Modern endoluminal therapeutic modalities: the pathologist's perspective

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For most of the last 20 years, surgical resection has been the conventional therapy for not only invasive esophageal adenocarcinoma, but also high grade dysplasia (HGD).[54] Although curative for most cases, esophagectomy is associated with significant morbidity and mortality, ranging from 2% to 7% in centers with much experience and up to 20% in hospitals where the procedure is infrequently performed.[10,23] Furthermore, comorbid illnesses, particularly among older patients, preclude surgery for some patients.

The aim of endoscopic therapy is to achieve a cure for early stage neoplasms while avoiding the considerable mortality and morbidity of surgery, with low incidence of lymph node metastasis.[42,57,61] Among various methods, endoluminal therapies such as photodynamic therapy (PDT), laser therapy, and endoscopic mucosal resection (EMR) have shown promise for the treatment of superficial neoplasms arising in Barrett esophagus (BE).[5,6,13,46] Given the increasing popularity of these techniques, pathologists should become acquainted with these therapeutic modalities.

ENDOSCOPIC MUCOSAL RESECTION

In contrast to laser and PDT, which aim to destroy the pathologic tissue in situ, EMR represents a minimally invasive surgical procedure that enables microscopic examination of the specimen for histologic confirmation of the neoplastic grade and its depth of invasion. EMR, which was originally developed as a diagnostic procedure (“strip-off biopsy”), has been used in Japan for the resection of early gastric cancers and recently has been introduced in the West for the treatment of early esophageal neoplasms.[13,32,43]

The current guidelines for EMR are evolving, and no standard has been specifically set for BE-associated neoplasms. If we follow the evolving guidelines for gastric cancer, these include the treatment of well-differentiated mucosal neoplasms of the intestinal type, measuring less than 2 cm and with no lymph node involvement.[41] However, some have reported that early gastric cancers with slight invasion into the submucosa measuring less than 5mm horizontally were often lymph node negative and therefore could benefit from this modality.[25] Other investigators advocate even less stringent indications and have reported relative success in well-differentiated intramucosal cancers less than 30mm in size, non-ulcerated submucosal cancers measuring less than 20mm, and even poorly differentiated intramucosal carcinomas less than 10mm in size.[4]

Pathologic evaluation of EMR

Since EMRs are performed with a curative intent, they should be handled and reported as surgical specimens. Appropriate reporting is essential, since additional therapeutic options including extension of mucosal resections during a second endoscopic session or recourse to more invasive therapy, that is, surgery, will be directly decided upon the microscopic evaluation of the specimens. Practically, EMR specimens should be stretched and mounted on a firm surface such as a wax block before fixation. This avoids curling of the specimens' edges and allows better slicing. Obtaining a picture of the stretched specimens is a good practice, particularly when the specimens are fragmented. It also may facilitate reconstruction of the specimens if needed, as well as correlation with findings that are not predicted, such as an unexpected positive margin(s). After fixation, inking of the margins is cardinal in helping in assessing the overall completeness of the resections, or lack thereof. Serial sectioning allows optimal determination of the differentiation, depth of invasion, vascular involvement, and status of the lateral (circumferential) and deep margins with clearance. Piecemeal resections are usually difficult to stage accurately. The fragments may be too small for stretching and attempts to reconstruct the specimens may be challenging. In such circumstances, direct communication with the gastroenterologists is cardinal. In our own experience, 74% of EMRs consisted of an intact specimen, whereas 26% of specimens were fragmented (4 specimens consisted of two fragments and 3 consisted of three or more fragments).[35] This problem in fact may become more common, as the newly introduced band technique, which allows gastroenterologists to remove

larger lesions, usually yields several mucosal fragments and essentially prevents the pathologists from accurately reporting on the lateral/circumferential margin status.

In addition to the size, the pathologic evaluation should report on the degree of differentiation, the depth of invasion, the status of the margins (lateral, deep and en-face), and the clearance of the excision. The status of vascular invasion also should be noted, especially in the cases with submucosal extension. In our reported series of 27 EMRs, the resection was microscopically complete in only 4% of the cases. A lateral margin was positive in 52% of EMRs, both lateral margins were positive in 11%, and the deep and lateral margins were positive in 26% of EMRs.[35]

The assessment of the clearance has been shown to be important for gastric EMRs and is likely to be the same for esophagus. In one series, none of the patients with a minimal clearance of 2 mm developed local recurrence, but 16% of cases with less ample margin recurred.[20] When adenocarcinoma is present at the margin, recurrence is usually noted in 37–50% of the cases.[20,38,44] Not only the presence of a positive margin but also its extension (evaluated by the number of positive sections) is important. In our experience, the rate of recurrence in cases with a positive lateral margin rose from 33 to 50% depending on whether one section or more were involved.[29] Technical artifacts such as hemorrhage and electrodiathermic burns can be encountered and warrant being mentioned in the final report if they limit the histologic interpretation.

Therapeutic efficacy of EMR

Several studies have validated EMR as an alternative to esophagectomy. A recent prospective series of 100 patients with “low risk” adenocarcinomas (well to moderately differentiated, $\leq$ 20mm in diameter and confined to the mucosa without angiolymphatic invasion or ulcer on endoscopy) reported no death and an overall recurrence rate of 11% during a mean follow-up of 36.7 months (range 2-83 months).[14] In addition to its efficacy, EMR is relatively safe, with low complication rates. Significant bleeding and perforation have been reported in 0% to 14% and 1.8% of procedures, respectively, while deaths have not been reported.[3,14,16,32,43,63]

However, other recent series have reported disappointingly high percentages of positive margins, with figures as high as between 62.5% to 83% of cases.[30,35,52,67] The reasons for these disappointing results are unclear. It has been suggested that tumor grade might be important in the failure to obtain clear margins. In one series, 88% of high-grade neoplasms were resected

with positive margins as opposed to 12% of low-grade neoplasms.[30] Another factor may be the method of assessing margins. In several series, a detailed examination of resection margins is not described.[16,33,43,48] Various authors also define completeness of resection differently. Some authors report the margin status only for the final EMR specimen in patients undergoing sequential EMR.[3] Others define completeness of excision based on the status of postoperative biopsies of the lesional area regardless of the margin status of the actual EMR specimen.[48] Nevertheless, we have experienced a high rate of tumor recurrence: 91% of EMRs with positive margins showed persistent/recurrent tumor at the first follow-up biopsy. The overall persistence/recurrence rate of 47% is higher than in other series, which report a local persistence/recurrence rate of 7% to 19% after EMR and PDT.[22,51]

In our experience, 44% of EMRs with positive lateral/circumferential margin(s) and negative deep margin (including five also treated by PDT) had no residual tumor and/or recurrence at the last biopsy with median follow-up of 23 months. However, 86% of EMRs with positive deep margin showed residual tumors despite the use of photodynamic therapy in some cases.[35]

Diagnostic Advantage of EMR

Given the high rate of incomplete resections, several investigators have advocated the use of EMR as a staging and diagnostic tool.[3,29,35]

In our experience, a change in diagnosis from the original biopsies is noted in 37% of the cases, with the biopsies underreporting the neoplastic grade in 21% of the cases and overreporting it in 16% of the cases.[35] Others have reported similar results. Conio et al reported a change in diagnosis in 26% of cases based on examination of the EMR specimen.[12] In their series of 42 patients undergoing EMR, Lightdale et al reported that 5 of 27 patients with an initial diagnosis of HGD were upgraded to IMC and 6 of 15 patients with an initial diagnosis of IMC were upstaged to invasive carcinoma.[31] Obviously, these changes in grade and stage may have a significant impact on patient outcome, as lymph node metastases can be observed in up to 8% of IMC and up to 21% of submucosal tumors.[11,17,40,56,62]

Earlier last year, we showed that EMR is superior to biopsy for diagnosing superficial gastroesophageal tumors, particularly for large (>10 mm) lesions. Discrepancies between biopsies and EMRs were shown to occur with significantly larger lesions and less extensive

biopsy sampling. Maximal dimension, surface area, and biopsy sampling ratios of the lesions were shown to be significantly greater in the discrepant cases than in the concordant cases.[24]

EMR is more accurate in staging early neoplasms than EUS

Accurate staging to differentiate dysplasia and intramucosal carcinoma from adenocarcinoma with submucosal invasion is critical in determining individualized patient management. Despite significant advances, endoscopic ultrasound (EUS) has only a 72% to 95% accuracy rate in distinguishing between mucosal (T1m) and submucosal (T1sm) disease.[43,58] Overstaging by EUS occurs in 0% to 12.5% of cases and understaging in 16 to 20% of cases.[13,43,58]

In one series, EMR was avoided in 17% of patients with evidence of submucosal invasion on EUS.[27] However, EMRs allowed more precise identification of the level of invasion, with pathologic analysis showing submucosal invasion in 40% of patients staged as intramucosal adenocarcinoma by EUS.[27] All the submucosal cancers were associated with nodular lesions except in one case, while submucosal invasion in flat, non-nodular BE with HGD in biopsy specimens seems to be uncommon.[27] In our experience, EUS correctly staged 70% of the lesions as intramucosal (n=10) or invasive (submucosal) tumor (n=2). It overstaged 3 lesions (pT1sm for actual mucosal lesions) and understaged two (pTX for actual intramucosal neoplasms).[35]

EMR improves diagnostic consistency

Interobserver variation is a vexing problem for surgical pathologists. Reid et al. achieved only a 61% interobserver agreement when evaluating three categories (negative for dysplasia; indefinite for dysplasia and low-grade dysplasia; high-grade dysplasia and carcinoma). More recently, a group of 12 observers reviewing 125 biopsies could reach only an interobserver kappa value of 0.50 (representing about 75% of interobserver concordance) when distinguishing the same 3 categories.[39,55] The reasons for diagnostic differences can be multiple, including the experience of the observers (not the case in the publications cited above) and quality of material, a phrase including features ranging from quality of the slides (staining, sections) to size of the specimen sampled. Another cause is likely related to the very nature of dysplasia, a biologic process encompassing a continuum of changes for which defining a fixed point, i.e., a specific grade, is sometimes difficult.

We reported recently that interobserver agreement of BE-related neoplasia on EMRs is significantly higher compared to biopsy specimens.[36] The results may relate to the larger tissue sampling compared to biopsies and the ability to evaluate mucosal landmarks such as double muscularis mucosae. In our series, none of the 25 biopsies had 100% interobserver agreement among all reviewers, although 13 cases (52%) were given diagnoses that differed by only one grade and 36% of the cases (n=9) differed by 2 grades. Diagnoses spanning 4 different grades were recorded in 12% of the biopsies. Of the 25 corresponding EMRs, all reviewers gave the same diagnosis in 16% of the EMRs, including three intramucosal adenocarcinomas and one invasive adenocarcinoma. Another 13 cases were given diagnoses that differed by one grade. 24% of cases had a diagnostic spread of 3 grades, but a diagnosis spanning 4 grades was recorded in only one EMR (4%). The interobserver coefficient and Kendall Coefficient for the mucosal biopsies were 0.938 (95% CI = 0.880-0.965) and 0.677, respectively. Alternatively, the ICC and KC for the 25 EMRs were significantly improved at 0.977 (95%CI=0.957-0.987) and 0.831, respectively.

In conclusion, although the validity of EMR as a definitive therapeutic tool is still under investigation, it already has proven to be a staging procedure superior to EUS (for early lesions) and to yield better concordance between preoperative and operative diagnoses compared to mucosal biopsies, also enhancing diagnostic reproducibility between pathologists.

PHOTODYNAMIC THERAPY

PDT is the most extensively studied ablative method for superficial neoplasias arising in BE. In short, an inactive photosensitive drug that accumulates within the epithelium is activated by endoscopically delivered laser light of an appropriate wavelength. As the drug absorbs the light energy, the latter is transferred to the oxygen with generation of high energy cytotoxic singlet oxygen molecules that damage the tissue.[49] Other ablative therapies currently investigated include argon plasma coagulation and laser photoablation.[18,65,70]

Several groups have reported a good clinical response to PDT, with dysplasia and/or superficial adenocarcinoma disappearing in 67% to 100% of the cases, using 5-aminolevulinic acid sodium porfimer.[1,19,45,47,68,69,73] In addition, PDT has been shown to decrease the risk of metachronous adenocarcinomas significantly.[45]

It has been shown repeatedly that the higher the histologic grade, the lesser the response rate.[6] Thus, mucosal/submucosal invasive adenocarcinomas (pT1) are less likely to be treated successfully than high-grade dysplasia. For instance, some authors have reported no evidence of recurrence in only 25% of pT1b/limited pT2 tumors (with limited follow-up).[15,28] Alternatively, the success rate is significantly higher for HGD and IMC (90% and 82.1%, respectively, in our experience) and the progression of HGD or IMC to invasive cancer is low, varying from 4 to 13%.[28,45] Our numbers are comparable to previous results.[45-47,71,72] In most series, PDT is combined with other ablative methods, a strategy necessary to achieve significant success. In our experience, the eradication rate after a single PDT alone was 6.5% but increased to 87.3% when fulguration was added. Among the cases that resisted a single series of PDT, none responded to a single additional PDT alone; however, when combined with fulguration, the success rate improved to 68.4% after a second course of PDT and 100% after a third course.[28]

A broad band of squamous epithelium usually reappears after acid suppression and anti-reflux surgery,[6,9] and also after electrocoagulation, argon plasma coagulation,[64] and laser.[7,9] In a series of 33 patients, the authors have shown that expressed as a ratio of the total number of sampled areas, the percentage of biopsies with squamous islands changes from 36.7% before PDT to 77.5% post-PDT.[6] Usually, no squamous atypia is seen in the restored squamous epithelium. Reviewing the residual non-dysplastic BE, we found that goblet cells are usually significantly decreased. Stromal capillary proliferation and eosinophilia also is noted early after PDT, while fibromuscular proliferation may be prominent at 6 months and is usually associated with glandular atrophy. A similar tendency is observed in the dysplastic epithelium. Reactive atypia of the columnar epithelium is more prominent post-PDT than pre-PDT, but usually is mild and not diagnostically challenging in post-PDT biopsies.[37]

Clinically, the main complications include esophagitis and photoreactions with most patients experiencing rapidly resolving sunburn (face or hands). More rarely, solar dermatitis, severe burn with blistering, or skin fragility can be seen. Esophageal stricture requiring dilatation is variably reported (6.25% to 29%) depending on the center.[15,28]

The histopathology of resistance to photodynamic therapy

In most cases (62.5% in our experience), the histologic grade of persistent neoplasia is unchanged after PDT. Less commonly, the neoplasia is downgraded.[6] We recently confirmed in a larger cohort that, as originally noted in a series of 33 patients, distally located lesions are more

likely to persist after PDT (4% of proximal lesions versus 15.3%).[6,28] The reason is unclear. However, since the distal esophagus remains exposed to high concentrations of gastric acid (or bile), it is plausible that COX-2 overexpression is evoked, in turn promoting the persistence of neoplastic tissue.[21,50,60]

Diffuse and multifocal neoplastic disease is also prone to persist after PDT.[6] We recently noted that all patients who responded to a single PDT course (+/- fulguration) had a short segment of neoplasia (<4 cm) while 2/3 of patients with neoplasia spanning $\geq$ 4 cm needed more than one course of treatment (repeated PDT with fulguration). Since long segment BE frequently harbors multiple neoplastic clones, it is likely that post-PDT persistence is a reflection of resistant clones unaltered after PDT.[26,53] Further evidence is that most re-emergence of neoplasia after initial eradication (92% of the cases) arose at the original site, reflecting the persistence of genetic abnormalities.[28]

Post-PDT buried Barrett epithelium and neoplasia

After PDT, Barrett's mucosa concealed by restored squamous epithelium (buried BE) is reported in 0% to 40%[2,8,19,46,47,69,72,73] and buried neoplasms in 0% to 3.7% of the patients.[19,46,47,73] A concern associated with buried BE is the risk of unnoticed malignant transformation.[9,59,66]

In our cohort, completely buried BE (absent before PDT) was observed in 17.3% of patients after treatment. More importantly, completely buried neoplasms, observed in 1.9% of 52 patients (n=1) before treatment, rose to 35.1% (n=13) of those after PDT. Importantly, 7.4% of the residual neoplasms were completely concealed by squamous epithelium, and in most cases (57.9%), these represented the highest grade and usually the sole residual neoplastic focus.[28,34] Although the patients with buried neoplasms responded to further treatment similarly to those with only surface neoplasms, the detection of buried neoplasms is difficult without reliable clinicopathological characteristics.[28] Therefore, endoscopic surveillance with extensive biopsies and thorough pathologic evaluation is cardinal.

In conclusion, whether evaluating endoscopic mucosal resections or diagnosing post-PDT follow-up biopsies or other ablative therapies, the histopathologic interpretation, and thus the role of the pathologists, is crucial in the validation of these new therapeutic methods.

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