Thoracic and Cardiovascular Surgery

Endoscopic Mucosal Resection and Vagal-Sparing Esophagectomy for High-Grade Dysplasia and Adenocarcinoma of the Esophagus

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Once a rare tumor, adenocarcinoma of the esophagus is currently the cancer with the fastest rising incidence in America. In addition to the increasing prevalence of the disease, surveillance programs for patients with Barrett's have led to the identification of increasing numbers of patients with high-grade dysplasia or early-stage esophageal adenocarcinomas. Although traditional esophagectomy is curative in the majority of these patients, associated morbidity and mortality remains a hurdle for patient acceptance of the procedure. New endoscopic and surgical therapies offer the potential of decreased morbidity, but do not include a lymphadenectomy, and consequently, are not appropriate in patients that have a significant risk of lymph node metastases. Endoscopic mucosal resection allows precise determination of the depth of tumor invasion and facilitates accurate local staging of early esophageal cancers. A vagal-sparing esophagectomy accomplishes the goal of removing the diseased esophagus while minimizing the physiologic impact of an esophagectomy in patients with early-stage esophageal cancer.
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Scope of the Problem

Once a rare tumor, adenocarcinoma of the esophagus is currently the cancer with the fastest rising incidence in America. Recent data indicate that in the US since 1975 the rate of increase of adenocarcinoma of the esophagus has outpaced the next closest cancer, melanoma, by nearly three times.[1-3] The current average yearly increase in incidence in the US exceeds 20%, and among white males the incidence has increased >800% since the mid-1970s in some areas of the country.[4-6] These are alarming statistics, and this increase has propelled this tumor into 1 of the top 15 cancers in US white males and has led to a complete epidemiologic shift such that in the US and other industrialized countries adenocarcinoma has replaced squamous cell as the most common esophageal malignancy.[3,4,7]

In addition to the increasing prevalence of the disease, surveillance programs for patients with Barrett's have led to the identification of increasing numbers of patients with high-grade dysplasia or early-stage esophageal adenocarcinomas. Although esophagectomy is curative in the majority of these patients, associated morbidity and mortality remains a hurdle for patient acceptance of the procedure and has prompted patients to seek potentially less effective but less morbid endoscopic therapies. To minimize morbidity, surgeons have developed minimally invasive techniques for resecting the esophagus as well as methods to spare the vagus nerves and thereby reduce the incidence of postvagotomy diarrhea or dumping symptoms. However, some of these new therapies do not include a lymphadenectomy and are not appropriate in patients that have a significant risk of lymph node metastases. Thus, it is critical when planning therapy for a patient to understand the relationship between depth of tumor invasion and the likelihood of lymph node metastases.

Staging Early Esophageal Adenocarcinoma

Local/regional staging of esophageal adenocarcinoma is best done with endoscopic ultrasound. Standard 7.5- and 12-MHz endoscopic ultrasound probes can accurately assess the

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Table 1 Relationship between Depth of Tumor Invasion and Likelihood of Lymph Node Metastases

Tumor Depth	Prevalence of Lymph Node Metastases (%)
Intramucosal	3–6
Submucosal	20–30
Intramuscular	45–75
Transmural	80–85

depth of invasion once the tumor has gone through the submucosa and also provide information on the presence of abnormal or enlarged lymph nodes. However, neither the standard probes nor the newer high-resolution 20-MHz probes are able to accurately distinguish intramucosal from submucosal tumor invasion.[8-11] This distinction is critical because the likelihood of lymph node metastases changes significantly once a tumor breaches the muscularis mucosa and enters the submucosa (Table 1).[12] Since approximately 30% of patients with a tumor invading into the submucosa will have lymph node metastases, a therapy that does not include a lymphadenectomy is not appropriate. This clinical problem led us to begin using endoscopic mucosal resection (EMR) to precisely determine the depth of invasion of early esophageal adenocarcinomas to determine the appropriateness of a vagal-sparing esophagectomy.[13] As we have gained comfort with EMR, we now also use it to remove nodules and small tumors before Barrett's ablation in some patients in an effort to preserve the esophagus, either secondary to significant medical comorbidities that would preclude esophagectomy or because of limited lengths of Barrett's in otherwise healthy individuals as an option instead of esophagectomy.

Endoscopic Mucosal Resection

Endoscopic mucosal resection excises a disc of esophageal wall down to the muscularis propria and provides a specimen for histologic review that includes both mucosa and submucosa. Thus, from an EMR specimen a pathologist can accurately determine whether a tumor is limited to the mucosa or has penetrated beyond the muscularis mucosa into the submucosa. Although several techniques have been proposed for EMR, one commonly used method involves the use of a cap that fits over the end of a standard endoscope. Developed by Dr. Inoue from Japan, these caps are available in various sizes and configurations (flat versus angled) and come with a complete kit for the procedure by Olympus®.[14] EMR can be performed with conscious sedation, but I prefer to have the patient intubated in the operating room to minimize the chance of aspiration. The procedure is quick, and patients are typically discharged home a few hours later. Using the large cap for EMR, lesions up to 1.5 cm in size can be excised in one piece. However, piecemeal excision of a lesion is also acceptable. If the EMR is only done for staging and a surgical resection is planned, then the EMR resection margins are not important, and as long as an adequate portion of the tumor has been excised to allow assessment of the depth of invasion, no further efforts at excision are necessary. Using this technique, we found that EMR accurately determined the depth of tumor invasion in all cases and had completely excised the target lesion in 86% of patients.[13]

To accurately determine margins, I have found it best to personally orient the specimen for the pathologist, and have it pinned and fixed for permanent rather than frozen section. In my experience all patients with negative margins on the EMR specimen have had no evidence of tumor at the EMR site on pathologic assessment of the resected specimen. Thus, negative margins are a reliable indicator of complete excision with EMR. However, tumor at the cauterized margin of the specimen indicates the potential for residual tumor in the esophagus, and if surgical resection is not planned, then repeat EMR or other ablative technique is warranted in these patients. Additionally, high-grade dysplasia and intramucosal cancers are frequently multifocal, particularly in patients with long-segment Barrett's. In our initial series we noted that in two of seven patients (29%) an additional cancer was present in the resected specimen that had not been detected preoperatively despite multiple endoscopies and extensive biopsies.[13] This is in keeping with numerous series that report that an undetected adenocarcinoma is found in the surgical specimen in 30 to 50% of patients that undergo an esophagectomy for what is believed to be only high-grade dysplasia.[15,16] Thus if EMR is used as primary therapy in patients with adenocarcinoma, continued careful surveillance of the residual Barrett's is necessary. This concept has been confirmed recently in a German series where 57 patients with high-grade dysplasia or intramucosal cancer were primarily treated with EMR. Within 11 months of the procedure nine patients (16%) had local recurrence or developed a metachronous cancer.[17] In an effort to reduce this risk Wang and colleagues are combining EMR with photodynamic therapy to ablate the residual Barrett's. They have reported that no new or recurrent cancers developed in 16 patients during a median follow-up of 13 months, although residual Barrett's was present in 47% of the patients.[8]

It is important to realize that the use of EMR to precisely stage the depth of tumor invasion is necessary only if endoscopic therapy or a vagal-sparing esophagectomy is contemplated for the patient. Traditional forms of esophagectomy including transhiatal, transthoracic, and minimally invasive thoracoscopic/laparoscopic procedures all include a lymphadenectomy, and thus, the distinction between intramucosal and submucosal lesions is less critical. However, the morbidity of an esophagectomy, while acceptable when death from cancer is a significant concern, is a barrier to physician and patient acceptance for therapy of high-grade dysplasia and intramucosal cancer. This sentiment is reflected in the literature by statements such as "surgery remains radical prophylaxis . . . offering a massive macroscopic morbid solution for a microscopic mucosal problem."[18] To increase patient acceptance and reduce the long-term morbidity of an esophagectomy, we have refined a vagal-sparing technique and applied it increasingly to patients with high-grade dysplasia.[19] However, the inability to accurately determine intramucosal from submucosal invasion, and prior data indicating that