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McGill University
Health Centre

**Technology Assessment Unit of the
McGill University Health Centre
(MUHC)**

**Radiofrequency ablation for the treatment of
Barrett's esophagus with high-grade and low-
grade dysplasia: An update**

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Health Centre (MUHC)**

by

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**Update of TAU report #46: Radiofrequency ablation for treatment
of Barrett's esophagus: A systematic review and cost analysis**

Approved by the Committee of the TAU on April 20, 2016

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REPORT REQUESTOR

This report is an update of [TAU report #46](#) "*Radiofrequency ablation for treatment of Barrett's esophagus: A systematic review and cost analysis*" which was requested by Dr. Vicky Baffis, Interim Chief of Division of Gastroenterology at the MUHC, on July 22nd, 2009. The new report will be presented to Ms. Andréanne Saucier, Director of Nursing, Clinical Operations (Adult Missions), and Dr. Alain Bitton, Director of the Division of Gastroenterology at the MUHC.

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ABSTRACT

- Barrett's esophagus, a pre-malignant condition, may progress in a step-wise manner through a series of pre-cancerous stages including metaplasia, low-grade dysplasia (LGD) and high-grade dysplasia (HGD) before developing into esophageal adenocarcinoma.
- Due to the relatively high rates of progression of high grade dysplasia to cancer (approximately 6.6% per patient-year), aggressive treatment of high grade dysplasia is recommended. Until recently, esophagectomy was the standard of care for HGD.
- Radiofrequency ablation (RFA) is an endoscopic ablation procedure designed to eliminate intestinal metaplasia and dysplasia, without the complications associated with esophagectomy and endoscopic mucosal resection.
- In 2009, a report by the Technology Assessment Unit recommended the use of RFA as a first-line treatment for high-grade dysplasia based on a single randomized controlled trial (RCT). It was also recommended that the report be updated as more evidence accrued.
- We identified one additional randomized controlled trial and several observational studies that have established the effectiveness and durability of RFA in eliminating intestinal metaplasia and dysplasia in high grade dysplasia patients, and have documented its good safety profile.
- The use of RFA for the treatment of low-grade dysplasia remains controversial due to uncertainties in diagnostic accuracy of LGD, progression rates to HGD and cancer, and the reversible nature of LGD.
- Two small randomized controlled trials that we identified found RFA to be effective in eliminating dysplasia in LGD patients, but concerns remain about the generalizability of these results to a non-trial setting, and the necessity for treating low-risk patients when more than a quarter of confirmed cases spontaneously revert to non-dysplasia.
- Thus, TAU's previous recommendation that RFA be used and funded at the MUHC for the treatment of HGD still stands. However, we do not recommend that RFA be used to treat LGD patients at the MUHC.

- Since 2010, 38 patients with confirmed high grade dysplasia have been treated at the MUHC of whom only 1 had esophagectomy (5 years after diagnosis).

RÉSUMÉ

- L'oesophage de Barrett, une condition pré-maligne, peut se développer d'une manière progressive en une série de phases pré-cancéreuses incluant la métaplasie, la dysplasie de bas grade (DBG) et une dysplasie de haut grade (DHG), avant de se transformer en un adénocarcinome oesophagien.
- Étant donné les taux de progression relativement élevés de la dysplasie de haut grade vers le cancer (environ 6.6% par patient-année), un traitement agressif de la dysplasie de haut grade est recommandé. Jusqu'à récemment, l'oesophagectomie était la norme de soins ("standard of care") pour la DHG.
- L'ablation par radiofréquence (ARF) est une procédure de résection endoscopique conçue pour éliminer les métaplasies et les dysplasies intestinales, sans les complications associées à l'oesophagectomie et à la résection muqueuse endoscopique.
- En 2009, un rapport de la Technology Assessment Unit recommandait l'utilisation de la ARF comme traitement de première ligne pour la dysplasie de haut grade, basée sur une seule étude randomisée. Il était aussi recommandé que ce rapport soit mis à jour suite à l'obtention de plus de preuves.
- Nous avons identifié une étude randomisée supplémentaire et plusieurs études par observation qui ont démontré l'efficacité et la viabilité de la ARF en éliminant la métaplasie et la dysplasie intestinales chez les patients avec une dysplasie de haut grade, et qui ont documenté un bon profil d'innocuité.
- L'utilisation de la ARF dans le traitement de la dysplasie de bas grade demeure controversée due à certaines incertitudes quant à la précision du diagnostic de la DBG, des taux de progression vers la DHG et le cancer ainsi que de la nature réversible de la DBG.
- Nous avons identifié deux petites études randomisées qui ont souligné que la ARF est efficace pour éliminer la dysplasie chez les patients avec une DBG mais des inquiétudes demeurent quant à la généralisation de ces résultats dans un contexte non dédié à la recherche et à la nécessité de traiter des patients à faible risque lorsque plus du quart des cas confirmés retournent à une condition de non-dysplasie.

- Par conséquent, la recommandation précédente du TAU selon laquelle la ARF peut être utilisée et financée au CUSM (Centre Universitaire de Santé McGill) pour le traitement des DHG, demeure. Cependant, nous ne recommandons pas que la ARF soit utilisée pour traiter les patients avec une DBG au CUSM.
- Depuis 2010, 38 patients avec une dysplasie de haut grade confirmée ont été traités au CUSM, parmi lesquels un seul patient a subi une oesophagectomie (5 ans suivant le diagnostic).

LIST OF ABBREVIATIONS

| | |
|--------|---------------------------------------------------------------|
| AIM | Ablation of Intestinal Metaplasia Containing Dysplasia trial |
| APC | Argon plasma coagulation |
| BE | Barrett's esophagus |
| CE-D | Complete eradication of dysplasia |
| CE-IM | Complete eradication of intestinal metaplasia |
| CI | Confidence interval |
| EAC | Esophageal adenocarcinoma |
| EMR | Endoscopic mucosal resection |
| ESD | Endoscopic surgical dissection |
| GERD | Gastrointestinal reflux disease |
| HGD | High grade dysplasia |
| HTA | Health technology assessment |
| INESSS | Institut National d'Excellence en Santé et en Service Sociaux |
| LGD | Low grade dysplasia |
| MUHC | McGill University Health Centre |
| NICE | National Institutes for Health and Clinical Excellence |
| PDT | Photodynamic therapy |
| RCT | Randomized controlled trial |
| RFA | Radiofrequency ablation |
| SURF | Surveillance vs. Radiofrequency ablation trial |
| TAU | MUHC Technology Assessment Unit |

EXECUTIVE SUMMARY

BACKGROUND

Barrett's esophagus (BE) is a pre-malignant condition that may progress from a non-dysplastic phase (metaplasia) to low-grade (LGD) or high-grade dysplasia (HGD), before progressing to esophageal cancer. Due to the higher progression rates of HGD to cancer, HGD has previously been treated with esophagectomy. More recently, endoscopic eradication therapies such as radiofrequency ablation (RFA) have replaced esophagectomy, which is associated with severe morbidity.

Since our previous report in 2009, which evaluated a single randomized controlled trial of RFA treatment for HGD and recommended its use at the MUHC, several observational studies have established the safety, durability and effectiveness of RFA. However, the use of RFA to treat low-grade dysplasia remains controversial because of uncertainty both in the diagnostic accuracy and in the progression rates of LGD to cancer. Thus, the current report evaluates the most recent evidence for the use of RFA in the treatment of low-grade and high-grade dysplasia.

OBJECTIVES

The objectives of this report were to update the evidence presented in our [previous report](#) on the effectiveness, durability, and safety of radiofrequency ablation for the treatment of Barrett's esophagus with high grade dysplasia when compared with other treatment modalities; to evaluate the evidence on the effectiveness, durability, and safety of RFA treatment for low-grade dysplasia versus endoscopic surveillance; and to update the cost and budget impact estimates associated with RFA use at the MUHC.

METHODS

We conducted a review of the literature from July 2009 up to September 2015 for RFA treatment of HGD and LGD, focussing on randomized controlled trials, controlled observational studies, and recent systematic reviews.

RESULTS: LITERATURE REVIEW

High-grade dysplasia: We identified one observational study (an update of the AIM RCT evaluated in our earlier report) assessing the durability of RFA; one observational study

of RFA versus esophagectomy; one RCT of RFA versus endoscopic resection; and one systematic review published in 2013. Effectiveness of RFA in completely eradicating dysplasia (CE-D) in these studies ranged from 81% to 100%, and in completely eradicating intestinal metaplasia (CE-IM) ranged from 68% to 92%. Durability of eradication in the AIM follow-up study at two years remained high (CE-D:93%; CE-IM:89%). In terms of safety, risk of esophageal strictures was far lower (0-14%) in RFA versus either endoscopic mucosal resection (88%) or esophagectomy (28%).

Low-grade dysplasia: In addition to the AIM RCT which assessed RFA versus sham endoscopy, we identified a further RCT (SURF) and one observational study, both of which evaluated RFA versus endoscopic surveillance. We also identified two recent meta-analyses assessing the use of RFA for the treatment of LGD. Complete eradication of dysplasia in these studies ranged from 90% to 98%, and complete eradication of intestinal metaplasia ranged from 72% to 98%. Rates of progression from LGD to cancer among RFA-treated patients ranged from 0.51% to 0.66% per patient-year, and from 0.37% to 3.90% for patients managed with endoscopic surveillance. The most common complication associated with RFA treatment of LGD patients was esophageal stricture, occurring in 11% of the patients in the SURF RCT.

RFA FOR BARRETT'S ESOPHAGUS AT THE MUHC

Only patients with high grade dysplasia are treated with radiofrequency ablation at the MUHC, and 38 such patients have been treated since 2010. 20% of these patients received RFA alone; the remainder were treated with a combination of endoscopic mucosal resection and RFA. Only 1 of the 38 patients with confirmed high grade dysplasia had an esophagectomy (5 years after diagnosis). On average, patients receive three RFA sessions (1 circumferential, and 2 focal).

COSTS

After accounting for costs of capital and disposable equipment, and nursing costs, and assuming that 10 cases of high-grade dysplasia would be treated annually at the MUHC with an average of three RFA sessions, we estimated the cost per case of HGD treated with RFA to be \$9,479. Thus, the budget impact for 10 HGD cases treated per year would be \$94,790. The potential costs of treating cancers that might have developed in some of these cases had they not received RFA are not considered here.

CONCLUSIONS

- Radiofrequency ablation is now the standard of care for the treatment of Barrett's patients with high grade dysplasia because there is good evidence for its effectiveness and safety in eliminating dysplastic tissue, and because the alternative treatment with esophagectomy is associated with higher morbidity.
- Ablation therapy for LGD remains controversial because of the lack of data on diagnostic accuracy, and uncertainty surrounding the progression rates from LGD to cancer. Although recent evidence from two randomized controlled trials suggest RFA is effective in treating LGD, uncertainties in diagnostic accuracy and progression rates to cancer, and the spontaneous reversion of LGD in some patients do not warrant routine treatment of LGD patients with endoscopic ablation therapies.
- Currently, the MUHC only treats patients with confirmed HGD with radiofrequency ablation, and 38 HGD patients have been treated since 2010. Of these, one patient required esophagectomy 5 years after diagnosis.

RECOMMENDATIONS

- The current evidence reinforces the previous TAU recommendation that RFA be used and funded at the MUHC for the treatment of Barrett's esophagus with high grade dysplasia.
- The TAU does not recommend the routine use of RFA for the treatment of low grade dysplasia given the lack of consistent evidence at this time for progression rates of LGD to cancer, and the reversible nature of LGD. However, in LGD patients with risk factors suggestive of higher risk of progression to HGD/cancer, such as multifocal, long segment or persistent BE, RFA may be considered after comprehensive discussion of potential risks and benefits with the patient. This recommendation should be reviewed if new evidence becomes available on biomarkers or other risk factors that better predict progression of LGD to cancer.

SOMMAIRE

CONTEXTE

L'oesophage de Barrett (OB) est une condition pré-maligne qui peut progresser vers une phase non-dysplasique (métaplasie) à une dysplasie de bas grade (DBG) ou à une dysplasie de haut grade (DHG), avant de devenir un cancer oesophagien. Étant donné les taux de progression plus élevés de la DHG vers le cancer, la DHG était précédemment traitée par oesophagectomie. Plus récemment, les thérapies d'éradication endoscopique, telle l'ablation par radiofréquence (ARF), ont remplacées l'oesophagectomie qui est associée à une morbidité sévère.

Depuis notre rapport précédent publié en 2009 qui évaluait une seule étude randomisée du traitement de la DHG par radiofréquence et qui recommandait son utilisation au CUSM (Centre Universitaire de Santé McGill), plusieurs études par observation ont démontré l'innocuité, la viabilité et l'efficacité de la ARF. Cependant, l'utilisation de la ARF pour traiter la dysplasie de bas grade demeure controversée due à certains doutes quant à la précision du diagnostic et des taux de progression de la DBG vers le cancer. Par conséquent, le présent rapport évalue les plus récentes preuves concernant l'utilisation de la ARF pour le traitement des dysplasies de bas et de haut grade

OBJECTIFS

Les objectifs de ce rapport étaient de faire la mise à jour des preuves présentées dans notre rapport précédent sur l'efficacité, la viabilité et l'innocuité de l'ablation par radiofréquence pour le traitement de l'oesophage de Barrett avec une dysplasie de haut grade lorsque comparée aux autres modalités de traitement, d'évaluer les preuves de l'efficacité, de la viabilité et de l'innocuité de la ARF pour le traitement des dysplasies de bas grade versus la surveillance endoscopique, et de faire une mise à jour des coûts et des estimés de l'impact budgétaire associés à l'utilisation de la ARF au CUSM.

MÉTHODOLOGIE

Nous avons effectué une revue de la littérature, du mois de juillet 2009 au mois de septembre 2015, pour le traitement par ARF de la DHG et de la DBG en ciblant les études randomisées, les études par observation et les revues systématiques récentes.

RÉSULTATS: REVUE DE LA LITTÉRATURE

Dysplasies de haut grade: Nous avons identifié une étude par observation (une mise à jour de l'étude randomisée AIM évaluée dans notre rapport précédent) évaluant la viabilité de la ARF; une étude par observation de la ARF versus l'oesophagectomie; une étude randomisée de la ARF versus la résection endoscopique et une revue systématique publiée en 2013. L'efficacité de la ARF dans ces études pour complètement éradiquer la dysplasie (CE-D) s'échelonnait de 81% à 100% et pour complètement éradiquer la métaplasie intestinale (CE-MI), de 68% à 92%. La viabilité de l'éradication dans le suivi de l'étude AIM demeure élevée après 2 ans (CE-D: 93%; CE-IM: 89%). En termes d'innocuité, le risque de sténoses oesophagiennes était beaucoup plus faible (0-14%) lors de la ARF versus la résection muqueuse endoscopique (88%) ou de l'oesophagectomie (28%).

Dysplasie de bas grade: En plus de l'étude randomisée AIM qui évaluait la ARF versus l'endoscopie placebo, nous avons identifié une étude randomisée additionnelle (SURF) ainsi qu'une étude par observation, ces deux études évaluant la ARF versus la surveillance endoscopique. Nous avons aussi identifié deux meta-analyses récentes évaluant l'utilisation de la ARF pour le traitement de la DBG. L'éradication complète de la dysplasie dans ces études variait de 90% à 98% et l'éradication complète de la métaplasie intestinale variait de 72% à 98%. Les taux de progression de la DBG vers le cancer chez les patients traités par ARF s'échelonnaient de 0.51% à 0.66% par patient-année, et de 0.37% à 3.90% pour les patients suivis par surveillance endoscopique. La complication la plus fréquente associée au traitement par ARF des patients avec une DBG était la sténose oesophagienne observée chez 11% des patients de l'étude randomisée SURF.

L'ABLATION PAR RADIOFRÉQUENCE POUR L'ŒSOPHAGE DE BARRETT AU CUSM

Seuls les patients avec une dysplasie de haut grade sont traités par ablation par radiofréquence au CUSM et ce nombre se chiffre à 38 patients traités depuis 2010. 20% de ces patients ont été traités par ARF, seulement, tandis que les autres ont été traités par une combinaison de la résection muqueuse endoscopique et de la ARF. Seulement un patient eut une oesophagectomie (5 ans suivant le diagnostic). En moyenne, les patients ont reçu trois sessions de ARF (1 circonférentielle et 2 focalisées).

Coûts

Si l'on tient compte des coûts d'immobilisation, des coûts des équipements à usage unique, des coûts des soins infirmiers et que l'on estime que 10 cas de dysplasie de haut grade seraient traités annuellement au CUSM selon une moyenne de trois sessions de ARF par cas, le coût du traitement par ARF d'un patient avec une DHG serait de 9 479 \$. Par conséquent, l'impact budgétaire pour traiter 10 patients par année avec une DHG serait de 94 790\$.

CONCLUSIONS

- L'ablation par radiofréquence est maintenant la norme de soins ("standard of care") pour le traitement des patients avec un oesophage de Barrett et une dysplasie de haut grade car il existe des preuves supportant son efficacité et son innocuité en éliminant les tissus dysplasiques et que le traitement alternatif par oesophagectomie est associé à une morbidité plus importante.
- La thérapie par ablation pour les cas avec DBG demeure controversée due à un manque de données sur la précision du diagnostic et à une incertitude quant aux taux de progression de la DBG vers le cancer. Malgré des preuves récentes de deux études randomisées suggérant que la ARF est efficace pour traiter les patients avec une DBG, des incertitudes quant à la précision du diagnostic, des taux de progression vers le cancer et de la nature réversible spontanée de la DBG chez certains patients, ne justifient pas le traitement de routine des patients avec une DBG à partir des thérapies endoscopiques d'ablation.
- Actuellement, le CUSM ne traite que les patients avec une DHG confirmée à partir de l'ablation par radiofréquence. Depuis 2010, 38 patients avec une DHG ont été traités, dont seulement un patient eut une oesophagectomie (5 ans suivant le diagnostic).

RECOMMANDATIONS

- Les preuves actuelles consolident les recommandations précédentes du TAU selon lesquelles la ARF soit utilisée et supportée financièrement au CUSM pour le traitement de l'oesophage de Barrett avec une dysplasie de haut grade.

- Le TAU ne recommande pas l'utilisation de routine de la ARF pour le traitement des patients avec une DBG étant donné l'absence actuelle de preuves cohérentes concernant les taux de progression de la DBG vers le cancer, et la nature réversible de la DBG. Cependant, chez les patients avec une DBG et des facteurs de risque suggérant un risque plus élevé de progression vers une DHG ou un cancer tel qu'un oesophage de Barrett persistant, multifocal ou en segment allongé, la ARF peut être considérée après une discussion franche avec le patient des risques potentiels et des bénéfices. Cette recommandation devrait être revue si de nouvelles preuves deviennent disponibles via des marqueurs biologiques ou via des facteurs de risque prédisant mieux la progression de la DBG vers le cancer.

RADIOFREQUENCY ABLATION FOR TREATMENT OF BARRETT'S ESOPHAGUS WITH HIGH- GRADE AND LOW-GRADE DYSPLASIA: AN UPDATE

1. BACKGROUND

Barrett's esophagus (BE) is a pre-malignant condition that predisposes to esophageal adenocarcinoma and affects approximately 2 to 6% of the adult population.^{2,3} BE is characterized by replacement of the normal squamous epithelial lining of the esophagus with columnar epithelia normally found in the stomach and intestine.⁴ Such replacement of one cell type by another, known as [metaplasia](#), is thought to be due to chronic tissue injury resulting from conditions such as gastroesophageal reflux disease (GERD). Current evidence suggests that only intestinal metaplasia, wherein the replaced cells resemble intestinal epithelia, clearly predisposes to esophageal cancer, and hence US gastroenterology societies require the presence of intestinal metaplasia extending beyond the gastroesophageal junction for a diagnosis of BE to be confirmed. However, British gastroenterology societies define BE as the presence of either intestinal or gastric cardiac metaplasia (replaced cells resemble stomach epithelia).

BE may progress in a step-wise manner from pre-malignant metaplasia to cancer-predisposing [dysplasia](#), and eventually to esophageal adenocarcinoma (EAC) [**Figure 1**]. Based on the degree of architectural and cytological changes, dysplasia can be divided into either low-grade dysplasia (LGD) or high-grade dysplasia (HGD),⁵ with the latter carrying the highest risk of progressing to [EAC](#). While the rate of progression to EAC is approximately 0.60% (95% CI: 0.51, 0.69) per patient per year among those with non-dysplastic BE, it is 1.70% (95% CI: 1.31, 2.09) per patient-year in LGD patients, and 6.58% (95%CI: 4.97, 8.18) per patient-year in HGD patients.¹ However, the subjective nature of distinguishing between non-dysplastic BE, low-grade dysplasia, and high-grade dysplasia confers a high possibility of misclassification. This uncertainty in diagnosis is also why the true risk of progression from low-grade dysplasia to high-grade dysplasia or cancer remains unclear.

Current guidelines recommend that patients with [GERD](#) symptoms and at least one risk factor for [EAC](#) (being male, white, ≥ 50 years of age, having chronic GERD, an elevated BMI, hiatal hernia, and intra-abdominal distribution of fat) undergo screening for BE. Those with non-dysplastic BE are recommended to undergo endoscopic surveillance every 3-5 years, while patients with confirmed HGD are recommended for endoscopic eradication therapy (**Figure 2**).⁴ However, recommendations are less clear for patients with LGD, who may undergo screening every 6-12 months, or may opt for endoscopic

eradication therapy. Some researchers argue for more aggressive treatment of LGD by citing evidence that when an LGD diagnosis is confirmed by at least two expert gastrointestinal pathologists, the rate of progression to HGD or cancer is much higher (13.4% per patient-year) than when a consensus diagnosis is not used, presumably because non-dysplastic BE cases, which have a lower rate of progression, are excluded.⁶

Until recently, the standard treatment for HGD or intramucosal cancer has been esophagectomy, which is associated with considerable morbidity and mortality.⁷ Advances in technology have paved the way for less invasive endoscopic techniques, which include endoscopic mucosal resection and endoscopic ablation therapies (**Figure 2**). [Endoscopic mucosal resection](#) (EMR), wherein the mucosal and submucosal esophageal layers are removed, is recommended if visible nodules or ulcers are detected. If the dysplasia is flat, i.e. nodules or ulcers are not visible, then various ablation techniques such as [photodynamic therapy](#) (PDT); [argon plasma coagulation](#) (APC); radiofrequency ablation (RFA); laser ablation; cryotherapy; and multipolar electro coagulation may be used (**Figure 2**).

Radiofrequency ablation (RFA) delivers high frequency alternating current to the mucosa using the BÂRXX (formerly HALO) system (Covidien, Sunnyvale, CA), with the aim of destroying neoplastic mucosa and allowing for the regeneration of normal squamous epithelia. RFA is typically administered to mucosa that is flat (i.e. there are no villi or pits) because RFA is not recommended if there is submucosal invasion of the dysplastic cells. The BÂRXX system provides two types of devices, the BarxxTM360, which administers circumferential treatment, and the BarxxTM90 device which provides focal treatment of smaller areas.

In 2009, the [TAU](#) published a report on RFA for Barrett's esophagus,⁸ which was mainly based on a single randomized controlled trial (RCT), the AIM trial, comparing RFA to sham therapy.⁹ This RCT by Shaheen et al. demonstrated significantly higher rates of complete elimination of intestinal metaplasia and dysplasia, and lower rates of progression to cancer for patients treated with RFA compared to sham therapy. Based on these results and the lack of significant adverse effects, the TAU recommended that RFA be approved for use at the MUHC for the treatment of HGD.⁸ The TAU also recommended that, due to the relatively short follow-up of the Shaheen trial, the evidence be re-evaluated within two years. Since the publication of these trial results in 2009, RFA has become standard practice for the treatment of HGD. However, it remains unclear whether this approach is suitable for the treatment of LGD, as has been recommended by some gastroenterological societies and health technology assessments.¹⁰

This report is an update of [TAU report #46](#) which evaluated the effectiveness of RFA for BE patients with high-grade dysplasia, and assessed the cost of RFA and esophagectomy from the point of view of the MUHC.⁸ The original report was requested by Dr. Vicky Baffis, Interim Chief of Division of Gastroenterology at the MUHC, on July 22nd, 2009. The new report updates the evidence of RFA treatment for high grade dysplasia, and summarizes recent evidence on the use of RFA in low grade dysplasia patients.

2. OBJECTIVES

The objectives of this report are to

- update the evidence on the safety and efficacy of radiofrequency ablation for the treatment of high grade dysplasia when compared with esophagectomy or other modalities;
- assess the safety and efficacy of radiofrequency ablation for the treatment of low grade dysplasia when compared with endoscopic surveillance;
- estimate the cost and budget impact of using RFA at the MUHC.

3. METHODS

3.1 Literature search and quality assessment

We updated our last literature search on high grade dysplasia Barrett's esophagus, which was conducted on September 3, 2009, by searching Pubmed, the Cochrane library and the health technology assessment (HTA) database of the Centre for Reviews and Dissemination. We also conducted a search for articles assessing the safety and efficacy of RFA in low grade dysplasia patients. The most recent search was conducted on June 9th, 2015.

Our systematic literature search was limited to randomized controlled trials (RCT). We also searched for cohort studies or systematic reviews/meta-analyses that evaluated the safety and efficacy of RFA in treating LGD, HGD or intramucosal cancer, when directly compared to esophagectomy, endoscopic mucosal resection, or endoscopic surveillance. Thus, uncontrolled studies, case reports, and studies or reviews evaluating ablative techniques other than RFA were excluded. We also identified relevant HTAs and clinical guidelines assessing the use of RFA in HGD and LGD patients.

3.2 MUHC experience

We describe the current treatment policy for Barrett's esophagus at the MUHC, and the MUHC experience with using radiofrequency ablation.

3.3 Cost analysis

We updated the cost estimates reported in our previous document for treatment of HGD Barrett's esophagus at the MUHC. Average resource use was estimated by Dr. Serge Mayrand at the Montreal General Hospital (MGH), and procedure and equipment costs were obtained from Mr. Philippe Lachapelle, Financial Advisor at the Department of Finance of the MUHC. The cost analysis included material and nursing costs; physician fees were not included.

4. LITERATURE REVIEW

4.1 High grade dysplasia (HGD)

We identified an update of the AIM (Ablation of Intestinal Metaplasia Containing Dysplasia) trial,^{9,11} which was evaluated in [our original report](#).⁸ The AIM study was an RCT that assessed the safety and efficacy of RFA *versus* a sham endoscopic procedure in the treatment of HGD and LGD patients.⁹ There have been no RCTs to date comparing RFA to esophagectomy, and hence we summarize the sole observational study assessing RFA vs. esophagectomy. We identified one RCT comparing RFA to EMR,¹² and one meta-analysis evaluating the efficacy and durability of RFA in BE patients.¹³

4.1.1 Effectiveness

As the incidence of esophageal adenocarcinoma is extremely rare, studies generally evaluate the effectiveness of radiofrequency ablation by assessing the proportion of patients who achieve complete eradication of [dysplasia](#) (CE-D) and complete eradication of intestinal [metaplasia](#) (CE-IM) after ablation therapy. Results are summarized in **Table 1**.

A. RFA versus sham endoscopy⁹

The **AIM** (Ablation of Intestinal Metaplasia Containing Dysplasia) trial randomized 127 BE patients with either high-grade or low-grade dysplasia to receive endoscopic

radiofrequency ablation or a sham endoscopic procedure.⁹ Diagnoses of dysplasia were made by consensus with at least two pathologists. Of the 63 HGD patients, 42 received RFA and 21 received the sham procedure, and an [intention-to-treat](#) analysis was performed on all randomized patients. Patients, outcome assessors (pathologists) and the study statistician were blinded to the treatment received. 81% of the RFA-treated HGD patients achieved [CE-D](#) compared to 19% in the sham group, and 74% vs. 0% attained [CE-IM](#) in the RFA and sham arms, respectively (**Table 1**). 2% of RFA-treated patients progressed to cancer compared to 19% in the sham group (p -value 0.04).

B. RFA versus endoscopic mucosal resection (EMR)¹²

van Vilsteren et al. randomized 47 patients with HGD and early cancer to either stepwise radical endoscopic resection (SRER) (n=25), in which the entire BE segment in removed in consecutive sessions, or to RFA (n=22) with or without prior focal endoscopic resection.¹² [CE-D](#) was achieved in 100% of SRER-treated patients versus 96% of RFA-treated patients (**Table 1**). [CE-IM](#) was reached in 92% and 96% of SRER and RFA patients, respectively.

C. RFA versus esophagectomy¹⁴

Zehetner et al., in 2011, published results of a retrospective study of patients treated for HGD or intramucosal cancer with either RFA or esophagectomy.¹⁴ 22 HGD patients received RFA (with or without prior [EMR](#)) and 13 were treated with esophagectomy. Of the 19 RFA-treated patients with follow-up data, 17 (89%) achieved [CE-D](#) and 12 (71%) achieved [CE-IM](#) (**Table 1**). As esophagectomy effectively removes the entire affected area, all patients were free of intestinal metaplasia at follow-up. Survival at 3 years was similar for the two groups (94%).

D. Systematic review of RFA in general¹³

In 2013, **Orman** and colleagues published a systematic review and meta-analysis of the efficacy and durability of RFA in the treatment of dysplastic and non-dysplastic BE patients.¹³ Of the 18 included studies and abstracts of efficacy, only 6 reported results separately for HGD patients. Most studies were uncontrolled cohort studies. The authors used a random-effects model to pool results from each study. There was a great degree of variability in patient inclusion criteria. Patients may have received [EMR](#) for staging purposes before RFA, or as escape treatment after RFA. The type (circumferential or focal) and number of ablation sessions also varied between studies. Complete eradication of dysplasia (CE-D) at follow-up was achieved in 607 of 714 (85%)

HGD patients, and complete eradication of intestinal metaplasia (CE-IM) was attained in 490 of 721 (68%) HGD patients.

4.1.2 Durability

Table 2 summarizes the results of the long-term durability of RFA treatment in HGD patients.

- In the follow-up of the [AIM](#) trial, **Shaheen et al.** allowed patients who received the sham procedure to cross-over to the RFA arm upon completion of the 12-month assessment.¹¹ Thus, the follow-up study was a prospective study to evaluate the long-term durability of RFA treatment in HGD and LGD patients. 58 of the original 63 HGD patients completed 12-month assessment, including 20 patients treated with sham who were eligible for crossover to the RFA group. 54 and 24 patients completed two-year and three-year follow-up, respectively. [CE-D](#) was maintained in 93% (50/54) of patients at 2 years and 96% (23/24) at 3-year follow-up. [CE-IM](#) was 89% (48/54) at 2-year follow-up. The rate of progression to cancer for HGD patients at the end of 3 years was 0.60% per patient per year.
- In the meta-analysis by **Orman et al.** described above, the authors do not report durability of RFA treatment separately for HGD and LGD patients.¹³ From the 6 included studies, 52% of patients had HGD, and 13% had LGD. Studies varied considerably by pre-treatment histology, timing of endoscopy, and start of follow-up after treatment. Included studies had a median sample size of 80 (range: 20–218), and a median follow-up length of 16.5 months (range: 13–51). The pooled maintenance of CE-IM was 87% (95% CI: 82%,91%).

4.1.3 Safety

A. RFA versus sham endoscopy⁹

The [AIM](#) trial authors reported the occurrence of three (4%) serious adverse events in the RFA treatment arm, but they do not specify whether they occurred in the HGD or LGD groups.⁹ There was one occurrence of gastrointestinal bleeding, one episode of overnight hospitalization for chest pain, and one episode of chest discomfort and nausea immediately after treatment. 5 patients (6%) developed [stricture](#), which were all successfully treated with dilatation.

B. RFA versus endoscopic mucosal resection (EMR)¹²

In the RCT comparing EMR to RFA, **van Vilsteren** reported that esophageal strictures occurred in 88% vs. 14% (p-value <0.001) of SRER and RFA patients, respectively. Additionally, there was one severe complication (perforation) in the SRER group versus none in the RFA arm, and 5 vs. 3 mild complications in the SRER and RFA arms, respectively.

C. RFA versus esophagectomy¹⁴

Zehetner et al. reported that procedure-related complications were significantly higher in the esophagectomy group compared to the RFA group (39% vs. 0%; p-value <0.001), as were long-term complications (61% vs. 0%) which included stricture (28%), reflux (59%), and diarrhea (23%).

4.1.4 Summary of the effectiveness, durability and safety of RFA for HGD

In randomized controlled trials, RFA was found to be far more effective than a sham endoscopic procedure in completely eradicating dysplasia and intestinal metaplasia, and equivalent to endoscopic mucosal resection (EMR). EMR and esophagectomy were associated with greater morbidity, notably esophageal strictures. The durability of RFA was maintained at 2 years after treatment, with close to 90% of treated patients still free from intestinal metaplasia or dysplasia.

4.1.5 Guidelines for the treatment of HGD

A. NICE guidelines

In March 2010, the National Institute for Health and Care Excellence (NICE) published guidelines for the treatment of Barrett's esophagus with HGD. The guidelines with respect to RFA were based on two studies: the AIM trial,⁹ judged to be of very high quality, and a case series,¹⁵ of very low quality. Based on the results from the AIM RCT (**Table 1**), and their cost-effectiveness analyses (approximately £25,000 per QALY compared to surveillance), NICE recommended that RFA treatment alone (i.e. without EMR) may be considered for the treatment of flat HGD.

The NICE guidelines also summarized five studies that evaluated the use of RFA after EMR; all were small, single-arm studies judged to be of very low quality. [CE-IM](#) for the five studies ranged from 54% to 83%, and [CE-D](#) ranged from 79% to 100%. The NICE guidance recommended that if EMR was used as first-line treatment, further treatment with an ablative procedure like RFA should be considered.

B. Delphi consensus guidelines for the management of HGD¹⁶

In 2012, consensus guidelines for the treatment of HGD were published using the Delphi process, which combines evidence from the literature with an anonymous voting process to reach a consensus.¹⁶ The consensus panel included experts from 68 centres including the US, UK, Europe, Australia and Japan. A consensus was reached if 80% of respondents agreed or strongly agreed with the draft statements and their level of evidence after four rounds of voting. The experts strongly agreed that RFA is presently the best ablation technique for treating flat HGD and for the eradication of residual Barrett's esophagus after endoscopic mucosal resection (EMR). HGD treated by EMR must be followed by ablation techniques to reduce recurrence rates, and HGD patients who receive ablative or surgical therapy require endoscopic follow-up. The experts also agreed that all Barrett's biopsies need to be evaluated by at least two experienced gastrointestinal pathologists when making a diagnosis of dysplasia.

4.2 Low Grade Dysplasia (LGD)

In addition to the [AIM](#) trial described above that also included LGD patients,^{9,11} we identified another RCT¹⁷ and one cohort study,¹⁸ both of which evaluated RFA versus endoscopic surveillance in LGD patients. We also report the results of two meta-analyses. Results are summarized in **Table 3**.

4.2.1 Effectiveness

A. RFA versus endoscopic surveillance

- The [AIM](#) RCT randomized 64 LGD patients to receive either RFA (n=42) or a sham procedure (n=22).⁹ 81% of the RFA-treated LGD patients achieved [CE-IM](#) compared to 4% in the sham group, and 90% vs.23% attained [CE-D](#) in the RFA and sham arms, respectively (**Table 3**).
- The **SURF** (Surveillance vs. Radiofrequency ablation) study was a randomized controlled trial conducted in 9 centres across 5 European countries, which assessed progression to HGD and adenocarcinoma in BE patients with confirmed LGD receiving either radiofrequency ablation or endoscopic surveillance.¹⁷ 140 LGD patients were randomized to receive either RFA (n=70) or standard endoscopic surveillance (n=70). 2 patients in each arm did not receive the treatment, and thus 68 patients in each group were analysed in a modified [intention-to-treat analysis](#). Outcome assessors (pathologists) were blinded to exposure status. The trial was terminated early due to superiority of RFA for the primary outcome, and median

follow-up at that time was 36 months. The proportion of patients who progressed to HGD or cancer (primary outcome) after 3 years was 1.5% vs. 26.5% in the RFA and surveillance arms, respectively (risk difference: 25%; 95% CI:14.1-35.9) [Table 3]. 93% (63/68) and 88% achieved CE-D and CE-IM, respectively.

- In 2015, **Small et al.** published a retrospective cohort study of confirmed cases of LGD receiving either RFA or endoscopic surveillance, with the primary objective of determining rates of progression to HGD or cancer.¹⁸ Of the 45 patients receiving RFA (with or without EMR), 1 (2.2%) developed intramucosal cancer, versus 36 of the 125 surveillance patients (28.8%) who progressed to either HGD (n=29), IMC (n=5) or submucosal cancer (n=2) [Table 3]. 96% and 78% of RFA patients achieved CE-D and CE-IM, respectively. However, in the surveillance group, a third of patients (31%) reverted spontaneously to non-dysplastic BE without treatment.

B. Reviews of RFA in general

- **Orman et al.** assessed the efficacy and durability of RFA in the treatment of dysplastic and non-dysplastic BE patients.¹³ Of the 18 included studies and abstracts of efficacy, 6 reported results separately for LGD patients. Most studies were uncontrolled cohort studies. The authors used a random-effects model to pool results from each study. Complete eradication of dysplasia (CE-D) at follow-up was achieved in 581 of 633 (92%) HGD patients, and complete eradication of intestinal metaplasia (CE-IM) was attained in 458 of 633 (72%) LGD patients.
- In 2014, **Almond et al.** published a meta-analysis of all endoscopic therapies for the treatment of LGD, with the specific aim of evaluating progression rates to cancer.¹⁹ They included 37 studies, 9 of which evaluated the use of RFA alone and an additional 5 assessed RFA with another endoscopic modality. Rates of progression to cancer were calculated as the total number of outcomes over the total number of patient-years of follow-up, while a random-effects meta-analysis was conducted for rates of CE-IM and CE-D. From the 14 studies that evaluated the use of RFA to treat LGD patients, the authors calculated the pooled rate of progression to cancer to be 5.25 per 1000 patient-years (95% CI: 0.64, 18.98) versus a pooled progression rate using other endoscopic treatments of 3.33 (0.69, 9.73) per 1000 patient-years. Pooled rates of CE-IM and CE-D from studies using RFA were 87.2 (76.2, 93.5) and 90.6 (81.0, 95.6), respectively, versus 42.2 (21.8, 65.7) and 87.8 (80.4, 92.6) for other modalities.

4.2.2 Durability of treatment with RFA

- The [AIM](#) trial authors reported that CE-IM was maintained in 98% (51/52) of LGD patients at the end of 2 years of follow-up.¹¹ Over the three year follow-up period, 3 cases of LGD treated with RFA progressed to HGD (rate of progression: 1.5% per patient-year) and 1 LGD case progressed to cancer, for an annual rate of progression to cancer of 0.51% per patient-year.
- Results from the [SURF](#) RCT showed that CE-D was maintained in 62 of the 63 patients (98.4%) who achieved CE-D after RFA treatment. 28% (19/68) of control patients reverted to non-dysplastic tissue at 3 year follow-up. CE-IM was maintained in 90% (54/60) of RFA patients, and occurred in 0% of the control patients. The rate of progression to cancer at the end of 3 years for the surveillance group was 3.9% per patient per year. Although the authors did not report the progression rate for the RFA group, we calculated the rate as 0.66% (1 case/152.5 person-years), assuming the same number of person-years of follow-up as in the surveillance group (**Table 3**).

4.2.3 Rates of progression from LGD to esophageal adenocarcinoma (EAC)

Due to the uncertainty in accurately diagnosing LGD, the rates of progression from LGD to cancer among both untreated and treated patients vary from one study to the next (**Table 3**):

- A meta-analysis by **Wani et al.** attempting to determine the incidence of [EAC](#) in Barrett's patients pooled 16 studies of 1,512 LGD patients undergoing surveillance endoscopy without any previous ablation or surgery, and found a weighted average incidence rate of 1.7% (1.7 cases per 100 patient-years) [95% CI: 1.3-2.1].¹ In a separate analysis, the authors pooled 239 LGD patients from 45 studies who had undergone some form of ablative treatment, and found an incidence rate of EAC of 0.16% (95% CI: 0.07-0.38). As the vast majority of studies included in this meta-analysis were non-comparative studies without control groups, the authors felt that they could not directly compare the incidence rates in the two populations, and hence calculations of relative risk reductions after ablative therapy or the number needed to treat (NNT) would not be accurate.
- The [SURF](#) trial by Phoa et al. is the only randomized controlled trial to date comparing LGD patients managed with surveillance to those undergoing RFA treatment.¹⁷ The study found that over a median follow-up of 36 months, 1 patient in the RFA arm and 6 in the surveillance arm developed cancer, for a

progression rate per person-year of 0.66% and 3.90%, respectively (**Table 3**). The authors argue that the high progression rate in the surveillance arm was a result of requiring a consensus diagnosis of LGD by at least two expert pathologists, which may not have been the case in previous studies. Based on the estimated risk reduction of 3.24% (3.9%-0.66%), the number of LGD patients needed to be treated with RFA to prevent one case of cancer (NNT) in this population would be 31.

- In the retrospective study by [Small et al.](#) comparing surveillance with RFA, only confirmed cases of LGD were included, where diagnosis was reached by consensus with up to three GI pathologists.¹⁸ This study, which included 145 patients in the surveillance arm over a follow-up of 544 patient-years, reported a progression rate to submucosal cancer per person-year of 0.37%, versus 0% in the RFA arm (**Table 3**). Thus, the NNT in this population would be 270.

4.2.4 Safety

The authors of the [SURF](#) RCT reported three serious adverse events occurring in 2 RFA patients: one hospitalization for abdominal pain, and one hospitalization for bleeding, and fever/chills. 8 (11.8%) RFA patients developed [stricture](#) requiring dilation. No adverse events occurred in the control patients.

4.2.5 Summary of the effectiveness, durability and safety of RFA for LGD

In two RCTS comparing RFA to endoscopic surveillance, treatment of LGD with RFA achieved high rates of complete eradication of metaplasia and dysplasia [**Table 3**]. However, a quarter of patients managed with endoscopic surveillance spontaneously reverted to non-dysplastic tissue by the end of follow-up. Rates of progression to cancer in the RFA-treated patients ranged from 0% to 0.5% per patient-year,^{11,18} while it ranged from 0.37% to 3.9% in patients managed with surveillance.^{1,17,18}

4.2.6 Guidelines for the use of radiofrequency ablation in LGD

A. NICE guidelines

In March 2014, the National Institute for Health and Care Excellence (NICE) published a guidance for the use of RFA in the treatment of LGD, and based on the AIM follow-up study¹¹ and the SURF trial,¹⁷ determined the evidence was adequate to recommend the use of RFA in low grade dysplasia patients.

B. BOB-CAT (Benign Barrett's and Cancer Taskforce) consensus guidelines for LGD²⁰

In 2014, new consensus guidelines suggested a strategy of risk stratification wherein LGD patients may be classified as high or low-risk, and their treatment amended accordingly.²⁰ LGD patients with high risk factors such as multifocality, long BE segment length, and persistence may have their treatment escalated to ablative therapy to decrease the risk of progression to cancer. On the other hand, patients with an absence of LGD on two consecutive endoscopies may have their treatment downgraded to less intensive surveillance.

4.3 Limitations of the AIM and SURF randomized controlled trials

Generalizability

In both the [AIM](#)⁹ and [SURF](#)¹⁷ trials, LGD was diagnosed by consensus reviews of two expert pathologists, which may be impractical in non-trial settings. Furthermore, the rate of progression to cancer for the control (surveillance) group in the SURF trial of 3.9% per patient-year was far higher than that reported in other studies (1.3¹⁸-1.7%¹), which raises further questions about the generalizability of these results.

Necessity

In the [SURF](#) trial,¹⁷ 28% of LGD patients managed with surveillance reverted to non-dysplastic tissue without treatment. The [AIM](#) trial found a similar proportion (23%) of LGD control patients had no dysplasia at 12 month follow-up,⁹ and in the observational study by Small et al. a third of confirmed LGD cases had no dysplasia during follow-up.¹⁸ If more than a quarter of LGD patients revert spontaneously, is treatment of all LGD patients with ablation therapy warranted?

5. RADIOFREQUENCY ABLATION FOR BARRETT'S AT THE MUHC

5.1 Current treatment policy

Patients with Barrett's esophagus are referred to the MUHC from across Quebec. The standard of care at the MUHC for Barrett's esophagus with HGD is radiofrequency ablation (RFA). Since 2010, 38 patients with HGD have been treated with RFA at the MUHC. The MUHC does not use RFA to treat patients with low grade dysplasia; these patients are managed with endoscopic surveillance. Diagnoses of HGD made by the

referring hospital's pathologist is confirmed after endoscopy and biopsy by an MUHC pathologist. Only about 20% of patients receive RFA alone. The vast majority (80%) are treated with a combination of RFA and [endoscopic mucosal resection](#) (EMR). EMR before RFA is performed both for staging purposes and to remove visible nodules, and EMR may be used after RFA as an escape treatment for intractable cases of BE with incomplete response. Cases that do not respond completely may also be referred for surgery (endoscopic surgical dissection or esophagectomy). In a minority of cases, RFA is used in conjunction with [argon plasma coagulation](#) (APC) if the residual BE island is very small.

Most patients receive an average of 3 RFA sessions (1 circumferential and 2 focal at intervals of 2 months or more), with the maximum number of sessions not exceeding 4-5 per patient. Each circumferential RFA treatment lasts approximately 60 minutes, and each focal session takes 45 minutes to administer.

Of the 38 HGD patients treated to date, only 1 patient has had an esophagectomy (5 years after diagnosis).

5.2 Cost and budget impact estimates

We updated the cost estimates calculated in our previous report. The capital cost of the Barxx™ 360/90 generator is \$82,041, resulting in an equivalent annual cost (EAC) of \$16,164, assuming a service life of 6 years, and an annual interest rate of 5%. **Table 4** shows the breakdown of costs if 10 patients with HGD, each requiring 3 sessions of RFA (1 circumferential and 2 focal), are treated at the MUHC per year, resulting in a total of 30 sessions of RFA performed at the MUHC annually. These cost calculations take into account the initial capital cost of the Barxx™360/90 generator, the sizing balloon and catheter costs, as well as nursing costs. We thus estimated the cost per case of HGD treated with RFA to be \$9,479. The budget impact for 10 HGD cases treated per year would be \$94,790.

6. DISCUSSION

6.1 The use of RFA for treating HGD

Radiofrequency ablation is now the standard of care for the treatment of Barrett's patients because numerous studies have now demonstrated the effectiveness of treating HGD with RFA. Although other modalities such as endoscopic resection and

esophagectomy achieve similar rates of eradication of dysplasia, these latter methods are associated with significantly higher rates of adverse events such as stricture.

6.2 The use of RFA for treating LGD

Radiofrequency ablation therapy for LGD remains controversial because of the lack of data on diagnostic accuracy, and progression rates from LGD to cancer. Below, we summarize some of these controversies regarding the use of RFA for treating LGD.

6.2.1 Controversies in treating LGD patients

Ambiguity in diagnosis

As diagnoses of LGD and HGD are based on subjective morphological criteria, there is considerable intra-observer and inter-observer discordance. In a study of 12 expert gastrointestinal pathologists tasked with categorising 125 biopsies as either negative; indefinite for dysplasia/LGD; HGD; or carcinoma, the [kappa statistic](#) for inter-observer agreement was 0.42 or moderate agreement.²¹

Furthermore, LGD is often over-diagnosed in a clinical setting. Curvers et al. found that only 15% of patients initially diagnosed with LGD received a confirmatory consensus diagnosis of LGD by two expert gastrointestinal pathologists.⁶ The majority were downgraded to non-dysplastic BE (75%). Because of this potential for overdiagnosis, some experts suggest that any treatment of LGD with RFA be prefaced by the requirement of a consensus diagnosis by expert gastrointestinal pathologists. However, such a recommendation may be unrealistic outside a controlled trial setting.

Lack of certainty in rates of progression to cancer

We found great uncertainty in published estimates of the rate of progression from LGD to cancer, ranging from 0.51% to 0.66% per patient-year^{11,18} in RFA-treated patients, and from 0.37% to 3.90% in patients managed with surveillance,^{1,17,18} even when limiting to studies that required a consensus diagnosis ([see section 4.2.3](#)). The corresponding estimates of an absolute risk reduction attributable to RFA range from 0.37% to 3.24% and the estimated number needed to treat ranges from 31 to 270. Furthermore, in the two RCTS that have included LGD patients, almost a quarter of confirmed LGD cases reverted to non-dysplasia,^{9,17} raising further concerns about the reliability of the reported rates of progression. The absence of a sufficiently precise estimate of efficacy of RFA in LGD patients made it impossible for us to study its cost-effectiveness.

7. CONCLUSIONS

- Radiofrequency ablation is now the standard of care for the treatment of Barrett's patients with high grade dysplasia because there is good evidence for its effectiveness and safety in eliminating dysplastic tissue, and because the alternative treatment with esophagectomy is associated with higher morbidity.
- Ablation therapy for LGD remains controversial because of the lack of data on diagnostic accuracy, and progression rates from LGD to cancer. Although recent evidence from two randomized controlled trials suggests RFA is effective in treating LGD, uncertainties in diagnostic accuracy and progression rates to cancer, and the spontaneous reversion of LGD in some patients do not support the routine treatment of LGD patients with endoscopic ablation therapies.
- Currently, the MUHC only treats patients with confirmed HGD with radiofrequency ablation, and 38 HGD patients have been treated since 2010. Of these, one patient required esophagectomy 5 years after diagnosis.

8. RECOMMENDATIONS

- The current evidence reinforces the previous TAU recommendation that RFA be used and funded at the MUHC for the treatment of Barrett's esophagus with high grade dysplasia.
- The TAU does not recommend the routine use of RFA for the treatment of low grade dysplasia given the lack of consistent evidence at this time for progression rates of LGD to cancer, and the reversible nature of LGD. However, in LGD patients with risk factors suggestive of higher risk of progression to HGD/cancer, such as multifocal, long segment or persistent BE, RFA may be considered after comprehensive discussion of potential risks and benefits with the patient. This recommendation should be reviewed if new evidence becomes available on biomarkers or other risk factors that better predict progression of LGD to cancer.

FIGURES

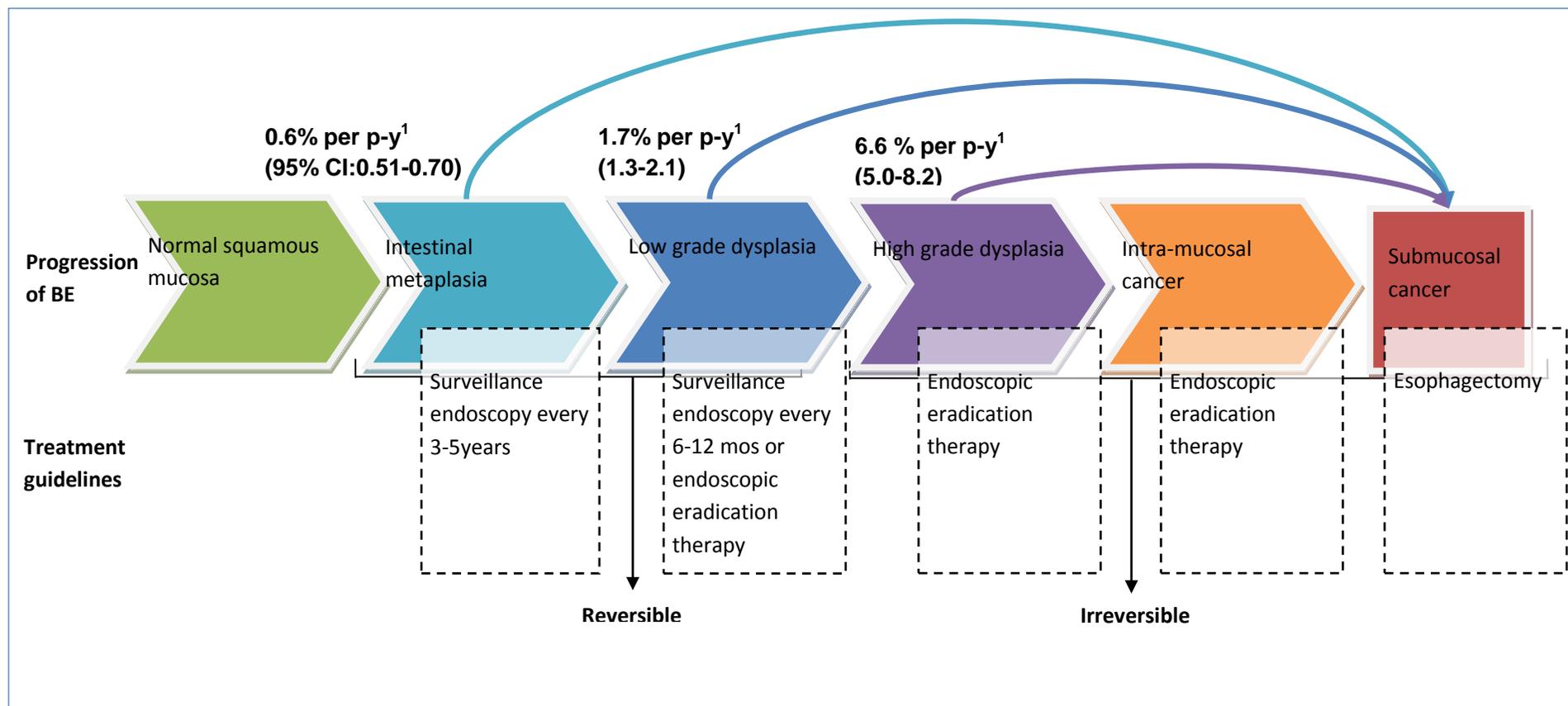


Figure 1: Stages in the progression of BE to cancer and treatment guidelines for each stage

¹Rates of progression in patients managed with surveillance, obtained from study by Wani et al.¹

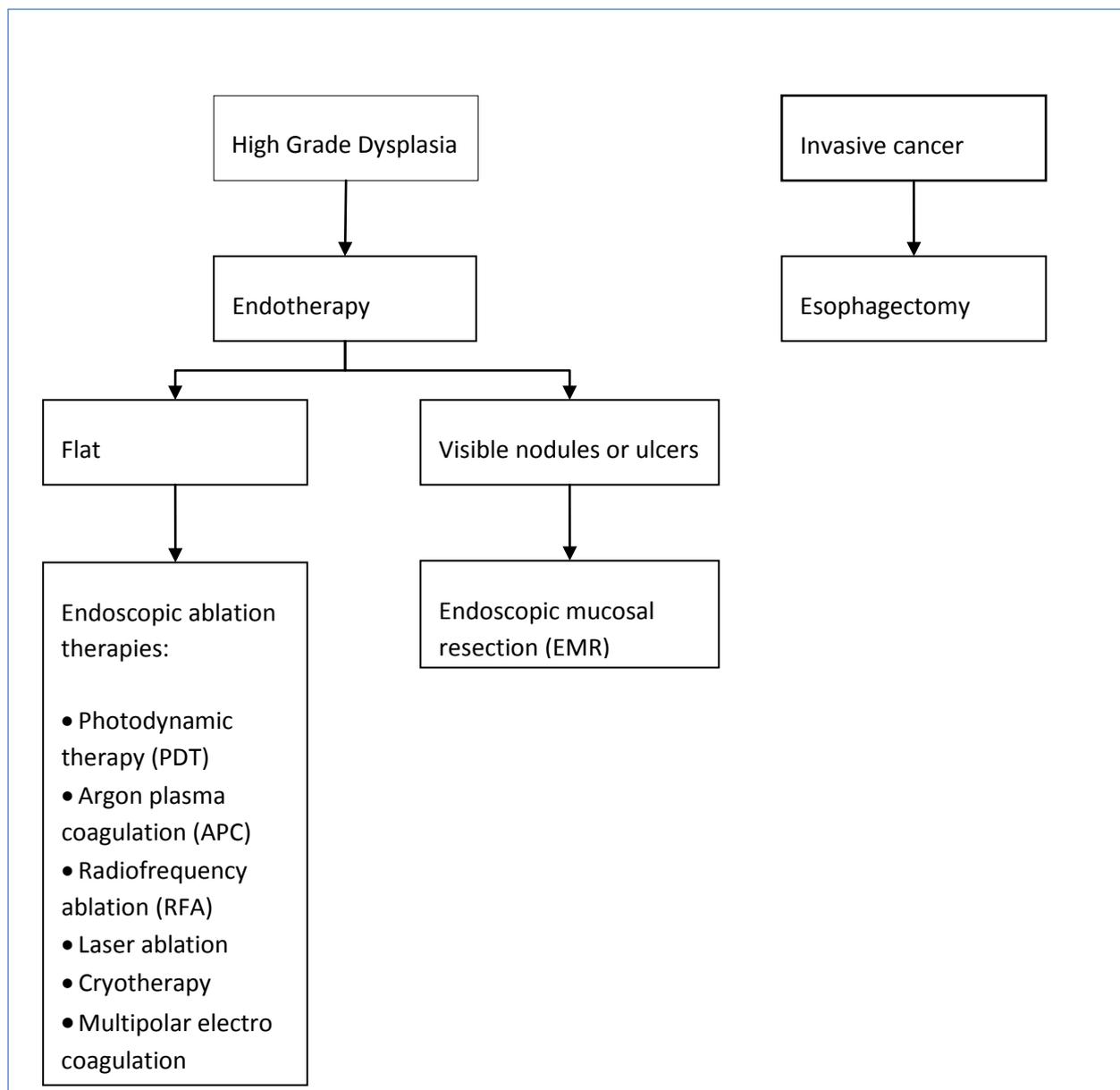


Figure 2: Treatment modalities for HGD and invasive cancer

TABLES

Table 1. Studies assessing the effectiveness of RFA for the treatment of HGD Barrett's esophagus

| Study (design) | Median follow-up (months) | Groups | N | <u>CE-IM</u> N(%) | <u>CE-D</u> N(%) | Cancer N(%) |
|----------------------------------------------------------|---------------------------|-------------------------|----|----------------------|---------------------|----------------|
| Shaheen 2009 (AIM RCT)⁹ | 12 | RFA | 42 | 31(74) | 34 (81) | 1(2) |
| | | Endoscopic surveillance | 21 | 0 | 4 (19) | 4(19) |
| van Vilsteren 2011 (RCT)¹² | 24 | RFA(+/-EMR) | 22 | 24 (96) | 24 (96) | 0 |
| | | SRER | 25 | 20 (92) | 22 (100) | 0 |
| Zehetner 2011 (retrospective cohort)¹⁴ | 17 | RFA(+/-EMR) | 19 | 12 (71) | 17 (89) | 0 |
| | 34 | Esophagectomy | 13 | 13 (100) | 13 (100) | 0 |
| Orman 2013 (review)¹³ | | RFA | | 490/721 (68) | 607/714 (85) | |

Table 2: Studies assessing the durability of RFA treatment in HGD Barrett's esophagus

| Study (design) | Groups | N | Median follow-up (months) | <u>CE-IM</u> N(%) | <u>CE-D</u> N(%) | Cancer N(%) |
|-------------------------------------------------------|-----------------------------|-------------|---------------------------|----------------------|---------------------|----------------|
| Shaheen 2011 (prospective cohort)¹¹ | RFA (2-yr follow-up) | 54 | 24 | 48 (89) | 50 (93) | 1* |
| | RFA (3-yr follow-up) | 24 | 36 | NR | 23 (96) | |
| Orman 2013 (review)¹³ | RFA in HGD and LGD patients | 80 (median) | 16.5 | 87% | NR | |

* This case of cancer was detected in the original RCT and not during the 2-year follow-up study

Table 3. Studies assessing the use of RFA in the treatment of LGD Barrett's esophagus

| Study (design) | Consensus diagnosis of LGD | Groups | N | Median follow-up (months) | CE-IM N(%) | CE-D N(%) | Progression to cancer or HGD N(%) | Progression to cancer N(%) | Rate of progression to cancer (per patient-year) |
|-------------------------------------------------------|----------------------------|-------------------------|-----------------------|---------------------------|--------------------------|---------------------------|-----------------------------------|----------------------------|--------------------------------------------------|
| Shaheen 2009 (AIM RCT)⁹ | Yes | RFA | 42 | 12 | 34 (81) | 38 (90) | | 0 | 0% |
| | | Endoscopic surveillance | 22 | 12 | 1 (4) | 5 (23) | | 0 | 0% |
| Shaheen 2011 (prospective cohort)¹¹ | Yes | RFA | 52 | 24 | 51 (98) | 51 (98) | 4 | 1 | 0.51% |
| Phoa 2014 (SURF RCT)¹⁷ | Yes | RFA | 68 | 36 | 60 (88) | 63 (93) | 1 (1.5) | 1 (1.5) | 0.66% ^a |
| | | Endoscopic surveillance | 68 | 36 | NR | NR | 18 (26.5) | 6 (8.8) | 3.90% ^b |
| Small 2015 (retrospective cohort)¹⁸ | Yes | RFA | 45 | 29 | 35 (78) | 43 (96) | 1 (2.2) | 0 ^c | 0 |
| | | Endoscopic surveillance | 125 | 28 | | 39 (31) | 36 (28.9) | 2 (1.6) ^c | 0.37% |
| Orman 2013 (review)¹³ | Not all studies | RFA | 633 | | 458 (72) | 581 (92) | | | |
| Almond 2014 (review)¹⁹ | | Ablation methods | 255 (for cancer rate) | | 87% (76,93) ^d | 91% (81, 96) ^d | | | 0.53% (0.06, 1.90) |

^a Calculated assuming same person-years as controls i.e. 152.5p-ys; ^b Calculated person-years from overall disease progression rate in controls of 11.8% per p-y i.e. 152.5 p-ys; ^c 1 (2.2%) and 5 (4%) developed intramucosal cancer in the RFA and surveillance arms, respectively.; ^d Pooled rate

Table 4: Estimated cost in Canadian dollars of RFA for the treatment of 10 HGD patients at the MUHC

| Item | Unit cost a | Resource use b | Average cost a x b |
|---------------------------------------------------------------------|-------------------|-------------------|-----------------------|
| Device cost | | | |
| 1. EAC of Barxx™360/90 generator* | \$539/procedure** | 1 | \$ 538.78 |
| 2. Barxx™360 sizing balloon | \$1,004.04 | 1 | \$ 1,004.04 |
| 3. Barxx™360 ablation catheter | \$2,536.51 | 1 | \$ 2,536.51 |
| 4. Barxx™90 ablation catheter | \$1,902.38 | 1 | \$ 1,902.38 |
| Procedure costs | | | |
| 5. Nursing, circumferential session | \$50.30/hr | 2 nurses*1 hour | \$ 100.60 |
| 6. Nursing, focal session | \$50.30/hr | 1 nurse*0.75 hour | \$ 37.73 |
| 7. Recovery room | \$113.73/hr | 1 hour | \$ 113.73 |
| Circumferential RFA (1+2+3+5+7) | | | \$ 4,293.66 |
| 1st Focal RFA (1+4+6+7) | | | \$ 2,592.62 |
| 2nd Focal RFA (1+4+6 +7) | | | \$ 2,592.62 |
| Total cost per case (1 circumferential and 2 focal sessions) | | | \$ 9,478.89 |

*EAC= Equivalent Annual Cost= $\frac{\text{Capital cost}}{\frac{1 - (\frac{1}{1+r})^t}{r}}$, where t is the service life of the Barxx™ generator = 6 years, and r is the annual discount rate=5%, and capital cost of generator=CAD 82,041. EAC = \$16,164.

** EAC per session (10 patients x 3 sessions=30 sessions) =\$16,164/30=\$539

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APPENDICES

APPENDIX A: CHARACTERISTICS OF STUDIES INCLUDED IN REPORT

Table A-1: Characteristics of all studies included in the TAU report

| Study | Design | Objective | Inclusion criteria | Population (n) | Follow-up | Groups (n) | Outcomes | | | | |
|---------------------|--------|---------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------|----------------|-----------|---------------------|---------------|----------------|--------------------------------|------------------------------|-------------------------------|
| | | | | | | | CE-D N (%) | CE-IM N (%) | Progression to cancer N (%) | Progression to HGD or cancer | Rate of progression to cancer |
| Shaheen 2009 | RCT | Assess safety and efficacy of RFA vs sham | Non-nodular dysplastic BE. Pts may have received EMR upto 8 weeks before inclusion. Consensus diagnosis of dysplasia by 2 pathologists. | HGD (63) | 1 year | RFA (42) | 34 (81) | 31(74) | 1(2) | | |
| | | | | | | Sham endoscopy (21) | 4 (19) | 0 | 4(19) | | |
| | | | | LGD (64) | 1 year | RFA (42) | 38 (90) | 34 (81) | 0 | 2 (5) | 0 |
| | | | | | | Sham endoscopy (22) | 5 (23) | 1 (4) | 0 | 3 (14) | 0 |
| Shaheen 2011 | Cohort | Assess the durability of RFA at 2 and 3-year f/up | Sham pts were eligible to cross-over to RFA arm after 12 mo assessment Pts who had CE-IM at 2 yrs | HGD (54) | 2 years | | 50 (93) | 48 (89) | 1* | | 0.60% per ptyr |
| | | | | LGD (52) | 2 years | RFA | 51 (98) | 51 (98) | 1 | 4** | 0.51% per ptyr |
| | | | | HGD (24) | 3 years | | 23 (96) | NR | | | |
| | | | | LGD (32) | 3 years | RFA | 32 (100) | NR | | | |

| | | | | | | | | | | | |
|---------------------------|-------------------------------|----------------------------------------------------|--------------------------------------------------------------------------------------------|------------|-----------|--------------------------------------------|------------|------------|-------|---------|----------------|
| Phoa 2014 | RCT (multi-centre, Europe) | Assess safety and efficacy of RFA vs sham | Expert-confirmed LGD within previous 18 mos. No HGD, cancer or visual abnormalities | LGD (136) | 3 years | RFA (68) | 62/63 (98) | 54/60 (90) | 1 (2) | 1(2) | 0.66% * |
| | | | | | 3 years | Endoscopic surveillance (68) | 19 (28) | 0 | 6 (9) | 18 (27) | 3.9% per pt-yr |
| Van Vilsteren 2011 | RCT | Assess safety and efficacy of RFA vs EMR | HGD or IMC conformed by study pathologist. No prior endoscopic treatment | HGD or IMC | 2 years | RFA +/- EMR(22) | (96) | (96) | 0 | | |
| | | | | | 2 years | Stepwise radical endoscopic resection (25) | 25 (100) | (92) | 0 | | |
| Zehetner 2011 | Retro-spective cohort | Assess safety and efficacy of RFA vs Esophagectomy | | HGD | 1.4 years | RFA +/- EMR(19) | 17 (89) | 12 (71) | 0 | | |
| | | | | | 2.8 years | Esophagectomy (13) | 13 (100) | 13 (100) | 0 | | |
| Small 2015 | Retro-spective cohort | Assess safety and efficacy of RFA vs surveillance | LGD confirmed by at least 1 expert pathologist; HGD, cancer of Indefinite BE excluded | LGD | 2.4 years | RFA (45) | 43 (96) | 35(78) | | | |
| | | | | | 2.3 years | Surveillance (125) | 39 (31) | | | | |

* Calculated assuming same person-years as controls i.e. 152.5p-ys

APPENDIX B: GLOSSARY OF TERMS

Argon plasma coagulation

A thermal ablative technique using ionized argon gas (argon plasma) to deliver evenly distributed thermal energy to the targeted tissue.

Dysplasia

A change in cell or tissue type due to more disordered growth than metaplasia. It is still reversible; however, once the transformation to neoplasia is made, the change is irreversible.

Endoscopic mucosal resection

An endoscopic procedure that may be used for staging and diagnosis of BE, or for the treatment of unresponsive BE after RFA. It is used when the BE segment is small, since there is a high risk of stricture when used on larger BE areas. It involves the removal of the mucosal and submucosal layers of the affected esophagus via various techniques:²²

- Lift and cut technique using a submucosal injection to separate the polyp from the rest of the esophagus, enabling easier resection
- Multiband mucosectomy to form a pseudopolyp with band ligation, and resection with a snare
- Cap technique, using submucosal injection and suction into a cap, followed by resection of the suctioned lesion with a snare
- Strip biopsy technique, using a double channel endoscope. After submucosal injection, a polypectomy snare is placed around the lesion, and a forceps passed through the second channel grasps and lifts the lesion for excision by the snare.

Intention-to-treat analysis

Analysis where results are analyzed based on the initial treatment assignment and not on treatment actually received, in order to preserve the integrity of randomization.

Kappa coefficient (κ)

The kappa coefficient provides a measure of inter-observer agreement for categorical data, taking into account observed agreement as well as the probability of random agreement.

| Kappa | Agreement |
|-----------|----------------|
| 0 | Poor |
| 0.01-0.20 | Slight |
| 0.21-0.40 | Fair |
| 0.41-0.60 | Moderate |
| 0.61-0.80 | Substantial |
| 0.81-0.99 | Almost perfect |

Metaplasia

A benign reversible change in cell type, wherein one differentiated cell type is replaced by another differentiated cell type. This change typically arises as a result of the inability of the original cells to withstand some stimulus or factor, giving way to more robust cell types. Metaplasia may progress to dysplasia, a more disordered growth of tissue, and eventually to neoplasia, an abnormal proliferation of cells resulting in a tumour.

Neoplasia

Abnormal proliferation resulting in the growth of a tumour.

Photodynamic therapy

An endoscopic eradication therapy utilizing a photosensitive chemical delivered via a laser to destroy dysplastic tissue. PDT has been associated with several side-effects including esophageal strictures and cutaneous photosensitivity and has largely been replaced by radiofrequency ablation.

Stricture

Narrowing of the esophagus, with or without dysphagia, identified on endoscopy.