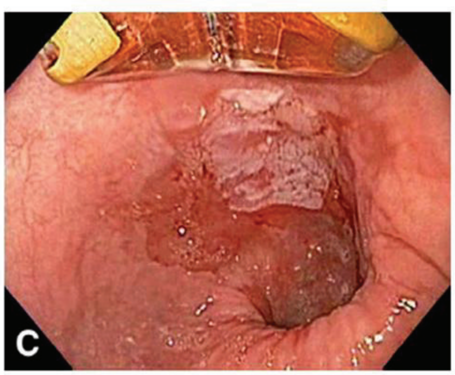
Figure 3: Endoscopic images of RFA treatment

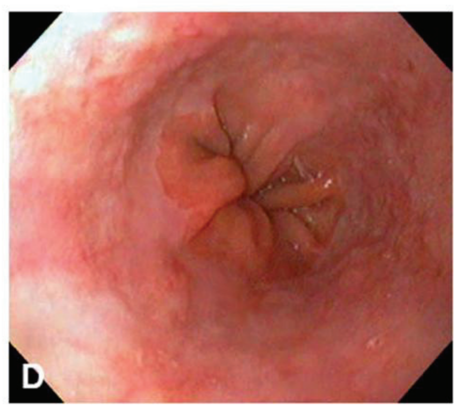




A: Baseline appearance of a 6-cm segment of BE with classic findings of both circumferential involvement of distal esophagus as well as tongue-like projections more proximally.

B, Immediate appearance after circumferential ablation with complete sloughing of esophageal epithelium.





C: After 1 year, focal ablation performed for any residual disease; note presence of endoscope-mounted ablation device at 12 o'clock in the endoscopic image, a small island of BE tissue, and an ablated area within that island.

D: 30-month follow-up endoscopy showing no visible BE tissue and no IM on biopsy.

Adapted from Fleischer et al. *Gastrointest Endosc* 2008; 68: 867-876.

Figure 4: Flow diagram of literature search in Pubmed and study selection

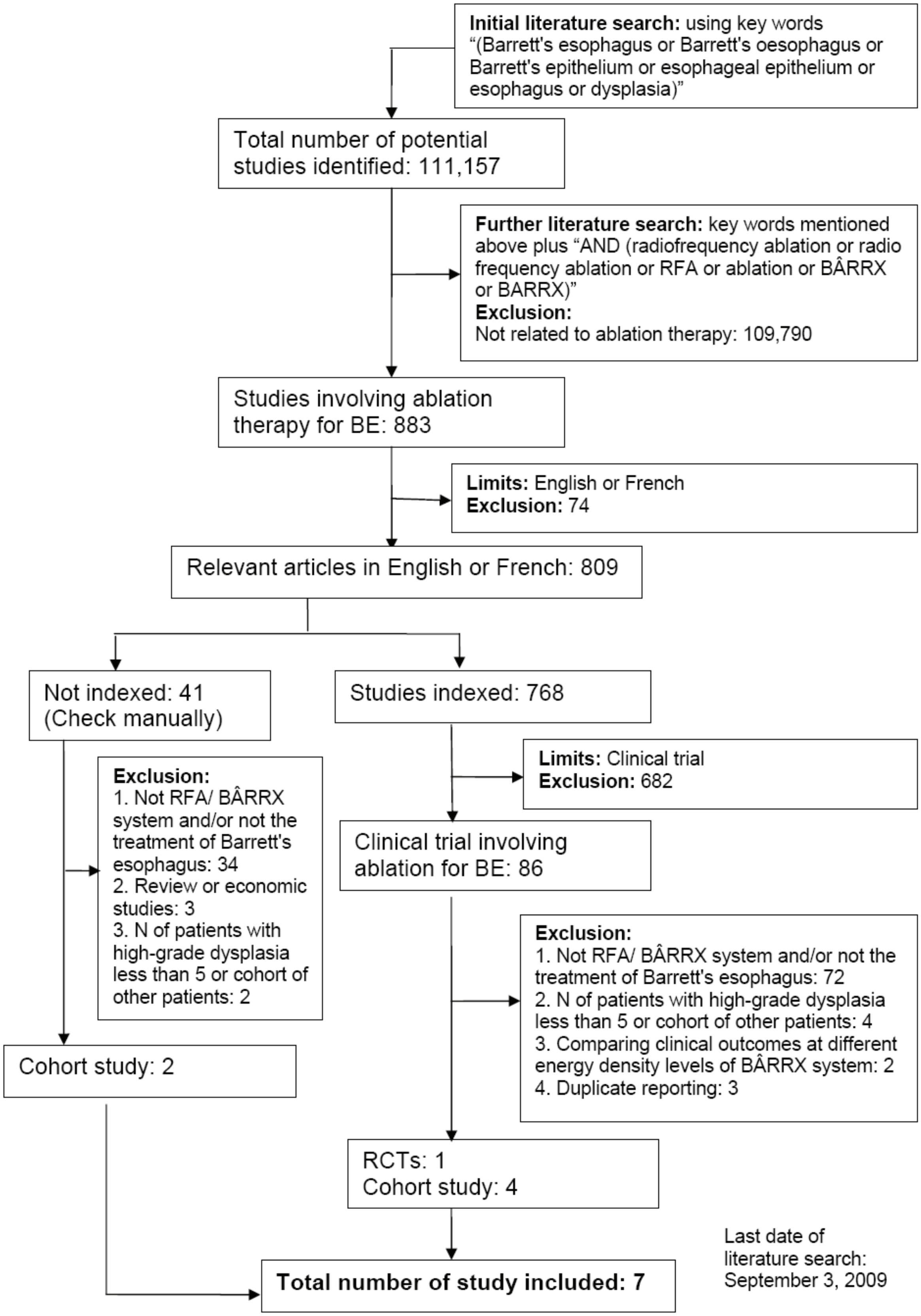


Table 1: Patient and study characteristics

Author (year)	Sample Size(group)	Age	Male (%)	Length of BE (cm) at recruitment	Follow-up time (months)	Number of RFA sessions	Financial support from manufacturer !
RCT							
Shaheen et al. (2009)[11]	42 (RFA)	65.9±1.4[a]	88	5.3±0.3 [a]	12	3.5*	Yes
	21(Sham)	67.3±1.8 [a]	100	5.3±0.5 [a]	12		
Cohort Study							
Vassiliou et al. [12](2009)	10† (RFA)	66(57-74)[b]*	88*	10(8-12) [b]*	20(10-29) [b]*	2.5(2-3)[b]*	NA
Velanovich [13](2009)	7$ (RFA)	62[a]*	80*	3(1-14)[b]*	19(12-28)[c]	1(1-3)[b]*	NA
Sharma et al.[14] (2009)	24 (RFA)	73(51-81)[c]	92*	6(1-12)[c]	23(6-38)[c]	CA: 1(0-4); FA: 1(0-3)	Yes
Ganz et al.[15] (2008)	92‡ (RFA)	66(59-75) [b]*	88	6(3-8) [b]*	12(8-15) [b]*	1(1-2) [b]*	Yes
Gondrie_1 et al.[16] (2008)	11§ (RFA)	60(57-67)[c]*	73	5(4-7) [c]*	19(18-22) [b]*	4(4-5) [b]*	Yes
Gondrie_2 et al.[17] (2008)	12# (RFA)	70(53-76) [b]*	75	7(6.5-8) [b]*	14(13-15) [b]*	3(3-4) [b]*	Yes

a: Mean±SE; b: Median (interquartile range (IQR): 25th percentile to 75th percentile); c: Median (range)
BE: Barrett's esophagus; RCT: randomized clinical trial; RFA: Radio frequency ablation; CA: circumferential ablation; FA: focal ablation; NA: not available, since authors did not declare conflict of interest or source of support.
*: Results are based on all cohort patients, because authors did not report high-grade and low-grade dysplasia separately, or authors reported baseline characteristics of initial cohort, rather those with follow-up biopsies.
†: This study included 15 patients with high-grade dysplasia, but only 10 of them had at least one follow-up biopsy.
$: This study included a total of 12 patients with high-grade dysplasia, but follow-up information was available on only 7 of them.
§: A majority of patients (n=9) had high-grade dysplasia. The other 2 had low-grade dysplasia.
#: A majority of patients (n=11) had high-grade dysplasia. The other 1 had low-grade dysplasia.
‡: Ninety-two out of 142 patients had at least 1 follow-up biopsy session that qualified them for the efficacy cohort.
!:Financial support: the study was supported or partly supported by BÂRRX Medical Company; or one or more authors received research grants, consulting fee, lecture fee etc. from BÂRRX Medical Company.

Table 2: Clinical outcomes

Author (year)	Sample Size	Eradication of Dysplasia N (%)	Eradication Metaplasia N (%)	Progression to Cancer N (%)	Adverse events N(%) §
RCT					
Shaheen et al.[11] (2009) †	42 (RFA)	34(81)	31(74)	1/42(2)	1 hemorrhage requiring esophagectomy, 2 chest pain requiring 1 day hospitalisation. 5 (6%) stricture requiring average 2.6 dilatations).
	21(Sham)	4(19)	0(0)	4/21(19)	None reported.
Cohort Study					
Vassiliou et al.[12] (2009)	10	10/(100)	8(80)	0/10(0)#	*(Based on 25 patients, 59 ablations). No buried glands. 1 mild hemorrhage (4%), 2 esophageal stricture requiring dilation (8%), 2 post-procedure nausea and vomiting (8%).
Velanovich [13] (2009)	7	7(100)	7(100)	0/7(0)	*(Based on 66 patients). No immediate procedure-related complications. 4 esophageal strictures (7%).
Sharma et al. [14] (2009)	24	19(79)	16(67)	2/24	No complications reported.
Ganz et al.[15] (2008)	92	74(80)	50(54)	2/92(2)	* ‡ (Based on 142 patients, 229 ablations). No serious adverse events. No buried glands. 1 stricture (1%), 2 underwent an esophagectomy for IMC (1%).
Gondrie_1 et al.[16] (2008)	11	11(100)	10(91)	0/11(0)#	*(Based on 11 patients, 46 ablations). No severe complications. 1 admitted for fever and chest pain (9%), 1 retrosternal pain (9%).
Gondrie_2 et al.[17] (2008)	12	12(100)	12(100)	0/12(0) #	*(Based on 12 patients, 41 ablations). No severe complications. 1 esophageal stricture (8%).

PPI: proton pump inhibitor; N: number; RCT: randomized clinical trial; IMC, intramucosal adenocarcinoma; bid: twice daily.
*: Results are based on all cohort patients, because authors did not report high-grade and low-grade dysplasia separately, etc.
§: The percentage of adverse events is out of the number of patients and not the number of sessions).
†: The analyses were based on an intention-to-treat approach.
‡: Authors did not use standardized approach for collecting adverse event data. Therefore, some events may have been underreported.
#: Progression to cancer was not reported in the articles. We obtained this information by communicating with the authors, Dr. Vassiliou and Dr. Bergman by e-mail.

Table 3: Estimated cost of radio-frequency ablation (RFA) therapy with the HALO 360/90 system

Item	Unit cost ($)	Resource use (average) †	Average cost ($)
	a	b	a×b
1. Nursing	30/hour	2×1 hours	30
2. Recovery room	203/hour	1 hour	203
3. HALO 360/90 generator	770 / procedure	1	770
4. HALO 360 sizing balloon	901	1	901
5. HALO 360 Ablation catheter	2703	1	2,703
6. HALO 90 Ablation catheter	1802	1	1,802
7. Hospitalization for complications‡	320/day	0 days	0
Circumferential RFA (Initial,1+2+3+4+5+7)	--	--	4,637
Circumferential RFA (Secondary, 1+2+3+5, without sizing balloon)	--	--	3,736
Focal RFA (1+2+3+4+6)	--	--	2,835
Cost/case (2 circumferential and 1 focal RFA)	**--**	**--**	**11,208**

†: The average resource uses were estimated by Dr. Mayrand.
‡: Serious complications following RFA treatment are very rare. Dilation for esophageal stricture is an outpatient procedure. Therefore, we assume the hospitalization cost due to complications is zero.

Table 4a: Estimated cost of esophagectomy

Item	Unit cost ($)	Resource use (average)	Average cost ($) †	Range used for sensitivity analysis ($)
	a	b	a x b	
Anesthesia (Technician fees)	33 /hour	6.5 (6-7) hours	215	198 — 231
Operating room	836/hour	6.5 (6-7) hours	5,434	5,016 — 5,852
Nursing & ICU	466/day	1.5(1 - 2) days	699	466 — 932
Consumables (tube, catheter, etc.)	--	--	2,000	--
Hospitalization after procedures	320/day	11 (8 -15) days	3520	2,560 — 4,800
Additional hospitalization for complications ‡	320/day	6 days	1,920	1,280 — 2,560
Sum	**--**	**--**	**13,788**	**--**

Abbreviations: d= day/days; hrs=hour/hours.
†: The average resource use was estimated by Dr. Ferri.
‡: Only the costs of hospitalization for serious complications were included. Dr. Ferri estimated the major complication rates and length of additional hospitalization (See Table 4b).

Table 4b: Complication rates following esophagectomy*

Complication	Rate (%)	Additional hospitalization (days)
Stricture	40	0 days (5-6 dilations are done as outpatient visits)
Pneumonia	30-40	14 days
Wound infection	5-10	--
Anastomotic leak	10	10 days
Arrhythmia	15-20	--
Empyema/effusion	5	Done as anastomotic leak
Reintubation	5-10	--
Sepsis	--	--
Ventilator dependence	5-10	--
Urinary tract infection	--	--
Sum	**--**	**6 days Per patient** (35% (Pneumonia) ×14+ 10% (Anastomotic leak) ×10)

* estimated by Dr. Ferri, MUHC
--: Complications are related to other complications, so the additional hospitalization is difficult to estimate. Or it is rare at MUHC. i.e. sepsis.

Table 5: Univariate sensitivity analysis

Variable (range)	Average cost of RFA / case ($)	Average cost of esophagectomy /case ($)	Budget impact of RFA ($)	Cost saving by using RFA per year ($)§
Number of eligible patients / year (10 – 15 cases)	10,514 – 9,976†	13,788	105,140 – 149,640	32,740 – 57,180
Sessions of RFA / case (2 – 4 sessions)	8,241 – 13,272†	13,788	57,687– 92,904	38,829 – 3,612
Esophagectomy: operating room (6 – 7 hours)	11,208	13,370 – 14,206	78,456	15,134 – 20,986
Esophagectomy: hospitalization after procedure (8 – 15 days)	11,208	12,828 – 15,068	78,456	11,340 – 27,020
Esophagectomy: additional hospitalization for complications (4 – 8 days)	11,208	13,148 – 14,428	78,456	13,580 – 22,540

RFA: Radio frequency ablation (BÂRRX)
§: Cost saving by using RFA per year= (average cost of esophagectomy - average cost of RFA per case) x number of patients per year. Except the first variable (number of eligible patients), we assumed 7 patients per year when examining the effects of other variables in the sensitivity analysis.
†: The equivalent annual cost (EAC) of BÂRRX generator is fixed. Therefore, whether there are 10 patients (30 sessions) or 15 (45 sessions) eligible patients per year at MUHC, each session contributes $539 and $359 to whole EAC ($16,164), respectively. Furthermore, if patients need 2 RFA sessions and 4 RFA sessions in average, each session contributes $1,155 and $577 to whole EAC, respectively.

Table 6: Results from the study by Inadomi et al*

Strategy	Cost (US$)	QALYs	ICER (US$)
No surveillance	1,859	12.43	--
RFA with surveillance	20,776	15.67	5,839
APC ablation with surveillance	22,117	15.62	(Dominated)
PDT ablation with surveillance	34,580	15.67	32,588,150
Surveillance	48,354	14.82	(Dominated)
Esophagectomy	58,973	15.02	(Dominated)

*(Cost-Utility Analysis of Barrett's Esophagus Patients with High-grade Dysplasia, Adapted from Inadomi et al., GASTROENTEROLOGY 2009;136:2101–2114)

RFA: radiofrequency ablation; APC: argon plasma coagulation; PDT: photodynamic therapy; QALYs: quality-adjusted life-years; ICER: incremental cost-effectiveness ratio; Dominated: Lower cost and greater effectiveness.
The study by Inadomi et al. was partly supported by BÂRRX Medical Company; and some authors received research grants from this company.

Appendix 1: Treatment of Barrett's esophagus by HALO system for radiofrequency ablation

Generally, the RFA therapy for Barrett's esophagus starts with circumferential ablation using the HALO360 system, as follows:

> ***Measuring inner diameter of esophagus[18]:*** A sizing balloon is introduced over a guidewire and positioned 10 cm above the top of the gastric folds. The balloon is automatically inflated and the displayed inner diameter measurement is recorded. The measurement step is repeated to extend 1 cm above the proximal edge of the intestinal metaplasia until entering the gastric cardia. According to inner diameter measurements, an appropriately sized ablation catheter is selected.
>
> ***Circumferential ablation[18]:*** An ablation catheter of the appropriate size is introduced over the guidewire together with the endoscope in a side-by-side manner. The proximal edge of the electrode is 1 cm above the edge of the intestinal metaplasia. The balloon is automatically inflated and energy applied at 300 W and 10 J/cm^2. The electrode is then moved distally by about 3 cm. Inflation and ablation is repeated, allowing 5—10 mm overlap with the previous ablation zone, until entire area affected by Barrett's esophagus is ablated. The ablation catheter is removed and cleaned. After that, the ablation process is repeated to ablate the entire BE area a second time.

If the residual circumferential area affected by BE is greater than 2 cm in size and/or if multiple isles or tongues remain, a second circumferential ablation would be performed[19]; whereas, if the BE area is small (< 2 cm) or if the remaining isles/tongues are deemed small, it would be more appropriate to use focal ablation[19]. The interval between successive ablation sessions must be 8 weeks or more[19].

> ***Focal ablation[18]:*** For focal ablation, the ablation catheter is mounted onto the endoscope and positioned at the 12 o'clock position in the endoscopic video image. The physician begins the upper endoscopy procedure, when the ablation catheter attaches the distal end of the endoscope. The ablation catheter is positioned at target areas by manipulating the endoscope. The physician applies energy to the affected tissue twice[14, 19], then moving to the next

abnormal area. The endoscope and catheter are removed and cleaned. Then, all ablated areas are treated repeatedly with a double application of energy.

Post-procedure care: After ablation therapy, patients will take high-dose proton pump inhibitors (i.e. esomeprazole 40 mg bid) as maintenance medication[3, 14]. Patients are advised to adhere to a liquid diet in the first 24 hours after the RFA procedure; then they gradually return to soft and normal diet at their own discretion[19]. Aspirin and nonsteroidal anti-inflammatory drugs should be avoided[3].

Follow-up: To determine the response to the first ablation, the patient is typically evaluated after a 2 to 3 month interval[3, 19]. Follow-up treatment strategy is determined based on the endoscopy and biopsy results. No long-term follow-up data for RFA therapy are available thus far[19]. Pouw et al. suggest scheduling follow-up endoscopy at 2 and 6 months following the last treatment, and then annually[19].

The endoscopic images of a BE patient undergoing ablation treatment with 30-months follow-up are shown in Figure 3 (adapted from a study by Fleischer et al[3]).

Appendix 2: Methods used in Literature Search

A systematic literature search of articles in English and French was performed using online databases of PubMed, the International Network of Agencies for Health Technology Assessment (INAHTA), the Canadian Agency for Drug and Technologies in Health (CADTH), the Cochrane Collaboration, and the website of BÂRRX Medical Company[18] to identify health technology assessment reports, systematic reviews and cost-effectiveness studies.

We included randomized controlled trials (RCTs) and cohort studies whose full texts were published in peer reviewed journals before September 3, 2009. If studies had both high-grade and low-grade patients, only results of the sub-group of high-grade dysplasia were reported. If results of high-grade and low-grade patients were mixed together and the proportion of high-grade patients was not more than 60%, then we excluded them. We further excluded studies based on the following criteria:

- Sample size: cohort study < 5; RCTs, no minimum requirement.
- Follow up time: < 6 months (mean/median).
- Outcomes: Did not report eradication of dysplasia or intestinal metaplasia.

A flowchart summarizing the study selection process is given in Figure 4. We extracted data on effectiveness and safety, including: 1) eradication of dysplasia, 2) eradication of intestinal metaplasia, 3) progression to cancer, and 4) adverse events. When necessary, we contacted authors to clarify issues. We used random effects generalized linear mixed model to pool results[20].

Appendix 3: Methods used in the Cost Analysis

We carried out a cost analysis to estimate the procedure cost and budget impact of RFA and the alternative, esophagectomy separately, from the point of view of the MUHC. Thus, physician fees were excluded. For simplicity, we focused only on the major cost components: costs of equipment, procedures, hospitalization and serious complications requiring inpatient visits. We excluded costs of diagnosis, complications of outpatient visits, follow-up, overhead, etc. We also excluded details of medication use as these were difficult to estimate.

The main components of the BÂRRX system are described in Appendix 1. The equivalent annual cost (EAC) is the cost per year of owning and operating an asset over its entire life. To estimate the EAC of the capital investment for the BÂRRX system, we assumed that HALO 360/90 generators would have a service life of 6 years; there was no additional maintenance fee; and the discount rate was 5% annually. Dr. Mayrand (gastroenterologist) estimated the resource use (equipment, operating room, intensive care unit (ICU), hospitalization, etc.) for RFA therapy, and Dr. Ferri (surgeon) estimated those for esophagectomy and estimated complication rates. Unit cost was derived from costs data provided by Mr. Robert, Department of Finance, MUHC, and the purchasing prices for the HALO 360/90 system was supplied by the BÂRRX Company. The cost of each item was the unit cost multiplied by the amount of resources used. The procedure cost of each intervention was the sum of all relevant items.

The annual budget impact is the total net cost per case multiplied by the estimated number of cases. We compared the cost of RFA to that of esophagectomy. Roughly 10 patients have high grade dysplasia and 7 of 10 are assumed to have metaplasia over a large section of the esophagus. Those 7 patients would be candidates for RFA with multiple RFA sessions. We assumed these patients would go through 3 sessions (2 circumferential and 1 focal ablation) in base case analysis, varying from a low of 2 (1 circumferential and 1 focal) to 4 (2 circumferential and 2 focal) sessions in sensitivity analysis. We also conducted univariate sensitivity analyses to allow us to evaluate the procedure costs and budget impact attributable to different variables.

Appendix 4: Critique of the Economic Study by Inadomi et al. [10]

The authors systematically reviewed the literature on the efficacy of different types of ablation technologies for eradication of metaplasia and dysplasia among BE patients[10]. A complex Markov decision analysis model was created to examine 6 different treatment strategies for 50 year old BE patients(e.g. no intervention, surveillance alone, RFA with surveillance, argon plasma coagulation (APC) ablation with surveillance, PDT ablation with surveillance, esophagectomy). The authors analyzed patients with no dysplasia, low grade dysplasia and high grade dysplasia separately.

This study has some serious limitations. For instance, the authors assumed that the effectiveness of the RFA procedure (in terms of eradication of metaplasia) was the same for patients with low grade dysplasia and high grade dysplasia. This would imply that the efficacy for high grade patients was overestimated. The authors assumed a higher mortality rate following esophagectomy (5% to 8%) than has been reported in the literature (approximately 1% for high-grade dysplasia)[21], thus favoring alternatives to surgical treatment. The follow-up time for many interventions was not more than 3 years, but the authors extrapolated results to 30 years (life-time) by making assumptions, which would potentially overestimate the effectiveness of all treatments. The model was too complicated to obtain reliable data on transition probabilities from the literature. Some strategies were uncommon in practice for high-grade patients, e.g. APC ablation and no surveillance. Finally, the assumed utilities for quality of life seem unrealistically high[22], e.g. assuming perfect health equals 1, utility estimates of 0.97 for postesophagectomy and 1 for high grade dysplasia seem too high.

But, overall, the quality of this study is good and it provides a useful insight into the cost-effectiveness of different treatments for BE. The main results of base-case analysis by Inadomi et al. [10] for high-grade patients are summarized in Table 6. Three ablation approaches (RFA, APC and PDT) showed very similar effectiveness (15.62 to 15.67 quality-adjusted life-years(QALYs)), but PDT was associated with a significantly higher cost of 34,580 US$, RFA of 20,776 US$ and APC of 22,117 US$, respectively. The esophagectomy strategy was dominated by ablation therapies for its higher costs (58,973 US$) and lower effectiveness (15.02 QALYs). Compared with no intervention, ablation strategies extend around 3 QALYs, and the incremental cost effectiveness ratio (ICER) is less than 6,000 US$. Authors concluded that “endoscopic ablation could be the preferred strategy for managing patients with BE with high-grade dysplasia (HGD)”[10].

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