RADIOLOGIC STAGING OF ESOPHAGEAL AND GASTROESOPHAGEAL JUNCTION CARCINOMA

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Radiologische stagering van oesofagus- en cardiacarcinoom

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Chapter 1

Introduction

Esophageal and Gastroesophageal Junction Carcinoma

1.1 Anatomy

The esophagus is a muscular tube that connects the pharynx to the stomach. In craniocaudad direction it passes through the neck, the posterior mediastinum and the diaphragm, to terminate in the gastroesophageal junction. Here the esophageal tube transforms into the pouch of the stomach [1-3].

The relationship of the esophagus to adjacent anatomical structures is as follows. In the neck, the esophagus lies anterior to the prevertebral fascia and posterior to the trachea. In the thorax, the esophagus is bounded on the right side by the mediastinal pleura, lung and azygos arch, and on the left side by mediastinal pleura, lung, aorta and pulmonary artery. In the upper mediastinum, the vertebral bodies lie posterior to the esophagus, anterior are the trachea and left recurrent laryngeal nerve. In the middle mediastinum, the thoracic duct and azygos vein lie posteriorly and to the right of the esophagus, the spine lies posteriorly and the carina and bronchi lie anteriorly. In the lower mediastinum, the aorta lies between the esophagus and vertebral column, anterior to the esophagus is the pericardium. At the esophageal hiatus, the esophagus is most commonly surrounded by the right diaphragmatic crus. In the abdomen, the left lobe of the liver lies anterior to the esophagus and gastroesophageal junction. The caudate lobe of the liver lies to the right and the fundus of the stomach to the left [1-3].

The esophageal and gastroesophageal wall consists of the following layers (Fig 1.1): the mucosa, lined with a thick layer of nonkeratinizing stratified squamous epithelium in the esophagus. The gastroesophageal junction is marked by an irregular boundary between this epithelium and simple columnar epithelium. The submucosa, a layer of loose connective tissue. The muscularis propria (externa). The serosa is the outer layer of the wall of the intraabdominal esophagus and gastroesophageal junction. The wall of the intrathoracic esophagus does not contain a serosa but is covered by an adventitia, loose connective tissue of the mediastinum [1-3].

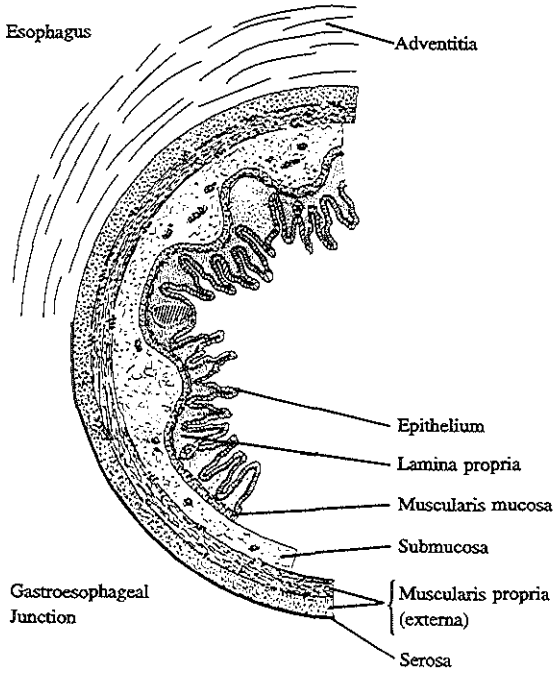

Figure 1.1 Layers of the wall of the esophagus and gastroesophageal junction.

1.2 Pathogenesis

In western countries the incidence of esophageal carcinoma is relatively low [4]. France has the highest incidence rate in Europe [4,5]. In the Netherlands, esophageal carcinoma comprise about 1.5% of all malignant tumors [6]. The estimated annual incidence of esophageal carcinoma in the Netherlands is 4.4 per 100,000 men and 2.5 per 100,000 women [6]. The true incidence of gastroesophageal junction carcinoma is less well known because it is frequently impossible to determine the exact site of origin of tumors in this area, and many authors do not distinguish tumors of the gastroesophageal junction from those of the esophagus and other parts of the stomach in their reports [7]. In a recent study from the south part of the Netherlands the incidence of gastroesophageal junction carcinoma was reported to be slightly higher than for esophageal carcinoma [6].

The risk of developing esophageal and gastroesophageal junction carcinoma increases with age and the majority of patients are in the sixth and seventh decade [6-9]. In France and other European countries, alcohol and tobacco are important factors in developing esophageal carcinoma. Dietary factors seem to play an important role in Iran, Northern China and the Transkei region of South Africa where a high incidence of esophageal carcinoma is observed [8,9]. Also associated with an increased risk of esophageal carcinoma is Barrett's esophagus. The estimated risk of esophageal cancer in such patients is 30-40 fold above that in the general population [10]. Other factors possibly associated with esophageal and gastroesophageal cancer are achalasia and lye strictures [8,9].

1.3 Pathology

The majority of malignant tumors in the esophagus are squamous cell carcinomas. Adenocarcinomas are reported to account for 1-24% of all esophageal cancers [11-14], an important number of these tumors arise in patients with Barrett's esophagus [10]. The great majority of gastroesophageal junction tumors are adenocarcinomas. Other tumors such as undifferentiated carcinoma, leiomyosarcoma, rhabdomyosarcoma and carcinosarcoma of the esophagus and gastroesophageal junction are rare [11].

1.4 Routes of spread

Spread of esophageal and gastroesophageal junction carcinoma may occur via direct extension, lymphatic spread or hematogenic metastases.

Direct extension

Carcinomas of the esophagus and gastroesophageal junction are usually well advanced at the time of diagnosis. Of 224 esophageal and gastroesophageal junction carcinomas resected in Rotterdam during the period 1978-1984, only 82 (37%) were confined to either the mucosa or submucosa [15].

According to some authors, spread of esophageal carcinoma into the surrounding mediastinum is facilitated by the fact that the esophagus lacks a serosa and is separated from neighbouring structures by only a loose adventitia [8,16]. Autopsy studies report invasion of the trachea in 13-32%, the bronchi in 16-17%, the pleura in 4-17%, the pericardium in 1-13%, the aorta in 3-18% and the diaphragm in 19% of patients, respectively [5,9,17].

Lymphatic spread

The lymphatic network of the esophagus is primarily longitudinally. Sakata was one of the first to report this and to describe lymphatic vessels in the mucosa and muscularis that run long longitudinal courses. He also reported that lymph drainage occurred in a cranial direction in the upper and middle part of the esophagus, some of these vessels went directly to nodes in the supraclavicular fossa. In the lower part of the esophagus, lymph drainage occurred in a caudad direction [18].

McCort pointed out that drainage to unexpected sites may occur when normal pathways become blocked and collateral circulation opens up [19]. Groups of lymph nodes draining the esophagus and gastroesophageal junction are illustrated in Figure 1.2. Due to the rich distribution of lymph vessels and their nonsegmental type of drainage, spread by way of the lymphatics is frequent and the site is unpredictable in esophageal and gastroesophageal junction carcinoma. Lymph node metastases are found in 59-65% of patients with esophageal carcinoma [19-21] and 70-80% of patients with gastroesophageal junction carcinoma [22-24] who undergo surgery. In one series, supraclavicular metastases were found in 27% of patients with esophageal carcinoma who underwent dissections of these nodes [25].

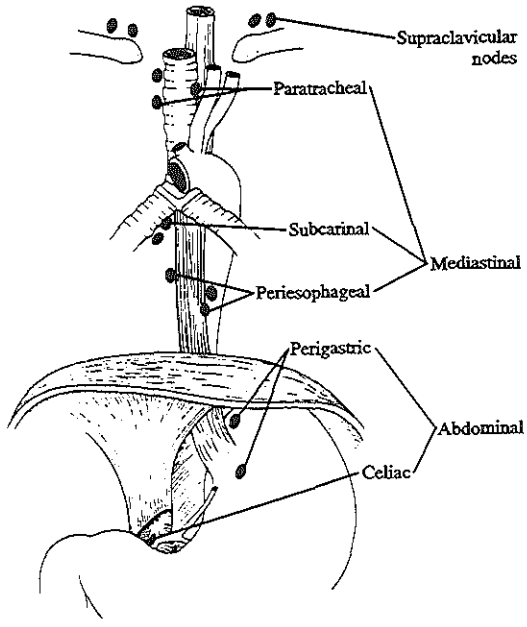

Figure 1.2 Lymph nodes draining the esophagus and gastroesophageal junction.

Hematogenic spread

The venous drainage of the upper two-thirds of the esophagus is to the systemic veins, that of the lower one-third and of the gastroesophageal junction is to the portal system. However, numerous areas of anastomosis exist both on the surface and within the wall of the lower esophagus [3]. Hematogenic metastases are often found in patients with advanced carcinomas. The most frequently involved sites at autopsy are the liver (21-47%), the lung (8-52%), the adrenals (3-20%), the kidney (5-13%), the peritoneum (4-5%) and bone (5-14%) [5,9,17].

1.5 Treatment and Prognosis.

At present, surgical resection of the tumor is generally accepted as the standard treatment for esophageal and gastroesophageal junction carcinoma. There is no unanimous opinion regarding the type and extent of resection to be performed [26]. Whereas some authors recommend radical resections and extensive lymph node dissections [20,21,27], others advocate more limited surgical procedures [22,28,29]. During the last 15 years, an increasing number of surgeons have favoured transhiatal resection without thoracotomy of the esophagus and gastroesophageal junction because this procedure theoretically reduces the operative risk for the patient [30]. Since 1986 this approach has become the standard surgical procedure for esophageal and gastroesophageal junction carcinoma in our institution [31]. The long-term survival of surgically treated patients with esophageal and gastroesophageal junction carcinoma is poor [26,32]. Due to the late onset of symptoms, many of these patients have well-advanced disease at the time of diagnosis and survival rates after resection are negatively affected by an advanced tumor stage [15,21,22,24,27-29]. Involvement of lymph nodes is especially associated with a poor prognosis [20,21], in one series the 5-year survival rates following resection dropped from 48% to 6% in patients with metastatic lymph nodes [33]. A critical review of the results of surgical treatment of esophageal carcinoma was published by Earlam and Cunha-Melo who analyzed the literature on esophageal carcinoma during the period 1953-1978 [32]. They estimated that of 100 patients with the disease, 58 were surgically explored, 39 of 58 (67%) had their tumor resected and 19 (33%) had an irresectable tumor at surgery. Forty-five percent of those resected and leaving the hospital survived for 1 year, 29% for 2 years and 18% for 5 years. The postoperative mortality was 29% for those patients in whom a resection was performed. Müller et al reviewed the literature on esophageal carcinoma during the period 1980-1988 [26]. They estimated that of 100 patients, 56 had their

tumor resected. Fifty-six percent of all resected patients survived for 1 year, 34% for 2 years and 20% for 5 years. The postoperative mortality in their review was 13%. They concluded that since the report of Earlam and Cunha-Melo 10 years previously, the postoperative mortality had been reduced by half but that efforts to improve long-term survival had failed [26]. Furthermore, they did not find evidence that adjuvant radiation therapy or chemotherapy improved either tumor resectability or long-term survival.
Although it is the current opinion that adenocarcinomas of the gastroesophageal junction are unsuitable for radiation therapy, there is no consensus regarding the role of primary radiation therapy in squamous cell carcinoma of the esophagus [34,35]. Pearson et al reported promising results with radiation therapy in these patients, but there has never been a controlled randomized trial of radiation therapy versus surgery [35,36]. Several chemotherapeutic drugs have shown some demonstrable activity in squamous cell carcinomas of the esophagus but their definitive role needs to be determined [37]. At present the prognosis of patients with symptomatic esophageal and gastroesophageal junction carcinoma continues to be poor, regardless of the therapy employed.

1.6 Staging

The goal of preoperative staging in esophageal and gastroesophageal junction carcinoma is twofold. The depth of invasion of the primary tumor and the local resectability should be assessed. Presence or absence of metastases must be evaluated.

Nonradiologic staging

Physical examination is performed to detect metastases. Esophagoscopy is used not only to obtain a tissue diagnosis, but also to determine the upper and lower limits of the tumor and to detect ulceration, fistula and submucosal metastases [9]. Bronchoscopy is used to exclude tracheobronchial invasion [9,38]. Some authors advocate mediastinoscopy to assess mediastinal lymph nodes [39].

Radiologic staging

Lindell et al analyzed the influence of radiographic chest film abnormalities, such as an abnormal azygoesophageal line or a widened mediastinum, on the resectability rate in patients with carcinoma of the esophagus but did not find any of these to be of prognostic value [40]. Esophageal axis deviation on barium studies has been used by Akiyama et al and others to assess resectability [41,42]. Furthermore, craniocaudad extent of the tumor, submucosal metastases and esophageal-airway fistula can be demonstrated on these studies [43]. McCort described the identification of metastatic lymph nodes on barium studies in patients with esophageal carcinoma. He also noted

that metastatic nodes should enlarge before they can be detected on these studies and that enlargement is not always due to metastases [19]. Other techniques that have been used selectively to assess tumor resectability and metastases are scintigraphy [38], azygos venography [42] and lymphography [44].

Computed Tomography

The appearance of the normal esophagus and of esophageal carcinoma on computed tomographic (CT) studies was first described in detail by Halber and Daffner in 1979 [45,46] and was followed by a description of the gastroesophageal junction on CT in 1981 by Marks et al [47]. CT seemed to be an ideal method of assessing the extent of mediastinal invasion by esophageal carcinoma because it was the first noninvasive technique that separately delineated the esophageal wall and the surrounding structures [45]. The gastroesophageal junction was slightly more difficult to evaluate because focal thickening or a pseudomass, due to absence of gastric distension and the transverse plane of CT sections through the gastroesophageal junction, were observed in a significant number of normal individuals [47,48]. Enlarged metastatic lymph nodes and hepatic metastases were also demonstrated on CT [46].

Earlier reports evaluating the ability of CT to stage esophageal carcinoma were enthusiastic [46,49-51]. Moss et al even reported an accuracy of 100% in assessing invasion of adjacent mediastinal structures and mediastinal lymph node involvement [49]. Others, however, reported CT to be of limited value in staging [52-56]. The accuracy of CT to assess either invasion or lymph node metastases was as low as 66% and 39% in these series [52,53]. The accuracy of CT to stage gastroesophageal junction carcinomas is also disputed [48,57,58]. These conflicting conclusions in the literature can be explained by the following reasons: differences in patient populations, lack of adequate correlation in some studies, different scanning techniques and different criteria used on CT studies [59]. At present controversy persists regarding the role and accuracy of CT in staging esophageal and gastroesophageal junction carcinoma [59].

Ultrasound

Only few reports are published that concern the use of transcutaneous ultrasound (US) for staging esophageal and gastroesophageal junction carcinoma [60]: the main reason is probably due to the fact that the primary tumor and the mediastinal lymph nodes generally cannot be displayed on these studies. US is an established technique for detection of hepatic metastases [61-63] and has also proved to be a valuable modality for assessment of cervical lymph node metastases in patients with head and neck tumors [64,65]. In one study US was clearly more sensitive than palpation in detecting these nodes [64].

US-guided Fine-Needle Aspiration Biopsy

CT- and US-guided biopsies are widely accepted techniques to obtain material for cytologic and histologic studies [66-69]. Recent studies have shown that the combination of US-guided fine-needle aspiration biopsy (FNAB) and cytologic study is a useful method to diagnose metastases in patients with carcinomas. Most importantly, false positive diagnoses are extremely rare and are reported in only 0-2% of biopsies [69-71]. There are, however, no reports concerning the utility of US-guided biopsies in esophageal and gastroesophageal junction carcinoma.

Magnetic Resonance Imaging and Endosonography

A few studies have been published that concern the use of magnetic resonance (MR) imaging, using spin-echo techniques and obtaining T1-weighted and T2-weighted images, for staging esophageal carcinoma [72-74]. Preliminary results of these studies indicate that MR is not superior to CT in predicting tumor resectability or assessing metastases.

Endosonography (ES) is a relatively new imaging modality to stage esophageal and gastroesophageal junction carcinoma that became available at our institution only during the late period of this study [75-77]. With this technique, an echoprobe is introduced endoscopically to and beyond the level of the tumor. The main advantage of ES compared to CT is that the different layers of the esophageal wall can be displayed separately. A major limitation of the technique is that in an important number of patients (16-50%) accurate staging is not possible because the echoendoscope cannot pass through the tumor [76,77]. Preliminary results indicate that ES is more accurate than CT to assess the depth of invasion of the primary tumor in those cases in which the tumor stenosis can be passed by the echoendoscope [75,77]. ES is reported to be more sensitive but less specific than CT in assessing regional lymph node metastases which carries the risk of overstaging [75,76] and ES is limited in detecting distant lymph node metastases [76]. The liver cannot be accurately examined with ES because of the limited penetration depth of the ES probe [76].

1.7 Purpose of the study

Pretreatment radiologic staging can, theoretically, improve the effectiveness and results of surgical treatment in esophageal and gastroesophageal junction carcinoma. Ideally, on these studies it is possible to select only patients with limited local disease for surgery, whereas those with nonresectable tumors or metastases to distant sites are excluded from surgery and submitted to other treatment modalities. The purpose of this study was

to evaluate the utility of CT, US and US-guided FNAB for pretreatment staging of esophageal and gastroesophageal junction carcinoma. In assessing distant metastases, these techniques were evaluated at different sites. Because little has been published regarding the examination of supraclavicular lymph nodes in esophageal and gastroesophageal junction carcinoma, a retrospective study was first performed to determine the number of patients with squamous cell carcinoma of the intrathoracic esophagus in whom supraclavicular metastases could be demonstrated with US and US-guided FNAB (Chapter 2). Subsequently, palpation, CT and US were prospectively evaluated for assessing supraclavicular metastases in patients with either esophageal or gastroesophageal junction carcinoma (Chapter 3). Accuracy of either CT, US, or a combination of both studies, to assess distant metastases in general and at the various sites was determined (Chapter 4). The utility of US-guided FNAB for diagnosing metastases was evaluated (Chapter 5). Assessment of resectability of the primary tumor was analyzed on CT studies alone because, generally, this cannot be displayed on US studies (Chapter 6). Finally a survival analysis was performed to estimate the influence on survival of distant metastases, assessed on US or CT studies, or diagnosed by means of US-guided FNAB and cytologic study (Chapter 7).

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Chapter 2

Ultrasound and Ultrasound-guided Fine-Needle Aspiration Biopsy of Supraclavicular Lymph Nodes in Patients with Esophageal Carcinoma

(Supraclavicular US and US-guided FNAB)

2.1 Abstract

The use of ultrasound (US) combined with US-guided fine-needle aspiration biopsy (FNAB) of supraclavicular lymph nodes in the pretreatment staging of 37 patients with squamous cell carcinoma of the esophagus is described. All patients underwent computed tomography of the chest and the abdomen and US of the abdomen and supraclavicular regions. Supraclavicular lymph node metastases (Stage IV disease according to the tumor nodes metastasis (TNM) classification) were cytologically diagnosed in seven (18.9 %) of the 37 patients. In two of these patients, no other metastases were found. In the other five patients, US-guided FNAB replaced more invasive diagnostic procedures. Due to their superficial location, US and US-guided FNAB of the supraclavicular lymph nodes was relatively simple to perform, and contributed to an improved staging of squamous cell carcinoma of the esophagus.

2.2 Introduction

Carcinoma of the esophagus has a poor prognosis. Due to the advanced stage of disease frequently present at the time of diagnosis, survival rates remain low. Surgical treatment is generally associated with a high postoperative morbidity and mortality and does not seem justified in patients with distant metastases [1-3]. Therefore, accurate pretreatment staging is of great importance to select the subgroup of patients who can benefit from an operation.

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Computed tomography (CT) of the chest and abdomen is generally accepted as the single most accurate noninvasive study for the pretreatment staging of carcinoma of the esophagus [4]. Some authors claim that CT is accurate in demonstrating local invasion of the tumor [5-7], although opposing opinions have been reported [8-9]. CT however, is not a sensitive predictor of metastatic involvement of periesophageal lymph nodes [6,8-10] and also seems limited in its ability to detect involvement of abdominal nodal areas [8-11]. Patients are usually not excluded from operative treatment on the basis of CT findings alone, and more invasive procedures are necessary to obtain cytologic or histologic evidence of metastatic spread.

According to the tumor node metastasis (TNM) classification, metastatic involvement of the supraclavicular lymph nodes in patients with carcinoma of the intrathoracic esophagus is associated with Stage IV disease (distant metastases) [12]. Due to their superficial location, the supraclavicular lymph nodes are accessible to ultrasound (US) and US-guided fine-needle aspiration biopsy (FNAB). In a previous study from our department the accuracy of US in combination with US-guided FNAB was good in detecting nonpalpable lymph node metastases in the neck [13]. This encouraged us to use US and US-guided FNAB of the supraclavicular lymph nodes when staging patients with squamous cell carcinoma of the esophagus.

2.3 Patients and methods

Thirty-seven patients with histologically proven primary squamous cell carcinoma of the intrathoracic esophagus who were referred to the Rotterdam Esophageal Tumor Study Group and underwent US of the supraclavicular lymph nodes in the period January 1987 - December 1988 were retrospectively studied. The patients, 26 men and 11 women, ranged from 42 to 77 years (mean, 59 years). Three patients had carcinoma of the upper esophagus, 16 had carcinoma of the middle esophagus, and 18 had carcinoma of the lower esophagus. Twenty-two patients had already undergone CT or US in other hospitals to rule out metastases to the chest and the abdomen. CT scans performed elsewhere were reevaluated at our department. In seven patients they were found to be adequate. The remaining 30 patients underwent CT scanning using a Tomoscan 350 (Philips Medical Systems, Eindhoven, The Netherlands) total body scanner with 1 cm thick contiguous slices through the chest and the abdomen, including the entire liver. Mediastinal and abdominal lymph node metastases were suspected if lymph nodes were greater than 1 cm in diameter. All patients underwent US of the neck and upper abdomen using a 7.5-MHz and a 3.5-MHz transducer (Aloka SSD-650). US-guided FNAB with a 23-gauge needle was done in

supraclavicular lymph nodes larger than 5 mm in diameter. In cases of multiple unilateral nodes, the largest node was aspirated. In cases of bilateral nodes, the largest nodes on both sides were aspirated. A negative outcome of the aspiration biopsy was accepted when the smears showed lymphocytes and no malignant cells.

2.4 Results

CT and US findings in the 37 patients are summarized in Table 2.1. Ten patients had supraclavicular lymph nodes larger than 5 mm in diameter on US and underwent US-guided FNAB. In two of these patients, enlarged, suspiciously firm lymph nodes were also palpable.

Table 2.1 CT and US findings in 37 patients with esophageal carcinoma

Findings	No.patients	%
Supraclavicular lymphadenopathy* (US)	10°/37	(27)
Mediastinal lymphadenopathy° (CT)	5/37	(14)
Abdominal lymphadenopathy° (CT and US)	7/37	(19)
Liver metastasis (CT and US)	1/37	(3)
Adrenal metastasis (CT and US)	2/37	(5)
Pleural metastasis (CT)	1/37	(3)

US: ultrasound; CT: computed tomography.
* Lymph nodes larger than 5 mm in diameter.
◇ In two patients, enlarged lymph nodes were also palpable.
° Lymph nodes larger than 1 cm in diameter.

Cytologic examination revealed metastatic involvement in seven patients, two patients with palpable nodes and five with nonpalpable nodes. In four patients, the left side, in two, the right side, and in one, both sides of the neck were involved. Of these seven patients, four had a carcinoma in the middle third of the esophagus and three in the lower third. Two patients with supraclavicular metastases did not show metastatic spread to the chest or the abdomen on CT and US. Abdominal adenopathy was found in the other five patients and mediastinal adenopathy in one. Two of these patients were also suspected of having distant metastases elsewhere (Table 2.2).

Cytologic examination of the supraclavicular lymph nodes did not show malignant involvement in three patients, nor were they suspected of metastatic spread to the chest or

abdomen on CT and US.
On the basis of US-guided FNAB of the supraclavicular lymph nodes, Stage IV disease was diagnosed in seven patients who were subsequently excluded from operative resection.

Table 2.2 CT and US findings in seven patients with esophageal carcinoma and cytologically proven supraclavicular metastases

	Patient no.						
Findings	1	2	3	4	5	6	7
Mediastinal lymphadenopathy (CT)	-	-	-	-	-	-	+
Abdominal lymphadenopathy (CT)	-	-	+	-	+	-	+
Abdominal lymphadenopathy (US)	+	-	+	-	-	+	+
Liver metastasis (CT and US)	-	-	+	-	-	-	-
Adrenal metastasis (CT and US)	-	-	-	-	-	-	+
Pleural metastasis (CT)	-	-	-	-	-	-	+

CT: computed tomography; US: ultrasound.

2.5 Discussion

Carcinoma of the esophagus has a poor prognosis because the diagnosis is rarely made before the development of local invasion and distant metastases. This explains why the 5-year survival remains low in western countries despite the recent advances in surgery and radiation therapy [1,3].
Spread by way of the lymphatics occurs frequently: at surgery, lymph node metastases are found in 41.3% to 59%, [14,15] and at autopsy, in 74.5% of cases [16]. The presence of lymph node metastases suggests an omnious prognosis [10,14,15], and in case of distant nodal metastases, resection of the tumor is at least questionable as an operation is generally associated with high postoperative morbidity and mortality rate of 14% to 29% [1,3].
In the past 10 years, CT has improved the accuracy of preoperative staging. A limitation of CT scanning is its inability to detect tumor in lymph nodes that are of normal size. Also, enlarged lymph nodes may not contain tumor [10]. Therefore CT is insensitive in predicting involvement of the periesophageal lymph nodes [6,8-10] and, to a lesser degree, in predicting the involvement of abdominal lymph nodes [8-11]. More invasive procedures are usually necessary to obtain cytologic or histologic evidence of tumor spread.
The incidence of metastatic spread of esophageal carcinoma to the supraclavicular lymph

nodes is often underestimated. Reports on pretreatment staging by CT are invariably limited to the chest and abdomen. To our knowledge there has been only one report in articles published in English that concerns sonographic evaluation of cervical lymph node metastases in esophageal carcinoma [17]. At surgery, metastatic involvement of the supraclavicular lymph nodes has been reported in 18% to 27% of cases [18]. We were able to detect supraclavicular metastases in 18.9% of patients, a finding that correlates well with these data. The 37 patients were not referred at random. Most had been selected elsewhere by excluding thoracic and abdominal metastases before their referral. In an unselected group of patients, the incidence of supraclavicular metastases may be even higher.

Due to the superficial location of the supraclavicular lymph nodes, US-guided FNAB is a relatively simple procedure with only little patient discomfort. The ease with which the exact nature of adenopathy can be established is a major advantage. According to the TNM classification all seven patients with supraclavicular metastases had Stage IV disease [12], and it is the policy of our Tumor Study Group that operation is not indicated in this group of patients with distant metastases.

On the basis of CT findings alone, Patients 3, 5 and 7 were suspected of having Stage IV disease, and, on the basis of abdominal US, Patients 1 and 6 were also suspected of having Stage IV disease (Table 2.2). Without supraclavicular US-guided FNAB, abdominal US-guided FNAB and/or surgical exploration would have been necessary in these 5 patients for correct assessment of distant metastases. Supraclavicular US-guided FNAB prevented an extensive operation in Patients 2 and 4 as distant metastases were not found on CT and US of the chest and the abdomen.

We recommend supraclavicular ultrasound and ultrasound-guided fine-needle aspiration biopsy in addition to CT of the chest and abdomen and ultrasound of the abdomen to improve the staging of squamous cell carcinoma of the esophagus.

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Chapter 3

Supraclavicular Lymph Node Metastases in Carcinoma of the Esophagus and Gastroesophageal Junction: Assessment with CT, US, and US-guided Fine-Needle Aspiration Biopsy

(Supraclavicular Metastases: CT, US and US-guided FNAB)

3.1 Abstract

The preoperative assessment of supraclavicular lymph node metastases was prospectively studied in one hundred patients with carcinoma of the esophagus and gastroesophageal junction. Findings at computed tomography (CT), ultrasound (US), and palpation were compared, and US-guided fine-needle aspiration biopsy of nodes with a small axis of 5 mm or greater was performed. Supraclavicular metastases were detected on CT scans in 11 of 13 patients (85%) and on US scans in 14 of 16 patients (88%) but were palpable in only three of the 16 patients (19%). The predictive value of a supraclavicular node indicating metastases was 0.74 at US and 0.85 at CT. Metastases were diagnosed in 10 of 46 patients with squamous cell carcinoma (22%) and five of 50 patients (10%) with adenocarcinoma. Nodes with metastases had a round configuration, with a statistically significant greater short-axis to long-axis ratio than that of benign nodes (0.89 vs 0.54; $p = 0.05$). In four of 16 patients (25%) with supraclavicular metastases proved with cytologic examination, neither CT nor US of the mediastinum and abdomen showed enlarged nodes.

3.2 Introduction

Lymph node metastases in carcinoma of the esophagus and gastroesophageal junction are associated with a poor prognosis. The 5-year survival rate after resection of esophageal carcinoma is as high as 47.9% - 53.8% in patients without lymph node metastases but only 6.3% - 15.3% in patients with them [1,2].

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The survival rates after resection of gastroesophageal junction carcinoma also drop significantly when lymph node metastases are found [3,4].
Preoperative assessment of lymph node metastases is therefore one of the most important factors in selecting therapy and estimating the prognosis. Many reports concern assessment of mediastinal and abdominal lymph node metastases with computed tomography (CT) [5-12]. Although CT evaluation of supraclavicular adenopathy in general has been reported by Goldberg and Austin [13], we are unaware of any study in which CT has been systematically used to determine supraclavicular lymph node metastases in esophageal and gastroesophageal junction carcinoma. In addition, few articles report the use of ultrasound (US) for detection of supraclavicular metastases in these cases [14,15]. Supraclavicular metastases are often detected with palpation only, despite the fact that palpation is an unreliable method [16,17].
The use of US and US-guided fine-needle aspiration biopsy (FNAB) to diagnose supraclavicular metastases in carcinoma of the thoracic esophagus was discussed by us in a previous report [15]. This study was undertaken to compare palpation, US and CT findings and to reevaluate the use of US-guided FNAB. Morphologic characteristics of malignant and benign nodes were studied, and the relative frequency of supraclavicular metastases was established in relation to the location of and histologic findings in the primary tumor. In cases of supraclavicular metastases the presence of radiologically detectable mediastinal and abdominal adenopathy was evaluated.

3.3 Patients and Methods

One hundred consecutive patients, 81 men and 19 women aged 40-85 years (mean, 63 years), were prospectively studied between January 1989 and June 1990. All patients had a primary malignant tumor of the thoracic esophagus and/or gastroesophageal junction that had been proved with histologic examination, and all were referred to the Rotterdam Esophageal Tumor Study Group for treatment. Forty-six patients had squamous cell carcinoma (carcinoma of the upper thoracic esophagus, n = 3; middle esophagus, n = 23; lower esophagus, n = 20), which was staged according to the classification put forth by the American Joint Committee on Cancer [18]. Fifty patients had adenocarcinoma of the middle thoracic esophagus (n = 2) or lower esophagus and gastroesophageal junction (n = 48). Four patients had undifferentiated carcinoma.
Palpation of the supraclavicular regions of all patients was done by members of the surgical and gastroenterologic departments. All patients underwent CT scanning of the chest and upper abdomen, including the entire liver, in 8- or 12-mm-thick contiguous

sections by means of a Somatom Plus Scanner (Siemens, Erlangen, Federal Republic of Germany) or a Tomoscan 350 (Philips Medical Systems, Eindhoven, The Netherlands). Ninety patients also underwent CT scanning of the neck from the cricoid cartilage to the sternal angle, with 5- or 6-mm-thick contiguous sections. CT scanning of the neck was not done in 10 patients during the initial period of the study. Contrast material was administered intravenously in all patients to better define the vascular structures, and a swallow of contrast material was routinely given. All patients underwent US of the neck and upper abdomen by means of a 7.5-MHz and a 3.5-MHz transducer, respectively (SSD-650; Aloka, Tokyo, Japan). The short and long axes of the supraclavicular nodes were measured at CT and US. Measurements on CT scans were taken in the axial plane and were considered representative of the true values because they did not differ significantly from the values obtained with US when nodes were detected with both modalities. Short-axis to long-axis ratios (S/Ls) were calculated with the mean of the US and CT values. When nodes were detected with either CT or US only, we used the values obtained with this modality. Supraclavicular lymph nodes were considered abnormal when they had a short axis of 5mm or more.

Palpation, CT and US of the supraclavicular regions were initially performed independently without knowledge of the other examiners' findings, and the results were documented. However, in patients with nodes seen on CT scans only, the US examination was repeated to confirm the CT finding before US-guided FNAB was performed.

US-guided FNAB with a 23-gauge needle was done in all but three patients with supraclavicular lymph nodes with a short axis of 5 mm of more. In cases of multiple nodes the largest node was aspirated. Mediastinal and abdominal lymph nodes were considered abnormal when they had a diameter of 1 cm or more. Patients with metastases proved by means of cytologic study were excluded from surgery. All patients in whom the tumor was resected underwent transhiatal esophagectomy with gastric interposition and cervical gastroesophageal anastomosis. This type of surgery does not include dissection of the supraclavicular lymph nodes, and therefore, further verification of the status of nodes with a short axis of less than 5 mm at US and CT was not possible. Thus, false-negative findings cannot be reported.

The comparisons between US and CT are based on the predictive value of a positive test finding (a lymph node with a short axis of 5 mm or more indicated metastases). The Student t-test was used for statistical analysis of the S/Ls. Test-based 95% (α = 0.05) confidence intervals (CIs) of relative risks (RRs) and exact CIs of the predictive values of positive test results were calculated.

Table 3.1 Supraclavicular lymph nodes and supraclavicular lymph node metastases in 100 patients with carcinoma of the esophagus and gastroesophageal junction: CT and US findings

Lymph nodes at CT	Lymph nodes at US		Total no. of lymph nodes at CT
	Present	Absent	
Present	11 (9)	4 (2)	15 (11)
Absent	7 (2)	68 (0)	75 (2)
Examination not done	4 (3)	6 (0)	10 (3)
Total (US)	22 (14)	78 (2)	100 (16)

Note: Numbers are the number of patients with supraclavicular lymph nodes. Numbers in parentheses are the number of patients with supraclavicular metastases proved by means of cytologic examination.

3.4 Results

Supraclavicular lymph nodes were detected in a total of 26 patients, on the initial US scan in 22 of the 100 patients, and on CT scans in 15 of the 90 patients who underwent supraclavicular CT. In seven patients, nodes were present on the initial US scan but absent on CT scans. In four patients, nodes were present on CT scans but absent on the initial US scans; however, in two of these four patients, nodes were found on a second US scan with the aid of the positive CT finding, and US-guided FNAB was subsequently performed (Table 3.1). Twenty-three of the 26 patients with supraclavicular nodes underwent US-guided FNAB. This procedure was not done in three patients; two patients already had liver metastases proved with cytologic examination, and in one patient it was impossible to avoid major blood vessels. Cytologic examination revealed metastases in 16 patients and benign cells in five patients. In two patients it was not possible to obtain adequate material for cytologic examination by means of repeat biopsies. No complications were observed in patients who underwent US-guided FNAB. Metastatic nodes were detected at the initial US examination in 14 of the 16 patients (88%) and at CT in 11 of the 13 patients (85%) but were palpable in only three of the 16 patients (19%). Benign nodes were found on US scans in five patients and on CT scans in two of these patients and were not found on clinical examination.

On the basis of the initial US examination, 14 of the 19 cytologically tested lymph nodes were metastatic. The predictive value of a lymph node on a US scan that indicated metastasis was 0.74 (CI, 0.49-0.91). Eleven of the 13 lymph nodes studied with cytologic tests and seen on CT scans were metastatic. The predictive value of a

Table 3.2 Location of and histologic findings in the primary tumor in 16 patients with supraclavicular metastases proved by means of cytologic examination

Location of primary tumor	Histologic findings			
	Squamous cell carcinoma	Adenocarcinoma	Undifferentiated carcinoma	Total
Upper esophagus[1]	1/3 (33)	0 (0)	0/1 (0)	1/4 (25)
Middle esophagus[2]	7/23 (30)	0/2 (0)	0/1 (0)	7/26 (27)
Lower esophagus[3] and gastroesophageal junction	2/20 (10)	5/48 (10)	1/2 (50)	8/70 (11)
Total	10/46 (22)	5/50 (10)	1/4 (25)	16/100 (16)

Note: Data represent number of patients with supraclavicular metastases per number of patients.
Numbers in parentheses are percentages.
[1]Thoracic inlet to tracheal bifurcation.
[2]Proximal half of the esophagus between the tracheal bifurcation and the gastroesophageal junction.
[3]Distal half of the esophagus between the tracheal bifurcation and the gastroesophageal junction.

lymph node on a CT scan indicating metastasis was 0.85 (CI, 0.55-0.98).

The short axis of the metastatic nodes ranged from 9 mm to 23 mm (mean, 12 mm), and of benign nodes, from 5 mm to 8 mm (mean, 6 mm). The S/L of malignant nodes (0.89) was significantly greater than that of benign nodes (0.54) ($p=0.05$). Lymph nodes with a hypoattenuated necrotic center were observed in five cases of metastatic enlarged nodes with short axes of 10 mm or longer, but such a center was not seen in cases of benign nodes.

The relationship between the percentage of patients with supraclavicular metastases and the location of and histologic findings in the primary tumor is shown in Table 3.2. Supraclavicular metastases were found more frequently in patients with squamous cell carcinoma (22%) than in patients with adenocarcinoma (10%) (RR, 2.2; CI, 0.83-5.7). A relationship exists between the location of the primary tumor and the frequency of supraclavicular metastases, which were mainly found in patients with carcinoma of the upper third (25%) and middle third (27%) of the esophagus. However, even in patients with carcinoma of the lower esophagus and gastroesophageal junction, supraclavicular metastases were proved in 11% of cases. The RR of the prevalence of supraclavicular metastases in carcinoma of the upper and middle thirds of the esophagus compared with that of the lower third and gastroesophageal junction is 2.3 (CI, 0.97-5.60).

On the basis of CT and US examinations, mediastinal lymph node metastases were also suspected in 50% and abdominal lymph node metastases in 35% of patients with

supraclavicular metastases (Table 3.3). In 25% of patients with supraclavicular metastases, radiologically detectable mediastinal and abdominal adenopathy was absent.

Table 3.3 Mediastinal and abdominal adenopathy: CT and US findings in 16 patients with supraclavicular metastases proved by means of cytologic examination

Adenopathy/Modality	No. of patients	%
Mediastinal/CT	8	50
Abdominal/CT	6	35
Abdominal/US	5	31
Mediastinal and abdominal/CT and US	6	35
None/CT and US	4	25

Note: All lymph nodes had a diameter of 1 cm or greater.

3.5 Discussion

The longitudinal orientation of the lymphatic network of the esophagus was reported by Sakata in 1903 [19]. Sakata noticed that many lymphatics of the middle esophagus drained into the neck nodes and that lymphatics of the lower esophagus drained into cardiac nodes. He expressed strong indications for the existence of connections between the deep layers of the esophagus and nodes in the supraclavicular fossa.

This nonsegmental type of drainage is responsible for metastases to lymph nodes far from the primary tumor [20]. It was observed by Akiyama et al [1], who performed extended lymph node dissections, and it explains the high percentage (22%) of supraclavicular metastases we found in patients with squamous cell carcinoma of the esophagus. This percentage does not differ significantly from the 18.9% that we reported previously in another group of patients [15]. Sannohe et al even found supraclavicular metastases in 27% of patients with esophageal carcinoma when these nodes were systematically dissected [21], but their selection criteria for performing neck dissections were not specified. In our study, supraclavicular metastases were found most commonly in patients with squamous cell carcinoma of the upper and middle esophagus, a finding consistent with the findings of Sakata et al [19]. The lower percentage of supraclavicular metastases in patients with adenocarcinoma is probably due to the more distal location of the primary tumor in these cases (Table 3.2). In patients with carcinoma of the lower esophagus and gastroesophageal junction, supraclavicular metastases might spread through collateral circulation when normal pathways to the stomach become blocked [22]. Although supraclavicular metastases are less frequent in these patients, we were able to detect them in a significant number of cases.

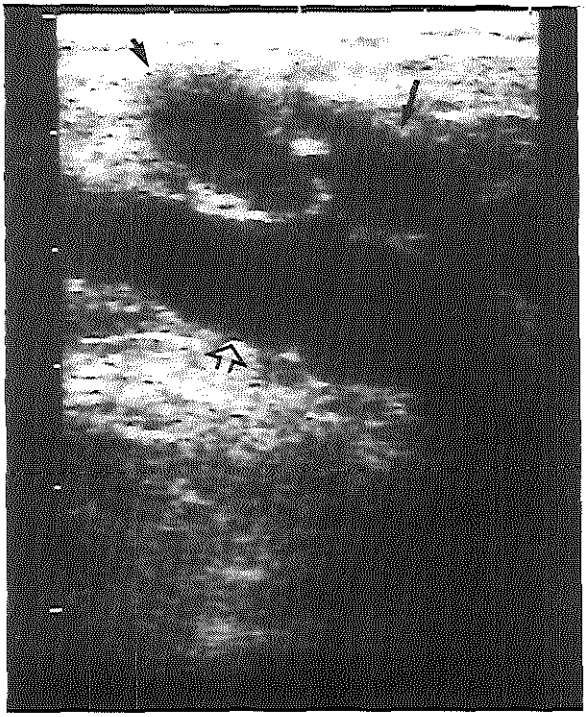

Figure 3.1
Axial sonogram of the right supraclavicular fossa in a 58-year-old woman with squamous cell carcinoma of the middle thoracic esophagus. Round, hypoechoic lymph node (short solid arrow) in the angle of the jugular vein (long solid arrow) and subclavian vein (open arrow). The lymph node was also detected at CT. US-guided FNAB revealed metastases.

Supraclavicular lymph nodes in general were found slightly more often with US than with CT, and neither modality was superior in enabling prediction of the metastatic status of the nodes. We prefer US as the initial examination to enable US-guided FNAB. In cases of a negative initial US examination, an additional CT examination can be performed. With the aid of the CT findings we were able to locate metastatic nodes at a second US examination and subsequently perform US-guided FNAB in two patients with previously negative US findings.

Unlike abdominal US-guided FNAB, supraclavicular US-guided FNAB is not hindered by respiratory movements or overlying bowel shadow, and the superficial location of the nodes also contributes to the easiness of the procedure. The direct visualization of the needle point enables precise puncturing of the nodes while one avoids the blood vessels. We found supraclavicular US-guided FNAB to be a safe technique that caused little discomfort to the patient. Supraclavicular lymph nodes were invariably found around the angle of the jugular and subclavian veins (Fig.3.1) and between the carotid artery and the thyroid gland or the trachea (Fig.3.2), and these areas are not systematically examined during transhiatal esophagectomy. Therefore, we are unable to report the percentage of cases in which supraclavicular metastases were falsely excluded

at US and CT. Metastatic nodes were palpable in only a minority of patients, and therefore examination of the supraclavicular regions should not be confined to palpation only (Fig.3.3). Sonographic examination of the shape of cervical lymph nodes in patients with carcinoma of the esophagus was done by Tohnosu et al [14]. Metastatic nodes tended to be round and had an increased S/L, exceeding 0.5 when compared with that of benign nodes. The average S/L of metastatic nodes in our series was also significantly greater than that of benign nodes. The greater size of benign nodes in our series is caused by the selection of only lymph nodes with a short axis of 5 mm or greater for US-guided FNAB. We agree with Tohnosu et al that round nodes are more likely to contain metastases, but because lymph nodes may also enlarge as a result of inflammatory processes [9], the diagnosis of metastases should not be confirmed with CT or US findings alone but should be confirmed with either cytologic or histologic examination. This is probably also true in cases of enlarged lymph nodes with necrotic

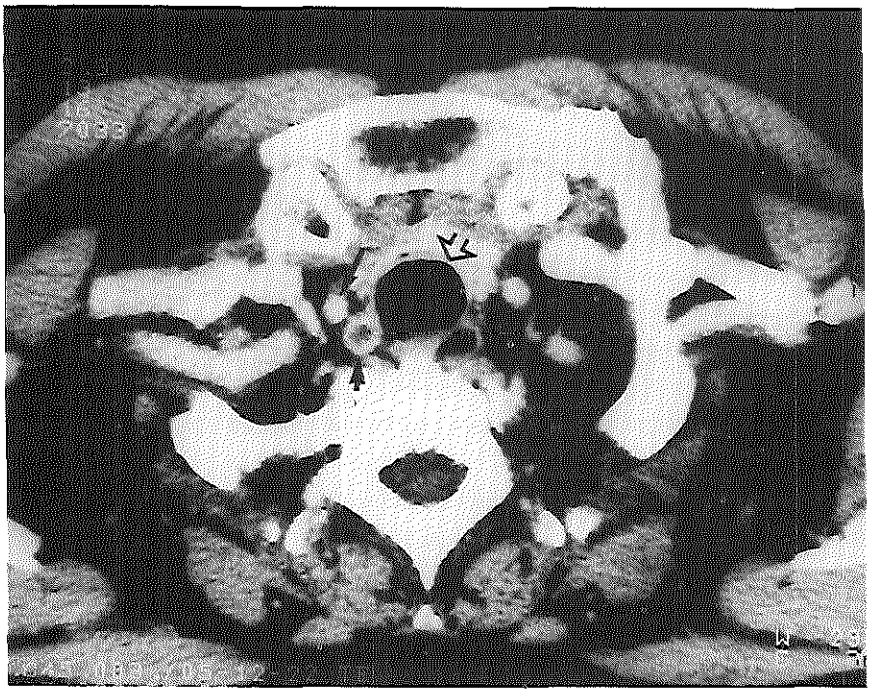

Figure 3.2 Axial contrast material-enhanced CT scan from a 67-year-old man with squamous cell carcinoma of the middle thoracic esophagus. An enhancing lymph node with a hypoattenuated, necrotic center (short solid arrow) is localized between the right carotid artery (long solid arrow) and the trachea (open arrow). Metastasis was proved at cytologic examination.

centers, even though the presence of such nodes was invariably associated with metastases in all cases we observed. Supraclavicular metastases were not always associated with adenopathy in other locations. Mediastinal and abdominal adenopathies were absent on US and CT in 25% of patients with supraclavicular metastases proved at cytologic examination. Diagnosing supraclavicular metastases (stage IV disease in the classification of the American Joint Committee on Cancer) is especially important in this group of patients because it changes the preoperative stage of the patient and influences the choice of therapy. In patients with carcinoma of the esophagus and gastroesophageal junction, examination of the supraclavicular regions should not be confined to palpation but should include US. An additional CT examination can be performed in patients with negative results on US examination. Cytologic confirmation of metastases can be safely obtained by means of ultrasound-guided fine-needle aspiration biopsy, which should especially be done in patients with round nodes.

Figure 3.3 Axial contrast-enhanced CT scan form a 64-year-old man with squamous cell carcinoma of the lower esophagus. A hypoattenuated, enlarged lymph node (solid arrow) is seen posterior to the left clavicle (open arrow). The node was not palpable at clinical examination because of the overlying clavicle and sternocleidomastoid muscle. Metastases were proved at cytologic examination.

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Chapter 4

Improved Assessment of Supraclavicular and Abdominal Metastases in Oesophageal and Gastro-oesophageal Junction Carcinoma with the Combination of Ultrasound and Computed Tomography

(Assessment of Distant Metastases with US and CT)

4.1 Abstract

The purpose of the study was to evaluate ultrasound and computed tomography in the assessment of distant metastases, supraclavicular and abdominal, in 113 patients with carcinoma of the oesophagus and gastro-oesophageal junction. Ultrasound and computed tomographic findings were compared with the cytological data in 29 patients and with the surgical data in 84 patients. In assessing distant metastases, ultrasound and computed tomography had a sensitivity of 61% and 70%, and a specificity of 93% and 85%, respectively ($p = 1.0$). When ultrasound and computed tomography were combined the sensitivity increased to 83% and the specificity decreased to 81%. There was no significant difference in the assessment of supraclavicular metastases ($p = 0.8$), coeliac metastases ($p = 1.0$) or liver and other nonlymphatic abdominal metastases ($p = 1.0$) on ultrasound or computed tomography. The results show that both ultrasound and computed tomography should be used for assessment of distant metastases and abnormalities confirmed by imaging guided biopsy.

4.2 Introduction

In patients with carcinoma of the oesophagus and gastro-oesophageal junction, pretreatment staging is required to select the optimal therapeutic approach.

Assessment of distant metastases is of great importance because metastatic spread to distant sites either obviates the need for surgery or limits it to palliative resection.

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The longitudinal orientation of the lymphatic network of the oesophagus is responsible for early metastases to the supraclavicular and coeliac lymph nodes in these tumours.
In assessing distant metastases both computed tomography (CT) and ultrasound (US) have certain advantages. On CT scans the primary tumour, the mediastinum and the lungs can be examined during the same session that is used for examining the supraclavicular nodes and the abdomen [1-3]. US scans can be performed more quickly than CT scans and a cytological diagnosis can be obtained almost immediately by means of US-guided fine-needle aspiration biopsy (FNAB) from any masses detected [4-6].
The purpose of this study was to evaluate the assessment of distant metastases with US, CT, and a combination of both techniques by comparing US and CT findings with cytological and surgical data.

4.3 Patients and Methods

Between January 1989 and December 1990 113 patients, 88 men and 25 women, aged 42-76 years (mean 61 years) with oesophageal (92 patients) and gastro-oesophageal junction (21 patients) carcinoma were studied prospectively. Histology of the primary tumour was squamous cell carcinoma in 57, adenocarcinoma in 50 and undifferentiated carcinoma in six patients. Staging was performed according to the classification of the American Joint Committee on Cancer (AJCC) [7] with one exception: whereas the AJCC considers coeliac nodes as regional nodes (N2) in carcinoma of the gastro-oesophageal junction and as distant nodes (M1) in carcinoma of the oesophagus, in our study they were considered distant in all cases.

Palpation, US and CT

Palpation of the supraclavicular regions of all patients was performed by physicians of the surgical and gastroenterological departments. Patients underwent US of the supraclavicular regions and the abdomen by means of a 7.5-MHz linear array transducer and a 3.5-MHz curvilinear transducer, respectively (SSD-650; Aloka, Tokyo, Japan).
All patients underwent CT scanning of the supraclavicular regions from the cricoid cartilage to the sternal angle with 5-or 6-mm-thick contiguous sections and contiguous CT scanning of the chest and upper abdomen, in 8-12-mm-thick sections by means of a Somatom Plus Scanner (Siemens, Erlangen, Germany) or a Tomoscan 350 (Philips Medical Systems, Eindhoven, The Netherlands). Contrast material was routinely administered intravenously by means of a drip infusion to better define the vascular structures. The supraclavicular lymph nodes were bilaterally studied on US and CT scans and were considered abnormal when they had a short axis of 5 mm or more. US

and CT scans of the abdomen included examination of the coeliac lymph nodes which were considered abnormal when they had a short axis of 10 mm or more, the liver and other nonlymphatic abdominal sites; the peritoneum, the kidneys and the adrenal glands. Palpation of the supraclavicular regions and CT and US of the supraclavicular regions and the abdomen were performed independently without knowledge of the other examiners' findings and the results were documented. In patients with enlarged supraclavicular nodes and nonlymphatic abdominal lesions present on CT but absent on US, US studies were repeated and US-guided FNAB performed in those cases when the lesions could now be detected.

US-guided FNAB

All but two patients with US and/or CT findings indicating supraclavicular, liver and other nonlymphatic abdominal metastases underwent US-guided FNAB of one suspect lesion. Biopsies were not performed in two patients with enlarged supraclavicular nodes present on CT scans but absent on US scans because the nodes could not be found on repeated US scans and in our experience it is not possible to perform CT-guided biopsies of these small (< 1 cm) and often mobile nodes. FNABs were only occasionally performed of enlarged coeliac nodes, because these nodes are usually removed at surgery when the primary tumour is resectable. In patients with multiple lesions biopsies were preferentially performed of supraclavicular nodes because these are easier to perform and are less distressing and invasive for the patient compared with abdominal biopsies. FNABs of supraclavicular lymph nodes were performed with a 23-gauge needle in a "free-hand" method and of abdominal lesions with a 22-gauge needle usually with an attachable needle guide. Patients with distant metastases proved by means of cytologic studies were excluded from surgery. The remaining patients, including those with negative cytological examinations, underwent surgery.

Surgery

At surgery laparotomy was performed as the first step of a planned resection; the liver was bimanually palpated, the coeliac lymph nodes were removed for histological examination and resectability of the tumour was determined. Patients with a surgically resectable tumour underwent transhiatal oesophagectomy (THE). In these patients the lower oesophagus was dissected transhiatally and the cervical oesophagus was dissected through a right sided neck incision. Enlarged lymph nodes on the right side of the neck were removed for histological examination. The intrathoracic oesophagus and the gastro-oesophageal junction were resected, a stomach tube was brought up to the neck and an anastomosis was made with the cervical oesophagus. Patients with an unresectable tumour underwent laparotomy only.

Data Analysis

Sensitivity and specificity of US and CT were estimated and are reported with 95% exact confidence intervals, by using the cytological data as standard of reference in the patients with cytologically proven metastases, and by using the data of the surgically assessed sites as the standard of reference in the patients who underwent surgery. The sensitivity was the chance of demonstrating positive findings on US or CT in a patient with metastases, whereas the specificity was the chance of demonstrating negative findings when no metastases were present. For the combination of US and CT the sensitivity was the chance of demonstrating positive findings on either US or CT in a patient with metastases whereas the specificity was the chance of demonstrating negative findings on both studies when no metastases were present. Statistical analysis of false positive and false negative findings on US and CT was performed in a patient-by-patient comparison by means of McNemar's test for paired data.

4.4 Results

Thirty-nine of 113 patients underwent US-guided FNAB. Distant metastases were proven by means of cytologic studies in 29 of these patients who were subsequently excluded from surgery. The sites of the cytologically proven metastases in these 29 patients are shown in Table 4.1.

Table 4.1 Number of patients with cytologically or surgically assessed sites

	No surgery	Surgery			Total
Distant sites	Cytologically proven metastases	Metastases	No metastases	Total	
Supraclavicular nodes	19	0	70	70[a]	89
Coeliac nodes	2	25	59	84	86
Liver and other non-lymphatic abdominal sites	8[b]	2	82	84	92
Total	29	25[c]	59	84[d]	113

[a] Supraclavicular nodes: surgically assessed in 70 patients at THE. Not assessed in 14 patients who underwent laparotomy alone.

[b] Liver metastases in 5 patients, peritoneal carcinomatosis in 2, renal metastases in 1.

[c] 2/25 patients had both liver metastases and coeliac lymph node metastases at surgery.

[d] 10/84 patients had negative cytology studies prior to surgery (supraclavicular lymph nodes, 8; adrenal glands, 2).

Metastases were not found in the cytological smears of 10 other patients who underwent US-guided FNAB; of the supraclavicular nodes in eight patients and of the adrenal glands in two patients. These patients subsequently underwent surgery at which metastases were not found at the cytologically tested sites.

Eighty-four patients underwent surgery. Seventy patients underwent THE. The remaining 14 patients underwent explorative laparotomy only, due to advanced local spread of the primary tumour (10 patients), the presence of multiple abdominal metastases (two patients) or other reasons (two patients).

At surgery distant metastases were found and proved by histopathological examination at 27 sites in 25 of 84 patients (Table 4.1). Twenty-five patients had coeliac lymph node metastases and two of these patients also had liver metastases. Supraclavicular metastases were not found on the right side in the 70 patients who underwent THE. In the remaining 14 patients surgery was abandoned after laparotomy and the supraclavicular nodes were not surgically assessed.

Supraclavicular metastases

Nineteen patients had supraclavicular metastases. In four of 19 (21%) patients with metastatic nodes, enlarged nodes were palpable. Metastatic nodes were detected on US scans in 15 of 19 (79%) patients (Fig. 4.1) and on CT scans in 16 of 19 (84%) patients (Fig. 4.2) (Table 4.2).

Table 4.2 Correlation of US and CT findings with cytological and surgical data in assessing supraclavicular metastases

Results of US and CT studies	Supraclavicular lymph nodes: numbers of patients (n = 89)	
	US	CT
True positive	15	16
False negative	4	3
False positive	6	5
True negative	64	65
Sensitivity[a] (%)	79[b] (54-94)	84 (60-97)
Specificity (%)	91 (82-97)	93 (84-98)

US and CT findings were correlated with the cytological data in 19 patients with supraclavicular metastases cytologically proven and were correlated with the surgical data in 70 patients who underwent THE, 8 of whom had negative cytology.

[a] Sensitivity = true positive/(true positive + false negative); specificity = true negative/(true negative + false positive). [b] 95% confidence interval in parentheses.

There was no significant difference between US and CT in assessing supraclavicular metastases ($p = 0.8$), but both techniques were superior to palpation in detecting metastatic nodes. A false negative diagnosis was made in four patients on US scans; in these patients nodes were absent on initial US scans but present on CT scans, however, enlarged nodes were found on repeated US scans with the aid of the positive CT findings and metastases were subsequently proven by US-guided FNAB and cytological examination. In six patients metastases were predicted on US studies, but proved incorrect by cytological study and at THE. A false negative diagnosis was made on CT scans in three patients with metastatic nodes, absent on CT scans but present on US scans. In five patients supraclavicular metastases were predicted on CT scans, but proved incorrect at THE; three of these patients also had previously negative cytological studies.

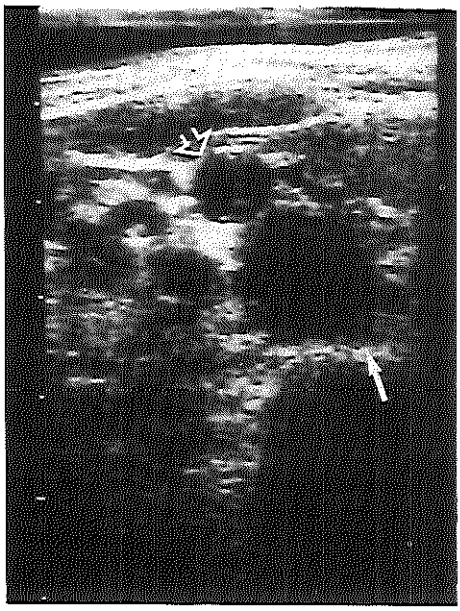

Figure 4.1
Axial sonogram of the right supraclavicular fossa in a patient with squamous cell carcinoma of the lower oesophagus. A round hypoechoic lymph node (solid arrow) is seen posterior to the sterno-cleidomastoid muscle and the carotid artery (open arrow). US-guided FNAB revealed metastases.

Figure 4.2
Axial contrast material-enhanced CT scan in a patient with squamous cell carcinoma of the middle thoracic oesophagus. A hypoattenuated, enlarged supraclavicular node (arrow) is localized posterior to the thyroid gland and lateral to the left carotid artery. Metastases were proven at cytologic examination.

Abdominal metastases

Table 4.3 summarizes the results of US and CT studies in assessing distant abdominal metastases.

Coeliac lymph node metastases

There was no significant difference in assessing coeliac metastases on US or CT studies ($p = 1.0$). Metastases were correctly predicted on US scans in eight of 27 (30%) patients (Fig. 4.3) and on CT scans in 13 of 27 (48%) patients (Fig. 4.4). Nineteen patients had metastatic nodes at surgery that were not detected on US scans. Metastatic nodes were not detected on CT scans in 14 patients but were proved cytologically in one patient and at surgery in 13 patients. Metastases were incorrectly predicted on CT in four patients without metastases at surgery. There were no false positive findings on US scans.

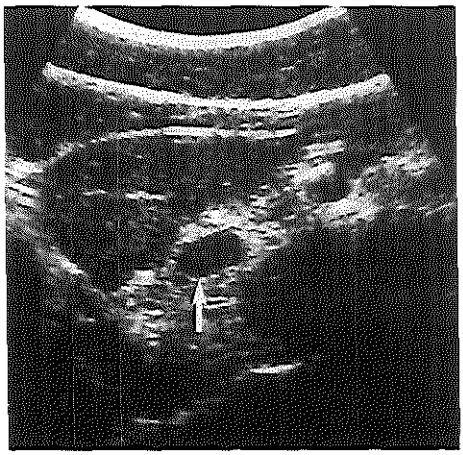

Figure 4.3
Saggital sonogram of the upper abdomen in a patient with squamous cell carcinoma of the middle third of the oesophagus shows an enlarged, hypoechoic, metastatic lymph node (arrow) posterior to the left hepatic lobe.

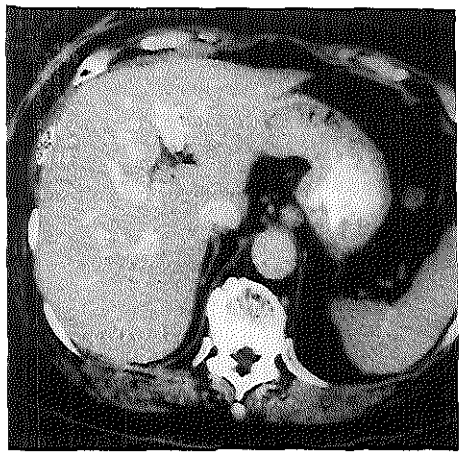

Figure 4.4
Axial contrast material-enhanced CT scan in a patient with squamous cell carcinoma of the lower oesophagus shows an enlarged metastatic coeliac lymph node between the aorta and the stomach.

Liver and other nonlymphatic metastases

There was no significant difference between the assessment of these metastases by US or CT ($p = 1.0$). Metastases were correctly predicted on US and CT scans in eight of 10 patients (80%) (liver metastases in five, peritoneal carcinomatosis in two and renal metastasis in one) (Figs. 4.5 and 4.6). Liver metastases were not detected on either US or CT scans in the two patients with small (< 1.0 cm) metastases at surgery. Adrenal metastases were incorrectly predicted on CT scans in two other patients and on US scans in one of these patients, but proved incorrect by cytologic study and subsequently at surgery.

Distant metastases

Table 4.4 summarizes the results of US and CT studies in assessing the presence or absence of distant metastases in each of 113 patients with cytological (29 patients) or surgical (84 patients) correlation. Fifty-four patients had distant metastases, either supraclavicular or abdominal. There was no significant difference between US or CT scans in assessing distant metastases ($p = 1.0$). Distant metastases were correctly predicted on US scans in 33 of 54 (61%) patients and on CT scans in 38 of 54 (70%) patients. The combination of US and CT correctly predicted distant metastases in 45 of 54 (83%) patients. A false positive diagnosis was made in four patients on US scans, in nine patients on CT scans and in 11 patients when both techniques were combined, respectively.

Table 4.3 Correlation of US and CT findings with cytological and surgical data in assessing distant abdominal metastases

Results of US and CT studies	Coeliac nodes[a], n = 86		Liver and other non-lymphatic sites[b], n = 92	
	US	CT	US	CT
True positive	8	13	8	8
False negative	19	14	2	2
False positive	0	4	1	2
True negative	59	55	81	80
Sensitivity (%)	30[c] (14- 50)	48 (29-68)	80 (44- 98)	80 (44- 98)
Specificity (%)	100 (94-100)	93 (84-98)	99 (93-100)	98 (92-100)

[a] Correlated in 86 patients; by cytology in 2, at surgery in 84.

[b] Correlated in 92 patients; by cytology in 8, at surgery in 84, including 2 with negative cytology of the adrenal glands prior to surgery.

[c] 95% confidence interval in parentheses.

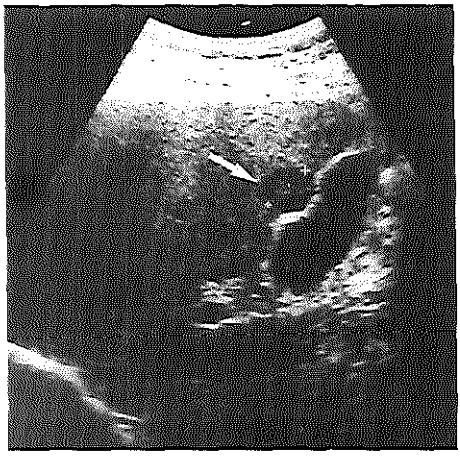

Figure 4.5
Oblique intercostal sonogram through the liver in a patient with adenocarcinoma of the gastro-oesophageal junction shows a hypoechoic metastatic nodule (arrow) adjacent to the gallbladder

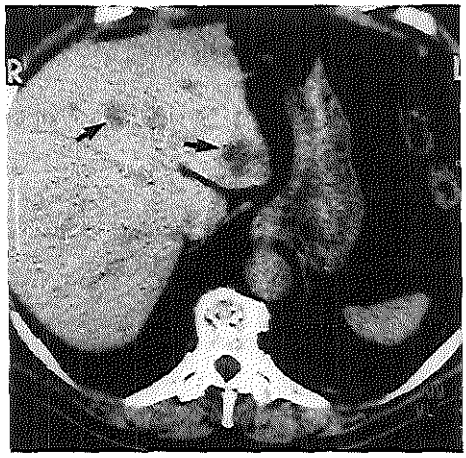

Figure 4.6
Axial contrast material-enhanced CT scan in a patient with adenocarcinoma of the gastro-oesophageal junction shows multiple hypoattenuated hepatic metastases (arrows).

Table 4.4 Correlation of US and CT findings with cytological and surgical data in assessing presence or absence of distant metastases (supraclavicular and abdominal) in each of 113 patients.

Results of US and CT studies	Distant sites, total numbers of patients (n = 113)		
	US	CT	US + CT
True positive	33	38	45
False negative	21	16	9
False positive	4	9	11
True negative	55	50	48
Sensitivity (%)	61 (47-74)	70 (56-82)	83 (71-92)
Specificity (%)	93 (84-98)	85 (73-93)	81 (69-90)

95% confidence interval in parentheses.

4.5 Discussion

Carcinoma of the oesophagus and gastro-oesophageal junction has a poor prognosis because many patients have advanced widespread disease at the time of clinical presentation and are not curable by surgical resection [8-11]. This is reflected by the fact that 54 of 113 (48%) patients who were staged had distant metastases proven by either cytological or histopathological examination.

In our institution THE is the standard procedure for resection of oesophageal and gastro-oesophageal junction carcinoma because the postoperative morbidity and mortality are less than with transpleural oesophagectomy including thoracotomy [12]. However, the supraclavicular lymph nodes are not systematically dissected in patients who undergo THE and enlarged neck nodes are removed and examined only unilaterally.

This limited verification of the state of the supraclavicular nodes in the present study means that the false negative findings and the specificity of the US and CT studies should be interpreted with caution. In order to achieve the best available nonsurgical estimate of the numbers of false negative findings on CT and US studies, these studies were reevaluated in cases of conflicting results. Furthermore, biopsies were performed in cases when nodes could be detected on repeated US studies after they had initially been detected on CT studies alone. Optimal verification of the state of the supraclavicular nodes can only be obtained when these nodes are bilaterally dissected at surgery. However, it was not considered ethical to extend the surgical procedure by performing these dissections.

The significance of examining the supraclavicular lymph nodes radiologically in patients with carcinoma of the oesophagus and gastro-oesophageal junction has been reported previously and is confirmed in the present study [6]. Both US and CT were clearly superior to palpation in the assessment of supraclavicular metastases. The relatively high numbers of false positive diagnoses on US and CT studies of the supraclavicular lymph nodes were due to the fact that these lymph nodes were considered abnormal when they had a short axis of 5 mm or more. When supraclavicular nodes were considered abnormal only when they had a short axis of 10 mm or more the number of false positive diagnoses decreased from six to one on US studies and from five to one on CT studies. However, the numbers of false negative findings increased from four to eight on US studies and from three to six on CT studies with consequent decreases in sensitivity to 58% and 68%, respectively (results not shown). Therefore, we prefer to perform FNABs of supraclavicular nodes with a short axis of 5 mm or more to confirm or exclude the presence of metastases by cytology.

US and to a lesser degree CT were limited in the assessment of coeliac lymph node metastases. Only a minority of metastatic nodes were detected on US scans and normal sized nodes were invariably not seen. The relatively low sensitivity of CT in detecting coeliac metastases has been reported by others [2,3] and is explained by the fact that normal sized lymph nodes may harbor metastases. The number of false positive findings on CT scans confirms the reports of other authors that lymph nodes may enlarge because of inflammatory processes [3].

Our results in assessing liver metastases with US and CT are comparable to the CT results reported by Halvorsen and Thompson [3]. In the present study neither US nor CT was superior in detecting metastatic nodules. However, at CT contrast was administered with a drip infusion, and better results of CT scanning of the liver may be obtained by dynamic bolus injection of contrast and rapid table incrementation during injection, but this technique is rather demanding to use for screening purposes [13].

Although peritoneal carcinomatosis was correctly predicted on US and CT studies in two patients with ascites, it can be very difficult to diagnose in the absence of ascites. However, because of the low prevalence of peritoneal carcinomatosis in the present study, the use of intraperitoneal contrast for better CT detection of peritoneal metastases is not advocated in patients with oesophageal and gastro-oesophageal junction carcinoma [14]. In assessing distant metastases US and to a lesser degree CT were characterized by a relatively low sensitivity and relatively high specificity. Although CT was slightly more sensitive than US in detecting distant metastases the difference was not statistically significant. This was not altered by including pulmonary findings on CT, as although one patient had pulmonary metastases, coeliac lymph node metastases were correctly predicted by both scanning techniques in this patient (results not shown).

With the combination of US and CT the sensitivity increased to an acceptable level. Although this was accompanied by a decrease in specificity this is considered to be less important because FNABs can be performed to enable cytological examination. In our study US guidance was used for biopsies. However, CT guidance is a well established alternative, especially for biopsies of abdominal lesions and can be performed in patients with abdominal lesions only detected on CT scans [15].

In conclusion, the combination of US and CT should be used for the assessment of distant metastases in carcinoma of the oesophagus and gastro-oesophageal junction. For logistic and cost-effective reasons we recommend US as the initial examination and the use of US-guided FNAB to confirm positive findings. Patients without lesions on US scans should undergo CT. When lesions are detected on CT scans either US-guided or CT-guided biopsies can be performed.

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Chapter 5

Assessment of Distant Metastases with Ultrasound-guided Fine-Needle Aspiration Biopsy and Cytologic Study in Carcinoma of the Esophagus and Gastroesophageal Junction

(Assessment of Metastases with US-guided FNAB)

5.1 Abstract

The use of ultrasound (US)-guided fine-needle aspiration biopsy (FNAB) for the assessment of distant metastases was prospectively studied in 135 consecutive patients with carcinoma of the esophagus and gastroesophageal junction. Patients with accessible lesions on US and computed tomographic studies of the supraclavicular regions and the abdomen underwent US-guided FNAB. In patients with multiple lesions biopsies were preferentially performed on enlarged supraclavicular nodes. Forty-nine patients underwent US-guided FNABs of 53 lesions. A cytologic diagnosis was established in 46 of 53 (87%) biopsies. Seven of 53 (13%) biopsies were nondiagnostic. Distant metastases were diagnosed by means of cytologic study in 33 of 135 (24%) patients. Supraclavicular metastases were diagnosed in 22 patients and abdominal metastases were diagnosed in 12 patients, including one patient who also had supraclavicular metastases. US-guided FNAB can improve the selection of patients for surgical and nonsurgical treatment by diagnosing distant metastases in an important number of patients.

5.2 Introduction

Carcinoma of the esophagus and gastroesophageal junction has a poor prognosis [1-5]. Surgical treatment is associated with a high postoperative morbidity and mortality, and the long-term survival of surgically treated patients is negatively affected by an advanced stage of disease [2-4].

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Preoperative assessment of distant metastases is of great importance, because in cases of metastatic spread to distant sites surgery can be refrained from, or can be limited to, a palliative resection. Search for metastases is usually performed with ultrasound (US), computed tomography (CT), and endosonography. Recent reports [6-8], however, show that none of these techniques is reliable enough to correctly predict the presence of metastases and, thus, in case of a suspect lesion, cytologic or histologic proof of metastases is mandatory to avoid overstaging. Diagnosing metastases by means of cytologic study will prevent unnecessary surgical procedures in some patients, and will improve selection of patients that can benefit from surgery. The purpose of this study was to evaluate the use of ultrasound (US)-guided fine-needle aspiration biopsy (FNAB) for the assessment of distant metastases in carcinoma of the esophagus and gastro-esophageal junction. The utility of US-guided FNAB was determined by the number of biopsies in which adequate material for cytologic examination could be obtained and by the number of patients in which distant metastases could be proved by means of cytologic study.

5.3 Materials and methods

Between January 1989 and December 1990, 135 consecutive patients with a biopsy-proven carcinoma of the intrathoracic esophagus and/or gastroesophageal junction were referred to the Rotterdam Esophageal Tumor Study Group for treatment. Sixty-six patients had squamous cell carcinoma, 63 patients had adenocarcinoma and six patients had undifferentiated carcinoma. Staging was performed according to the classification of the American Joint Committee on Cancer [9].

Forty-nine patients underwent US-guided FNABs of accessible lesions on US and/or CT studies to confirm or exclude the presence of distant metastases (stage IV disease) by means of cytologic study. In patients with multiple lesions, biopsies were preferentially performed of supraclavicular nodes. Forty-five patients underwent biopsies of one lesion and four patients underwent biopsies of two lesions. An average of two needle passes was made in each biopsy session. All biopsies were performed by using real-time sonographic guidance (Aloka SSD-630 and Aloka SSD-650, Tokyo, Japan). US-guided FNAB of supraclavicular lymph nodes with a short axis that ranged from 0.5 - 2.0 cm was performed in 34 patients. US-guided FNAB of hepatic lesions with a diameter that ranged from 1.0 - 6.0 cm was performed in seven patients and of celiac lymph nodes with a short axis that ranged from 1.0 - 4.0 cm in seven patients. US-guided FNAB of a solid renal mass was performed in one patient, of enlarged adrenal glands in two patients and of ascites in two patients. Supraclavicular biopsies were performed in a

"free-hand" manner using a 7.5-MHz linear array transducer and a 23-gauge needle (Sherwood Medical, Ballymoney, Northern Ireland). Aspiration of ascites was done in a "free-hand" manner using a 5.0-MHz linear array transducer. All other abdominal biopsies were performed using a 3.5-MHz sector scanner with an attachable needle guide and a 22-gauge needle (Cook, Spencer, Indiana, USA). In all cases the needle was connected with a 24-cm hollow flexible cannula (Polystan, Almere, The Netherlands) which was connected with an empty 12-ml syringe held by an assistant who applied suction after the lesion had been punctured (Fig. 5.1).

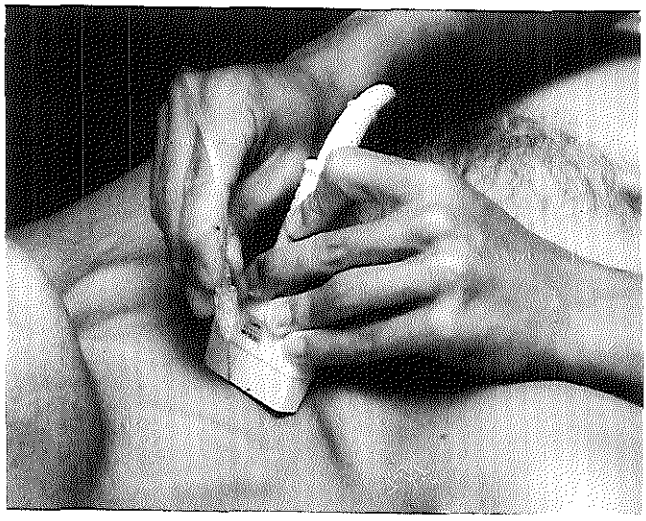

Figure 5.1
US-guided FNAB of a supraclavicular lymph node with a 23-gauge needle and an interconnecting cannula.

Smears obtained from the aspirated material were air dried for 10 minutes, stained with May-Grünwald-Giemsa staining methods, and examined by an experienced cytopathologist. Biopsies were considered diagnostic when the specimens contained either metastatic cells or benign cells of the biopsied tissue in an adequate amount to be classified as negative for malignancy. Biopsies were considered nondiagnostic in cases of bloody, necrotic, or hypocellular specimens.

Patients with distant metastases proved by means of cytologic study were excluded from surgery. The remaining patients, with the exception of 11 patients who had a poor general condition, underwent surgery. Patients with a resectable tumor at surgery underwent transhiatal esophagectomy (THE) with gastric interposition and cervical gastroesophageal anastomosis [10]. In patients with an irresectable tumor surgery was abandoned after laparotomy.

5.4 Results

Table 5.1 summarizes the results of US-guided FNAB and cytologic studies in the assessment of distant metastases.

Supraclavicular metastases

Thirty-four patients underwent US-guided FNAB of supraclavicular lymph nodes with a short axis of 5 mm or more. A cytologic diagnosis was established in 30 of 34 (88%) biopsies. Four of 34 (12%) biopsies were nondiagnostic.

Supraclavicular metastases were diagnosed in 22 of 135 (16%) patients; 15 of 66 (23%) patients with squamous cell carcinoma, six of 63 (10%) patients with adenocarcinoma and one of six (17%) patients with undifferentiated carcinoma. In only five of 22 (23%) patients with supraclavicular metastases, enlarged nodes were also palpable.

Metastatic nodes were not found at THE in six of eight patients with benign cells at cytologic examination and in three of four patients with nondiagnostic biopsies. In the other three patients, the supraclavicular regions were not surgically assessed because the tumor was considered irresectable at surgery.

Table 5.1 Results of US-guided FNAB and cytologic studies in assessing distant metastases

	US-guided FNAB	Cytologic diagnosis		
		Metastases	Benign cells	Nondiagnostic
Supraclavicular nodes, total	34	22	8	4
Squamous cell carcinoma	19	15 [a-c]	3	1
Adenocarcinoma	13	6	5	2
Undifferentiated carcinoma	2	1	0	1
Abdominal lesions, total	19	12	4	3
Squamous cell carcinoma	9	4 [a]	3 [b]	2 [c]
Adenocarcinoma	10	8 [d]	1	1 [d]
Distant metastases, total	53	34	12	7
Squamous cell carcinoma	28	19	6	3
Adenocarcinoma	23	14	6	3
Undifferentiated carcinoma	2	1	0	1

Numbers are numbers of biopsies. Forty-nine patients underwent 53 biopsies; 45 patients underwent one biopsy and four patients underwent two biopsies.

[a] Supraclavicular and liver metastases cytologically proven in one patient.

[b] Supraclavicular metastases cytologically proven in one patient with benign results on cytologic studies of the celiac nodes.

[c] Supraclavicular metastases cytologically proven in one patient with a nondiagnostic biopsy of the celiac nodes.

[d] Peritoneal carcinomatosis cytologically proven in one patient with a nondiagnostic biopsy of the liver.

Abdominal metastases

US-guided FNAB of 19 abdominal lesions was performed in 18 patients. A cytologic diagnosis was established in 16 of 19 (84%) biopsies. Three of 19 (16%) biopsies were nondiagnostic.

Abdominal metastases were diagnosed in 12 of 135 (9%) patients; four of 66 (6%) patients with squamous cell carcinoma and eight of 63 (13%) patients with adenocarcinoma. The sites where abdominal metastases were cytologically proven are shown in Table 5.2. Three of four patients with benign results on cytologic studies of abdominal lesions underwent surgery. Benign results on cytologic studies of the adrenal glands were confirmed at surgery in two of these patients.

Table 5.2 Results of US-guided FNAB and cytologic studies of abdominal metastases

	US-guided FNAB	Cytologic diagnosis		
		Metastases	Benign cells	Nondiagnostic
Abdominal lesions, total	19	12	4	3
Liver	7	6	0	1
Squamous cell carcinoma	1	1 [a]	0	0
Adenocarcinoma	6	5	0	1 [d]
Celiac nodes	7	3	2	2
Squamous cell carcinoma	6	2	2 [b]	2 [c]
Adenocarcinoma	1	1	0	0
Adrenal glands	2	0	2	0
Squamous cell carcinoma	1	0	1	0
Adenocarcinoma	1	0	1	0
Peritoneum (ascites)				
Adenocarcinoma	2	2 [d]	0	0
Kidney				
Squamous cell carcinoma	1	1	0	0

Numbers are numbers of biopsies. Eighteen patients underwent 19 biopsies of abdominal lesions.

[a] Supraclavicular metastases and liver metastases cytologically proven in one patient.

[b] One of two patients with benign results on cytologic studies of the celiac nodes also had cytologically proven supraclavicular metastases.

[c] One of two patients with nondiagnostic biopsies of the celiac nodes also had cytologically proven supraclavicular metastases.

[d] Peritoneal carcinomatosis was cytologically proven in one patient with a nondiagnostic biopsy of the liver.

In the third patient cytologic studies of the celiac nodes showed benign cells only, however, celiac metastases were nevertheless found at surgery. Surgery was not performed in another patient with a benign cytologic result of a celiac biopsy because the patient also had cytologically proven supraclavicular metastases. One of three patients with nondiagnostic biopsies of abdominal lesions underwent surgery; metastases were not found at surgery in this patient with a nondiagnostic biopsy of the celiac nodes. Two other patients with nondiagnostic biopsies of abdominal lesions were excluded from surgery because of cytologically proven metastases at other sites; one patient with a nondiagnostic biopsy of the celiac nodes also had supraclavicular metastases and one patient with a nondiagnostic biopsy of the liver also had peritoneal carcinomatosis.

Distant metastases

In total, US-guided FNAB of 53 lesions was performed in 49 patients. A cytologic diagnosis was established in 46 of 53 (87%) biopsies. Seven of 53 (13%) biopsies were nondiagnostic.

Distant metastases were diagnosed by means of cytologic study in 33 of 135 (24%) patients; 18 of 66 (27%) patients with squamous cell carcinoma, 14 of 63 (22%) patients with adenocarcinoma, and one of six (17%) patients with undifferentiated carcinoma. In one patient with squamous cell carcinoma, both supraclavicular and hepatic metastases were cytologically proven. No complications, other than localized mild discomfort, were observed in patients undergoing US-guided FNAB.

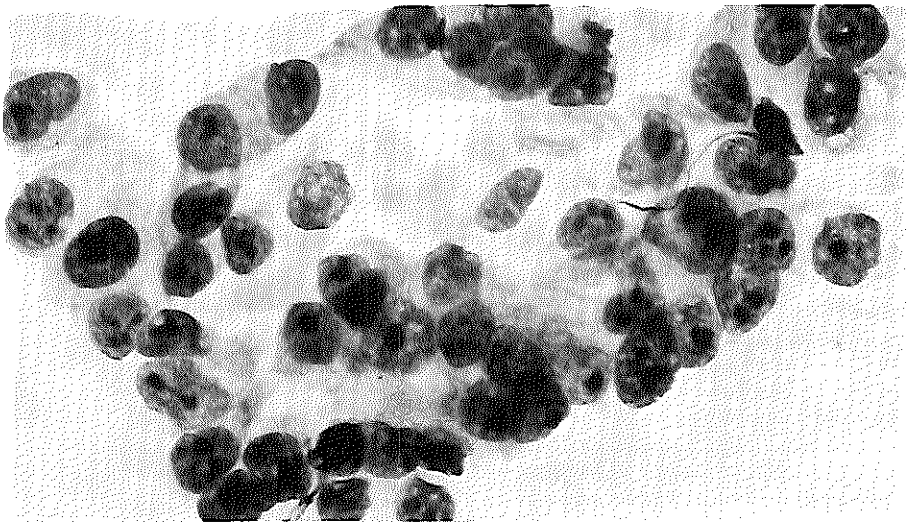

Figure 5.2 Needle aspirate of a metastatic lymph node in a patient with adenocarcinoma of the gastro-esophageal junction shows atypical epithelial cells with finely vacuolated cytoplasm in acinar arrangement (x400, May-Grünwald-Giemsa stain).

5.5 Discussion

In most institutions the presence of cytologically proven distant metastases will importantly affect the therapeutic approach in carcinoma of the esophagus and gastroesophageal junction. The number of diagnostic biopsies in the present series shows the value of US-guided FNAB in obtaining material for cytologic examination (Figs. 5.2 and 5.3).

CT guidance is a well-established alternative for US guidance, but it is more time consuming and expensive [11,12]. Furthermore we believe that real time visualization of lesions provided by US guidance is an advantage in cases of mobile and superficial lesions [11]. We agree with Reading et al. that clear visualization of the biospy needle is the key element in a successful biopsy [13]. With small target lesions, such as supraclavicular lymph nodes, there is a risk of displacing the needle tip out of the lesion during suction required to obtain cells. Therefore, in cases of FNABs with small-caliber needles for cytologic studies we use an interconnecting cannula which allows the operator to hold both the US probe and the needle during the whole procedure. Thus, subtle adjustments can be made while puncturing the lesion and the tip of the needle can be kept inside the lesion while it is moved up and down under direct US visualization during the appliance of suction. US-guided FNABs of enlarged supraclavicular lymph nodes were preferentially performed. Supraclavicular biopsies cause less patient discomfort compared with abdominal biopsies, do not require the use of local anesthetics and are not hindered by respiratory movements or overlying bowel shadow.

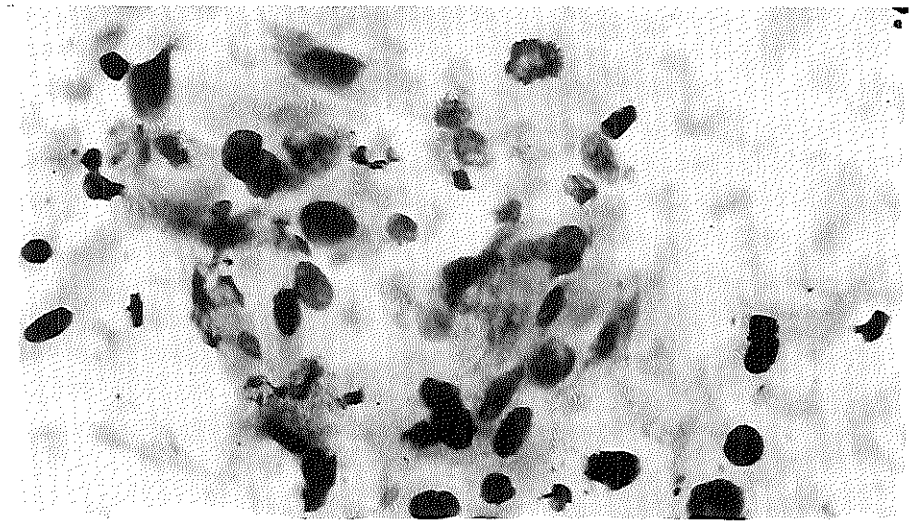

Figure 5.3 Needle aspirate of a metastatic lymph node in a patient with squamous cell carcinoma of the esophagus shows a cluster of, and some dispersed, atypical epithelial cells with hyperchromatic nuclei and keratinized cytoplasm (x400, May-Grünwald-Giemsa stain).

The superficial location of the nodes contributes to the ease of the procedure [8].
Rizzatto et al. reported successful US-guided FNABs of superficial lesions in 97% of cases [14]. In our series a cytologic diagnosis was established in 88% of supraclavicular biopsies. The greater number of nondiagnostic biopsies in our series is probably due to the small size of the nodes in these cases (5-10 mm).
A cytologic diagnosis was established in 84% of abdominal biopsies. US-guided FNAB of celiac lymph nodes was occasionally hindered by respiratory movements and overlying bowel shadow, which is reflected in the lower percentage of celiac biopsies (72%) that provided a cytologic diagnosis, compared to supraclavicular biopsies (88%), even though the supraclavicular nodes were usually smaller in size.
Distant metastases were diagnosed by means of cytologic study in 24% of patients who were subsequently excluded from surgery. By excluding these patients from surgery we hope to improve the selection of patients who will benefit from surgery and thus improve the long-term survival in this group of surgically treated patients.
Supraclavicular metastases were diagnosed more often in patients with squamous cell carcinoma than in patients with adenocarcinoma. The prevalence of supraclavicular metastases in both groups of patients, however, underlines the importance of examining these nodes thoroughly. Abdominal metastases were diagnosed more often in patients with adenocarcinoma, which is probably due to the more caudal location of adenocarcinomas compared to squamous cell carcinomas. In patients with benign results on cytologic studies, metastatic involvement of the cytologically assessed sites was nevertheless proven at surgery in one patient with a celiac biopsy. Probably cells were obtained from the nonmalignant part of the node. This stresses the importance of repeating biopsies in cases of unexpected negative cytologic findings. In the remaining patients with either benign results on cytologic studies or nondiagnostic biopsies, metastatic involvement of the cytologically assessed sites was not found at surgery. However, because surgery was not performed in all of these patients and because the supraclavicular nodes are not systematically dissected, but are only removed unilaterally when enlarged at THE, these results should be interpreted with caution.
In conclusion, distant metastases were proven by means of US-guided FNAB and cytologic study in an important number of patients. It is our opinion that cytologic proof of distant metastases will help to select patients for surgical and nonsurgical treatment.

5.6 References

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Chapter 6

CT Assessment of Resectability in Patients Undergoing Transhiatal Esophagectomy for Esophageal and Gastroesophageal Junction Carcinoma

(CT Assessment of Resectability)

6.1 Abstract

The ability of preoperative computed tomography (CT) to assess resectability and to stage carcinoma of the esophagus and gastroesophageal junction was studied in 71 patients who underwent transhiatal esophagectomy. Patients with preoperatively proven distant metastases who did not have surgery were not included in the present study. At surgery the tumor invaded adjacent mediastinal or abdominal structures in 18 patients (prevalence 25%), but was nonresectable in only seven of these 18 (39%) patients. Invasion of the tracheobronchial tree, the aorta and the diaphragm were correctly detected on CT in 5 of 6, 1 of 2 and 2 of 10 patients. There were four false positive results on CT; tracheobronchial invasion and pericardial invasion were incorrectly predicted in one and three patients, respectively. Invasion of adjacent structures was correctly assessed on CT in 58 (82%) patients and the depth of tumor invasion was correctly determined in 49 (69%) patients. CT correctly staged 57% of patients according to the classification of the American Joint Committee on Cancer. Understaging (31%) occurred more often than overstaging (11%). In the present study, CT was not effective in assessing nonresectability by diagnosing invasion because of the relatively low prevalence of invasion of adjacent structures and the fact that invasion was often not associated with nonresectability. In assessing invasion itself, CT was accurate in diagnosing tracheobronchial involvement, but was limited in diagnosing invasion of other adjacent structures. In assessing stage grouping, CT was limited in detecting either diaphragmatic invasion or lymph node involvement.

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J Comput Assist Tomogr: in press.

6.2 Introduction

In patients with carcinoma of the esophagus and gastroesophageal junction, pretreatment staging is used for planning the therapeutic management. Assessment of resectability is of great importance because in locally advanced, nonresectable tumors, patients can be spared unnecessary surgical procedures. At present, computed tomography (CT) is used for staging esophageal and gastroesophageal junction carcinoma in many institutions, but controversy persists regarding the accuracy of CT in preoperative staging [1-6]. At our institution, transhiatal esophagectomy with gastric interposition and cervical gastroesophageal anastomosis (THE) is performed for resection of both esophageal and gastroesophageal junction carcinoma [7-9]. This study was performed to define the role of CT in assessing resectability of these tumors and to determine the accuracy of CT in classifying esophageal and gastroesophageal junction carcinoma according to the tumor node metastasis classification of the American Joint Committee on Cancer (AJCC) [10].

6.3 Patients and Methods

Seventy-one patients, 59 men and 12 women, 43-76 years old (mean, 61.8 years), with a histologically proven primary malignant tumor of the esophagus and gastroesophageal junction, who underwent both complete CT examinations and surgery at our institution between January 1989 and December 1990, were studied. Eleven of 71 patients had received either radiation therapy (one patient) or chemotherapy (10 patients) prior to CT scanning and surgery.

Not included in the present study are 32 patients with distant metastases detected on ultrasound (n=27) and CT (n=29) studies and proven by cytologic biopsy (n=29) and exploratory laparotomy (n=3), without surgical assessment of tumor resectability.

The tumors were classified by anatomic region as defined by the AJCC, as follows [10]. The upper thoracic esophagus extends from the thoracic inlet to the level of the tracheal bifurcation. The middle thoracic esophagus is the proximal half and the lower thoracic esophagus is the distal half of the esophagus between the tracheal bifurcation and the gastroesophageal junction.

All patients underwent CT scanning of the supraclavicular regions with 5-or 6-mm-thick contiguous sections and contiguous CT scanning of the chest and upper abdomen with 8-12-mm-thick contiguous sections by means of a Somatom Plus Scanner (Siemens, Erlangen, Germany) or a Tomoscan 350 (Philips Medical Systems, Eindhoven, the Netherlands). Additional 5-or 6-mm-thick contiguous sections were obtained at the level of the primary tumor in cases of an uncertain relationship between the tumor and the

surrounding structures. Contrast material was administered intravenously in all patients to better define the vascular structures and a swallow of diluted (1:20) contrast material (Meglumine-ioxithalamate; Telebrix, Laboratoires Guerbet, France) was routinely given. The CT scans were reviewed independently of the surgical records by two radiologists.

Evaluation of invasion of adjacent structures was based on the following criteria. In tumors of the upper and middle thoracic esophagus, involvement of the tracheobronchial tree was predicted when an esophageal tumor mass either caused inward bowing of the posterior tracheal or bronchial wall or displaced the trachea and/or bronchi away from the spine. In tumors of the middle and lower thoracic esophagus, involvement of the pericardium was predicted when the tumor extended directly to the pericardium, obliterating the fat planes at this level when normal fat planes were present immediately above and below the tumor mass. In tumors of the lower esophagus and gastro-esophageal junction, involvement of the diaphragm was predicted when the crura were surrounded by tumor mass. In all regions, involvement of the aorta was predicted when the tumor was in contact with the aorta, obliterating the periaortic fat in an arc greater than 90°. Anatomical extent of the primary tumor and involvement of lymph nodes were determined for all tumors on CT. Increased radiodensity of periesophageal or peri-gastroesophageal fat or ill defined outlines of the tumor indicated extramural tumor growth (pT3). Lymph nodes were considered abnormal when they had a short axis of 1 cm or more. Each tumor was classified into the stage groups designated by the AJCC [10]. The accuracy of CT for staging was determined by comparing the CT findings with the surgical and histopathologic findings. Patients underwent surgery within a mean of 20 days after CT scanning. Invasion of adjacent structures (pT4) was considered present when the tumor was seen macroscopically to have invaded these structures at surgery.

6.4 Results

Two patients had squamous cell carcinoma of the upper thoracic esophagus, 16 patients had carcinoma of the middle esophagus (squamous cell carcinoma, n=15; undifferentiated carcinoma, n=1), 37 patients had carcinoma of the lower esophagus (squamous cell carcinoma, n=14; adenocarcinoma, n=22; undifferentiated carcinoma, n=1) and 16 patients had carcinoma of the gastroesophageal junction (adenocarcinoma, n=14; undifferentiated carcinoma, n=2).

Table 6.1 CT assessment of tumor invading adjacent structures

	Results[a]						
	TP	FN	TN	FP	Sensitivity	Specificity	Accuracy
Tracheobronchial involvement	5 (1)	1	11	1	0.83	0.92	0.89
Aortic involvement	1	1 (1)[b]	69	0	0.50	1.00	0.99
Pericardial involvement	0	0	50	3	–	0.94	0.94
Diaphragmatic involvement	2 (1)	8 (4)[b]	43	0	0.20	1.00	0.85

Numbers are numbers of patients.
Numbers in parentheses are numbers of patients with nonresectable tumors.
Not shown is the false-negative result on CT in a patient with a nonresectable tumor that invaded the mesocolon transversum.
TP, true positive; FN, false negative; TN, true negative; FP, false positive. In one patient with a nonresectable tumor, neither aortic involvement nor diaphragmatic involvement was assessed on CT.

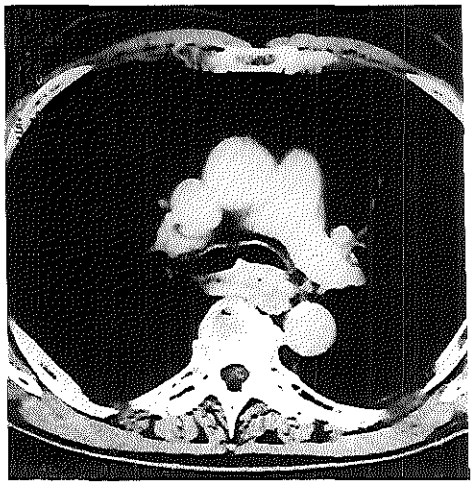

Figure 6.1
Axial contrast material - enhanced CT scan from a 61-year-old man with squamous cell carcinoma of the middle thoracic esophagus. A large esophageal mass indents the posterior wall of the left mainstem bronchus. Invasion and nonresectability were confirmed at surgery.

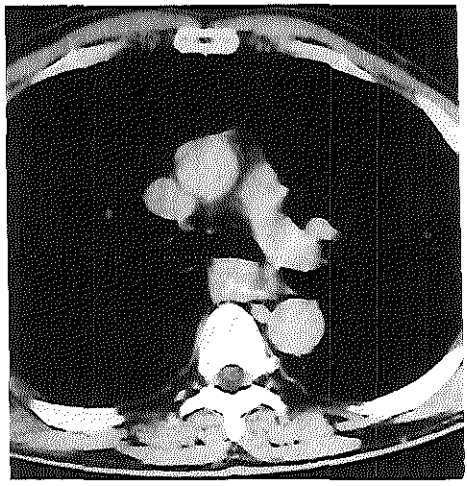

Figure 6.2
Axial contrast material - enhanced CT scan from a 62-year-old man with undifferentiated carcinoma of the middle thoracic esophagus. A large mass indents the posterior wall of the left mainstem bronchus. There was no invasion at surgery and at histopathologic examination the tumor only invaded the muscularis propria (pT2).

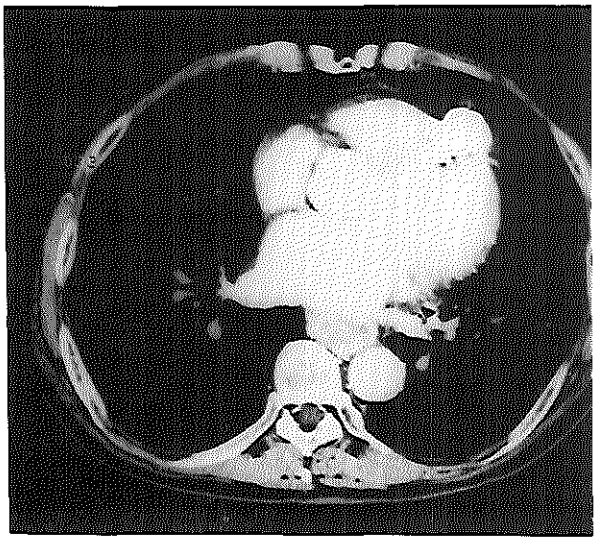

Figure 6.3
Axial contrast material-enhanced CT scan from a 74-year old man with squamous cell carcinoma of the lower thoracic esophagus. Fat planes are absent between the tumor mass and the pericardium. At surgery, however, pericardial invasion was absent.

CT Assessment of Resectability

In 53 of 71 (75%) patients, the tumor was not adherent to the adjacent mediastinal and abdominal structures at surgery and could be removed without difficulty. The tumor invaded adjacent structures in the remaining 18 patients (prevalence 25%) (Table 6.1). In seven (39%) of these patients the tumor was nonresectable. In the other 11 (61%) patients, the tumor could be resected. However, laceration of the left mainstem bronchus occurred in one of 11 patients and the surgical procedure had to be extended in six other patients: laryngectomy in one patient and partial resection of the diaphragm in five patients. Involvement of the tracheobronchial tree could be identified on CT in all but one patient (Fig. 6.1). In this patient the tumor was adherent to the left mainstem bronchus, but could nevertheless be resected. There was one false positive result in a patient with a large undifferentiated carcinoma that indented the posterior wall of the left mainstem bronchus on CT. However, at histopathologic examination the tumor invaded only the muscularis propria (pT2) (Fig. 6.2). Involvement of the aorta was correctly predicted on CT in one of two patients. In the other patient who had been preoperatively treated with chemotherapy, 60° of the aortic circumference was in contact with the tumor. None of the tumors was adherent to the pericardium at surgery. However, in three patients pericardial invasion was incorrectly predicted on CT (Figs. 6.3 and 6.4). Involvement of the diaphragm was correctly identified on CT in two of 10 patients. In one of these patients, the tumor was nonresectable, in the other the tumor could be resected by resecting a part of the diaphragm (Fig. 6.5).

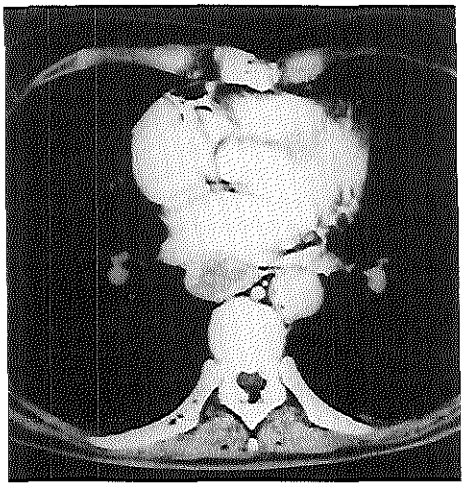

Figure 6.4 a
Axial contrast material - enhanced CT scan from a 72-year-old woman with squamous cell carcinoma of the lower thoracic esophagus. At this level fat planes are absent between the tumor mass and the pericardium.

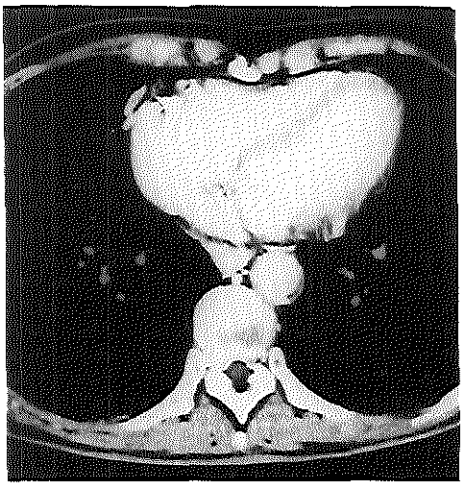

Figure 6.4 b
Axial CT scan from the same patient shows fat planes present at a lower level. At surgery, pericardial invasion was absent.

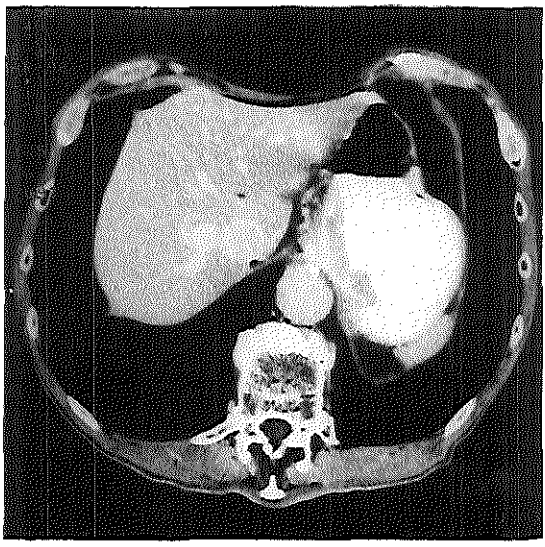

Figure 6.5
Axial contrast material - enhanced CT scan from a 76-year-old man with adenocarcinoma of the gastro-esophageal junction. The left diaphragmatic crus is surrounded by tumor. The CT findings were confirmed at surgery, the tumor was nonresectable.

False negative findings occurred in eight patients. In four of these patients, the tumor was considered nonresectable at surgery; due to invasion of the diaphragm and the pancreas in one patient, the diaphragm and the aorta in another patient, and the diaphragm alone in two patients. In another patient with a nonresectable tumor of the gastroesophageal junction, invasion of the mesocolon transversum was not assessed on CT studies.

CT Assessment of Depth of Invasion of Primary Tumor (pT)

At surgical/histopathological examination, the depth of invasion of the primary tumor was pTis - pT2 in 16 patients, pT3 in 37 patients and pT4 in 18 patients. The depth of invasion was correctly determined on CT in 49 of 71 (69%) patients. Thirteen of 71 (18%) patients were understaged and nine of 71 (13%) patients were overstaged.

When patients were excluded who had received chemotherapy or radiotherapy preoperatively, CT correctly staged 42 of 60 (70%) patients, understaged 12 of 60 (20%) patients and overstaged six of 60 (10%) patients. Preoperative CT could determine the absence (pTis-pT3) or presence (pT4) of invasion of adjacent structures with an accuracy of 82% (58 of 71 patients).

For those 10 patients who received chemotherapy preoperatively, CT findings (with a mean 56 day interval) before and after chemotherapeutic treatment were compared. A significant decrease in tumor size ($\geq$ 50% reduction of tumor size on axial CT scans) was observed in three patients. In addition, in one of these patients, one of two enlarged lymph nodes returned to normal size. A nonsignificant decrease in tumor size ($<$50%) was observed in two patients and a nonsignificant increase was observed in one patient. In four patients the tumor size remained unchanged. However, in all 10 patients, the depth of tumor invasion on CT scans before and after chemotherapy was identical. In the patient who received radiotherapy preoperatively, CT scans prior to radiation therapy were not available for comparison.

CT Assessment of Lymph Node Metastases

Mediastinal lymph nodes were surgically and histopathologically assessed in 64 of 71 patients and were not assessed in the remaining seven patients with a nonresectable tumor. Mediastinal lymph node metastases were found in the resected specimen of 10 of 64 (16%) patients. In assessing mediastinal lymph node metastases, CT had a sensitivity of 30%, a specificity of 85% and an accuracy of 77%.

Abdominal lymph nodes were surgically and histopathologically assessed in all 71 patients. Involvement of abdominal lymph nodes was found in 32 (45%) patients; perigastric nodes alone were found in 19 patients, celiac nodes alone were found in six patients and both perigastric and celiac nodes were found in seven patients.

CT had a sensitivity of 28%, a specificity of 90% and an accuracy of 62% in assessing abdominal lymph node metastases.

CT Assessment of Tumor Stage

Twenty-nine patients had stage I-II disease, 28 had stage III disease and 14 had stage IV disease. CT correctly staged 40 (57%) patients, understaged 23 (32%) patients and overstaged eight (11%) patients. Carcinomas of the esophagus were correctly staged in 30 of 55 (55%) patients and gastroesophageal junction carcinomas were correctly staged in 10 of 16 (63%) patients. When patients with preoperative chemotherapy or radiotherapy were excluded, CT correctly staged 37 (61%), understaged 19 (32%) and overstaged four (7%) of 60 patients. For the 10 patients who received chemotherapy preoperatively, tumor stages on CT scans before and after chemotherapeutic treatment were identical.

6.5 Discussion

Whether surgical resection for esophageal and gastroesophageal junction carcinoma should be regarded as a potentially curative or a palliative procedure remains a matter of controversy, but surgery is generally not recommended in patients with a nonresectable tumor. Thus, at our institution where THE is performed for both esophageal and gastroesophageal junction carcinoma, a major role of preoperative CT should be to determine suitability for resection.

Conflicting results are reported regarding the value of preoperative CT in staging esophageal and gastroesophageal junction carcinoma, partly because of the different prevalences of invasion of adjacent structures that are reported by different authors [2,3,11,12]. The prevalence of invasion will be determined by the selection of patients who have surgery. Whereas at some institutions patients have surgery regardless the presence of distant metastases [13], at our institution patients with cytologically proven distant metastases detected on ultrasound or CT studies are excluded from surgery [14,15]. The prevalence of invasion in our series was relatively low and in more than half the cases of invasion, the tumor could nevertheless be resected. This limited the value of CT to assess nonresectability by diagnosing invasion. Furthermore, CT was limited in assessing invasion itself.

CT was most accurate in assessing tracheobronchial involvement. Although this did not preclude resection in all patients, it occasionally complicated surgery, which is demonstrated by the accidental laceration of the bronchial tree in one of the patients.

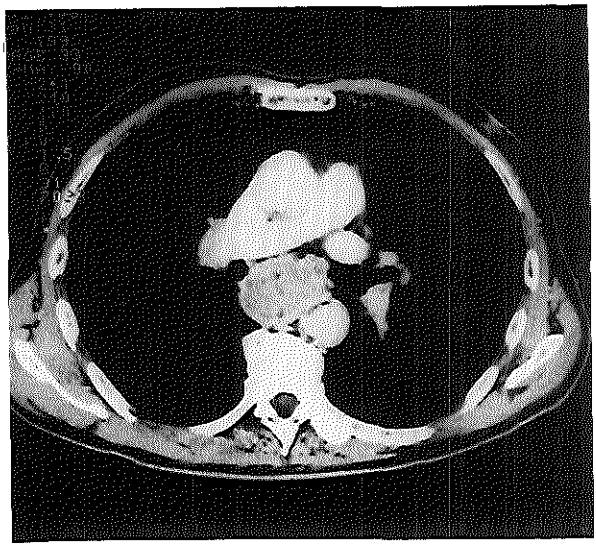

Figure 6.6
Axial contrast material - enhanced CT scan from a 67-year-old man with squamous cell carcinoma of the middle thoracic esophagus shows contact of 70° between the aorta and the tumor. A small atheromatous plaque is seen in the aortic wall. At surgery invasion was absent and the tumor could be resected without difficulty.

Our results in assessing tracheobronchial involvement on CT are comparable with those reported by Becker et al [11]. In their series, tracheobronchial involvement at THE was identified in all cases on CT. The false positive result in our series was caused by an undifferentiated carcinoma of the esophagus, and it has been suggested previously that CT is less accurate in staging these tumors [16].

The therapeutic management in patients with esophageal and gastroesophageal junction carcinoma will rarely be affected by aortic or pericardial invasion because these are only reported at autopsy in 3% and 1% of patients, respectively [17]. This is consistent with the results of the present study; aortic involvement was observed in only two of 71 patients and pericardial involvement was not found at surgery.

For the assessment of aortic involvement, we modified the CT criteria of Picus et al. [12]. According to their criteria, aortic invasion would have been considered indeterminate in eight patients with contact of 45-90° between the aorta and the tumor (Fig. 6.6). With the modified CT criteria (> 90° contact) there was one false negative result, but there were no indeterminate results. As reported by others, CT was of little help in assessing pericardial involvement [11,13]. However, pericardial involvement was occasionally simulated by motion artefacts and lack of periesophageal fat, which may be caused by the often poor nutritional status of patients with esophageal and gastroesophageal tumors [3]. With use of the criteria suggested by Halvorsen and Thompson, five patients with negative findings at surgery would have indeterminate findings on CT because of the lack of fat planes [1,16].

Similar to the reported experience, CT was inaccurate in predicting diaphragmatic invasion [6,11-13]. In our study, diaphragmatic involvement was considered present on CT scans only in cases in which the crura were surrounded by tumor mass. However, when invasion was predicted on the basis of broad contact between the tumor and the diaphragmatic crura over a length of 1 cm or more, there were no false negative findings, but 19 false positive findings on CT. Thus, the close relationship of the esophagus and the gastroesophageal junction with the diaphragm and the absence of intervening fat planes at this level cause great difficulty in assessing diaphragmatic involvement on CT scans (Figs. 6.7 and 6.8). Moreover, diaphragmatic involvement does not necessarily preclude resection, in our present study 50% of tumors with diaphragmatic invasion could be resected.

The different layers of the esophageal wall are not separately displayed on CT scans. Therefore, differentiation was only attempted among tumors within the wall (pT2 and less), tumors with extramural extension (pT3) and tumors invading the adjacent structures (pT4) [10]. Understaging was caused mainly by not recognizing diaphragmatic involvement. Overstaging may have been caused by inflammatory and desmoplastic reactions around the tumor that are often found at histopathologic examination. Excluding patients who received either chemotherapy or radiotherapy preoperatively did not improve the results.

CT was limited in assessing lymph node metastases and was characterized by a low sensitivity and a relatively high specificity, which has been reported previously by others [1,11,12]. This is explained because normal-sized nodes may harbor metastases [1]. The lower sensitivity of CT in assessing lymph node metastases in the present series compared to other series [1,6,11] is explained by the fact that our results concern only patients who underwent surgery. Patients with cytologically proven supraclavicular and celiac lymph node metastases detected on ultrasound and CT studies were excluded from surgery and these results are not included in the present report [14,15]. The false positive results of CT in assessing mediastinal lymph node metastases should be interpreted with caution, because the mediastinal nodes are not systematically dissected at THE [7-9]. This can also explain the lower prevalence of mediastinal lymph node metastases compared with abdominal lymph node metastases in our series.

In assessing stage grouping on CT, understaging occurred more often than overstaging. This was caused mainly by not detecting either diaphragmatic involvement or regional lymph node metastases in patients with a stage III tumor and by not detecting distant lymph node metastases in patients with a stage IV tumor. Excluding patients with preoperative chemotherapy or radiotherapy slightly decreased the number of understaged

patients, but the numbers of these patients are too small to draw any final conclusions. For those patients who received chemotherapy, similar results in assessing stage grouping on CT were obtained prior to and after chemotherapeutic treatment. However, only a limited number of patients were studied and the definitive role of CT in the follow-up of chemotherapeutically treated patients remains to be determined.

In conclusion, CT was not effective in assessing resectability of esophageal and gastroesophageal junction carcinoma in patients undergoing THE. This was caused by the relatively low prevalence of invasion of adjacent structures at surgery and the fact that invasion was often not associated with nonresectability. Furthermore, in assessing invasion, CT was accurate only in assessing tracheobronchial involvement.

In assessing stage grouping in surgically treated patients, CT had a tendency to understage rather than to overstage because of its limitation in detecting either diaphragmatic invasion or lymph node involvement.

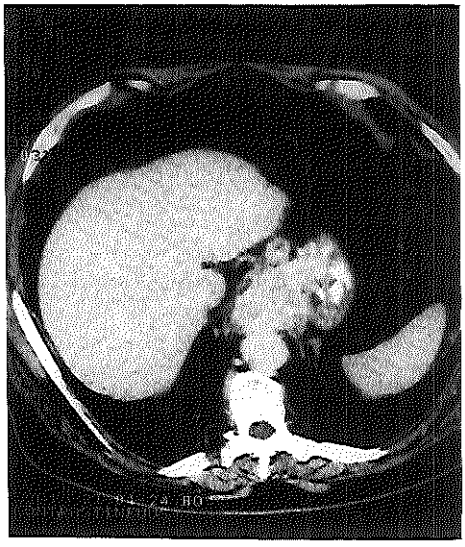

Figure 6.7
Axial contrast material - enhanced CT scan from a 67-year-old man with squamous cell carcinoma of the lower esophagus. Broad contact between the tumor and the diaphragmatic crura. However, at surgery invasion was absent (pT3).

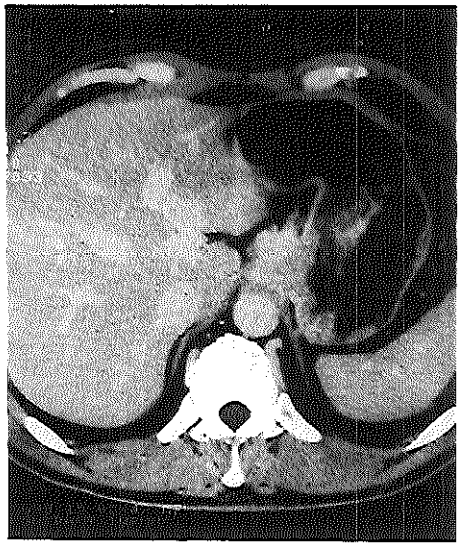

Figure 6.8
Axial contrast material - enhanced CT scan from a 44-year-old man with adenocarcinoma of the gastroesophageal junction. Broad contact between the tumor and the diaphragmatic crura. At surgery invasion was present and the tumor could not be resected (pT4).

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Chapter 7

Influence of Radiologically and Cytologically Assessed Distant Metastases on the Survival of Patients with Esophageal and Gastroesophageal Junction Carcinoma

(Survival in Esophageal and Gastroesophageal Cancer)

7.1 Abstract

Distant metastasis in carcinoma of the esophagus and gastroesophageal junction is associated with a poor survival following resection. In order to improve the selection of patients for surgical and nonsurgical treatment, the influence on survival of distant metastases, assessed on radiologic studies or proven on cytologic studies was determined. During the period 1989-1990, 135 patients were referred to our institution. On ultrasound or computed tomographic studies distant metastases were suspected in 62 patients and were absent in 73 patients. In 33 patients metastases were cytologically proven, 32 of these patients were subsequently excluded from surgery. Twelve other patients were unfit for surgery due to their general condition. The remaining 91 patients underwent surgery; 77 patients underwent transhiatal esophagectomy, the tumor was irresectable in 14 patients.

The 2-year survival for all patients suspected of distant metastases on radiologic studies was 11.2% and was 44.3% for patients without metastases on these studies ($p < 0.001$). For patients with cytologically proven metastases the 2-year survival (3%) was shorter than for patients suspected of distant metastases on radiologic studies that were not cytologically confirmed (21.1%) ($p < 0.001$). There was no statistically significant difference in survival between this last group of patients and those without metastases on radiologic studies ($p = 0.87$). Following resection the 2-year survival dropped from 53.9% to 0% when distant metastases were present on histopathologic studies of the resected specimen ($p = 0.04$). Following resection there was no significant difference in survival between patients with distant metastases suspected or absent on preoperative

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radiologic studies ($p = 0.47$). Surgery should be avoided in patients with cytologically proven distant metastases because the expected survival is low and surgery does not seem a life prolonging procedure in these patients. However, patients should not be excluded from surgery on the basis of metastases on radiologic studies alone.

7.2 Introduction

Carcinoma of the esophagus and gastroesophageal junction has a poor prognosis because many patients have disseminated disease at first presentation. When metastases are found at surgery, survival rates following resection drop significantly [1-5]. This explains the persisting low survival of surgically treated patients despite the decrease in postoperative mortality during the past 10 years [6,7].

In a previous report by our study group in 1987 it was concluded that effort should be directed to better selection of patients for surgery in order to improve the long-term survival of surgically treated patients and to avoid unnecessary surgery in patients with disseminated disease [1].

Radiologic studies such as computed tomography (CT) and ultrasound (US) have improved the pretreatment staging of esophageal and gastroesophageal junction carcinoma, but conflicting results are reported regarding the accuracy of these studies [8]. Thus, the decision to refrain from surgery in patients on the basis of radiologic studies alone remains controversial and some authors have stated that "no noninvasive test is of sufficient reliability to exclude patients from operative resection" [9].

US-guided fine-needle aspiration biopsy (FNAB) is a safe and minimal invasive technique to provide cytologic specimen of lesions suspected of metastases on radiologic studies. During the last 3 years we have systematically included this technique in the pretreatment staging of esophageal and gastroesophageal junction carcinoma [10]. Patients suspected of having distant metastases on US or CT studies underwent US-guided FNAB when these lesions were accessible to biopsies. With the exception of one patient, patients with cytologically proven distant metastases were excluded from surgery whereas those without cytologically proven metastases underwent surgery.

This study was performed to evaluate the survival of patients after having been selected for surgery according to our staging strategy. Furthermore, the influence on survival of distant metastases assessed on radiologic studies or diagnosed on cytologic studies was determined.

7.3 Patients and methods

Between January 1989 and December 1990, 135 patients, aged 40-84 years (mean 63 years) with a biopsy proven carcinoma of the intrathoracic esophagus or gastroesophageal junction were referred to the Rotterdam Esophageal Tumor Study Group for staging and treatment. Patient characteristics are shown in Table 7.1.

Staging was performed according to the classification of the American Joint Committee on Cancer (AJCC) [11]. In the present report, however, malignant involvement of N2 nodes in carcinoma of the gastroesophageal junction is also considered as distant metastasis. All patients underwent US of the supraclavicular regions and the abdomen by means of a 7.5-MHz linear array transducer and a 3.5-MHz curvilinear transducer, respectively (SSD-650; Aloka, Tokyo, Japan). All patients underwent CT scanning of the chest and upper abdomen including the entire liver in 8-12-mm-thick contiguous sections and all but 11 patients also underwent CT scanning of the supraclavicular regions from the cricoid cartilage to the sternal angle in 5- or 6-mm-thick contiguous sections by means of a Somatom Plus Scanner (Siemens, Erlangen, Germany) or a Tomoscan 350 (Philips Medical Systems, Eindhoven, The Netherlands). Distant sites systematically examined on US and CT scans were the lungs, the liver, the peritoneum, the kidneys and the adrenal glands (visceral sites), the supraclavicular nodes and the celiac nodes which were considered enlarged when they had a short axis of 5 mm and 10 mm or more, respectively. Patients with US or CT findings indicating distant metastases that were accessible to biopsies underwent US-guided FNAB of one suspect lesion. In patients with multiple lesions biopsies were preferentially performed of supraclavicular nodes because supraclavicular biopsies are easier to perform and are less invasive for the patients compared with abdominal biopsies [12,13]. FNABs of supraclavicular lymph nodes were performed with a 23-gauge needle and of abdominal lesions with a 22-gauge needle. With the exception of one patient, those patients who had distant metastases proven by means of cytologic study were excluded from surgery. Also excluded from surgery were patients who had a poor general condition. The remaining patients, including patients with US or CT findings indicating distant metastases that were not accessible to biopsies or patients who had negative results on cytologic studies of biopsies, underwent surgery.

At surgery laparotomy was performed as the first step of planned resection. Patients with a surgically resectable tumor underwent transhiatal esophagectomy (THE) with gastric interposition and cervical gastroesophageal anastomosis [14]. Survival rates following resection with this technique are almost identical to those obtained with a transthoracic approach [7].

In patients with an irresectable tumor surgery was abandoned after laparotomy.
Data on squamous cell carcinomas and adenocarcinomas were combined because the radiologic staging and the surgical approach in these tumors are similar in our institution and recent reports do not show significant differences in survival [15,16].
Survival was measured from the date of radiologic staging. Survival curves were derived by the Kaplan-Meier method and comparisons of survival rates of different subgroups of patients were made by using the log-rank test. In addition, a multivariate analysis was separately performed for both the surgically treated and nonsurgically treated groups by using the Cox proportional hazards model. Results are reported with P values and associated 95% confidence intervals (CIs). Operative mortality rate was defined as the in-hospital death after surgery. Overall mortality rate represents death due to any cause during follow up.

Table 7.1 **Characteristics and two year survival of 135 patients with esophageal and gastroesophageal junction carcinoma**

Characteristics		No.(%) of patients	2-year survival*
All patients		135	28.9 (21.1-37.2)
Sex:	Male	105 (78)	27.5 (18.8-36.9)
	Female	30 (22)	34.1 (17.4-51.6)
Age:	< 60	45 (33)	27.5 (15.1-41.4)
	≥ 60	90 (67)	29.5 (19.7-39.9)
Tumor type:	squamous cell carcinoma	66 (49)	20.9 (11.6-32.0)
	adenocarcinoma	63 (47)	37.3 (24.6-49.9)
	undifferentiated carcinoma	6 (4)	33.3 (4.6-67.6)
Tumor location:	upper esophagus	5 (4)	40.0 (0.8-58.2)
	middle esophagus	38 (28)	27.1 (13.8-42.4)
	lower esophagus	66 (49)	30.0 (18.8-42.0)
	gastroesophageal junction	26 (19)	27.5 (11.3-46.5)
Distant metastases on US and CT:	present	62 (46)	11.2 (4.5-21.3)
	- cytologically proven	33 (24)	3.0 (0.2-13.4)
	- negative cytology or cytology not done	29 (22)	21.1 (7.4-39.4)
	absent	73 (54)	44.3 (32.5-55.8)
Surgery:	not performed	44 (33)	8.2 (2.3-19.1)
	performed	91 (67)	39.5 (28.8-50.0)

Note: * 95% confidence interval in parentheses.

7.4 Results

Sixty-two patients were suspected of having distant metastases on US and/or CT studies (Tables 7.1 and 7.2). Distant metastases were proven by means of US-guided FNAB and cytologic study in 33 patients; 32 of these patients were excluded from surgery, in another patient surgical resection was attempted despite the presence of cytologically proven celiac metastases but it was abandoned after these metastases were confirmed histopathologically. In 29 patients the cytologic smears did not show malignant cells (17 patients) or US-guided FNAB could not be performed (12 patients). Two of these patients were excluded from surgery because they had a poor general condition, 27 patients had surgery at which the tumor was resected in 20 patients (resection rate 74%). Seventy-three patients did not have metastases on US and/or CT studies; 10 of these patients were excluded from surgery because they had a poor general condition, the remaining 63 patients had surgery with resection of the tumor in 57 patients (resection rate 90%). In total, 44 patients were excluded from surgery; because of cytologically proven distant metastases in 32 patients and because of a poor general condition in 12 patients. These patients were treated with radiation therapy (n = 7), chemotherapy (n = 6), tube insertion (n = 8), laser therapy (n = 3), a combination of radiation therapy and chemotherapy (n = 3), chemotherapy and tube insertion (n = 14) or radiation therapy, chemotherapy and tube insertion (n = 1). Two patients did not receive any treatment. Ninety-one patients had surgery; 14 patients underwent laparotomy only because of major abdominal metastases and irresectability of the primary tumor, the other 77 patients underwent THE.

Table 7.2 Patients suspected of distant metastases on US and CT studies and patients with distant metastases proven on cytologic studies

Location of distant metastases	No. (%) of patients	
	Distant metastases on US and/or CT	Distant metastases cytologically proven
Lungs	2 (1)	0 (0)
Liver	10 (7)	6 (4)
Peritoneum	2 (1)	2 (1)
Kidneys	1 (1)	1 (1)
Adrenal glands	2 (1)	0 (0)
Supraclavicular lymph nodes	38 (28)	22 (16)
Celiac lymph nodes	30 (22)	3 (2)
Total	62 (46)	33 (24)

Survival

The duration of follow-up ranged from 19 to 995 days (mean 400). No patient was lost-to-follow-up. Ninety-six patients had died at the time of this study (January 1, 1992). The operative mortality rate was 4% and 4% of patients who did not have surgery died within one month. Thirty-nine patients were alive at follow-up study, the length of their follow-up period ranged from 402-993 days (median 696). Two-year survival rates according to several patient characteristics are shown in Table 7.1. There was no statistically significant difference in survival between patients regarding sex, age or location of the primary tumor. Survival was better for patients with adenocarcinoma compared to patients with squamous cell carcinoma, the difference in survival became evident only after the first year but did not reach statistical significance (p = 0.12).

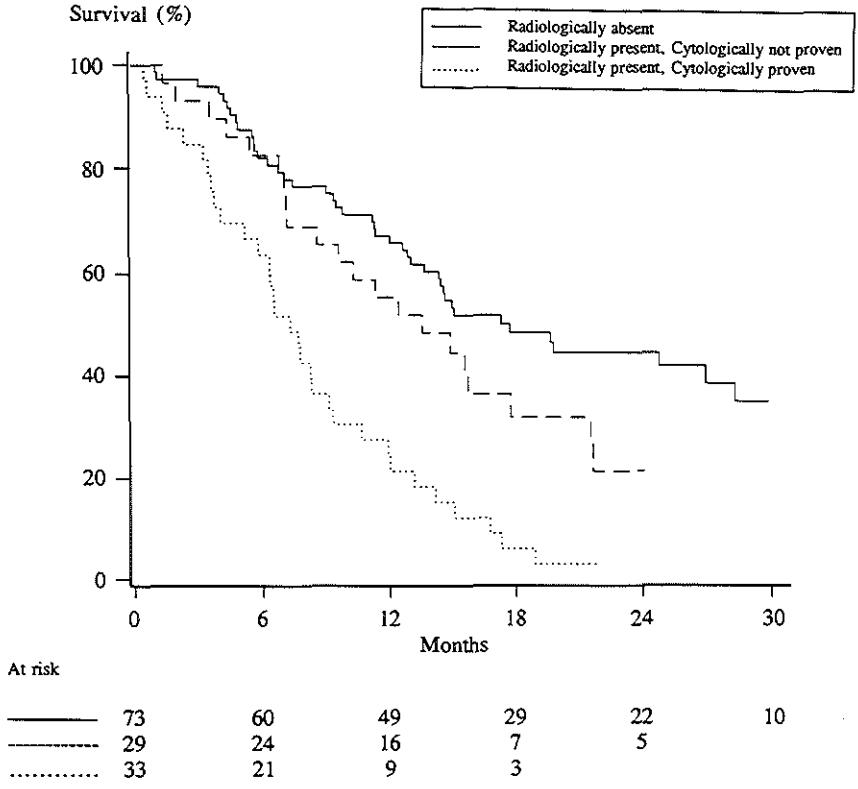

Figure 7.1 Survival rate according to the presence or absence of distant metastases on radiologic (ultrasound or CT) studies and cytologic studies.

When the patients were subdivided on the basis of their radiologic findings, patients suspected of distant metastases on US and CT studies had a 2-year survival of 11.2% whereas patients without metastases on these studies had a 2-year survival of 44.3% ($p < 0.001$). Patients with cytologically proven metastases had a shorter survival than either patients suspected of metastases on radiologic studies that were not cytologically proven ($p < 0.001$) or patients without metastases on radiologic studies ($p < 0.001$) (Table 7.1, Fig.7.1). The difference in survival between these last two groups of patients was not statistically significant ($p = 0.87$). Within the group of patients suspected of metastases on radiologic studies that were not cytologically proven, there was no significant difference in survival between patients without metastases on cytologic studies and those who did not undergo US-guided FNAB ($p = 0.11$).

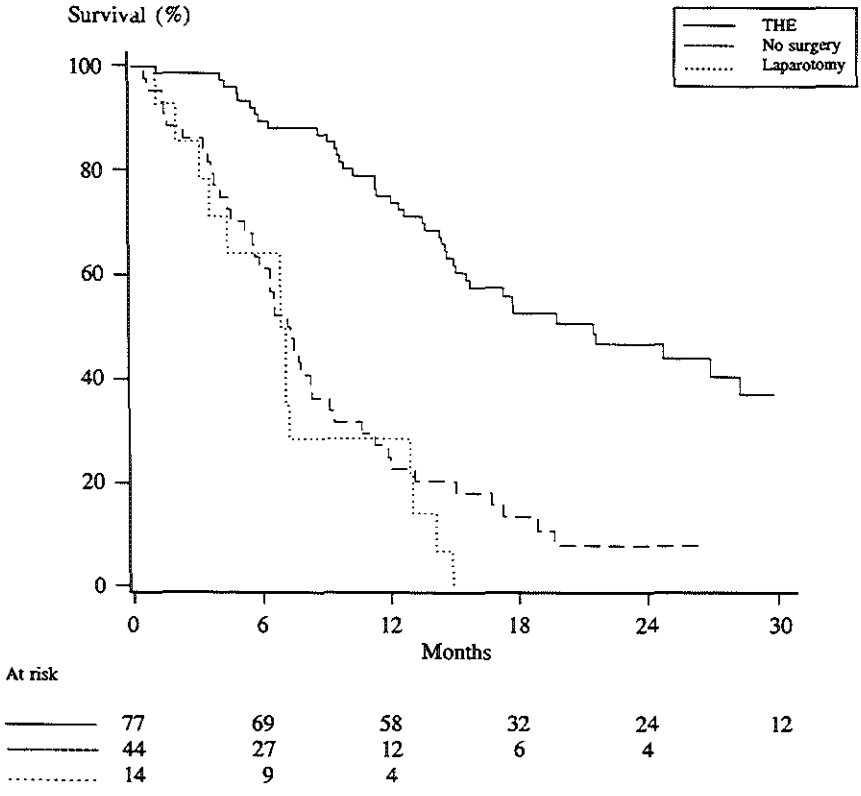

Figure 7.2 Survival rate according to the treatment patients received.

Table 7.3 One year and two year survival of 44 patients excluded from surgery

Characteristics	No. of patients	1-year survival	2-year survival
Poor general health	12	33.3 (10.3-58.8)	22.2 (4.1-49.2)
Cytologically proven metastases	32	25.0 (11.8-40.7)	3.1 (0.2-13.7)
- Cytologic or radiologic evidence of visceral metastases	12	8.3 (0.5-31.1)	0
- Cytologic or radiologic evidence of lymphatic metastases only	20	35.0 (15.7-55.2)	5.0 (0.3-20.5)

Note: 95% confidence interval in parentheses.

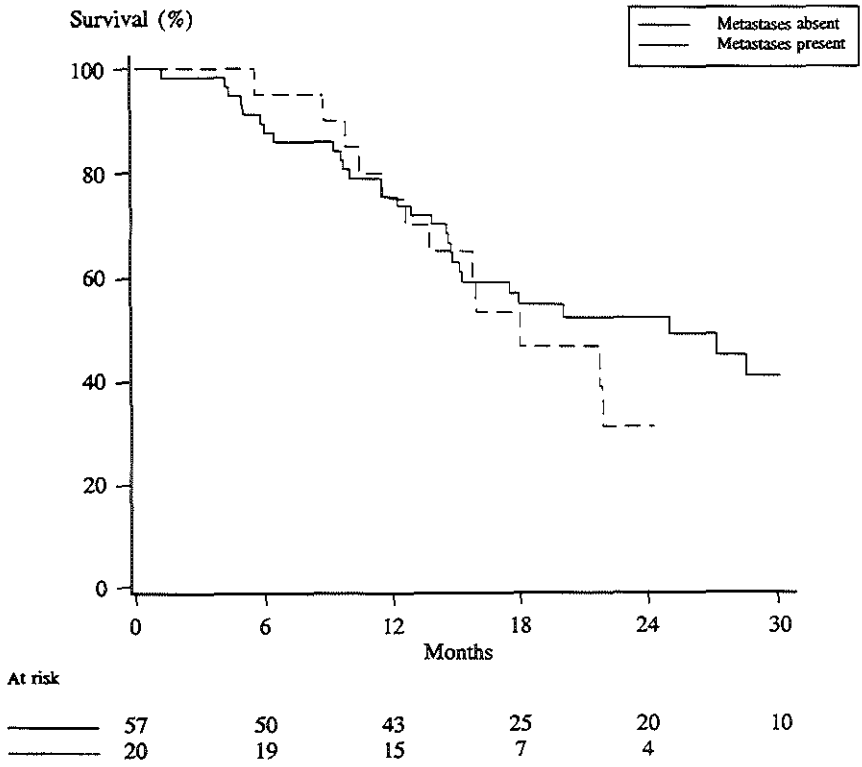

Figure 7.3 Survival rate according to the presence or absence of distant metastases on radiologic studies, within the group of patients who underwent transhiatal esophagectomy (THE).

When the patients were subdivided on the basis of the treatment they received, surgically treated patients had a 2-year survival of 39.5% whereas patients excluded from surgery had a 2-year survival of 8.2% ($p < 0.001$) (Table 7.1, Fig. 7.2). Further statistical analysis of survival was performed separately for surgically and nonsurgically treated patients. For the group of patients excluded from surgery, patients excluded because of cytologically proven distant metastases had a worse prognosis than those with a poor general health, but the difference did not reach statistical significance ($p = 0.13$) (Table 7.3).

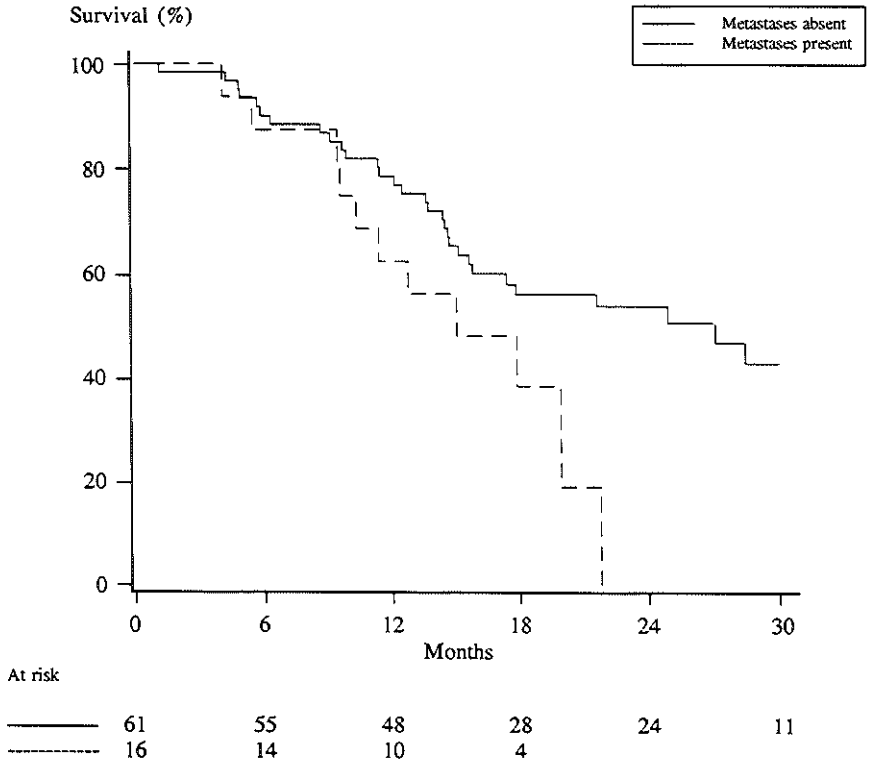

Figure 7.4 Survival rate according to the presence or absence of distant metastases on histopathologic studies of the resected specimen within the group of patients who underwent transhiatal esophagectomy (THE).

Within the group of patients with cytologically proven distant metastases, those with cytologic or radiologic evidence of visceral metastases had a worse prognosis than those with evidence of lymphatic metastases alone ($p = 0.024$) (Table 7.3). For the group of surgically treated patients, those who underwent THE had a statistically better survival than those who underwent laparotomy only ($p < 0.001$) (Table 7.4, Fig. 7.2). There was no statistically significant difference in survival between patients who were radiologically suspected of distant metastases and those without distant metastases on radiologic studies within the groups of patients who underwent either THE ($p = 0.47$) or laparotomy ($p = 0.52$) (Table 7.4, Fig. 7.3). For patients who underwent THE, those with distant metastases on histopathologic study had a worse survival compared to those without distant metastases ($p = 0.04$) (Table 7.4, Fig. 7.4). A multivariate model using patient characteristics as variables did not show any independent effect on survival within the group of surgically treated patients. Within the group of nonsurgically treated patients, for those patients with cytologically proven distant metastases, the presence of visceral metastases was associated with a hazard ratio of 2.7 (95% CI, 1.2-6.1) compared to the presence of lymphatic metastases alone.

Table 7.4 One year and two year survival of 91 surgically treated patients

Characteristics		No. of patients	1-year survival	2-year survival
Laparotomy		14	28.6 (8.8-52.4)	0
- Radiologic evidence of distant metastases:	present	8	25.0 (3.7-55.8)	0
	absent	6	33.3 (4.6-67.6)	0
Transhiatal esophagectomy		77	75.3 (64.1-83.5)	46.8 (34.5-58.2)
- Radiologic evidence of distant metastases:	present	20	75.0 (50.0-88.7)	31.0 (10.7-54.1)
	absent	57	75.4 (62.1-84.7)	52.1 (37.7-64.6)
- Histopathologically proven distant metastases:	present	16	62.5 (34.9-81.1)	0
	absent	61	78.7 (66.1-87.0)	53.9 (40.1-65.8)

Note: 95% confidence interval in parentheses.

7.5 Discussion

While numerous articles have been published that evaluate the accuracy of CT in staging esophageal and gastroesophageal junction carcinoma, there are only few articles that have correlated the findings on CT or US studies with the length of patient survival [17,18]. Halvorsen et al who compared the length of patient survival with pretherapy CT findings in 89 patients with esophageal carcinoma reported that regardless of therapy, evidence of abdominal metastases on CT studies decreased the mean patient survival of 320.6 days to 102.4 days [17]. Similar observations are shown in our study, the 2-year survival of patients decreased significantly when distant metastases were suspected on US or CT studies. However, within this group of patients the worst survival was observed in patients with distant metastases proven on cytologic studies, these patients had a significantly shorter survival than those without cytologic proof of metastases. This can be explained by the limited specificity of US and CT in diagnosing metastases, in our study for example 13 of 62 patients suspected of distant metastases on radiologic studies eventually had their tumor resected without evidence of distant metastases on histopathologic studies of the resected specimen (results not shown). Consequently, although the group of patients suspected of metastases on US and CT has a poor prognosis, by excluding all these patients from surgery some patients without metastases will be withheld their optimal treatment. By obtaining cytologic proof of metastases the risk of overstaging is minimized which is reflected in the significantly worse prognosis in cases metastases were cytologically proven. A critical remark may be that bias was introduced regarding survival because patients were excluded from surgery in cases when metastases were cytologically proven. However, the 2-year survival rate of these patients is comparable to the 2-year survival rate of patients with distant metastases following resection in our study and reported by others [4,5,14].

Naturally, in some patients correctly suspected of distant metastases on US and CT, the cytologic examination will be false negative or cytologic biopsies cannot be performed. This can explain the lower 2-year survival and the lower resection rate at surgery in patients without cytologic confirmation of lesions suspected of metastases on US and CT studies compared to patients not suspected of metastases on these studies. However, because the difference in survival is not statistically significant and because suboptimal treatment should be avoided in individual patients without metastases, we recommend not to exclude patients from surgery on the basis of metastases on radiologic studies alone. In patients with cytologically proven distant metastases surgery does not seem a life prolonging procedure. The 2-year survival of these patients who were excluded from surgery in our study was 3% whereas following resection there were no survivers

after 2 years in patients with distant metastases in our study and in studies of other authors [4,5,19]. In our study 75% of patients with cytologically proven metastases had died within one year, thus if surgery is considered a palliative procedure in patients with distant metastases, maximally 25% of these patients can be palliated for one year including the duration of their hospital admission. Since surgery is a formidable procedure with a postoperative morbidity of at least a few months [1], we do not consider palliative surgery indicated in this group of patients although opposite opinions have been reported in selected cases [15]. For patients with cytologically proven metastases, survival was worst for those patients who had cytologic or radiologic evidence of visceral metastases. However, patients with evidence of lymphatic metastases alone also had a very poor prognosis with only 5% of patients alive after 2 years. For patients who underwent surgery, as expected, the survival rates were best for those patients who had their tumor resected. Patients with irresectable tumors at surgery had a poor prognosis, none of these patients was alive after 2 years and continuous effort should be made to keep the numbers of patients that suffer from unnecessary surgery as low as possible. Although the resection rate at surgery at our institution increased from 81% in 1987 to 85% at present, the postoperative mortality rate remained at the same level during this period which indicates that the higher resection rate is not the result of a more agressive surgical approach with the goal to achieve resection, but is more likely the result of better patient selection [1]. This is supported by the fact that the 2-year survival following resection in our study is relatively high compared to the survival after resection reported by others [5,7,19]. For patients who underwent resection those suspected of distant metastases on US or CT did not have a significantly worse prognosis compared to those without metastases on these studies which is consistent with our current belief that patients should not be excluded from surgery on the basis of metastases on radiologic studies alone. However, when distant metastases were proven at histopathologic examination of the resected specimen the survival following resection deteriorated, none of these patients was alive after 2 years.
In conclusion, in patients with carcinoma of the esophagus and gastroesophageal junction, pretreatment assessment of distant metastases is of great importance to select the optimal treatment. Surgery should be avoided in cases of distant metastases because the expected survival is very poor and surgical treatment does not seem life prolonging in these patients. However, metastases should be proven by means of cytologic studies and patients should not be excluded from surgery on the basis of radiologic findings alone in order to avoid suboptimal treatment in individual patients with potentially curable disease.

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Chapter 8

FINAL REMARKS

A Radiologic Staging Strategy

When surgery is considered, radiologic staging of esophageal and gastroesophageal junction carcinoma should begin with the assessment of distant metastases. The presence of distant metastases is associated with a poor prognosis (Chapter 7) [1-4] and most surgeons do not consider resection in these patients [5-7]. The combination of ultrasound (US) and computed tomography (CT) is the best choice for noninvasive assessment of distant metastases (Chapter 4) and should include examination of the supraclavicular lymph nodes, since supraclavicular metastases are such a common finding in esophageal and gastroesophageal junction carcinoma (Chapters 2 and 3). For logistic and cost-effective reasons we recommend US as the initial examination and the use of US-guided fine-needle aspiration biopsy (FNAB) when metastases are suspected. Patients without metastases on US should undergo CT and US- or CT-guided biopsies in those cases when lesions are detected. Distant metastases can thus be proven in 24% of patients (Chapter 5) in whom surgery can be avoided (Chapter 7).

Presence or absence of regional lymph node metastases cannot be determined accurately (Chapter 6) and there is no consensus regarding the therapeutic consequences in those patients who have regional lymph node metastases [5,7].

Assessment of the invasion depth of the primary tumor is unsatisfactory. Furthermore, assessment of resectability of the primary tumor by determining invasion of adjacent structures on radiologic studies may be hazardous, because invasion does not necessarily preclude resection (Chapter 6).

A flow chart for a radiologic staging strategy is presented (Fig 8.1).

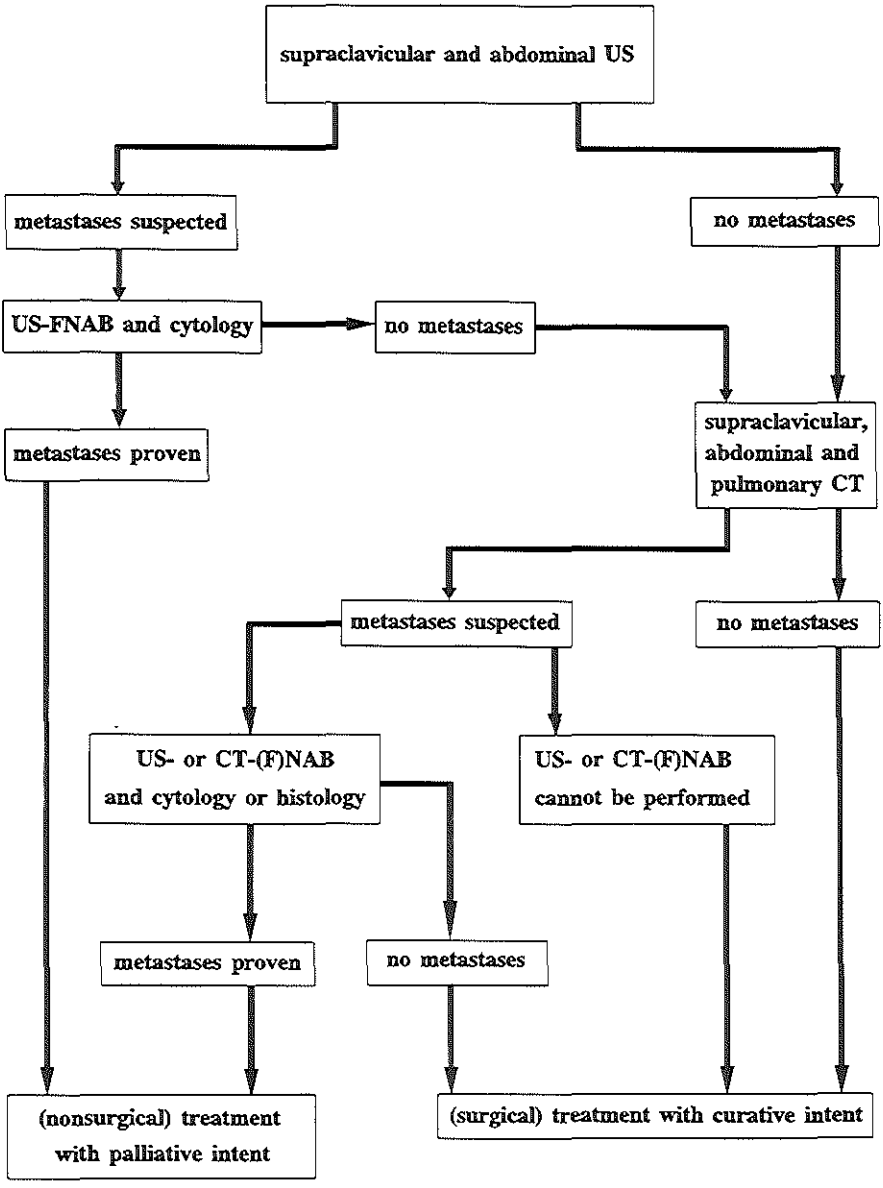

Figure 8.1 Flow chart of radiologic staging for patients with esophageal and gastroesophageal junction carcinoma.

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APPENDIX

TNM classification and Stage Grouping (AJCC 1988)

Tumor Nodes Metastasis (TNM) classification for tumors of the esophagus

Primary Tumor (T)

T_0	No evidence of primary tumor
T_{is}	Carcinoma in situ
T_1	Tumor invades lamina propria or submucosa
T_2	Tumor invades muscularis propria
T_3	Tumor invades adventitia
T_4	Tumor invades adjacent structures

Regional Lymph Nodes (N)*

N_0	No regional lymph node metastasis
N_1	Regional lymph node metastasis

Distant metastasis (M)

M_0	No distant metastasis
M_1	Distant metastasis

* For the upper and middle thoracic esophagus the mediastinal lymph nodes are considered regional lymph nodes.
For the lower thoracic esophagus the mediastinal and perigastric lymph nodes are considered regional lymph nodes.
Involvement of more distant nodes including the supraclavicular and celiac nodes is considered distant metastasis.

Tumor Nodes Metastasis (TNM) classification for tumors of the gastroesophageal junction

Primary Tumor (T)

T_0 No evidence of primary tumor

T_{is} Carcinoma in situ

T_1 Tumor invades lamina propria or submucosa

T_2 Tumor invades the muscularis propria or the subserosa

T_3 Tumor penetrates the serosa (visceral peritoneum) without invasion of adjacent structures

T_4 Tumor invades adjacent structures

Regional Lymph Nodes (N)*

N_0 No regional lymph node metastasis

N_1 Metastasis in perigastric lymph nodes within 3 cm of the edge of the primary tumor

N_2 Metastasis in perigastric lymph nodes more than 3 cm from the edge of the primary tumor, or in lymph nodes along the left gastric, common hepatic, splenic, or celiac arteries

Distant Metastasis (M)

M_0 No distant metastasis

M_1 Distant metastasis

* Involvement of more distant nodes including the supraclavicular nodes is considered distant metastasis.

Stage Grouping for tumors of the esophagus

Stage O	T_{is}	N_0	M_0
Stage I	T_1	N_0	M_0
Stage IIA	T_2	N_0	M_0
	T_3	N_0	M_0
Stage IIB	T_1	N_1	M_0
	T_2	N_1	M_0
Stage III	T_3	N_1	M_0
	T_4	Any N	M_0
Stage IV	Any T	Any N	M_1

Stage Grouping for tumors of the gastroesophageal junction

Stage O	T_{is}	N_0	M_0
Stage IA	T_1	N_0	M_0
Stage IB	T_1	N_1	M_0
	T_2	N_0	M_0
Stage II	T_1	N_2	M_0
	T_2	N_1	M_0
	T_3	N_0	M_0
Stage IIIA	T_2	N_2	M_0
	T_3	N_1	M_0
	T_4	N_0	M_0
Stage IIIB	T_3	N_2	M_0
	T_4	N_1	M_0
Stage IV	T_4	N_2	M_0
	Any T	Any N	M_1

SUMMARY

The purpose of this thesis was to evaluate the utility of computed tomography (CT), ultrasound (US) and US-guided fine-needle aspiration biopsy (FNAB) for pretreatment staging of esophageal and gastroesophageal junction carcinoma. Aspects of assessing the depth of invasion of the primary tumor and the presence or absence of metastases are discussed.

In *Chapter 1*, general information on esophageal and gastroesophageal junction carcinoma is provided.

Chapter 2 presents a retrospective pilot study that was performed to determine the prevalence of demonstrable supraclavicular metastases with US and US-guided FNAB in patients with squamous cell carcinoma of the intrathoracic esophagus. Supraclavicular metastases were cytologically proven in 19% of patients. In these patients US-guided FNAB of supraclavicular nodes replaced more invasive diagnostic procedures or avoided extensive surgical procedures.

In *Chapter 3*, the assessment of supraclavicular metastases with palpation, US and CT is compared in patients with carcinoma of the esophagus and gastroesophageal junction. Morphologic characteristics of benign and malignant nodes are studied. The relative frequency of supraclavicular metastases is related to the location of and histologic findings in the primary tumor. CT and US were equally sensitive and both modalities were superior to palpation in detecting supraclavicular metastases. Metastases were found more frequently in patients with squamous cell carcinoma compared to adenocarcinoma and were most frequently observed in those patients who had carcinoma of the upper and middle thoracic esophagus. Metastatic nodes tended to have a round configuration. Neither CT nor US was superior in predicting the metastatic status of nodes and in cases of enlarged nodes on either study, US-guided FNAB should be performed to obtain material for cytologic examination.

Chapter 4 evaluates US and CT in assessing distant metastases in carcinoma of the esophagus and gastroesophageal junction by comparing these findings with cytological and surgical data. In assessing distant metastases US, and to a lesser degree, CT were characterized by a relatively low sensitivity and a relatively high specificity. With the combination of US and CT, the sensitivity increased to an acceptable level of 83%. Although this was accompanied by a decrease in specificity it was considered to be less important because FNAB can be performed to enable cytological examination.

Chapter 5 describes the utility of US-guided FNAB for diagnosing distant metastases in esophageal and gastroesophageal junction carcinoma by determining the number of biopsies in which adequate material for cytologic study could be obtained and the number of patients in whom distant metastases could be proven. A cytologic diagnosis was established in 87% of biopsies, 13% of biopsies were nondiagnostic. Distant metastases were diagnosed by means of cytologic study in 24% of patients. No complication, other than localized mild discomfort was observed.

Chapter 6 discusses the ability of preoperative CT to assess resectability and to stage carcinomas in patients who undergo transhiatal esophagectomy. CT was not effective to assess nonresectability by diagnosing invasion; this was due to the relatively low prevalence of invasion of adjacent structures and the fact that invasion was often not associated with nonresectability. In assessing invasion itself, CT was accurate in diagnosing tracheobronchial involvement, but was limited in diagnosing invasion of other structures. In assessing stage grouping, CT was limited in detecting either diaphragmatic invasion or lymph node involvement.

In *Chapter 7*, the influence on survival of distant metastases, assessed on US or CT studies or proven on cytologic studies is evaluated. Patients with cytologically proven distant metastases and those unfit to be operated were excluded from surgery, which was performed in the remaining patients. The 2-year survival for patients with cytologically proven metastases (3%) was shorter than for patients suspected of metastases on US and CT studies that were not cytologically confirmed. There was no significant difference in survival between this last group of patients and those without metastases on US and CT studies. Following resection the 2-year survival dropped from 53.9% to 0% when distant metastases were present on histopathologic studies of the resected specimen. Because the expected survival of patients with distant metastases is low, it is recommended to avoid surgery when these are cytologically proven. Due to

the limited specificity of US and CT, patients should not be excluded from surgery on the basis of metastases suspected on these studies alone.

In *Chapter 8*, final remarks are given within the scope of a pretreatment staging strategy for patients with esophageal and gastroesophageal junction carcinoma. A flow chart for a radiologic staging strategy is presented.

SAMENVATTING

Doel van dit proefschrift was het bepalen van de gebruikswaarde van computer tomografie (CT), echografie en echogeleide cytologische punctie voor de pretherapeutische stagering van oesofagus- en cardiacarcinoom. Aspecten van het bepalen van de lokale uitbreiding van de primaire tumor en de aanwezigheid van metastasen worden behandeld.

In *Hoofdstuk 1* worden enkele algemene aspecten van het oesofagus- en cardiacarcinoom besproken.

Hoofdstuk 2 geeft de resultaten weer van een retrospectief vooronderzoek met als doel het bepalen van de prevalentie van met echografie en echogeleide cytologische punctie aantoonbare supraclaviculaire lymfkliermetastasen in patiënten met een plaveiselcelcarcinoom van de thoracale oesofagus. Supraclaviculaire metastasen waren in 19% van de patiënten cytologisch aantoonbaar. Echogeleide cytologische punctie van supraclaviculaire lymfklieren verving in deze patiënten meer invasieve diagnostische procedures of voorkwam een uitgebreide operatie.

Hoofdstuk 3 geeft de resultaten weer van het vaststellen van supraclaviculaire lymfkliermetastasen met palpatie, echografie en CT in patiënten met een oesofagus- en cardiacarcinoom. Morfologische kenmerken van benigne en maligne lymfklieren worden besproken. Het relatief voorkomen van supraclaviculaire metastasen wordt gerelateerd aan de lokatie en het histologisch type van de primaire tumor. CT en echografie waren even gevoelig en beide technieken waren superieur aan palpatie in de detectie van supraclaviculaire metastasen.
Metastasen werden vaker gevonden in patiënten met een plaveiselcelcarcinoom dan in patiënten met een adenocarcinoom en werden het meest frequent aangetroffen in patiënten met een carcinoom van het bovenste en middelste éénderde deel van de oesofagus. Door metastasen aangedane lymfklieren hadden vaker een ronde configuratie. CT en echografie waren gelijkelijk beperkt in het voorspellen van metastasen wanneer vergrote lymfklieren werden waargenomen. Wanneer vergrote lymfklieren met deze onderzoeken worden gevonden moet aansluitend echogeleide punctie worden verricht om materiaal te verkrijgen voor cytologisch onderzoek.

Hoofdstuk 4 behandelt de betrouwbaarheid van echografie en CT voor het vaststellen van metastasen op afstand door de bevindingen bij deze onderzoeken te vergelijken met de cytologische en operatieve resultaten. Echografie en in mindere mate CT werden gekenmerkt door een relatief lage sensitiviteit en een relatief hoge specificiteit in het vaststellen van deze metastasen. Wanneer de bevindingen van beide onderzoeken samengevoegd werden bereikte de sensitiviteit een acceptabel niveau van 83%. De hiermee gepaard gaande daling in specificiteit wordt van minder belang geacht, omdat met cytologische punctie nadere diagnostiek kan worden verricht.

Hoofdstuk 5 beschrijft de bruikbaarheid van echogeleide cytologische punctie voor het diagnostiseren van metastasen op afstand in patiënten met een oesofagus- en cardiacarcinoom. Graadmeters voor de bruikbaarheid waren het percentage diagnostische biopsieën en het aantal patiënten bij wie metastasen op afstand cytologisch konden worden aangetoond. Van de biopsieën was 87% diagnostisch, in 13% van de biopsieën werd geen cytologische diagnose verkregen. In 24% van de patiënten konden metastasen op afstand worden aangetoond. Complicaties anders dan lokale gevoeligheid werden niet waargenomen.

In *Hoofdstuk 6* wordt de mogelijkheid onderzocht om met preoperatief CT onderzoek de resectabiliteit van de tumor te bepalen en deze te stageren in patiënten die transhiatale oesofagusresectie ondergaan. Het voorspellen van irresectabiliteit van de tumor door middel van het vaststellen van ingroei in naburige organen met CT bleek niet doeltreffend. Dit werd enerzijds veroorzaakt door de lage prevalentie van ingroei en anderzijds doordat ingroei vaak geen irresectabiliteit ten gevolge had. CT was betrouwbaar in het vaststellen van ingroei in de trachea en de bronchi, maar was weinig betrouwbaar in het voorspellen van ingroei in andere organen. Ten aanzien van de stagering was CT weinig gevoelig in het diagnostiseren van diafragma-ingroei en het detecteren van lymfkliermetastasen.

Hoofdstuk 7 bespreekt de invloed van metastasen op afstand, gedetecteerd met echografie en CT of bewezen met cytologisch onderzoek, op de overleving van patiënten met een oesofagus- en cardiacarcinoom. Patiënten met cytologisch bewezen metastasen op afstand en patiënten ongeschikt vanwege andere redenen werden uitgesloten van operatie; de overige patiënten werden geopereerd.
De 2-jaars overleving was lager voor patiënten met cytologisch bewezen metastasen (3%) dan voor patiënten verdacht van metastasen op echo en CT onderzoeken, die niet

cytologisch waren aangetoond. Er was geen significant verschil in overleving tussen deze laatste groep patiënten en patiënten zonder metastasen op echo en CT onderzoeken. Na operatieve resectie van de tumor daalde de 2-jaars overleving van 53,9% tot 0% voor de patiënten bij wie metastasen op afstand in het resectie preparaat werden aangetroffen. Omdat de verwachte overleving van patiënten met metastasen op afstand gering is, wordt geadviseerd niet te opereren wanneer deze cytologisch worden aangetoond. Patiënten behoren niet te worden uitgesloten van operatie alleen op grond van voor metastasen verdachte afwijkingen op echo en CT onderzoeken, omdat de specificiteit van deze onderzoeken beperkt is.

Hoofdstuk 8 bevat enkele laatste opmerkingen in het kader van een radiologisch protocol ten behoeve van de stagering van patiënten met een oesofagus- en cardiacarcinoom. Het protocol wordt in een stroomschema weergegeven.

EPILOOG

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CURRICULUM VITAE

HANS VAN OVERHAGEN

1959	4 september, geboren te Leiden
1977	eindexamen Atheneum B, Rijnlands Lyceum te Oegstgeest
1978	kandidaatexamen I Nederlands Recht, Rijksuniversiteit te Leiden
1985	artsexamen, Rijksuniversiteit te Leiden
1985-1986	onderzoeker, afdelingen Klinische Immunologie en Chirurgische Oncologie, Academisch Ziekenhuis te Groningen
1986-1991	arts-assistent in opleiding tot radiodiagnost, Academisch Ziekenhuis Rotterdam
1991-heden	stafmedewerker afdeling Radiodiagnostiek, Academisch Ziekenhuis Rotterdam