Endoscopic mucosal resection for high-grade dysplasia and intramucosal carcinoma: a Canadian experience

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Background: Endoscopic mucosal resection (EMR) is increasingly being used as a first-line treatment for Barrett esophagus (BE) with high-grade dysplasia (HGD) and intramucosal adenocarcinoma (IMC). We reviewed our experience with endoscopic treatment of BE with HGD and IMC at our institution with respect to eradication rates, complications and long-term recurrence.

Methods: We performed a single-centre retrospective review of all patients referred between October 2010 and August 2014 for EMR with dysplastic BE or IMC. We performed EMR using a cap-fitted endoscope, and the procedure was repeated every 3 months until eradication or progression of disease.

Results: A total of 28 patients were identified: 16 with dysplastic BE (14 HGD, 1 low-grade dysplasia, 1 intermediate dysplasia) and 12 with IMC. Complete eradication of HGD was achieved in 11 of 14 (79%) patients. Three of 12 (25%) patients initially referred with suspected IMC were found to have invasive adenocarcinoma on EMR. Eradication was successful in 8 of 9 (89%) patients with true IMC, with 1 patient progressing to salvage esophagectomy. Complications occurred in 2 of 28 (7%) patients; both had esophageal strictures managed with dilatation. Median duration of follow-up was 371 days.

Conclusion: Our experience supports the safety of EMR as a first-line treatment for patients with BE with dysplasia and IMC in early short-term follow-up.

Contexte : La mucosectomie endoscopique est de plus en plus utilisée en première intention pour l'œsophage de Barrett avec dysplasie de haut grade (DHG) et pour l'adénocarcinome intramuqueux. Nous avons passé en revue notre expérience du traitement endoscopique de l'œsophage de Barrett avec DHG et de l'adénocarcinome intramuqueux dans notre établissement aux plans des taux d'éradication, des complications et des récurrences à long terme.

Méthodes : Nous avons procédé à une revue rétrospective de tous les cas d'œsophage de Barrett dysplasique ou d'adénocarcinome intramuqueux d'un seul centre adressés pour mucosectomie endoscopique entre octobre 2010 et août 2014. Nous avons effectué les mucosectomies endoscopiques à l'aide d'un endoscope muni d'un capuchon, et les interventions étaient répétées tous les 3 mois jusqu'à éradication ou progression de la maladie.

Résultats : En tout, 28 patients ont été recensés : 16 présentaient un œsophage de Barrett dysplasique (14 DHG, 1 dysplasie de bas grade, 1 dysplasie intermédiaire) et 12 présentaient un adénocarcinome intramuqueux. Une éradication complète de la DHG a été obtenue chez 11 patients sur 14 (79 %). Chez 3 patients sur 12 (25 %) initialement adressés pour un adénocarcinome intramuqueux, la mucosectomie a révélé un adénocarcinome envahissant. Huit patients sur 9 (89 %) atteints d'un adénocarcinome intramuqueux avéré ont subi le traitement d'éradication avec succès, et 1 patient a dû subir une œsophagectomie de sauvetage. Des complications sont survenues chez 2 patients sur 28 (7 %); les 2 patients ont présenté des sténoses œsophagiennes corrigées par dilatation. La durée médiane du suivi a été de 371 jours.

Conclusion : Notre expérience confirme l'innocuité de la mucosectomie endoscopique comme traitement de première intention chez les patients présentant un œsophage de Barrett dysplasique ou un adénocarcinome intramuqueux dans le contexte d'un suivi à court terme.

The incidence of esophageal adenocarcinoma is increasing 2% per year.¹ The most clinically important risk factor for the development of esophageal adenocarcinoma is Barrett esophagus (BE), a premalignant change from normal esophageal squamous epithelium to metaplastic columnar epithelium-containing goblet cells resulting from gastroesophageal reflux.² Endoscopic surveillance of BE is the standard of care to identify development of dysplasia. The development of dysplasia further enhances the risk of progression to adenocarcinoma.

The management of BE with high-grade dysplasia (HGD) is controversial. Multiple guidelines exist with respect to the management of HGD.^{3,4} Traditionally, the main options were endoscopic surveillance or eradication of HGD through surgical resection of the esophagus. There has been some controversy about the risk of progression of HGD to adenocarcinoma during surveillance. Some studies have reported a relatively high risk of progression,⁵ whereas other larger studies have argued that “low-risk” HGD lesions can be safely managed with endoscopic surveillance.^{6,7} Conversely, the surgical option, an esophagectomy, remains a complex and morbid operation.⁸

Novel targeted endoscopic techniques, such as endoscopic mucosal resection (EMR) and radiofrequency ablation, are associated with lower morbidity and should be considered.³ Complete eradication of dysplasia can be achieved with these techniques in up to 96% of patients.^{9–12} We previously argued that a balanced approach should be taken: selected patients with HGD can be followed closely with endoscopic surveillance and EMR of any nodular lesions, followed by radiofrequency ablation for long segments as required.¹³ At our centre, thoracic surgery and surgical endoscopists work collaboratively to select appropriate patients for endoscopic eradication therapy.

Endoscopic mucosal resection can also be used to diagnose and treat selected patients with intramucosal adenocarcinoma (IMC) and is now considered first-line therapy for discrete unifocal IMC.¹⁴ As a resection technique, EMR yields a pathology specimen that can be used to diagnose local submucosal invasion. In the absence of invasion, IMC can be adequately treated with EMR and continued regular surveillance endoscopy. Successful curative resection rates of IMC with EMR have been in the range of 57%–96%.^{15,16}

In the present study, we sought to review our experience with endoscopic treatment of BE with HGD and IMC at our institution with respect to eradication rates, complications and long-term recurrence.

METHODS

Patients were identified from a pre-established prospectively collected endoscopic procedures database (Clinical Outcomes Research Initiative [CORI]). We obtained research ethics board approval. We performed a search

using “esophagogastroduodenoscopy” as procedure in conjunction with the keywords “Barrett’s esophagus” and “malignancy.” Results were then manually searched to identify patients who underwent EMR between October 2010 and August 2014. Follow-up data were retrospectively collected from electronic records for endoscopy, imaging, operative and pathology reports; ambulatory clinic reports; and the last documented hospital visit.

The EMR procedure was performed using the Duette Multi-Band Mucosectomy device (Cook Medical). Dysplastic lesions were identified with a combination of location of prior biopsy sites, mucosal and vascular pattern abnormalities, and narrow band imaging. We used a cap-fitted endoscope to aspirate and band the selected mucosal area, followed by a snare resection supplemented with electrocautery according to the manufacturer’s instructions. We used this technique to resect all lesions that appeared dysplastic, either as a single specimen or in a piecemeal fashion to achieve complete gross resection.

We then reviewed pathology specimen results, and follow-up was determined depending on the findings. In the presence of invasive adenocarcinoma, the patient was referred for consideration of esophagectomy. In margin-negative IMC and HGD, patients were followed with endoscopy at 3-month intervals with repeat EMR of any suspicious lesions until there was eradication of all dysplastic mucosa, followed by an endoscopic surveillance regimen with 4-quadrant biopsies. In the presence of persistent long-segment BE, radiofrequency ablation was performed with a BarrX catheter after resection of discrete lesions amenable to EMR.

RESULTS

We identified 28 consecutive patients undergoing EMR. Sixteen patients were referred with BE with dysplasia, and 12 were referred with IMC. Five of the patients referred for BE with dysplasia were eventually referred for radiofrequency ablation. Twenty patients were men and 8 were women. The mean age of patients was 67 (range 49–86) years. The median duration of follow-up was 371 days. A summary of patient results is shown in Figure 1.

Barrett esophagus with dysplasia

Of the 28 patients with BE referred for EMR, 14 patients had HGD, 1 patient had low-grade dysplasia (LGD), and 1 had intermediate dysplasia. Of those, 11 patients had biopsy-proven complete eradication of dysplasia. These results were achieved after a median of 1 (range 1–2) EMR session; the patients were followed for a median of 175 days and underwent a median of 3 endoscopy sessions, including the initial EMR sessions.

At final follow-up, 6 of these 11 patients had normal squamous epithelium on biopsy. These patients were

followed for a median of 193 days, receiving a median of 1 (range 1–2) EMR session and 3.5 (range 2–5) total endoscopy sessions. Three of these patients were referred for radiofrequency ablation, as they had long-segment BE.

At follow-up, 5 of these 11 patients had BE with no evidence of dysplasia on random biopsy. However, this patient subgroup has the shortest follow-up at a median of 121 days, receiving a median 2 (range 1–2) EMR sessions and 2 (range 2–4) total endoscopy sessions. Their follow-up is ongoing, with the intention of complete eradication of BE.

Three patients referred for EMR management of HGD did not achieve eradication of dysplasia. One patient died of unrelated acute lymphoblastic leukemia after a single EMR session. One patient had a single EMR session revealing HGD, and then surveillance endoscopy revealing BE without dysplasia followed by LGD on the last 2 sessions. In spite of persistent LGD on biopsy, this patient has been followed with close endoscopic surveillance for

almost 4 years, and there has been no recurrent nodular disease. One patient has been followed with serial endoscopy and EMR over a period of 1.6 years, having received 4 EMR sessions and 2 surveillance endoscopy sessions during this time. Unfortunately, this patient has had persistent biopsies showing HGD. This patient had severe refractory reflux and, in the interim of endoscopic follow-up, underwent antireflux surgery. At the last surveillance endoscopy, pathological review confirmed BE with HGD, but the disease was limited to a discrete unifocal area. Endoscopic surveillance continues, with consideration of radiofrequency ablation.

Intramucosal adenocarcinoma

Twelve patients referred for EMR management had IMC. Three of these patients were referred for consideration of esophagectomy after a single EMR session, based on pathology results compatible with invasive disease. One

Fig. 1. Summary of patient distribution, results and follow-up. BE = Barrett esophagus; EMR = endoscopic mucosal resection; HGD = high-grade dysplasia; IMC = intramucosal adenocarcinoma; LGD = low-grade dysplasia.

patient had prohibitive comorbidities that precluded surgery and died of their disease. Two patients went on to esophagectomy. Final pathology on surgical specimen was T3N1 and T0N1, respectively.

One patient was eventually found to have invasive adenocarcinoma on EMR specimen after 6 endoscopy sessions spread over a period of 1.3 years. Initial EMR pathology was IMC. Subsequent EMR specimens showed HGD. The sixth EMR session showed invasive adenocarcinoma, and the patient was referred for esophagectomy. Final pathology from their esophagectomy showed no evidence of invasive adenocarcinoma, but a background of HGD.

Eight of the 12 patients referred for IMC had complete R0 resections with no endoscopic evidence of recurrence after a median of 1 (range 1–3) EMR session. These patients were followed for a median of 4.5 endoscopy sessions over a median of 1.6 years of follow-up. Six of 8 patients had normal squamous esophageal mucosa on random biopsy at the last documented surveillance. Two patients had evidence of BE without dysplasia at the last biopsy. For both patients, routine surveillance endoscopy is ongoing.

Complications

There were no perforations, and no patients experienced postoperative bleeding requiring repeat intervention. Strictures developed in 2 patients, who had 2 and 3 EMR sessions for HGD, respectively. Both patients were treated successfully with a single balloon dilatation.

DISCUSSION

Results from our experience are consistent with those of other series of endoscopic management of HGD. In our cohort referred for HGD, 11 of 14 (79%) patients had complete eradication of dysplasia. Although 2 patients have persistent dysplasia, HGD and LGD, they have been followed over the course of 570 and 1170 days, respectively, with close endoscopic surveillance and have shown no evidence of disease progression.

For patients referred for IMC, we achieved complete eradication of neoplasia in 8 of 9 (91%) patients.

Four patients were referred for consideration of esophagectomy in a fashion that did not affect oncologic outcome. Three of these 4 patients were immediately referred based on endoscopic appearance of submucosal invasion and corresponding pathologic confirmation of invasive adenocarcinoma. These were appropriate, timely referrals, as the 2 patients who underwent esophagectomy had evidence of nodal disease; final pathology was T3N1 and T0N1. One of these 4 patients had a delayed diagnosis of invasive adenocarcinoma after 6 endoscopy sessions over 466 days; however, the carcinoma detected after this time was an early curable carcinoma in situ.

Patients selected for our endoscopic management program had discrete unifocal nodules amenable to complete endoscopic resection. However, they must adhere to rigorous endoscopic surveillance. Our experience adds to the evidence that close endoscopic follow-up will detect progression of disease in a timely fashion.

Endoscopic ultrasonography was not used as a screening tool for patients selected for endoscopic management. This is consistent with other studies documenting the limited accuracy of endoscopic ultrasonography in staging early IMC and HGD.^{17,18}

Radiofrequency ablation was offered selectively to patients with long-segment BE after nodular regions were pathologically assessed by EMR. We chose to refer these patients for ablation, as serial EMR of long-segment BE has been associated with a higher rate of postoperative strictures, ranging from 37%–86%.^{12,19} A recent systematic review comparing serial EMR with EMR plus radiofrequency ablation for eradication of BE with HGD or IMC revealed similar rates of eradication of neoplasia (94.9% v. 93.4%, respectively) and metaplasia (79.6% v. 73.1%) at the expense of a significantly higher rate of structuring (33% v. 10%).²⁰

Esophageal varices are a potential comorbidity limiting the ability to safely perform EMR. Although our series did not capture this scenario, case reports have described preoperative transjugular intrahepatic portosystemic shunt to decrease portal pressure to diminish varices, allowing for EMR. An alternative approach is band ligation of nodular regions of HGD or IMC with biopsy as opposed to resection. The disadvantage of this technique is the lack of documentation of negative margin status.²¹

Limitations

Limitations of our study include the retrospective nature of the data, which limits our interpretation of the potential long-term results. Despite a median follow-up of more than a year, there was significant heterogeneity in the follow-up data, as a group of patients was still actively undergoing endoscopic therapy for BE. This limited number of patients may not capture rare but potentially important complications, such as post-EMR bleeding or delayed stricturing. Also, the candidate patient population must be motivated and able to adhere to strict follow-up, as complete resolution with EMR may take several sessions, depending on the extent of the BE.

CONCLUSION

Endoscopic mucosal resection demonstrated safe management of this high-risk population of patients with BE with HGD and IMC. The lone patient in the IMC group who had a delayed diagnosis of invasive esophageal cancer actually turned out to have only in situ cancer.

Two patients in the HGD group have persistent dysplasia but have undergone close endoscopic surveillance for a long time period (570 and 1170 d, respectively) with no progression of disease. Complications were minor (stricture), and were readily treated with endoscopic therapy.

Our multidisciplinary experience supports that endoscopic management can be safely performed as first-line treatment for patients with BE with dysplastic changes and also for selected patients with IMC.

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References

1. Simard EP, Ward EM, Siegel R, et al. Cancers with increasing incidence trends in the United States: 1999 through 2008. *CA Cancer J Clin* 2012;62:118-28.
2. Haggitt RC. Barrett's esophagus, dysplasia, and adenocarcinoma. *Hum Pathol* 1994;25:982-93.
3. Spechler SJ, Association AG. American Gastroenterological Association medical position statement on the management of Barrett's esophagus. *Gastroenterology* 2011;140:1084-91.
4. Fernando HC, Murthy SC, Hofstetter W, et al. The Society of Thoracic Surgeons practice guideline series: guidelines for the management of Barrett's esophagus with high-grade dysplasia. *Ann Thorac Surg* 2009;87:1993-2002.
5. Weston AP, Sharma P, Topalovski M, et al. Long-term follow-up of Barrett's high-grade dysplasia. *Am J Gastroenterol* 2000;95:1888-93.
6. Buttar NS, Wang KK, Sebo TJ, et al. Extent of high-grade dysplasia in Barrett's esophagus correlates with risk of adenocarcinoma. *Gastroenterology* 2001;120:1630-9.
7. Schnell TG, Sontag SJ, Chejfec G, et al. Long-term nonsurgical management of Barrett's esophagus with high-grade dysplasia. *Gastroenterology* 2001;120:1607-19.
8. Finks JF, Osborne NH, Birkmeyer JD. Trends in hospital volume and operative mortality for high-risk surgery. *N Engl J Med* 2011;364:2128-37.
9. Konda VJ, Ruiz MGH, Koons A, et al. Complete endoscopic mucosal resection is effective and durable treatment for Barrett's-associated neoplasia. *Clin Gastroenterol Hepatol* 2014;12:2002-10.
10. Larghi A, Lightdale C, Ross A, et al. Long-term follow-up of complete Barrett's eradication endoscopic mucosal resection (CBE-EMR) for the treatment of high grade dysplasia and intramucosal carcinoma. *Endoscopy* 2007;39:1086-91.
11. Lopes CV, Hela M, Pesenti C, et al. Circumferential endoscopic resection of Barrett's esophagus with high-grade dysplasia or early adenocarcinoma. *Surg Endosc* 2007;21:820-4.
12. Chennat J, Konda VJ, Ross AS, et al. Complete Barrett's eradication endoscopic mucosal resection: an effective treatment modality for high-grade dysplasia and intramucosal carcinoma — an American single-center experience. *Am J Gastroenterol* 2009;104:2684-92.
13. Henteleff HJ, Ellsmere JC, Rizk N. CAGS and ACS Evidence Based Reviews in Surgery. 38: Guidelines for the management of Barrett esophagus with high-grade dysplasia? *Can J Surg* 2011;54:352.
14. National Comprehensive Cancer Network. esophageal and esophagogastric junction cancers; 2014. Available: www.nccn.org/professionals/physician_gls/pdf/esophageal.pdf (accessed 2015 Apr. 30).
15. Saligram S, Chennat J, Hu H, et al. Endotherapy for superficial adenocarcinoma of the esophagus: an American experience. *Gastrointest Endosc* 2013;77:872-6.
16. Guo H-M, Zhang X-Q, Chen M, et al. Endoscopic submucosal dissection vs endoscopic mucosal resection for superficial esophageal cancer. *World J Gastroenterol* 2014;20:5540.
17. Thota PN, Sada A, Sanaka MR, et al. Correlation between endoscopic forceps biopsies and endoscopic mucosal resection with endoscopic ultrasound in patients with Barrett's esophagus with high-grade dysplasia and early cancer. *Surg Endosc* 2016; epub ahead of print.
18. Qumseya BJ, Brown J, Abraham M, et al. Diagnostic performance of EUS in predicting advanced cancer among patients with Barrett's esophagus and high-grade dysplasia/early adenocarcinoma: systematic review and meta-analysis. *Gastrointest Endosc* 2015;81:865-74.e2.
19. Pech O, Ell C. Editorial: Resecting or burning: What should we do with the remaining barrett's epithelium after successful ER of neoplasia? *Am J Gastroenterol* 2009;104:2693-4.
20. Desai M, Saligram S, Gupta N, et al. Efficacy and safety outcomes of multimodal endoscopic eradication therapy in Barrett's esophagus-related neoplasia: a systematic review and pooled-analysis. *Gastrointest Endosc* 2016;S0016-5107:30591-0.
21. NeSmith M, Jou J, Fennerty MB, et al. Transjugular intrahepatic portosystemic shunt prior to endoscopic mucosal resection for Barrett's esophagus in the setting of varices. *ACG Case Rep J* 2014;1:189-92.