Endosonographic Staging of Esophageal Cancer

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Background: Endosonography (ES) is an important tool for staging malignant esophageal cancer with the TNM staging classification. ES is a safe procedure and an accurate method of staging tumor invasion (T) and lymph node involvement (N).

Methods: The author reviewed the literature on the comparative roles of computed tomography and ES as complementary staging procedures.

Results: Advantages of ES in staging esophageal cancer include the ability to accurately determine the layer depth of mural infiltration and to detect metastatic involvement of regional lymph nodes. Its disadvantages include its inability to identify distant metastases, to differentiate inflammation from malignant infiltration of wall layers or in lymph nodes, and to examine beyond obstructing tumors unless esophageal dilation is performed. A recent review indicates the accuracy for T staging to be 84% and N staging to be 77%.

Conclusions: ES is a valuable tool in staging esophageal cancer and should be used in combination with computed tomography for highest accuracy.

Introduction

The goal of staging esophageal cancer is as much to determine inoperability as operability.\(^1\)\(^-\)\(^3\) Currently, the TNM system is used most widely for staging esophageal cancer (Table 1).\(^4\) Because of known poor prognosis of cancer of the esophagus, accurate staging will benefit a majority of patients by providing reliable objective data to justify either potentially curative surgery or a nonsurgical approach to palliative therapy. It is essential for sound medical reasons to avoid needless surgical operations intended simply to stage a malignant condition as unresectable for cure or even resectable for palliation, when equally good non-operative palliation may be available.\(^1\)\(^,\)\(^2\)\(^,\)\(^5\)\(^,\)\(^6\) On the other hand, for patients who are found by endosonography (ES) to have cancer limited to the wall, T1-3, N0, M0 lesions can be advised with more confidence regarding the potential benefits of surgery with or without adjunctive therapy than otherwise would be possible.\(^7\)\(^,\)\(^8\) Accurate staging of patients with lesions favorable for curative resection allows proper counseling regarding risks and benefits of surgical therapy, especially for those who may have significant concomitant illness that makes the decision on operability difficult.

The accuracy of non-operative staging methods must be determined by a comparative study of the results obtained with the best equipment, used by the most experienced operators, and based on careful histopathologic analysis of the organs and tissues involved. Over the past decade, sufficient experience with esophageal ES has been reported to establish it as the single most accurate method for T and N staging of esophageal cancer.\(^3\)\(^,\)\(^8\)\(^-\)\(^10\) Surgical pathologic correlation remains the final arbiter or gold standard in determining the clinical stage diagnosed by an imaging technique.

Computed Tomography

The major sources of error in computed tomography (CT) staging of esophageal cancer are its inability to determine the extent of transmural invasion and its inability to detect lymph node metastases. Most studies have revealed a relatively low accuracy of CT for determining the degree of esophageal wall involvement in T1-3 stages.\(^8\)\(^,\)\(^11\)\(^-\)\(^13\) The extent of intramural spread of esophageal cancer is not accurately detected by either CT or standard endoscopy, and this failure can lead to understaging.

Esophageal carcinoma spreads intramurally in all directions and extramurally to involve the tracheobronchial tree, pleura, pericardium, aorta, vertebrae, and stomach by direct extension. CT evaluation of the mediastinum relative to cancer invasion depends, to a significant degree, on the visualization of fat planes between the esophagus and adjacent structures. However, even a normal individual’s fat planes, particularly in the mid-esophageal region where most tumors occur, may not be distinguishable by CT and are especially difficult to define in underweight patients.

Taylor\(^12\) reports that aortic invasion occurs in 2% to 19% of patients. The tracheobronchial tree is involved in 6% to 46% percent, and the pericardium is involved in up to 18% of patients. The accuracy of CT is reported to vary between 50% to 94% in detection of aortic invasion and in 55% to 97% for tracheal involvement. Bronchoscopy is generally used to assess airway involvement. Where only impingement of the airway is present, most tumors are considered still resectable.\(^12\)

Accurate staging of mediastinal and celiac lymph nodes is difficult because CT can reliably evaluate only those lymph nodes over 1 cm in size, and it is not capable of demonstrating important lymph node structural characteristics. Lymph node size alone has not been found to be predictive of tumor involvement, and most metastases and mediastinal lymph nodes have been shown to measure less than 7 mm in diameter. Conversely, lymph nodes may be enlarged by inflammatory disease and following surgery or chemoradiation therapy. The overall accuracy of CT in evaluating mediastinal nodes is less than 60% in most reports. Accuracy in staging celiac and abdominal lymph nodes is also low, varying from 39% to 87%.

In a review of the role of CT in staging esophageal neoplasms, Halvorsen and Thompson\(^11\) concluded that CT is useful in patients with squamous cell cancer of the thoracic esophagus but is not reliable for cancer in the cervical and gastroesophageal junction regions. CT is considered to be relatively specific when enlarged lymph nodes are found but has relatively low sensitivity in detecting both mediastinal and upper abdominal adenopathy. Using these provisos, it appears that CT is able to separate esophageal cancer patients into three groups: (1) potentially curable, (2) unresectable (distant metastases or direct mediastinal invasion), and (3) indeterminate.
Carcinoma of the gastroesophageal junction represents a diagnostic challenge for CT. A focal pseudomass is present at the gastroesophageal junction in up to 33% of normal patients. In patients with carcinoma of the esophagogastric junction, loss of the periesophageal fat plane in this region is an unreliable sign of tumor extension. Although it is possible to predict resectability in most cases, accuracy of both CT and ES for staging is reduced in many cases due to the presence of tumor metastases in normal-size lymph nodes. CT imaging is recommended more as a problem solving technique than as a routine preoperative test in patients with carcinoma of the gastroesophageal junction. The major advantage for CT in staging esophageal cancer is to evaluate for distant metastases. It is the best imaging technique for determining the M stage and should be used prior to and in conjunction with ES for staging all cases of esophageal cancer. The presence of gross mediastinal invasion or distant metastases obviates the need for ES. In their comparisons of T and N staging by CT and ES, Holden and colleagues reported T-stage accuracy for CT was 40% and 87% for ES; N-stage accuracy was 33% for CT and 73% for ES. Saunders et al also published a recent review of radiologic staging methods.

Endosonography

Ultrasound endoscopes currently are available with radial sector or linear array scanning configurations. These instruments are similar in design to standard diagnostic endoscopes but are more expensive and electronically complex. The ES procedure involves first a diagnostic endoscopy to confirm the surface features and location of the lesion, followed by passage of the ultrasound endoscope. Procedure time averages approximately 90 minutes for premedication and performance of both procedures. The risks are similar to those of standard endoscopy.

ES permits systematic and detailed examination of the esophageal wall, adjacent organs, vessels, and regional lymph nodes. The relatively high frequencies of ultrasound (7.5 to 12 MHz) now possible with current ultrasound endoscopes that have a 360° sector or linear array scanning capability provide excellent imaging of the four-layer wall structure and the adjacent adventitia of the esophagus. It can determine penetration of cancer into the various layers, adjacent organs, and especially periesophageal, celiac, and perigastric lymph nodes (Figs 2–5). Transendoscopic ultrasound probes with 12 or 20 MHz frequencies are under investigation and are proving helpful for staging intramucosal cancer and tight malignant strictures. However, these probes have a limited number of uses and are expensive.
Fig 2C. — ES image of esophagus, normal esophageal wall, several millimeters proximal to the abnormal wall shown in Fig 2B.

Fig 3A. — Endoscopic view of a rectal edematous adenocarcinoma associated with a columnar-lined Barrett’s esophagus.

Fig 3B. — ES image of the lesion showing thickening and distortion of the mucosa and submucosa, as well as involvement (arrow) but not penetration of the hypopharyngeal mucosal propria. An 8-mm round, smooth, hyperechoic lymph node suggestive of a nodal metastasis is at the 1 o’clock position. The lesion was staged T3, N1 by ES.

Fig 4A. — Endoscopic view of an ulcerated adenocarcinoma in the distal esophagus associated with a columnar-lined (Barrett’s) esophagus.

Fig 4B. — ES image of the lesion at the 24 cm level with destruction of all wall layers and invasion through the muscular propria, coming into the periesophageal adventitia (ES).

Fig 4C. — ES image at the 30-cm level showing a large 2.5 cm hyperechoic, oblong, smooth-margin lymph node and several smaller nodes in its vicinity. The lesion was staged T3, N1 by ES.
Transendoscopic needles have been developed to permit intramural and extramural aspiration cytology of tumor masses and lymph nodes. Though still investigational, these techniques may further improve the staging accuracy of ES.

**TNM Staging by Endosonography**

The 1992 version of the TNM system generally has been accepted as the best staging classification\(^8\) (Table 1). The staging accuracy of ES is greatest for depth of tumor invasion (T), intermediate for lymph node involvement (N), and inadequate for assessment of distant metastases (M). The high frequencies used provide excellent definition of the wall layers, but the range of effective ultrasound transmission is limited. Thus, the technique is of little value in determining distant metastases except for celiac axis region lymphadenopathy.

<table>
<thead>
<tr>
<th>Table 1 — System for Staging Esophageal Cancer</th>
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<tr>
<td><strong>Primary Tumor (T)</strong></td>
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<tr>
<td>T1. Primary tumor cannot be assessed</td>
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<tr>
<td>T2. No invasion of primary tumor</td>
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<tr>
<td>T3. Invasion to prepyloric submucosa</td>
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<tr>
<td>T4. Invasion to muscularis or submucosa</td>
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<td><strong>Regional Lymph Nodes (N)</strong></td>
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<tr>
<td>N0. No regional lymph nodes metastases</td>
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<tr>
<td>N1. Regional lymph node metastases</td>
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<tr>
<td><strong>Distant Metastases (M)</strong></td>
</tr>
<tr>
<td>M0. No distant metastases</td>
</tr>
<tr>
<td>M1. Distant metastases</td>
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Tio et al\(^{13}\) reported the results of ES and CT in the preoperative staging of esophageal carcinoma using the TNM system preoperatively in 74 patients with esophageal cancer. They found the overall accuracy of ES to be 89% and CT to be 59%. There was a remarkable discrepancy between ES and CT in the assessment of regional lymph nodes with an overall accuracy of ES of 80% compared to 51% for CT. As the depth of tumor infiltration progressed, the incidence of lymph node metastases also increased. Esophageal stenosis prevented passage of the instrument in 26% of their patients. This resulted in an incomplete examination and provided an edge for CT, especially in the diagnosis of celiac lymph node metastases. In those patients in whom the endoscope could not be passed, the overall accuracy for CT for celiac lymph node metastases was 82% compared to 68% for ES.

Recent reviews presented evidence from several countries that documents the high accuracy rates for ES in locoregional staging of esophageal cancer.\(^{6,10,19}\) In a review of 21 reports, the average accuracy for T and N staging by ES was 84% and 77%, respectively.\(^{19}\)

In a review of 15 reports by Rosch,\(^{19}\) the mean accuracy of locoregional staging by ES was broken down by stage as follows: T1 - 80.5%, T2 - 76%, T3 - 92%, T4 - 86%, N0 - 69%, and N1 - 89%. The results of understaging and overstaging in relation to T stages in 11 reports are shown in Table 2. (Please see printed version of journal.)\(^{19}\)

**Esophageal Obstruction and Pre-endosonography Dilation**
Esophageal stenosis due to cancer has been a limiting factor for accurate staging. One report indicated that esophageal stenosis prevented a complete examination in 16% of cases. In most reports, the inability to pass the instrument beyond a malignant stricture is found in 26% to 62.5% of cases. Peroral esophageal dilation reduces this hindrance, and if properly performed by gradual dilation in one or more sessions before ES, a more complete examination can be done. Because dilation risk is higher when a severely obstructing carcinoma is dilated at the same session followed by ES, some have recommended that dilation not be done before ES. The concern here should be more with assuring better dilation technique than with dilation before ES.

Kallimanis et al reported that ES either alone or after dilation is a safe procedure. The records of 63 patients with esophageal cancer who underwent ES were evaluated to investigate the risk of pre-ES dilation and its potential advantage in permitting a complete examination beyond the obstructing lesions. Thirty-nine patients (62%; group I) had lesions that allowed passage of the ultrasound endoscope, 10 patients (16%; group II) had lesions that did not permit passage of the scope after dilation, and 14 (22%; group III) had lesions dilated adequately to permit complete ES staging. All patients in groups II and III had the ES staging confirmed by CT and/or surgery, and no complications were encountered in any group. Based on this report and our experience over the past 11 years, properly performed esophageal dilation before ES usually permits a complete examination and is a safe procedure.

ES has proven helpful for triage of esophageal carcinoma into three groups: (1) local resectability, with a clearly demarcated intramural lesion without deep adventitial invasion and no distant node involvement, (2) palliative resectability, when distant node involvement is present, and (3) nonresectability, when there is deep adventitial invasion or invasion of contiguous organs, usually in association with widespread nodal involvement. Tio et al reported local resectability was correctly predicted in 5 of 6 esophageal cancers. ES accurately determined palliative resectability in 11 of 13 cancers and nonresectability in 6 of 7 cancers. As with other imaging methods, the staging errors found in this report were primarily the result of a failure to correctly differentiate inflammatory changes in lymph nodes from metastases.

In a recent study from Italy, 55 patients with squamous cell cancer of the esophagus were examined by ES. Forty of these patients subsequently had surgical exploration that provided the basis for determining the staging accuracy of ES vs CT. T stage was correctly defined in 36 (90%) of the 40 patients by ES compared to 20 patients (50%) by CT. Lymph node involvement was correctly diagnosed in 20 (87%) of 23 patients by ES compared to 39% by CT.

Murata et al reported the following ES criteria for lymph node metastasis: spherical or round shape, distinct border, and heterogeneous echogenicity or spots within the nodes. These criteria yielded a sensitivity of 87%, a specificity of 90%, and an overall accuracy of 89% based on comparison of ES and histology of resected lymph nodes. Other ES criteria suggestive of metastasis in lymph node sizes are diameter greater than 10 mm and a homogeneous, diffuse hypoechoic image. Normal lymph nodes typically have homogenous echogenicity and irregular borders, often have angular shapes, and are less than 1 cm in maximum diameter. However, size alone, especially for lymph nodes less than 1 cm, is not a reliable criterion for absence of metastasis.

Francioni et al recorded the size and site of 267 lymph nodes at the time of operation. They found the range of size of lymph nodes with metastasis to be great and not too different from the range for normal lymph nodes. In order to develop diagnostic criteria for abnormal lymph nodes, they compared size as well as intrinsic and extrinsic echo characteristics. The accuracy of lymph node diagnosis was approximately 80% when their criteria were used.

Significant problems remain with ES both in detecting lymph node presence and in determining benign from malignant involvement. Tytgat and Tio demonstrated in in vitro and pathologic studies that lymph nodes less than 5 mm on ES were not likely to be malignant, but it has been shown that micrometastases in such small nodes are missed. Another problem is that all malignant lymph nodes are not imaged. Abe and colleagues reported the detection of 43% of periesophageal lymph nodes larger than 5 mm and 58% of nodes larger than 10 mm. Forty-eight percent of regional lymph nodes greater than 10 mm and round in contour were malignant.

Murata et al reviewed the value of ES in the assessment of the extent of tumor invasion. In 173 cases of esophageal cancer, the depth of the cancer invasion was diagnosed correctly in 88%. In evaluation of lymph node metastases according to their own criteria, ES had a sensitivity of 84%, a specificity of 88%, and an overall accuracy of 88%.

Brugge et al recently reported that measurement of the maximal thickness (overall and extrasophageal) of a malignant esophageal mass by ES may be more accurate (91% for overall and 94% for extrasophageal) than the usual subjective assessment (muscularis propria disruption and irregular mass border) for staging T3 and T4 lesions (73%) (P<0.07).

ES presents problems in differentiating mucosal and submucosal cancer and in recognizing lymph node metastases in early esophageal cancer. Also, detection of invasion of the tracheobronchial system is a weak area for ES. Tracheobronchoscopy is the most accurate staging method for tracheobronchial invasion, with CT a distant second. The accuracy of ES for tracheobronchial staging is low, especially when nontraversable tumors are studied. Tracheobronchoscopy should be performed for staging all cases of cervical and thoracic esophageal carcinoma.

Endosonography for Cancer Recurrence

Lightdale et al reported the use of ES in an evaluation of 40 patients who had undergone resection of esophageal and gastric cancer and presented with symptoms suggesting recurrence. They found 24 of the 40 patients to have recurrent cancer in the area of the surgical anastomosis based on endoscopic biopsy in 16, repeat endoscopy in 2, and surgery after negative endoscopy in 6. Sixteen patients had no anastomotic recurrence. With ES, locally recurrent cancer was identified by nodular hypoechoic thickening at the anastomosis in 23 of 24 patients, with only 1 false negative. Absence of anastomotic recurrence was correctly diagnosed in 13 of 16 patients, with 3 false positives (sensitivity, 95%; specificity, 80%; positive predictive accuracy, 88%; and negative predictive accuracy, 82%). Other reports have confirmed the value of ES in assessing the posttherapy status of esophageal cancer.

Catalano et al reported the use of ES for detection of anastomotic recurrence in 30 asymptomatic and 10 symptomatic patients who had previously undergone resection of esophageal cancer. Anastomotic recurrences were found in 3 (10%) of the 30 asymptomatic patients. Standard endoscopy identified only one of these recurrent lesions, and CT did not detect any. One false-positive diagnosis by ES was due to presence of concentric hypertrophy of the esophageal wall near the anastomosis. Four of the 10 symptomatic patients were diagnosed correctly by ES, with tumor recurrence providing 100% sensitivity and specificity, as did esophagoscopy with biopsy.

Fockens and coworkers investigated the role of ES performed every six months for early detection of postoperative recurrent cancer. After exclusion of the finding of regional-free fluid, the positive predictive value of abnormalities on ES was 92%. Two thirds of patients were without symptoms when recurrences were found. The clinical value of early diagnosis of cancer recurrence by ES is yet to be determined.

Chak et al reported a US multicenter study of prognosis of esophageal cancers staged preoperatively as T4 by ES, ES was significantly more accurate than CT for T4 staging (87.5% vs 43.8%, respectively) (P=0.0002). Of a total of 79 patients studied, 42 had surgery and 37 had no surgery. The median survival times for these
two groups were 5.2 and 7.0 months, respectively (P=0.50). Surgical treatment of T4 lesions did not influence survival compared with other palliative methods.

The technique of esophageal cancer surgery has been developed in Japan and China for removal of early (intramucosal) esophageal cancer. ES is playing an essential role in staging and patient selection for use of this therapy. High-frequency (20 MHz) transendoscopic ultrasound probes appear especially useful for this purpose.30,31

Conclusions

Although problems with ES accuracy occur in some aspects of staging carcinoma of the esophagus, ES is recognized in most centers and in current research protocols as an essential procedure in the TNM staging of these malignancies. Current research protocols on therapy of esophageal cancer neoadjuvant/radiation therapy with or without surgery should include ES as an essential step in complete staging. Availability of ES is currently limited to academic centers where these research protocols are conducted, but some studies still do not require its application. The definitive study with a sufficiently large number of cases followed for five years to evaluate the true role and impact of ES on stage-dependent treatment protocols is yet to be performed.

The strengths of ES are its ability to accurately determine the layer depth of mural infiltration and to detect metastatic involvement of regional lymph nodes. Its weaknesses are inability to identify distant metastases, to examine beyond a significant number of obstructing tumors unless dilation is done, and to differentiate inflammation from malignant infiltration of wall layers or in lymph nodes because of the similarity of echogenic patterns of these two pathologic processes. Lymph node size is of little help since many reports indicate that histopathology of large nodes is often due to inflammation and small nodes may contain micrometastases. Overstaging by ES may occur due to inflammation and preoperative radiation effects. Ulcerating carcinomas tend to be associated with the most inflammation and hence are often overstaged. The most obvious cause of understaging is the inability to do a complete examination because the instrument can not be passed through a stenotic lesion in the esophagus. Proper dilation in one or more sessions prior to the scheduled ES will overcome this hindrance in most patients.

ES has proven to be an accurate method for staging esophageal cancer and should be used with CT as a component of all staging methods. The value of combining ES and CT has been reported by Botet and colleagues,32 who found a higher accuracy rate of 86% in TNM staging than when either modality was used alone. A recent consensus conference recommended that CT scan be used first to confirm or exclude distant metastases. If no distant metastases are identified, ES should be used for local T and N staging.17

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References


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