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TOPIC HIGHLIGHT

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Esophageal resection for high-grade dysplasia and intramucosal carcinoma: When and how?

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Abstract

High-grade dysplasia (HGD) and intramucosal carcinoma (IMC) in the setting of Barrett's esophagus have traditionally been treated with esophagectomy. However, with the advent of endoscopic mucosal resection and endoscopic ablative therapies, endoscopic therapy at centers with expertise is now an established treatment of Barrett's-esophagus-related neoplasia, including HGD and IMC. Esophagectomy is today reserved for more selected cases with submucosal invasion, evidence for lymph node metastasis, or unsuccessful endoscopic therapy.

Key words: Barrett's esophagus; High-grade dysplasia; Intramucosal carcinoma; Endoscopic mucosal resection; Esophagectomy

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INTRODUCTION

High-grade dysplasia (HGD) and intramucosal carcinoma (IMC) in the setting of Barrett's esophagus (BE) have traditionally been treated with esophagectomy. However, with the advent of endoscopic mucosal resection and endoscopic ablative therapies, endoscopic therapy at centers with expertise is now an established treatment of Barrett's-esophagus-related neoplasia, including HGD and IMC. Esophagectomy is today reserved for more selected cases with submucosal invasion, evidence for lymph node metastasis, or unsuccessful endoscopic therapy. This review highlights the updated role of and approaches for esophagectomy in the management of HGD and IMC in BE and discusses risk factors associated with submucosal invasion, lymph node metastasis, or unsuccessful endoscopic therapy.

TRADITIONAL APPROACH: ESOPHAGECTOMY AS THE STANDARD OF CARE FOR HGD

HGD in the setting of BE has been identified as a key risk factor in the progression to esophageal adenocarcinoma (EA). Patients with HGD are at a higher risk for progressing to EA than are patients with BE with no or low-grade dysplasia (LGD). This has given rise to performing prophylactic esophagectomy for the treatment of HGD to prevent EA. In addition to the risk of progression to EA, the surgical literature has reported a high risk of coexisting adenocarcinoma in patients with HGD that is

not diagnosed by endoscopic biopsy. The esophagectomy literature has reported varying prevalence of occult EA in patients with BE and HGD, ranging from 0% to 73%, and frequently approximates to a rate of around 40%[1-7]. Thus, the role of esophagectomy for the treatment of HGD is underlined by both prevention of cancer and cure of occult cancer.

Concerns have previously been raised as to whether esophagectomy is appropriate for most patients with HGD and IMC. Newer data have suggested that the incidence of invasive cancer is probably much lower than the 40% rate previously estimated[8]. This suggests that esophagectomy for HGD is unnecessary in more than 80% of patients in whom it is performed. At the same time, newer endoscopic techniques for evaluating and managing HGD and IMC have been developed and clinically tested. Currently, the approach to HGD and IMC is more complex and provides much more individualized care of patients than previously was available.

ENDOSCOPIC EVALUATION OF BARRETT'S-ESOPHAGUS-RELATED NEOPLASIA

The management of BE has been greatly influenced by the advent of endoscopic mucosal resection (EMR) and endoscopic ultrasound (EUS). Prior to the advent of endoscopic ablative techniques, whether intramucosal cancer was different from invasive cancer was a moot point, given that esophagectomy was indicated in either case. However, with endoscopic therapy now available for IMC, the distinction must be acknowledged. When evaluating treatment options it is crucial to understand the difference between the presence of intramucosal cancer limited to the mucosal lining, which only has a minimal nodal metastasis risk[9-11] and might be locally treatable, and the presence of cancer with invasion into the submucosa, which carries a higher nodal metastasis risk and requires surgery and/or systemic therapy[9,12-16].

Understanding pathological definitions is instrumental in managing a patient with Barrett's-related neoplasia. Dysplasia is neoplastic cytological and architectural atypia without evidence of invasion past the basement membrane. The diagnosis of LGD or HGD is based on the severity of cytological criteria that suggest neoplastic transformation of the columnar epithelium[17]. HGD and carcinoma *in situ* are regarded as equivalent. IMC is tumor that is limited to the lamina propria and is considered T1a by the American Joint Committee on Cancer staging. Submucosal carcinoma (SMC) is a tumor that invades past the muscularis mucosa into the submucosa, but not into the muscularis propria. Vessel invasion might be either venous or lymphatic channel invasion.

In a systematic review of the surgical literature that has reported the rates of cancer in patients who were undergoing esophagectomy for prophylactic treatment of HGD, the pooled average was 39.9% in the 441 patients who underwent esophagectomy for HGD among 23 studies[5]. These rates were largely based on retrospective studies with varying aims, sizes, definitions, and methodology. This average rate is consistent with previous pooled studies by Edwards *et al*[1], Ferguson *et al*[6], and Pellegrini *et al*[7] who have reported rates of 41%, 43% and 47%, respectively. However, the majority of these patients had IMC, whereas the rate of submucosal invasive cancer was decreased to 12.7% when applying both standardized criteria and strict definitions.

Prospective studies with rigorous endoscopic criteria in the EMR literature have reported lower rates of occult submucosal invasive disease. Among patients presenting with HGD and IMC who were undergoing complete BE EMR, the rate of occult submucosal invasive cancer was 4%[18]. Pech *et al*[19] have reported their long-term experience with EMR and other ablative procedures for Barrett's-esophagus-related neoplasia. They achieved a complete response in 96.6% and the 5-year survival rate was 84%. In their experience, esophagectomy was required in only 3.7% of patients initially presenting with HGD or IMC[19].

The management of HGD and IMC has now shifted from esophagectomy to endoscopic therapy to achieve total Barrett's eradication[18,20,21]. The concept of total Barrett's eradication highlights the importance of not only treating the known neoplasia, but also eradicating all of the at-risk Barrett's epithelium, to treat any synchronous lesions and hopefully prevent any metachronous lesions. Although expertise might vary from site to site and patient characteristics need to be taken into account, there is now acceptance of endoscopic therapy for HGD and IMC, and esophagectomy is no longer the standard of care[22].

Endoscopic modalities include tissue-acquiring therapies that include focal EMR, complete Barrett's EMR, and endoscopic submucosal dissection. Tissue-acquiring modalities are important to stage a visible lesion in the setting of HGD or for the treatment of IMC. HGD might also be treated with ablative therapies, such as photodynamic therapy, which has the longest experience of the ablative therapies[23], radiofrequency ablation, which has demonstrated initial success[24], and cryotherapy, which is a newer modality[25]. Chennat and Waxman have described these endoscopic therapies in further detail in their article in this issue.

HIGH-RISK CHARACTERISTICS OF BARRETT'S NEOPLASIA

Endoscopic therapy has advantages in that it is organ-preserving and does not have the same morbidity and mortality as surgery. However, not all cases are successful or appropriate for endoscopic therapy. Indications for esophagectomy include lymph node metastasis and failure of endoscopic therapy. Risk factors for submucosal invasion, lymph node metastasis, and failure of endoscopic treatment need to be incorporated into the management strategy of a patient with HGD and IMC. These risk factors are evident in endoscopic appearance, pathological characteristics, and results of endoscopic treatment (Table 1).

Table 1 High-risk characteristics associated with submucosal invasion, lymph node metastasis, or unsuccessful endoscopic therapy

Endoscopic characteristics
Long-segment Barrett's esophagus
Visible lesions with high risk endoscopic characteristics
Polypoid mass
Excavated lesions or ulcers
Evidence of lymph node involvement by EUS + FNA
Pathological characteristics
Multifocal HGD
Evidence of submucosal invasion
Deeper two thirds of the submucosa carries high risk of lymph node metastasis
Moderately or poorly differentiated tumor
Evidence of lymphatic channel invasion
Evidence of vascular invasion
Evidence of neural invasion
Treatment characteristics
Failure of ablation of remainder for Barrett's epithelium
Piecemeal endoscopic resection (as opposed to *en bloc* resection)
Longer time to achieve eradication

EUS: Endoscopic ultrasound; FNA: Fine needle aspiration; HGD: High-grade dysplasia.

Endoscopic characteristics

Long-segment BE has been identified as a risk factor for cancer[26] and for recurrence of neoplasia with endoscopic therapy[19]. Furthermore, visible lesions in the setting of HGD are more at risk for harboring occult cancer than flat dysplasia[5,27,28].

Careful white light examination is essential for targeting biopsies and resection of visible lesions because visible lesions in the setting of dysplasia have a high risk of occult cancer. Furthermore, the type of lesion is correlated with risk of submucosal invasion. Standardization of endoscopic appearance of visible lesions is now developing, and more attention is being given to non-protruding lesions. The updated Paris classification is based on the Japanese classification of gastric lesions. In the esophagus, superficial lesions based on endoscopic appearance include the following classifications: protruding pedunculated (type 0- Ⅰ p), protruding sessile (0- Ⅰ s), slightly elevated (0- Ⅱ a), completely flat (0- Ⅱ b), slightly depressed (0- Ⅱ c), excavated (0-Ⅲ), or a mixed pattern[29]. Type 0-Ⅲ is suspicious for submucosal invasion. Type 0- Ⅰ and type 0- Ⅱ c lesions are also associated with increased risk of submucosal penetration[30]. Thus, protruding or depressed lesions are at higher risk than those slightly raised or flat areas. EMR provides an opportunity to stage the depth of a lesion in areas of question.

Endoscopic ultrasound in BE demonstrates a thickened mucosal lining. It is not optimal for differentiation between a T1a tumor (IMC) and a T1b (SMC) tumor, and EMR is better suited for depth staging at this range[31]. However, given the risk of lymph node metastasis in patients with IMC, EUS with fine needle aspiration (FNA) might identify patients not eligible for endoscopic therapy[32]. EUS with or without FNA is a reasonable procedure in all patients with IMC and patients with visible lesions, who have a higher risk of occult cancer. Any patient found with lymph node involvement should be referred for esophagectomy. The utility of EUS in flat HGD might be questioned[33].

Pathological characteristics

The diagnosis of HGD, IMC, and invasive cancer represents a biological and histological continuum. Although pathological assessment is the gold standard, interpretation is subject to a great deal of variability among pathologists. There is high inter-interpreter variability in diagnosing HGD as reported in the literature[34-38]. Due to limited sample size and depth, as well as potential crush artifacts, pathologists might not reliably be able to distinguish between HGD, IMC and SMC on a single biopsy specimen. One of the advantages of EMR specimens is that pathologists are better able to stage lesions because they provide large and intact pathological specimens.

In evaluations of specimens from EMR for Barrett's neoplasia, moderately or poorly differentiated cancers are more likely to invade the submucosa[30,39]. HGD obtained from multiple levels throughout a BE segment has a higher risk of being associated with occult cancer[28]. Furthermore, in a risk analysis performed on patients with either HGD or IMC, multifocal neoplasia has been cited as a risk factor for recurrence after endoscopic therapy[19]. Risk factors for lymph node metastasis in EA are vascular invasion, lymphatic channel permutation, neural invasion, and grade of the tumor[40,41]. In EA, submucosal invasion of the most superficial third does not carry the same lymph node metastasis risk as the deeper two thirds[40]. Manner *et al*[42] have reported favorable outcomes with endoscopic resection of low-risk SMC in their long-term experience of endoscopic resection. However, larger trials are needed before adopting endoscopic therapy as standard practice for these superficial submucosal invading tumors.

Treatment characteristics

Endoscopic resection specimens not only provide a histological specimen that is important for accurate pathological diagnosis, but also provide a means for assessing treatment adequacy. Lateral margins might indicate that further endoscopic treatment is necessary, whereas positive deep margins indicate that surgery is appropriate. The following are associated with a higher risk of recurrence: length of time to complete eradication of neoplasia with multiple endoscopic treatment sessions; piecemeal resection; and no ablative therapy to target the remainder of the at-risk Barrett's epithelium[19].

Although there is ongoing interest and early investigations for genetic or molecular markers to predict endoscopic response[43], none of these markers has been validated for clinical use.

ADVANTAGES OF ESOPHAGECTOMY

The strategy of performing esophagectomy for HGD or IMC not only cures the index condition, but also addresses occult cancer and prevents cancer death[44]. Although endoscopic treatment is an appropriate and cost-effec-

tive[45] approach for the treatment of many patients with HGD and IMC, patients who are appropriate surgical candidates can benefit from esophagectomy. The surgical specimen enables accurate staging of disease to diagnose areas of occult cancer, and confirms treatment adequacy with negative margins and lymph nodes. Conventional approaches are transhiatal esophagectomy and transthoracic esophagectomy. Minimally invasive esophagectomy (MIE) techniques are growing in popularity because of their perceived benefits of reduced pain, lower incidence of postoperative complications, and faster recovery. These MIE techniques include video-assisted thoracoscopy surgery with laparotomy or laparoscopy, laparoscopy with a right thoracotomy, or laparoscopic transhiatal resections. These procedures have been studied in mostly retrospective studies and conclusions are limited in terms of direct comparisons to open surgery due to lack of prospective randomized trials[46,47].

The issue of the morbidity and mortality of esophagectomy is the major concern for either open esophagectomy or MIE. Adverse outcomes include pulmonary complications, hemorrhage, anastomotic leakage, infections, and recurrent nerve palsy. Although one study based on a national Veteran's Affairs database has reported morbidity of almost 50% and mortality of 10%[48], the expertise and volume of the center, the experience of the surgeon, the patient risk factors, and the indications for esophagectomy should be taken into account[49-51]. In institutions with expertise and high volumes, the mortality rate is 2%-3%[52]. It is also important to note that esophagectomy specifically for HGD has a different risk profile than that of esophagectomy for cancer. Comorbid diseases, debilitation from cancer and/or neoadjuvant therapy, and issues with locally advanced disease are not as predominant in patients with HGD. A pooled mortality rate of 1% was calculated among six studies that involved esophagectomy for HGD[49]. Quality of life indicators for patients who underwent esophagectomy for HGD and IMC are equivalent to those of the general population[53].

INDICATIONS FOR ESOPHAGECTOMY FOR BARRETT'S HGD OR IMC

Strong indications for esophagectomy include lymph node metastasis and failure of endoscopic therapy. Invasion of tumor into the submucosa is still considered a strong indication for esophagectomy, although invasion into the superficial third of the submucosa does not carry the same lymph node metastasis risk as the deeper two thirds, and potentially could be treated endoscopically[29,42]. Factors to consider in the management strategy for HGD and IMC include characteristics that are associated with lymph node metastasis, submucosal invasion, and failure of endoscopic therapy, as listed in Table 1, and may serve as milder indications for esophagectomy. Excavated lesions (Paris classification 0-Ⅲ) are not typically considered to be amenable to endoscopic therapy due to high suspicion of submucosal invasion, whereas protruding lesions (0-Ⅰ) and depressed lesions (0-Ⅱc) are a concern for submucosal invasion and should be approached with caution endoscopically (Table 2). These circumstances allow for endoscopic resection to serve as a diagnostic tool to stage the lesion accurately to determine if the lesion is amenable to endoscopic therapy. Multifocal high grade is a milder indication for esophagectomy than previously considered, due to the evolving options of ablative therapy. These risk factors, as listed in Table 1, need to be weighed with patient characteristics, patient preferences, available surgical expertise, available endoscopic expertise, and surgical approach options to decide if esophagectomy or endoscopic therapy is appropriate for each case.

Table 2 Relative risk of submucosal invasion associated with endoscopic appearance of lesions

Endoscopic appearance	Paris classification	Relative risk of submucosal invasion
Polypoid	0-Ⅰp	Higher
Sessile	0-Ⅰs	Higher
Slightly raised	0-Ⅰa	Low
Flat	0-Ⅰb	Low
Slightly depressed	0-Ⅰc	Higher
Excavated	0-Ⅲ	Very high

WHICH OPERATION FOR BARRETT'S HGD OR IMC?

Selection of the appropriate approach to esophagectomy for HGD or IMC is based on a number of factors (Table 3). Prior surgery in the chest or abdomen might require an open rather than a minimally invasive approach, and prior esophageal surgery such as fundoplication might limit consideration of a vagal-sparing approach. Comorbidity such as severe pulmonary disease, or advanced age might encourage some surgeons to pursue an approach associated with less postoperative pulmonary morbidity, such as transhiatal esophagectomy[54]. Whether minimally invasive approaches offer a lower risk of postoperative pulmonary morbidity compared to open transthoracic approaches has not yet been adequately determined[47,55-57].

The appropriate extent of operation for HGD or IMC is somewhat complex and controversial, and is related to the length of esophagus that must be resected, the extent of soft tissue resection around the esophagus, and the regions for lymph node dissection. It is appropriate to examine the surgical specimen at the time of resection, and usually to perform a frozen section analysis of the proximal margin, to ensure that all the Barrett's mucosa has been removed. Limiting the resection to encompass just the Barrett's segment is probably not a good long-term strategy, because most reconstructive techniques using a gastric tube create a model of frequent reflux, thus exposing patients to the possibility of developing Barrett's mucosa in the remaining esophagus[58]. Indeed, this phenomenon has been well documented in the esophageal remnant after standard subtotal esophagectomy, and theoretically, the risk would be increased if more esophagus were left in place[58-64]. Some cases of adenocarci-

Table 3 Selecting an appropriate surgical approach

Patient characteristics
Prior surgery (thoracic, abdominal, esophageal)
Obesity
Age
Pulmonary function
Other comorbid factors
Surgical options
Standard open resection
Transhiatal esophagectomy (2 or 3 holes)
Minimally invasive esophagectomy
Vagus sparing esophagectomy
Mucosal stripping esophagectomy?
Extent of operation
Extent of esophageal resection
Limited resection of Barrett's segment
Near-total esophagectomy
Extent of soft tissue resection
Minimal
Standard
Extended
Extent of nodal dissection
Minimal
Standard
Extended 3-field
Surgical results
Accuracy of staging
Number of lymph nodes
Effects on long-term survival
Effects on perioperative outcomes

noma arising in such metaplastic epithelium have been described[65,66]. Therefore, a near total esophagectomy is recommended for patients who are undergoing esophagectomy for HGD or IMC.

The lateral extent of soft tissue resection for HGD or IMC is a more controversial problem, with the possible range extending from a vagal-sparing esophagectomy, in which no additional soft tissues are removed, to an extended *en bloc* esophagectomy, which sometimes includes the azygos vein, thoracic duct, contralateral pleura, a rim of diaphragm, and in some cases, even the posterior pericardium. With the increasing accuracy of EUS in assessing the depth of penetration of the primary tumor, anything more than removing a standard amount of soft tissue representing the lateral margins is not likely to provide the patient with benefits regarding local recurrence, but might add to postoperative morbidity. Whether a vagal-sparing operation offers the same freedom from local recurrence has not been sufficiently studied to date[67].

The appropriate extent of nodal dissection for HGD or IMC is also controversial. In order to stage esophageal cancer accurately it has been suggested that a minimum of 10 lymph nodes be resected for early-stage cancers[68]. The use of more extensive nodal dissections, especially three-field lymphadenectomy, are controversial for regionally advanced cancers and are likely inappropriate for HGD and IMC, although this question has not been formally studied.

The best surgical option for HGD or IMC is the one that produces the least morbidity, balanced against the best long-term survival. As present, any standard resection technique including open transthoracic, minimally invasive, and transhiatal approaches provide similar long-term outcomes, and transhiatal esophagectomy might have an advantage in reducing postoperative morbidity. The more extensive resections (open transthoracic, and minimally invasive) are likely to improve staging accuracy, particularly with regards to nodal status. Long-term functional status is similar regardless of the surgical approach. The use of vagal-sparing techniques, especially for HGD, has potentially interesting advantages with regard to quality of life, but has not been adequately evaluated in terms of staging accuracy and long-term outcomes. In the end, it is the surgeon's training and experience, in combination with the individual patient's needs that determines the most appropriate approach to esophagectomy for HGD or IMC.

CONCLUSION

Barrett's HGD or IMC can be primarily treated endoscopically with endoscopic resection and endoscopic ablation with the goal of total Barrett's eradication. Evidence of submucosal invasion, lymph node metastasis or failure of endoscopic therapy or their risk factors, which can be ascertained by endoscopic appearance, pathological characteristics, and treatment course, need to be incorporated into the decision-making process for endoscopic versus surgical treatment. Longer-term studies with additional risk analysis need to be carried out to be able to predict reliably which patients are amendable to endoscopic therapy and who may benefit from esophagectomy.

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