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Endoscopic Mucosal Resection in the Management of Esophageal Neoplasia: Current Status and Future Directions

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Abstract

Endoscopic mucosal resection has expanded the role of the gastroenterologist in the management of esophageal neoplasia from screening and diagnosis to staging and endoscopic treatment. Its rise to prominence is a reflection of the long identified need to obtain histological information regarding depth of invasion and neoplastic margins during therapy that previously could not be achieved with ablative techniques. The resultant improvement in diagnosis and staging has allowed for better selection of patients for endoscopic therapy who may be spared invasive surgery. The clinical indications, endoscopic techniques, outcomes and complications in the management of esophageal neoplasia are reviewed in this manuscript. Training requirements to achieve proficiency in EMR as well as potential quality measures to assess competence are also proposed in this review.

Introduction

Endoscopic mucosal resection (EMR) has been adopted into advanced endoscopic practices in the United States as a diagnostic and therapeutic technique. The development of this technique has been a major advance in the management of early neoplastic lesions in the luminal gastrointestinal tract. EMR involves usually injecting fluid into the submucosa to lift the lesion from the deeper muscle layer and then removing the lesion with a combination of electrocautery and mechanical means. It was initially described in Europe and Japan several decades ago as a technique for the treatment of early gastric cancer^{1, 2}. Most of the early experience in EMR was in its application in the treatment of early esophageal and gastric cancers. It has since evolved into an effective diagnostic, staging and treatment strategy for superficial gastrointestinal cancers. Resection of small bowel lesions³ and colonic lesions⁴ have also been described. Its acceptance is a reflectance of the long identified need to obtain histological information regarding depth of invasion and neoplastic margins during therapy. Prior to this, endoscopic therapies were severely disadvantaged since they involved destruction

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of the mucosa without actually fully staging lesions which meant that ablation techniques were primarily reserved for those who were unsuitable for surgery. With the proliferation of ablation techniques, EMR is now recommended for the appropriate management of all suspicious neoplastic lesions in the gastrointestinal tract.

EMR has evolved to become a valid treatment alternative in the management of Barrett's high grade dysplasia (HGD), intramucosal adenocarcinoma (IMC) and squamous neoplasia with comparable outcomes to esophagectomy, the traditional mode of treatment⁵. Accurate staging of the target lesions is probably the most important reason for these excellent results as it allows for decisions on further treatment to be guided by the histology of resected specimens. Thus patients with deep invasion may still be considered for esophagectomy without jeopardizing outcomes while patients with superficially invasive lesions and adequate resection margins may be spared surgery.

EMR is one of several endoscopic treatment modalities employed in the treatment of esophageal neoplasia. Other endoscopic treatment modalities include endoscopic submucosal dissection (ESD) and mucosal ablation by the application of thermal energy (radiofrequency ablation, multipolar electrocoagulation, argon plasma coagulation), photochemical energy (photodynamic therapy) and cryotherapy. EMR is often used in conjunction with these methods because of its diagnostic value. EMR provides a more robust means of characterizing the degree of dysplasia and ascertaining the depth of tumour invasion than pinch biopsies and endoscopic ultrasound (EUS)^{6, 7} respectively. It also helps in clarifying the diagnosis that is often not obvious on pinch biopsies due to their distortion and size limitations. The improved diagnosis and staging has allowed for better selection of patients who may be candidates for endoscopic therapies and thus spared invasive surgery and the identification of those who may be better served by surgical techniques.

This article reviews the role of EMR in the management of esophageal neoplasia (arising in BE and squamous neoplasia) with specific focus on techniques, indications and outcomes.

General Considerations

The gastrointestinal wall consists of 2 major layers, the mucosa and the muscle layers, that are held together by the submucosa which consists of loose connective tissue. The mucosa and the muscle layers may be separated by the injection of fluid into the submucosa thus allowing for removal of the mucosa with minimal risk of injury to the muscle layer.⁸

Careful patient selection is crucial in ensuring that endoscopic resection offers adequate therapy as patients with disseminated disease will not benefit from EMR though partial resection of bulky tumors may be performed using snares to "debulk" tumors prior to application of ablative therapies such as PDT or cryotherapy for palliation. Presently, TNM staging is performed with computerized tomography (CT) of the chest and abdomen to detect disseminated metastases (M) and nodal involvement (N) and EUS to detect lymph node (N) involvement. The presence of these would preclude EMR as a curative treatment. However, EUS has only modest accuracy in delineating the T stage of esophageal cancers^{7, 9, 10} as overstaging may result from peritumoral inflammation causing wall thickening. The use of high frequency ultrasound probes has not improved the accuracy of T staging despite better delineation of the esophageal wall. The diagnostic accuracy is diminished in nodular lesions (type 0-I), submucosal cancers¹¹ and at the gastroesophageal junction¹². This may be partly attributed to the difficulties in obtaining perpendicular images with the probe at the gastroesophageal junction especially if there is a hiatus hernia¹³. Also, the standard balloon devices used for acoustic coupling compress lesions and make it difficult to even identify early neoplasia while the alternative, water filling the lumen, is not practical in certain areas of the esophagus or stomach.

The accuracy of miniprobe staging in differentiating mucosal (T1m) and submucosal (T1sm) is suboptimal at 73.5–80%^{11, 12, 14}.

EMR Technique

General Aspects

Prior to performing endoscopic resection, the entire esophageal mucosa should be carefully surveyed with high resolution white light endoscopy (WLE). The detection of subtle mucosal abnormalities that may not be apparent on WLE may be aided with the adjunctive use of chromoendoscopy with indigo carmine or acetic acid, or with other enhanced imaging modalities such as narrow band imaging (NBI) or the Fujinon intelligent chromoendoscopy (FICE) imaging system. NBI and FICE highlight mucosal surface patterns and details of microvasculature by utilizing light of short wavelength (blue and green light) which has more superficial tissue penetration and greater absorption by hemoglobin¹⁵. HGD is differentiated from non-dysplastic mucosa by the differences in mucosal surface and vascular pattern¹⁶. Though NBI offers better image quality than high resolution white light endoscopy, the interobserver variability is not improved with NBI and chromoendoscopy^{17–19}. The presence of blood in the esophagus following biopsies may reduce the visibility and hence decrease the utility of NBI after the acquisition of biopsies. In squamous lesions, Lugol's iodine is used to identify and localize dysplastic mucosa. Normal epithelium is stained by iodine, which interacts with glycogen present in the tissue. Dysplastic and neoplastic tissue containing no glycogen remain unstained and are thus demarcated from the normal mucosa²⁰. Given the limitations of enhanced endoscopic imaging modalities, their use should be coupled with meticulous mapping biopsies to identify neoplastic areas not visualized by imaging techniques. In addition, the exact location of EMR should be documented to facilitate subsequent resection of residual neoplastic tissue.

The endoscopic appearance of visible lesions should then be assessed for any clues to suggest submucosal spread. The Paris endoscopic classification characterizes superficial neoplastic lesions by their endoscopic appearance in order to predict the likelihood of submucosal invasion^{22, 23}. Most superficial esophageal squamous cell carcinoma lesions are non-protruding and these carry a lower risk of submucosal invasion as compared to protruding and excavated lesions.²¹ Most lesions in BE are flat lesions (type IIa and IIb)²². Ulcerated neoplasms are very rare in BE²². Submucosal infiltration in BE neoplasia is more often encountered in protruding and depressed lesions²³. The presence of nodularity in the setting of BE is associated with increased risk of coexistent carcinoma and should be targeted for EMR²⁴.

EMR allows for lesions to be resected in one piece (i.e. en bloc resection). Larger lesions (those more than 1–2 cm in maximal diameter) may require multiple, “piecemeal” resections and are associated with a higher risk of tumour recurrence²⁵ and should be performed with meticulous attention to avoid any residual islands of tissue being left behind. Though many different EMR methods have been described^{26, 27}, the basic technique involves the following steps. The lateral margins of the lesion can be delineated with dye based or virtual chromoendoscopy (techniques such as NBI or FICE). Electrocautery may be used to demarcate the lesion. This allows for better recognition of the boundaries after the injection of saline for lifting. The submucosa beneath the tumour is injected with saline to lift the lesion. The submucosal injection of saline is a crucial step in preventing perforation²⁸ as the injected saline acts as a cushion separating the mucosa from the muscularis propria. The needle is inserted almost tangential to the muscle wall and injected. The presence of a saline “bleb” or cushion indicates submucosal infiltration. Sufficient amounts of saline should be injected to completely lift the lesion as an inadequate saline cushion may result in the muscle layer being sucked into the snare together with the mucosa. The resultant resection may include the muscle layer thus resulting in a perforation.

The saline cushion also minimizes the transfer of thermal energy from electrocautery and thus protects from perforation. The failure of the lesion to lift with saline injection may also be a sign of submucosal invasion, inflammatory change or fibrosis²⁹. Diluted epinephrine in various strengths may be used to lift the lesion in order to provide better hemostasis. The authors use 1:200 000 epinephrine solution in their practice to mitigate the hemodynamic effects of epinephrine that may result from the large volumes (more than 20ml) often required to lift the lesion. Other materials used for submucosal injection include hypertonic saline and hydroxypropyl methyl cellulose (which may be helpful for the resection of larger lesions as it dissipates slowly)³⁰.

Electrocautery is applied following the closure of the snare to resect the mucosa. An energy setting of 16 W blend 2 is used with a Meditron unit [Meditron Devices Inc, Hackensack, NJ] to remove the resected specimen at our institution. This setting provides a balance of “cut” and “coagulation” as demonstrated by animal studies at our institution and has decreased the incidence of delayed bleeds in our experience. Energy settings and devices used by other institutions in prior reports have been summarized in Tables 2 and 3.

Methods

Strip biopsy—The strip biopsy was the first endoscopic resection technique to be described². This technique requires the use of a double-channel endoscope. The lesion is lifted with a grasping forceps while a snare, introduced through the second working channel, resects the lesion with cautery. The strip-biopsy and its modifications³¹ have several shortcomings. The resected specimens are small and often damaged by the grasping forceps³². Elevating the tumor with a grasping forceps may be difficult with tangential tumors³³. A double-channel scope is not widely available, has a large diameter, and an additional assistant (who assists with grasping the lesion of interest). The assistant could be another endoscopist or an experienced endoscopy nurse or technician) is required. The strip-biopsy is seldom used now and has been largely replaced by the cap and ligation methods.

Cap method—Inoue and colleagues described an EMR technique which uses a transparent cap affixed to the distal tip of the endoscope³⁴. The cap contains a groove on which a specially designed small-diameter crescent-shaped snare can be placed during the procedure to prevent it from slipping. The snare is opened and positioned on the internal circumferential ridge of the cap. The endoscope is then positioned over the target lesion and the mucosa is retracted into the cap by suction. The snare is closed to capture the lesion and resected by electrocautery (Figure 1 and Video 1). The available caps vary in their size and consistency. Oblique caps have been developed to facilitate the resection of tangential lesions in the esophagus³⁵. However perforation of the upper esophageal sphincter has been reported with its use³⁶. The crescent-shaped snare is more pliable than the conventional snare used in the removal of colonic polyps. This flexibility facilitates looping of the snare within the cap. This technique may be preferred in areas of prior resection or ablation as it achieves better suction and more satisfactory resection on a consistent basis in the authors' experience. However, multiple snares will be required with piecemeal resection as the snare tends to lose its configuration with repeated use. Retrieval of specimens individually may be considered during piecemeal resection as onset of bleeding may make subsequent specimen retrieval challenging.

Ligation-assisted EMR—A band ligation device is placed over the mucosal lesion either with or without prior submucosal saline injection. The mucosa is aspirated into the cap and a band is deployed. The captured mucosa is then resected with electrocautery with the aid of a snare deployed either above or below the band. The multiband mucosectomy device (Duette Multiband Mucosectomy Kit™, Cook Ireland Ltd, Limerick, Ireland) is a 6-band ligator attached to a therapeutic endoscope that allows for the passage of a hexagonal snare through

the accessory channel. This allows for multiple sequential ligations and resections to be performed with a single intubation (Figure 2 and Video 2). The resected specimens can then be retrieved with the aid of a Roth net, cap or snare. The band is not typically strong enough to capture the muscularis propria and so this limits the depth of the tissue that is caught within the band. Nevertheless, perforations have been reported with the use of ligation method³⁷ and caution is warranted.

Circumferential EMR—In this technique EMR is used to remove the entire visible BE segment instead of targeting visible abnormalities. Typically multiple EMRs are performed using the ligation assisted method or using a regular snare³⁸ in every session and multiple sessions are needed to completely remove all visible BE. Short term results appear promising^{39–41} but this approach is characterized by a higher rate of complications, particularly strictures. Residual strips of BE tissue left between EMR sites may need to be ablated or resected separately as well. Additional information on outcomes with this approach is summarized in Table 2.

Comparisons of methods

There is limited data available comparing the various EMR techniques. A prospective randomized study comparing the cap and ligation methods showed that the size of resected specimens and the rates of bleeding were similar with both methods⁴². Both techniques also provide specimens of similar depth of resection⁴³. The choice of technique is often determined by the cost, preference and experience of the endoscopist. Anticipation of multiple resections (necessary in larger lesions to obtain clear margins) may make the ligation method preferable.

Post EMR care and management of antiplatelet and anticoagulant use (see Table 1)

EMR is performed as an ambulatory procedure in the United States, with low immediate complication rates (no perforations, 3.8% bleeding : within 7 days)⁴⁴ though patients are often hospitalized after EMR in Asia and Europe. In high risk patients such as those who have multiple comorbidities and need immediate anticoagulation, short term inpatient observation may be considered. In our unit, patients are advised to be on clear liquids for 24 hours following EMR and avoid the use of aspirin and all non steroidal anti inflammatory medications for the next 2 weeks and clopidogrel for 2 days to reduce the risk of delayed bleeds. They are advised to seek medical attention should they experience any signs of overt gastrointestinal bleeding. Management of anticoagulants depends on the risk status of the patient for thrombosis. Generally, our unit follows ASGE guidelines⁴⁵ in terms of bridging patients at high risk with low molecular weight heparin after stopping anticoagulants and after the procedure until the patient can be anticoagulated with their normal regimen. Platelet inhibitors (Aspirin and Clopidogrel) are held for a week prior to EMR in patients who are at low risk of thrombosis.

Pathological interpretation of specimens

Resected specimens should be interpreted by dedicated GI pathologists. Some centres have suggested mounting the EMR specimens on a firm surface such as cork before fixation to avoid curling of the specimens' edges and to allow better sectioning⁴⁶. The submucosal side of the specimen is apposed to the plate. The specimen should not be over-stretched as it may cause distortion and fracture of the tissue. The margins of the specimens are inked, the specimens are fixed in formalin, serially sectioned (“bread-loaf” sectioning) and stained with hematoxylineosin. They are assessed for size, histology (figure 3: HGD), tumor grade, depth of tumor penetration (figure 4: IMC, figure 5: Submucosal EAC) and margins (lateral and deep), lymphovascular infiltration (figure 6) and completeness of resection (assessed using lateral and deep margin involvement⁴⁷). Distortion from cautery and hemorrhage may make assessment of margins challenging^{47, 48}. With multiple EMR, assessment of lateral margins

can be difficult as reconstruction of the lesion from the fragments may not be feasible. Frozen section analysis of EMR specimens has been shown to correlate well with permanent sectioning and may provide an option to guide real time decision-making on whether additional EMR is required or indicated (if submucosal invasion is detected on initial EMR, subsequent resections may be avoided)⁴⁹.

EMR provides effective T staging of mucosal abnormalities^{7, 19} seen on endoscopy. EMR provides additional information compared to biopsy specimens. The histopathology on resected specimens has better diagnostic reproducibility with significantly higher interobserver agreement than biopsies as the specimens are larger and mucosal landmarks can be assessed⁵⁰. The findings on EMR changes the eventual management by upstaging the grade of dysplasia originally seen on biopsy in as much as 34% of cases in one series⁶. The histological findings on EMR specimen also have excellent correlation with the pathological findings from esophagectomy specimens⁴⁷ reaffirming the validity of histological findings on EMR.

Clinical Applications and Outcomes

The choice of treatment would be influenced by local expertise. Esophagectomy is associated with significant morbidity and mortality. Morbidity rates of 30–50%⁵¹ and mortality rates of 1–2% in high-volume centres and 5–10% in lower volume centres⁵² have been reported. Conversely, the outcomes reported with endoscopic resection are obtained from centres of excellence with dedicated endoscopists experienced in recognizing subtle early lesions, careful patient selection and intensive endoscopic surveillance following resection to detect recurrences. The patient's preferences and values should also be considered - the fear of major surgery versus the fear of missing invasive cancer. Patients should be counseled on the need for multiple sessions of endoscopic treatment, continued endoscopic surveillance following treatment and the risk of neoplastic recurrence which can usually be managed endoscopically.

EMR is limited in its ability to achieve en bloc resection for lesions larger than 15–20mm in largest diameter, which may require piecemeal resections. Larger lesions removed by piecemeal resection are associated with an increased risk of tumour recurrence²⁵. The lateral margins are difficult to assess with multiple EMR. The rearrangement of multiple specimens obtained from piecemeal resection as well as the artifacts induced by electrocautery can cause uncertainty in pathological staging. As a result, lateral spread of tumour is not accurately assessed with reconstruction after piecemeal resection.

Barrett's HGD

EMR is a crucial component of endoluminal therapy (consisting of resection and ablation techniques) for HGD arising in BE. Long term outcomes of subjects treated with EMR alone or in combination with ablative techniques appear to be comparable to those treated with esophagectomy⁵.

Adenocarcinoma

The risk of lymph node metastases (LNM) for in EAC is related to the depth of tumour invasion and the presence of lymphovascular invasion. EAC that is confined to the mucosa has a low risk of LNM (1–5%)^{53–56} that may be comparable to the surgical mortality in high volume centers. A significant proportion of Barrett's neoplasia may be associated with a duplicated muscularis mucosa⁵⁷ which may be mistaken for the muscularis propria resulting in over-staging. Tumour invasion into the duplicated muscularis mucosa is associated with a 10% risk of LNM⁵⁸ as it provides potential access to the lymphatic space. This relatively small single center study, did not account for lymphovascular invasion as an additional factor determining

LN metastasis, and needs to be corroborated with larger studies. Tumors which extend to the submucosa have a much higher risk of LNM, as high as 25%⁵⁹ though cancers confined to the upper third of the submucosa (sm1) may have lower rates of LNM in some studies (0–12.9%)^{56, 60, 61}. Literature on the suitability of endoscopic resection in the therapy of superficially invasive (sm1) submucosal EAC is limited and conflicting. Some centers have reported excellent results in subjects with sm1 EAC treated endoscopically⁶² while others have reported substantial rates of metastatic lymphadenopathy in sm1 tumors with survival and recurrence rates similar to deeper invasion of the submucosa (sm2 and sm3) arguing against the use of endoscopic therapy in subjects who are surgical candidates^{63 61} given the inability of current endoscopic techniques to target LNMs. The Wiesbaden group has shown that patients with sm1 EAC may be considered for endoscopic resection if the cancers are low grade and do not demonstrate lymphovascular infiltration⁶². However accurate delineation of depth of submucosal infiltration requires a full thickness resection of the submucosa which presently, can only be achieved with surgical resection. Endoscopically resected specimens only contain part of the submucosa. Hence the fraction of submucosal penetration can only be estimated. The measurement of submucosal depth in endoscopically resected specimens may be confounded by artefacts from saline injection and electrocautery during EMR. Lymphovascular invasion may be a tool to help predict LNM in EAC but its accuracy is limited as shown in two recent studies performed on esophagectomy specimens to assess the depth of submucosal invasion^{61, 63}.

Squamous Cell Carcinoma

Superficial lesions (m1, m2 tumors invading the upper and middle third of the mucosa) which are less than 3 cm diameter and encompassing less than ¼ of the circumference may be considered for EMR⁶⁴. Lymphatic invasion occurs earlier in squamous cell carcinoma (SCC). Lesions confined to the epithelium and lamina propria (m1, m2) have a 0–5.6% risk of LNM^{65, 66} and may be treated endoscopically. However, nodal metastases occur in 6–18% of patients with muscularis mucosa (m3) involvement and 53% in sm1 cancers^{59, 66–68}. In m3 lesions with lymphovascular invasion, LNM occurs far more frequently - 41.7% in one surgical series⁶⁶. Hence patients with SCC confined to the superficial mucosa (m1 and m2) may be candidates for endoscopic resection. Tumors that have invaded the deeper mucosa (m3) or the submucosa generally should be considered for surgical resection as present endoscopic resection techniques do not allow for nodal dissection.

Outcomes

BE HGD and Adenocarcinoma—We have summarized data on outcomes with focal and circumferential EMR in Table 2. Data from single centre cohort studies report complete remission rates of 94–96% in patients undergoing endoscopic resection with or without ablation for HGD and intramucosal adenocarcinoma^{44, 69}. Endoscopic resection of nodular mucosa may be combined with ablation of the residual dysplastic mucosa by either radiofrequency ablation (RFA) or photodynamic therapy (PDT) in patients with long-segment Barrett's esophagus. The ablation is performed at least 4–6 weeks after the resection to allow for the resected mucosa to heal prior to ablation. The role of combination therapy is less well-defined. It may be associated with a lower risk of recurrence⁶⁹. RFA is well tolerated^{70, 71} but the risk of esophageal strictures is increased with PDT following EMR⁷². Circumferential EMR, which involves complete removal of at risk columnar mucosa, has lower rates of recurrence but the rate of esophageal stenoses is much higher at 12–56%^{39–41}. Our experience suggests that EMR may be performed safely without jeopardizing outcomes of subsequent esophagectomy should the patient require it later⁷³.

Recurrences of dysplasia or carcinoma have been reported in 12–21% of patients after a mean follow-up of 43–63 months^{44, 69}. These are usually amenable to endoscopic retreatment. The

risk of recurrence is higher in patients with long-segment Barrett's esophagus (RR 1.9 [95% CI 1.06 to 3.3]), multifocal neoplasia (2.1 [1.16 to 3.99]), those who had piecemeal resection (2.44 [1.13 to 4.89]) and those who needed a longer period to achieve complete remission⁶⁹. The risk of recurrence was significantly reduced in patients who underwent ablative therapy of the remaining non-neoplastic Barrett's epithelium with APC or PDT in one study⁶⁹ but this was not borne out by another study⁴⁴. Other factors that have been implicated in predicting recurrence include the presence of any residual BE (without dysplasia), increasing length of the BE segment at baseline, and presence of an incident carcinoma (carcinoma detected after 6 months of surveillance for HGD)⁴⁴. Patients who have undergone resection should undergo continued endoscopic surveillance for recurrences.

Squamous cell carcinoma (SCC)

Data on outcomes is summarized in table 3. A questionnaire-based Japanese study reported on outcomes for EMR for superficial esophageal cancer on 396 patients at 80 institutions. En bloc resection rates of 64.3% was achieved in tumors measuring <1 cm in diameter and 36.5% in those <2cm in diameter. Patients with submucosal cancers showed significantly worse 5-year survival rates than those with mucosal cancers²¹. A Western series of 65 patients with early SCC or high-grade dysplasia reported over 95% complete response rate and a 7- year survival rate of 77%⁷⁴. Another cohort of 51 patients of early SCC or high-grade dysplasia reported a 91% complete local remission and 58% 5-year survival rate⁷⁵. Local recurrence rates of 20–26% after a follow-up of more than 1 year have been reported^{74,76,77} mandating close endoscopic surveillance after EMR.

Complications of EMR

EMR is generally well tolerated when performed by experienced endoscopists. The overall complication rate is 13–17%^{44, 69} in the 2 largest reported series but these included minor bleeding which did not result in a drop in hemoglobin. Serious complications are rare. The main complications include bleeding, perforation and esophageal strictures.

The rate of esophageal stricture formation is 6–23%^{44, 74}. These are more likely to occur after circumferential EMR⁴⁰ and when used in combination with ablative techniques such as PDT^{54, 69}. These are usually amenable to serial dilations.

The risk of bleeding is 0.6%–11%^{21, 44, 69} depending on the definition used in studies. Most of the bleeding episodes reported refer to minor bleeding episodes that do not decrease hemoglobin levels or necessitate blood transfusion. Clinically significant bleeding requiring transfusion, hospitalisation or endoscopic therapy occurs in 3.8%⁴⁴. Arterial bleeding is uncommon. Hemostasis may be secured in the vast majority by the application of hemoclips.

Perforations have been reported in 0–2.5% of procedures^{21, 69}. The 2 largest series of EMR in Barrett's esophagus, with 132 and 279 patients respectively, did not report any perforations^{44, 69}. These may be managed conservatively with the application of hemoclips or stents if they are recognized during the EMR^{78, 79}. More recently the use of over-the-scope clips have been described in animal models⁸⁰.

Training and Quality in EMR

There is limited data on learning curves for EMR. In the authors' center, EMR is performed under the supervision of an experienced mentor who can takeover from the trainee and complete the procedure if necessary. The “self-taught” method may not be feasible as inadequate resection of the initial lesion may compromise outcomes for subsequent treatment due to scarring. Hence, EMR training should be undertaken in an established centre with extensive

experience. Training is required in at least 30 cases to gain technical proficiency. EMR can be practiced on porcine models before the procedure is performed on patients. Trainees should preferably begin performing EMR in treatment-naïve patients as scarring from prior resections make it more technically challenging. The ligation method would be the easiest method to learn for beginners as the technique is similar to variceal band ligation. Apart from the technical aspects of performing EMR, training should also encompass recognition of subtle lesions on WLE, NBI and chromoendoscopy to ensure that adequate treatment is provided. The endoscopists should preferably possess the endoscopic skills to cope with potential complications such as strictures, bleeding and perforation following EMR. EMR should be performed in a setting where surgical backup is available, in the event of a perforation, and mechanical ventilation is feasible in case of aspiration with cervical lesions.

Evidence-based quality measures to assess competence in EMR need to be defined. Potential quality measures would include appropriate indications for EMR, completeness of resection with negative margins, adequate number of biopsies of non-resected Barrett's mucosa and rate of complications (strictures, bleeding and perforation), and reporting of the pathological results. Further research needs to be performed to validate these and other potential quality measures.

Conclusion

EMR has evolved to become a valid treatment alternative to surgery in patients with mucosal neoplasia and carcinoma and has expanded the role of the gastroenterologist in the management of esophageal neoplasia from screening and diagnosis to endoscopic treatment. However the success of endoscopic resection is predicated on careful patient selection and close surveillance following therapy. EMR is curative for lesions restricted to the mucosa and may be considered in selected patients with submucosal disease and no lymphovascular invasion. Future research focusing on novel transmural endoscopic resection techniques could increase the spectrum of patients who may benefit from endoscopic resection.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations used

(EMR)	Endoscopic mucosal resection
(HGD)	high grade dysplasia
(IMC)	intramucosal adenocarcinoma
(EAC)	esophageal adenocarcinoma
(ESD)	endoscopic submucosal dissection
(EUS)	endoscopic ultrasound
(CT)	computerized tomography

(WLE)	white light endoscopy
(NBI)	narrow band imaging
(FICE)	Fujinon intelligent chromoendoscopy
(BE)	Barrett's esophagus

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Figure 1. Cap EMR

1a Saline infiltration.

1b Prelooping of snare within the cap.

1c Snare deployment.

Figure 2. Ligation technique
Deployment of snare over banded mucosa

Figure 3. HGD seen in a EMR specimen
 Note the nuclear pleiomorphism and the loss of nuclear polarity to the basement membrane.

Figure 4. Intramucosal EAC seen in an EMR specimen at low power characterized by loss of normal mucosal architecture
Intact muscularis mucosa without invasion of the submucosa.

Figure 5. Submucosal EAC seen on an EMR specimen
 Focus of invasive adenocarcinoma invading the submucosa beneath the muscularis mucosa.

Figure 6. EMR specimen showing lymphatic invasion by malignant cells

a

Table 1

EMR and anticoagulation

	Management of antiplatelets and anticoagulants use following EMR
General	<ul style="list-style-type: none"> • avoid aspirin and all non steroidal anti inflammatory medications for the next 2 weeks • advise patients to monitor for symptoms of overt gastrointestinal bleeding • consider prophylactic deployment of hemostatic clips to secure hemostasis though this is unproven.
warfarin	<ul style="list-style-type: none"> • Stop warfarin 5 days prior to the EMR. • An INR level below 1.5 is used as an arbitrary cutoff to proceed with EMR. • Resume warfarin 24 hours after the procedure with the usual daily dose. • Check INR levels 1 week later to ensure adequate anticoagulation. • In patients deemed to be at high risk of thrombosis, warfarin cessation is bridged with low molecular weight heparin.
Clopidogrel	<ul style="list-style-type: none"> • Discontinue clopidogrel 7 days before endoscopy. • In patients with high-risk cardiac conditions, cessation of clopidogrel is done after discussion with the cardiologist. This may entail deferring the EMR, where feasible, until a suitable time period following the insertion of coronary stents.

Outcomes following endoscopic resection (ER) of BE HGD and adenocarcinoma

Table 2

Author	Year	Study Design	Number of patients	Treatment Methods	Electrocautery equipment and settings	Tumour Stage	Complete Remission	Recurrence	Complications
Larghi et al ⁷	2005	Prospective single-centre cohort	48	EMR (40) Additional PDT/APC (9) Esophagectomy (8) Additional chemoradiation (1)	blended current cautery ICC 200 (Endocut; Erbe USA Inc, Marietta, Ga)	HGD (25) Early carcinoma (15) Submucosal invasion (8)	N/A	0/29 at mean follow-up of 22.9 mth	Perforations (0) Mild immediate bleeding (2) odynophagia (40)
Soehendra et al ⁸¹	1997	Case series	7	Endoscopic snare mucosectomy	Pure coagulation current (30–40W)	Limited to submucosa	100% (3 patients refused endoscopic follow-up, 2 patients died of unrelated causes within 8 months of EMR)	Nil after median follow-up of 7 mth (range 3–22)	Nil
May et al ⁴²	2003	Prospective randomized	72	Cap EMR (50 EMR) “Suck-and-ligate” (50 EMR)	Erbotome ICC-20 (Erbe, Inc., Tübingen, Germany)	Stage I adenocarcinoma without submucosal invasion (78) Stage I SCC (22)	97% complete local remission (60/62 patients) in whom ER was performed with curative intent	9.7% at mean followup of 20.7 (2.3) months	Minor bleeding (2)
Ell et al ⁸²	2000	Prospective case series	64	EMR	Erbotom ICC 200 (Erbe Inc., Tübingen, Germany)	“low risk” group: Lesion diameter of 20 mm or less; and Macroscopically type I, IIa, IIb, or IIc lesions <10 mm; and Well or moderately differentiated adenocarcinoma (G1/G2) or HGD; and intramucosal lesions “high risk”: Lesion diameter > 20 mm and intramucosal; and/or Macroscopically type III; and/or Poorly differentiated adenocarcinoma (G3); and/or submucosal infiltration	97% in “low risk” patients 59% in “high risk” patients	14% (mean follow-up 12+/- 8 months).	20% in “low-risk” 3.5% in “high risk” No perforations
Pech et al ⁶⁹	2008	Prospective case series	349	EMR (279) PDT (55) both (13) APC (2)	Erbotom ICC 200 (Erbe Inc., Tübingen, Germany)	High grade intraepithelial neoplasia (HGIN) (61) Intramucosal carcinoma (288)	96.6% with mean followup 63.6 (SD 23.1) mth 84% calculated 5 yr survival	21.5%	17.2% overall 0. 6% major complications
Manner et al ⁶²	2008	Prospective case series	21	ligation EMR or cap EMR additional APC in 14/19 patients	Erbotom ICC 200 (Erbe Inc., Tübingen, Germany)	“low-risk” submucosal cancer: (sm1) on initial EMR, absence of infiltration into lymph vessels/veins, histological grade G1–2 and macroscopic type I–II	95% after mean 5.3 mth 66% calculated 5-yr survival	28% after mean follow-up 62 months	No major complication 5.3% minor bleeding (1)
Prasad ⁴⁴	2009	Retrospective case series	178	EMR with or without PDT (132) Esophagectomy (46)	16 W blend 2 using a Meditron unit (Meditron Devices Inc, Hackensack, NJ)	T1a EAC	Cumulative mortality 17% with endoscopy vs 20% in esophagectomy (P 0.75)	Incident rate: 5.5/100 person-years vs 0.56/100 person-years	Overall 13% (18). Strictures (8) Significant bleeding (5) Photosensitivity (5)

Author	Year	Study Design	Number of patients	Treatment Methods	Electrocautery equipment and settings	Tumour Stage	Complete Remission	Recurrence	Complications
Pouw ⁷⁰	2009	multicenter, prospective cohort study	24	EMR (23) RFA (24)	Not available	Adenocarcinoma (16) T1m2(8) T1m3(6) T1sm1(2) HGIN (7).	96%	No recurrence after median 22 months	Perforation (1) Bleeding (1) Stenosis (1) Mucosal laceration (5)
Seewald ⁴⁰	2003	Case series	12	Circumferential EMR	Erbotom ICC 100/200 (Erbe Inc., Tübingen, Germany) at a setting 3- and 120-W output.	Intramucosal carcinoma (9) HGIN (3)	100%	No recurrence after median 9 mth	Bleeding (4/31 EMR sessions) Strictures (2)
Pouw ⁴¹	2008	Retrospective case series	34	Circumferential EMR	Endocut 2 ERBE ICC200, ERBE VIO300D	HGIN (22) Early carcinoma including T1sm1 (12)	100%	9% after median 23 mth	perforations, (2) delayed bleeding (1) dysphagia (19)
Larghi ³⁹	2007	Case series	26	Circumferential EMR	ICC 200 Endocut (Erbe USA Inc., Marietta, Georgia, USA) at a setting of 30W and 60W output	HGD 19 (79 %) Adenocarcinoma 5 (21 %)	87.5% eradication of intestinal metaplasia	Recurrence (1) after median 28 mth	Strictures (3) Bleeding during resection (2) No delayed bleeding or perforation

Table 3

Outcomes following endoscopic resection (ER) of squamous esophageal neoplasia.

Author	Year	Study design	Number of patients	Treatment Methods	Electrocautery equipment and settings	Tumour Stage	Complete Remission	Recurrent	Complications
Kodama ²¹	1998	Survey (93.4% SCC)	396	EMR	Not available	T1 & T1sm	NA	NA	6.8% Overall 2.5% perforation 2% stenosis 1.5% hemorrhage
Pech ⁷⁴	2007	Prospective case series	65	Ligation EMR	Erbotom ICC 200 (Erbe, Tübingen, Germany)	HGIN (12) Mucosal SCC (53)	HGIN: 91.7% mucosal SCC: 96.2%	26% at mean followup of 39.3 mth	23% (only esophageal stenosis)
Ciocirlan ⁷⁵	2007	Retrospective case series	51	Cap EMR	Endo-Cut ICC 200 (Erbe, Tübingen, Germany)	T0 (21) T1m (17) T1sm (16)	91%	26% mean local disease recurrence time: 65 months	Stenosis (3)
Pech ⁷⁷	2004	Prospective case series	39	Polypectomy technique Suck-and-ligate	Erbotom ICC 200 (Erbe Inc, Tübingen, Germany)	Carcino ma-in-situ (10) T1m (19) T1sm (10)	Carcino ma-in-situ 90% (9) T1m 100% (19) T1sm 80% (8)	Carcino ma-in-situ (2) T1m (3) T1sm (1)	Overall 15 % Minor bleeding (3) Esophageal stenoses (3)
Esaki ²⁵	2007	Retrospective case series	62 (64 lesions)	EMR Adjunctive APC or heater probe	Not available	m1/m2 (48) m3/sm1 (16)	NA	14/64 lesions 3–36 mth after EMR	Bleeding 2% (1) Perforation 2% (1)