The prognosis for patients with carcinoma of the esophagus remains poor despite the recent use of aggressive combination therapies and radical surgical resection. Attempts to improve the survival of patients with esophageal carcinoma have been confounded by a lack of effective therapeutic options in the later stages of the disease and an inability to accurately identify the early disease stages. Endoscopic ultrasound is a novel technique that affords close-proximity imaging of the esophageal wall and its adjacent structures. Endosonography is superior to CT scan for assessing depth of tumor penetration (T stage) and lymph node status (N stage). Recent advances in endoscopic ultrasonography include the ability to perform ultrasound-guided fine-needle aspiration of mediastinal masses and lymph nodes. Therefore, endosonography is ideally suited for staging esophageal cancers.

(CHEST 1997; 112:184S-190S)

The prognosis for patients with carcinoma of the esophagus remains poor despite aggressive combination therapies and radical surgical resection. Attempts to improve the survival of patients with esophageal carcinoma have been confounded by a lack of effective therapeutic options in the later stages of the disease and an inability to accurately identify the early disease stages. Ultrasound technology is a powerful diagnostic technique when applied to medical practice. Endoscopic ultrasonography (EUS) combines the access of endoscopy with the diagnostic versatility of ultrasonography to offer perhaps the most noteworthy advance in GI endoscopy during the last decade. This novel technique affords close-proximity imaging of the GI tract and provides detailed images of the esophageal wall and its adjacent structures. Therefore, endosonography is ideally suited for staging esophageal cancers.

Using endosonography, the GI tract wall may be imaged as a five-layered structure of differing echogenicities (alternating hyperechoic and hypoechoic layers), although some high-frequency ultrasound transducers may image additional layers. The endosonographically imaged layers correspond generally with mural histology. Cystic structures are readily identified by endosonography both in the esophagus and elsewhere in the GI tract. The thickness of the layers of the normal GI tract are not an exact measure of histologic thickness because the EUS images are a measure of time and not simply distance.

Ultrasound thickness represents the time required for an ultrasonic pulse emitted by a transducer to travel to and return from a reflective tissue interface, rather than the actual distance between tissue and transducer. Time (t) is related to distance (d) by the equation d = v t, where v is the velocity of sound in the tissue being imaged. Moreover, sound wave velocity varies with the acoustic impedance of each portion of the GI tract. Interpretation of endosonographic images therefore requires an understanding of the physical characteristics of ultrasound as well as a knowledge of three-dimensional anatomy.

STAGING

The approach to tumor staging is not a fixed science, but rather a dynamic process. Historically, as more was learned about the natural history of specific cancers, and as new technologies became available to diagnose and treat tumors, the classification and staging of cancer have been amended to take advantage of such modern advances (eg, the various modifications of the Dukes’ classification for staging colorectal cancer). The American Joint Committee on Cancer and the International Union Against Cancer collaborated on a uniform classification system of malignancy, including esophageal cancer, which was finalized in 1987. The result of this endeavor was the formulation of the new TNM classification for esophageal cancer in which T refers to depth of penetration of the primary tumor into or through the GI tract wall, N refers to status of regional lymph nodes with regard to malignant involvement, and M refers to presence or absence of distant metastases. The depth of tumor penetration and the existence of lymph node metastases are the most important factors for determining the prognosis and mode of treatment for patients with esophageal carcinoma. Involvement of nonregional lymph nodes (eg, malignant involvement of celiac axis lymph nodes) in patients with cervical esophageal carcinoma is considered metastatic disease (M1). Once classified, tumors are staged at all anatomic locations from stage 0 (best prognosis) to stage IV (poorest prognosis).

ENDOSONOGRAPHIC EVALUATION OF DEPTH OF TUMOR PENETRATION (T STAGE)

Endosonography is highly accurate and superior to CT scan for the preoperative staging of esophageal carcinoma8-23 (Tables 1-8, 15-28, and 19,29,30) (Figs 1-3). However, endosonography is not a substitute for CT scan but rather a useful adjunct for the preoperative staging of esophageal cancer. There is a learning curve for the endosonographic staging of esophageal tumors, as noted by Rice et al. The accuracy for preoperative T staging in their first 28 cases was 59% but improved to 81% in the next 52 patients evaluated.

Endosonography is accurate in identifying the early stages of disease and in detecting advanced, nonresectable esophageal carcinoma. The differentiation of mucosal and submucosal disease in early esophageal cancer (T1) is problematic and leads to overstaging in some cases. Assessment of vascular involvement in patients with esophageal cancer has important implications regarding...
the approach to therapy. When compared with CT scan, endosonography provides a more sensitive and reliable determination of local vascular involvement.33

ENDOSONOGRAPHIC EVALUATION OF LYMPH NODE METASTASES (N STAGE)

The endosonographic assessment of lymph node metastases has been shown to be more accurate than CT scan (Tables 324,26,37,34 and 418,20,30) (Figs 4, 5). However, the precise differentiation of malignant from benign lymph nodes remains problematic. Unlike CT scan, which can determine only lymph node size, endoscopic ultrasonography provides additional information, including lymph node shape, border characteristics, and central echogenicity.34 However, micrometastases, currently detectable only by histologic evaluation, may not produce endosonographically detectable changes leading to understaging, and large-sized, inflammatory lymph nodes may be incorrectly classified as metastatic and therefore overstaged. Attempts to classify lymph nodes by specific endosonographic features have improved the accuracy of lymph node classification but are cumbersome, subjective, and have not yet been widely studied.35,36 Heintz et al37 used computer-supported B-node analysis (Program Microscale; Digithurst; Nuremberg, Germany) to evaluate lymph node characteristics in vitro on resected specimens of patients with esophageal and gastric carcinoma. However, subjective evaluation or computer analysis did not reliably distinguish benign from malignant lymph nodes.37 A recognized association between depth of tumor penetration (T stage) and lymph node metastasis (N stage) may aid in reliably predicting lymph node metastases. In a review of the association between T stage and N stage for 103 patients with surgically resected specimens of esophageal carcinoma, lymph node involvement (percent) increased with depth of tumor penetration as follows: Tis (tumor in-situ) (n=4) N1 (0%); T1 (n=14) N1 (14.3%); T2 (n=18) N1 (33.3%); T3 (n=60) N1 (73.3%); T4 (n=7) N1 (85.7%).38 Similarly, in their series of >400 cases, Dittler et al39 viewed the accuracy of endosonography for assessing lymph node metastases and noted that the incidence of lymph node metastases increased with advancing T stage (T1, 4%; T2, 52%; T3, 82%; T4, 91%). Therefore, tumor

<table>
<thead>
<tr>
<th>Source</th>
<th>No. of Patients</th>
<th>Accuracy, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rice et al24</td>
<td>28</td>
<td>59</td>
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<tr>
<td>Souquet et al18</td>
<td>82</td>
<td>77</td>
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<td>Fok et al25</td>
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<td>82</td>
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<tr>
<td>Grimm et al30</td>
<td>63</td>
<td>86</td>
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<tr>
<td>Dittler and Siewert27</td>
<td>167</td>
<td>86</td>
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<tr>
<td>Binnmoeller et al23</td>
<td>38</td>
<td>89</td>
</tr>
<tr>
<td>Grimm et al25</td>
<td>57</td>
<td>90</td>
</tr>
</tbody>
</table>

*Compared with histopathologic staging of the resected specimen.

FIGURE 1. A 71-year-old man with a cancer at the gastroesophageal junction discovered incidentally while undergoing endoscopy for dyspepsia. The hypoechoic tumor shown in the endosonogram penetrated into the submucosa but not beyond (T1). There were no malignant-appearing lymph nodes detected by EUS (N0). The typical five-layer endosonographic appearance of the normal esophageal wall is shown in the upper right quadrant of the endosonogram, opposite the tumor. The patient underwent surgical resection. Surgical pathologic assessment revealed a 1.5-cm T1 tumor with no muscularis propria involvement. Twelve lymph nodes were harvested and assessed, and none was found to be positive for malignancy (T1N0).

Table 2—Endosonography Compared With CT Scan for Preoperative T Staging of Esophageal Carcinoma

<table>
<thead>
<tr>
<th>Source</th>
<th>No. of Patients</th>
<th>EUS, %</th>
<th>CT, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hordijk et al20</td>
<td>41</td>
<td>76</td>
<td>49</td>
</tr>
<tr>
<td>Kalantzis et al30</td>
<td>28</td>
<td>82</td>
<td>50</td>
</tr>
<tr>
<td>Chak et al22</td>
<td>79</td>
<td>87</td>
<td>43</td>
</tr>
<tr>
<td>Tio et al20</td>
<td>74</td>
<td>89</td>
<td>59</td>
</tr>
</tbody>
</table>

FIGURE 2. A 61-year-old man with adenocarcinoma of the esophagus. Endoscopy showed a 4-cm-long tumor in the lower one third of the esophagus. The endosonogram obtained at 39 cm from the incisor teeth showed a 2.5×4.0-cm tumor that did not penetrate beyond the muscularis propria (T2).
involvement of lymph nodes increases with advancing T stage and may be one of the most sensitive indicators of lymph node metastases.38,39

ENDOSCOPIC ULTRASOUND-GUIDED FINE-NEEDLE ASPIRATION

Endosonography is not equivalent to histologic assessment of sampled tissue, however, and the knowledge that lymph node tumor involvement increases with depth of tumor penetration provides only an indirect or statistical advantage to determining tumor stage. Newer, more direct approaches to regional lymph node evaluation include EUS-guided fine-needle aspiration (FNA) of suspicious lymph nodes. The ultrasound endoscope (Pentax/Hitachi FG-32UA; Pentax Precision Instruments; Orangeburg, NY) is designed to permit ultrasound scanning parallel to the long axis of the insertion tube and, thereby, ultrasound-guided tissue sampling. Preliminary reports using this system are promising, and the safety and efficacy of this exciting new technology require additional study.40,41 Wegener et al41 used EUS-guided FNA in 12 patients with extrinsic mass lesions adjacent to the gastrointestinal wall. A malignant lesion was identified in seven patients and a benign lesion in four patients. There were no complications with this procedure.

The most accurate and effective approach to esophageal tumor staging is the combination of endosonography and CT scan. Using this approach, CT scan should be performed first to detect distant metastases (M stage). If no distant metastases are detected, endosonography should be performed to determine depth of tumor penetration and the presence of regional lymph node adenopathy (T, N stage). If FNA is available, cytologic confirmation of endosonographically suspicious lymph nodes should be obtained.

ENDOSONOGRAPHIC EVALUATION AFTER MEDICAL/SURGICAL THERAPY

Despite improved surgical technique and preoperative and postoperative adjuvant therapy, recurrence of disease remains the most common cause of mortality in patients with esophageal cancer. Methods for patient surveillance after surgery and/or adjuvant therapy include patient history (dysphagia, weight loss, etc), upper GI contrast radiograph (barium swallow), endoscopy with biopsy, and CT scan. Endosonography has been used with variable success to detect residual tumor infiltration in the absence of endoscopic lesions after medical treatment of esophag-
geal cancer.42,44 Nousbaum et al42 studied 34 patients with inoperable esophageal cancer using endosonography and CT scan prior to treatment. In this study, patients were considered to have inoperable conditions because of distant metastasis (50%), poor general condition (42%), or concurrent cancer (8%). Ten patients receiving chemotherapy and radiation therapy had complete resolution of endoscopically detectable tumor, including endoscopic biopsy specimens negative for residual tumor. Combination therapy consisted of chemotherapy (three cycles of fluorouracil [5-FU], 800 mg/m²/d for 5 days and cisplatin, 70 mg/m² on day 2 of the cycle) and radiotherapy (three cycles of 3 Gy daily for 5 days). When endosonography suggested the persistence of tumor infiltration in patients who were endoscopically negative and biopsy negative for tumor, local tumor recurrence or distant metastases appeared within a few months. Alternatively, when endosonography failed to detect residual tumor in these patients, no tumor progression or regression was observed within 8 months, suggesting that endosonography is superior to endoscopy with biopsy and CT scan for assessing response of esophageal cancer to therapy.42

In contrast, Dittler et al44 examined 25 patients with T3 esophageal or gastroesophageal junction carcinomas who received either three or six cycles of chemotherapy (etoposide/doxorubicin/cisplatin or cisplatin/leucovorin/etoposide/5-FU) or combined chemotherapy/radiotherapy (5-FU and 30 to 60 Gy of radiation). All patients underwent endosonographic staging prior to and after therapy, followed by surgical resection. In all cases but one (T4), restaging demonstrated the tumor to be a T3 tumor. However, histopathologic examination of the resected specimen after therapy and restaging revealed T0 (no tumor cells) in two cases, T1 in one case, T2 in 12 cases, T3 in seven cases, and T4 in three cases. The authors concluded that endosonographic restaging of esophageal cancers was not a reliable predictor of tumor response to combination chemotherapy/radiation therapy.43

Similarly, Catalano et al44 and Souquet et al18 independently demonstrated that endosonographic surveillance after surgery with or without adjuvant chemotherapy/radiation therapy was limited by imaging artifact. Specifically, interpretation of endosonographic imaging was impeded by hypoechoic esophageal wall thickening resulting from either a surgical artifact in the region of the anastomosis or a benign inflammation or fibrosis.18,44 Despite the presence of imaging artifact, however, Catalano et al44 demonstrated that EUS was more sensitive than upper endoscopy and CT scan for the evaluation of anastomotic recurrence of esophageal carcinoma. Therefore, endosonography appears to be sensitive but relatively non-specific in detecting anastomotic recurrence of esophageal cancer.

**Endosonography in Patients With High-Grade Malignant Strictures**

Most patients with esophageal carcinoma present late in the course of their disease. The relative elasticity of the esophagus and its anatomic location within the chest, free of restricting adjacent organs or bony structures, allows for significant tumor growth before the onset of symptoms. Therefore, patients often remain relatively free of symptoms until the tumor has grown to an advanced stage, at which time it may produce dysphagia, odynophagia, weight loss, or bleeding. Patients with high-grade malignant strictures represent a subgroup of 20 to 37.5% of patients with esophageal carcinoma.42,44 In a recent study of 79 patients with esophageal carcinoma who underwent preoperative staging using EUS,42 21 patients (26.6%) presented with high-grade malignant stricture defined as a tumor obstruction precluding passage of an echoendoscope without prior dilation. Nineteen of the 21 patients (90%) had stage III or IV disease as determined by histopathologic assessment of the surgical specimen. Patients with high-grade malignant stricture were significantly more likely to have a relatively advanced disease stage (stage III or IV) (p<0.05) when compared to patients presenting with less severe malignant strictures, who were subsequently found to have a

**Table 5—Percentage of Patients Presenting With High-grade Malignant Strictures, Precluding Passage of the Echoendoscope**

<table>
<thead>
<tr>
<th>Source</th>
<th>Total No. of Patients</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rice et al 44</td>
<td>28</td>
<td>21.0</td>
</tr>
<tr>
<td>Grimm et al 28</td>
<td>67</td>
<td>21.0</td>
</tr>
<tr>
<td>Catalano et al 46</td>
<td>204</td>
<td>25.0</td>
</tr>
<tr>
<td>Tio et al 20</td>
<td>74</td>
<td>26.0</td>
</tr>
<tr>
<td>Van Dam et al 47</td>
<td>79</td>
<td>26.6</td>
</tr>
<tr>
<td>Kalantzi et al 30</td>
<td>28</td>
<td>28.5</td>
</tr>
<tr>
<td>Dittler et al 27</td>
<td>253</td>
<td>30.0</td>
</tr>
<tr>
<td>Grimm et al 26</td>
<td>63</td>
<td>31.6</td>
</tr>
<tr>
<td>Fok et al 25</td>
<td>89</td>
<td>36.0</td>
</tr>
<tr>
<td>Hordijk et al 34</td>
<td>41</td>
<td>36.4</td>
</tr>
<tr>
<td>Dancygier et al 46</td>
<td>38</td>
<td>37.5</td>
</tr>
</tbody>
</table>
relatively earlier disease (stage 0, I, or II). Therefore, the presence of malignant strictures severe enough to prevent passage of the echoendoscope represents an important prognostic factor.

Attempts to stage esophageal tumors from the region proximal to a stenosis (incomplete staging) has poor accuracy, usually <50%. Most (but not yet all) endosonographers now agree that esophageal dilatation to facilitate passage of the echoendoscope for staging is not warranted and poses a risk of esophageal perforation that outweighs the benefit of staging.

Alternative strategies for staging tumors with malignant strictures include high-frequency (20 MHz) ultrasound probes and newly designed nonoptical esophagoprobe. Grimm used a wire-guided endosonographic probe (7.5-MHz transducer; 7.9-mm outer diameter) to evaluate 41 patients with high-grade malignant strictures. The results demonstrated the probe to be safe and useful in that the tumor, esophageal wall layers, and regional lymph nodes could be visualized in all patients with no complications reported. In a similar study, Binmoeller et al evaluated the nonoptical esophagoprobe for use in highly stenosing esophageal carcinomas. Eighty-seven consecutive patients with high-grade malignant strictures were evaluated using the prototype probe. The esophagoprobe was successfully passed in all patients, although nine patients (10%) required preliminary bougienage to 33F. T-stage accuracy in 38 patients in whom surgical correlation was available was 89%. Souquet et al successfully used a high-frequency ultrasound miniprobe in 10 of 11 patients in whom preoperative endosonography using the dedicated echoendoscope could not be performed due to stenosing tumors. However, in this report, the limited depth of penetration provided by the miniprobe precluded correct classification of many periesophageal lymph nodes. In another study of patients evaluated using a high-frequency endosonographic probe, 13 of 14 patients were staged preoperatively as having at least a T2 tumor when the cancer was demonstrated to penetrate through the muscularis propria. McLoughlin et al used the high-resolution, 20-MHz, catheter-based ultrasound transducer to examine 14 of 15 patients with esophageal carcinoma. Of seven patients in whom surgical correlation was available, the high-frequency probe correctly staged the tumor in six patients. Continued refinement of ultrasound probes may eventually yield a tool capable of reliably staging tumors not evaluable by dedicated echoendoscopes. However, at the present time, most institutions are without these prototype instruments and high-resolution catheter-based systems.

**IMPACT OF ENDOSONOGRAPHIC EVALUATION OF PATIENTS WITH ESOPHAGEAL CARCINOMA**

Endosonography provides accurate pretherapeutic staging information, which aids both in the prognosis of patients presenting with variable stages of esophageal carcinoma and in posttreatment evaluation. Accurate preoperative staging of esophageal cancer is useful only if the results of such staging have an impact on treatment. When surgery is considered the only therapeutic option, patients benefit from endosonographic evaluation only when the results of such evaluation demonstrate advanced disease that precludes surgery. EUS is not useful when palliative treatment aimed at relieving dysphagia is the only measure under consideration.

EUS has been shown to predict survival in patients who undergo combined brachytherapy and external radiation. In such patients, lymph node abnormalities and tumor thickness were closely related to survival.

EUS has been shown to accurately predict the outcome of patients undergoing surgery for cancer of the esophagus or gastroesophageal junction. In a prospective analysis of 86 patients who underwent preoperative staging using EUS, patients with no endosonographic evidence of regional lymph node metastases (N0; n=17) had a median survival of 28 months, whereas patients who were endosonographically determined to have lymph node metastases (N1; n=60) had a median survival of 10 months, and patients in whom celiac axis lymph node metastases were detected by endosonography (M1; n=13) had a median survival of 3 months. Thus, the outcome for patients with esophageal or gastroesophageal junction cancer is strongly related to the results of endosonographic staging.

Chak et al conducted a multicenter retrospective evaluation of patients in whom EUS demonstrated esophageal tumor to be locally invasive (T4 disease). Of 79 patients included in the study, 42 were treated surgically (including preoperative multimodality treatment in many instances) and 37 were treated using nonsurgical therapies (radiotherapy, chemotherapy, esophageal dilation, esophageal endoprosthesis placement, or laser ablation). EUS was significantly more accurate than CT scan at detecting tumor invasion of adjacent structures (T4) (87.5% vs 43.8%, respectively). Overall mortality was not significantly different between treatment groups at 6-month follow-up (60% mortality for the surgically treated group vs 65% for the nonsurgically treated group). Survival curves for both groups were found to be virtually overlapping. Thus, EUS identified patients with T4 disease significantly more accurately than CT scan and predicted a poor prognosis irrespective of treatment modality.

When effective treatment options for patients with T4 esophageal carcinoma are not available, EUS can predict a poor outcome and avoid costly surgical intervention, thereby reducing morbidity and conserving diminishing health-care resources.

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