Staging Investigations in Patients with Esophageal Cancer: A Critical Re-Appraisal

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CHAPTER 1

General introduction

ESOPHAGEAL AND GASTRIC CARDIA CANCER

The incidence of esophageal cancer has been increased over the years. In 1989, the incidence was 6.9 cases of esophageal cancer per 100,000 men and 2.4 cases per 100,000 women in The Netherlands. In 2003, the incidence had increased to 11.9 cases per 100,000 men and 3.8 cases per 100,000 women. Currently, about 1,400 patients are annually diagnosed with esophageal cancer in The Netherlands (1). The two major types of esophageal cancer are squamous cell carcinoma and adenocarcinoma, which comprises more than 90% of esophageal cancer cases.

Complaints, such as weight loss, dysphagia or pain, usually arise in an advanced stage of the disease. As a consequence, more than 50% of patients have already locally advanced cancer, lymph node metastases, or distant metastases at the time of presentation (2). The 5-year survival rate for esophageal cancer is low, i.e., 10-15% (3).

Upper gastrointestinal endoscopy with the simultaneous taking of biopsies is presently the preferred investigation for diagnosing cancer in the esophagus or gastric cardia (4-6). After diagnosing esophageal or gastric cardia cancer by upper gastrointestinal endoscopy and biopsy and with the patients' physical condition permitting resection, tumor staging is the next step to determine which treatment modality is most appropriate (7, 8). Preoperative staging investigations that are most commonly used to determine the extent of esophageal or gastric cardia cancer include endoscopic ultrasonography (EUS), computed tomography (CT), positron emission tomography (PET), and ultrasound (US) of the cervical region and the abdomen. Bronchoscopy and bone scintigraphy are usually only used for specific indications. The preoperative TNM stage is established by a combination of these investigations. The extent of local invasion of the tumor through the esophageal wall is described by T stage (9). T stage is subdivided into stage T1 to T4, with a T1-carcinoma infiltrating into the mucosa (T1m) or submucosa (T1sm), a T2 into the muscularis propria, a T3 through the muscularis propria and a T4 infiltrating into surrounding organs or vessels (9). EUS is currently the standard investigation to determine T stage. CT scan and bronchoscopy are considered to be less sensitive and specific (10, 11). The N stage indicates the presence of malignant regional lymph nodes, with N0 indicating absence of regional lymph node metastases and N1 presence of these metastases (9). Both EUS, and to a lesser extent CT scan, can be used for assessing N stage (11). The M stage registers the presence of distant metastases, with M0 if no distant metastases are present and M1 if these metastases are present (9). Esophageal cancer commonly disseminates to the celiac and supraclavicular lymph nodes, the liver, lung and adrenal glands (12).

The diagnosis and staging of patients with esophageal or gastric cardia cancer is important for the selection of the most optimal treatment modality. Nevertheless, there are many preoperative investigations that can be performed in patients with esophageal or gastric cardia cancer, and it is questionable whether all these investigations should be performed.

AIM OF THIS THESIS

The aim of this thesis is to assess which preoperative staging investigations should be performed in patients with esophageal or gastric cardia cancer to determine whether localized cancer on the one hand or a locally advanced disease or metastases on the other hand are present. In addition, it is evaluated which determinants play a role in the performance and evaluation of staging investigations.

OUTLINE OF THE THESIS

In chapter 2, an overview of the existing literature about the advantages, limitations and results of preoperative staging investigations if used in patients with esophageal cancer is given. In addition, a meta-analysis is performed for the use of EUS, CT and PET in esophageal cancer staging. In chapter 3, US of the supraclavicular region, if indicated with fine-needle aspiration, CT, and the combination are compared to determine whether both investigations should be performed to detect whether malignant supraclavicular lymph nodes are present in patients with esophageal or gastric cardia cancer or only one of these. In chapter 4, the quality of preoperative metastasis detection in patients with esophageal or gastric cardia cancer obtained in a high volume referral center is compared with that in 63 low volume referring regional centers. In chapter 5, radiologists of referral centers, so-called expert radiologists, and radiologists of referring regional centers, i.e., non-expert radiologists, were prospectively compared in the evaluation of CT scans of patients diagnosed with esophageal or gastric cardia cancer to determine whether the quality of CT scan and the experience of the radiologist are important factors in the evaluation of CT scans. In chapter 6, the association between the number of EUS investigations performed in a center and the results of esophageal or gastric cardia cancer staging is investigated. In chapter 7, it is assessed whether publication bias is present in the reporting of EUS staging results in esophageal, gastric and pancreatic cancer. In chapter 8, it is determined whether CT, US abdomen, EUS, US of the cervical region and chest X-ray should all be performed in patients with esophageal or gastric cardia cancer or whether it is more effective to perform a selection of these investigations to detect metastases in these patients. In chapter 9, it is assessed whether a correlation exists between socio-economic status of esophageal cancer patients and tumor histology, staging approach, preoperative TNM stage and treatment in The Netherlands. In chapter 10, the results described in this thesis are summarized and discussed.

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CHAPTER 2

Staging investigations for esophageal cancer: review and meta-analysis

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ABSTRACT

Accurate staging of patients with esophageal cancer is important for the selection of the most optimal treatment modality. Staging investigations that are most commonly used to determine the extent of esophageal cancer include upper gastrointestinal endoscopy, endoscopic ultrasonography (EUS), computed tomography (CT), positron emission tomography (PET), and ultrasound (US) of the cervical region and abdomen. Bronchoscopy and bone scintigraphy are used for specific indications.

In this article, published results, and the pros and cons of the different staging investigations in patients with esophageal cancer will be discussed and a meta-analysis will be performed for the use of EUS, CT and PET in esophageal cancer staging. Based on these data, it can be concluded that EUS is the investigation of choice for the determination of T and N stage. For malignant supraclavicular lymph nodes, US of the cervical region is most accurate. CT and PET can both be used to detect the presence of distant metastases, however PET should be particularly be considered in patients with a tumor that is otherwise staged as T3N0-1, to detect metastases that were not seen with other investigations.

INTRODUCTION

In order to optimize the selection of patients for a curative resection and other treatment modalities, it is important to determine the depth of infiltration of the tumor into the esophageal wall (T stage), and the presence of malignant lymph nodes (stage N1) and distant metastases (stage M1). T stage is subdivided into stage T1 to T4, with a T1 carcinoma infiltrating into the mucosa (T1m) or submucosa (T1sm), a T2 into the muscularis propria, a T3 through the muscularis propria and a T4 infiltrating into surrounding organs or vessels (1). Whether a malignant lymph node is defined as N1 or M1 depends on the location of the primary cancer. Malignant lymph nodes in the mediastinum are classified as N1, if the tumor is located in the esophagus. Malignant lymph nodes in the cervical or supraclavicular region are staged as N1 in patients with cervical esophageal cancer, and as M1 in patients with cancer of the intrathoracic esophagus. Metastases to celiac lymph nodes are staged as M1a if the primary tumor is located in the distal part of the esophagus and as stage M1b if the tumor is located in the proximal part of the esophagus (2). Distant metastases from esophageal cancer are most often detected in celiac and supraclavicular lymph nodes, liver, lung and adrenal glands (3).

Investigations that can be used to stage esophageal cancer include upper endoscopy, barium swallow, endoscopic ultrasonography (EUS), computed tomography (CT), ultrasound (US) of the cervical region and abdomen, positron emission tomography (PET), bronchoscopy, chest X-ray, magnetic resonance imaging (MRI), and bone scintigraphy. In this article, these investigations will all be reviewed with regard to reported results, and the pros and cons if used in esophageal cancer patients. In addition, a meta-analysis will be performed for the use of EUS, CT and PET in esophageal cancer staging. Based on these data, we propose the most optimal staging strategy in patients diagnosed with esophageal cancer.

METHODS

Literature search and data extraction

A Medline literature search was performed identifying all articles relating to the use of staging investigations in patients with esophageal cancer. Search terms that were used to identify such articles were combinations of 'esophagus', 'oesophagus', 'cancer', 'neoplasm', 'carcinoma', 'endoscopy', 'barium examination', 'barium swallow', 'endoscopic ultrasonography', 'EUS', 'computed tomography', 'CT', 'positron emission tomography', 'PET', 'bronchoscopy', 'chest X-ray', 'chest', 'radiograph*', 'magnetic resonance imaging', 'MRI', 'bone scan', 'bone scintigraphy', and 'bone'. Abstracts obtained from these searches were evaluated to identify articles relating to results, and pros and cons of staging investigations in esophageal cancer patients.

For the part concerning the reported results of staging investigations, articles containing information on overall accuracy, sensitivity and/or specificity of these investigations for T, N

and/or M stage of esophageal cancer and published in the English literature before January 2006 were included. Excluded were articles published in abstract form only, case reports, editorials and reviews. In addition, articles containing results of patients who had undergone prior radiation and/or chemotherapy were excluded, if the result of the gold standard could have been influenced by the administration of radiation and/or chemotherapy. The references of included articles and reviews, found with the literature search, were also examined to find additional articles that met the inclusion criteria. From the included articles, accuracy, sensitivity and/or specificity of the investigations were obtained.

If more than 5 articles were included in the part concerning the reported results of the staging investigation for N or M stage, respectively, the staging investigation was included in the meta-analysis. This was the case for EUS, CT and PET. For these investigations, articles were included in the meta-analysis if the absolute numbers of true-positive (TP), false-negative (FN), false-positive (FP), and true-negative (TN) test results were available or derivable from data in an article, which allowed us to construct 2x2 contingency tables. Studies with potentially overlapping study populations were excluded. Two independent readers (E.P.M.v.V., P.D.S.) extracted the data from the included articles. The absolute numbers of TP, FN, FP, and TN test results were retrieved or calculated from the published data. Other characteristics that were extracted from each included study, were origin of article, publication year of article, mean age of patients, proportion of male (as percentage of total number of patients), histology of the tumor, whether the study was retrospectively or prospectively performed, whether the patients were consecutive or not, whether the test results were blindly interpreted or not, and the gold standard that was used in the study. For articles containing EUS results, the type of EUS probe, whether fine-needle aspiration was performed for suspicious lymph nodes or not, and whether dilation was performed in patients with a stenotic tumor or not were also extracted. For articles containing results of CT, the type of CT scanner and whether contrast was administered or not were extracted. For articles containing results of PET, the type of PET scanner was extracted. In case of inconsistent findings between the two readers, a consensus decision was made.

Statistical analysis: meta-analysis

Sensitivity and specificity of EUS, CT and PET, respectively, were pooled using a random effects model. With this method, the variability between studies is taken into account. To estimate the relationship between sensitivity and specificity of EUS, CT and PET, respectively, a random effects summary receiver operating characteristic (SROC) analysis was performed. In a SROC analysis, the logits (log odds) of sensitivity and 1-specificity are subtracted to calculate D [D = ln(sensitivity/(1-sensitivity)) – ln((1-specificity)/specificity)]. Sensitivity is the proportion of patients who are correctly identified as having metastases (true positive results), specificity is the proportion of patients who are correctly identified as having no metastases (true negative results), 1-sensitivity is the proportion of patients in whom the gold standard

is positive for metastases, but who are incorrectly identified as negative by the staging investigations (false negative results) and 1-specificity is the proportion of patients in whom the gold standard is negative for metastases, but who are incorrectly identified as positive by the staging investigations (false positive results). D is the log of the diagnostic odds ratio, which represents a summary measure of the diagnostic performance or discriminatory power of an investigation. D ranges from zero to infinity. A value close to zero or far from 1 represents an investigation with good diagnostic performance. The logits are summed to calculate S [S = ln(sensitivity/(1-sensitivity)) + ln((1-specificity)/specificity)]. S is a proxy for the positivity criterion of the diagnostic test. When institutions use different thresholds for scoring a test result as positive, different positivity criteria will exist among studies. Subsequently, a linear regression model D = a + bS is estimated, weighted by the inverse of the variance of D. Additional covariates are added to the model to adjust for differences in study characteristics. A study characteristic was considered statistically significant if $p < 0.05$. The *meta* and *metareg* commands of STATA 8.0 were used for the meta-analysis.

To determine whether publication bias, i.e., the selective reporting of manuscripts with more positive results, was present in this study, funnel plots were constructed. A funnel plot is an epidemiologic method for assessing the presence of publication bias, in which a measure of the study size is plotted against the measure of interest. In this study, the measure of study size was the number of patients and the measure of interest was the natural logarithm of the diagnostic odds ratio (D). The idea is that studies with the largest study size will estimate D most accurate, whereas studies with a smaller study size will have a more variable result, with both lower and higher values of D compared to the larger studies. If this is the case, the plot will have a symmetric, inverted funnel shape. If publication bias is present, the left base of the plot will disappear and the plot is asymmetric and skewed (4). Symmetry and shape of the funnel plots were determined by means of visual inspection of the plots.

DIAGNOSTIC AND STAGING PROCEDURES

Upper gastrointestinal endoscopy

Upper gastrointestinal endoscopy is the preferred investigation for diagnosing esophageal cancer and should always be performed in patients suspicious for esophageal cancer (5-7). It allows direct visualization of the esophagus and the sampling of biopsies. In addition, exact location and length of the primary tumor can be assessed. The appropriate number of biopsy specimens that should be obtained during endoscopy has been reported to be at least 6 to 7. This number of specimens enables a correct diagnosis of esophageal cancer in 96-100% of cases (5, 8). In patients with a stenotic tumor, biopsies are less frequently positive in comparison with patients with an exophytic tumor. To overcome the problem of missing a diagnosis in patients with stenotic esophageal cancer, brush cytology can be performed (6). It is useful

to inspect the stomach during the same procedure to evaluate its suitability for gastric tube reconstruction following esophagectomy.

Barium swallow

A barium swallow can be used to detect lesions in the esophagus and to show their extent, location and depth of infiltration (9, 10). Either a single or double contrast examination can be performed. The accuracy of a barium swallow to detect esophageal cancer of different sizes has been reported to vary between 73% and 96% (11, 12). It is difficult to detect cancers appearing as superficial depressions or flat lesions (9).

In a prospective study of 34 patients with squamous cell carcinoma of the esophagus, tumor length as detected by barium swallow was compared with that at resection. In only 3 patients, these lengths were equal, whereas in 13 patients the variation in length was more than 2 cm (13).

The information obtained with barium swallow can also be obtained with upper gastrointestinal endoscopy, whereas the last investigation also allows the taking of biopsies. Therefore, the use of barium swallow is nowadays considered to be obsolete in the staging logarithm of esophageal cancer.

Endoscopic ultrasonography (EUS)

EUS is the most accurate investigation to determine the T stage of esophageal cancer (14) as it is able to discern the different layers of the esophageal wall (15). Accuracy of EUS for T staging has been determined in 43 studies (14-56) and varied between 53% and 94%, with a median accuracy of 83%. In Figure 2.1, accuracies are plotted against T stage (T1-4). From this, it can be seen that accuracy increases with higher T stages (19, 21, 24-26, 29, 30, 32, 36, 37, 41, 44, 56-58).

EUS is also an useful investigation for the detection of regional and celiac lymph node metastases (20, 25, 27). Using EUS, lymph nodes are considered to be malignant if their size is larger than 8-10 mm, and they have an uniform hypoechoic echodensity, a sharp demarcation from surrounding fat, and a rounded shape (59). Accuracy for N stage was reported in 47 articles (14-16, 18-21, 23, 24, 26-28, 30-38, 40-44, 46-53, 55-58, 60-68), and sensitivity and specificity in 30 articles (15, 16, 18, 23-25, 31, 33, 34, 38, 44, 47-52, 54-58, 60-64, 66-68). Accuracy of EUS for N stage varied between 54% and 94%, sensitivity between 37% and 100%, and specificity between 50% and 100%. We included 31 articles reporting the absolute numbers of TP, FN, FP, and TN test results of EUS for N stage in the meta-analysis. Study characteristics are shown in Table 2.1. The random effects pooled sensitivity and specificity of EUS for N stage were 0.80 (95% confidence interval (C.I.) 0.75-0.84) and 0.70 (95% C.I. 0.65-0.75), respectively. D measured 1.94 (95% C.I. 1.71-2.17). The estimated SROC curve is shown in Figure 2.2. The differences between the curves of EUS, CT and PET for N staging were statistically not significant. Visual inspection of the funnel plot revealed that the plot was symmetric (Figure 2.3), which implies that publication bias was not present.

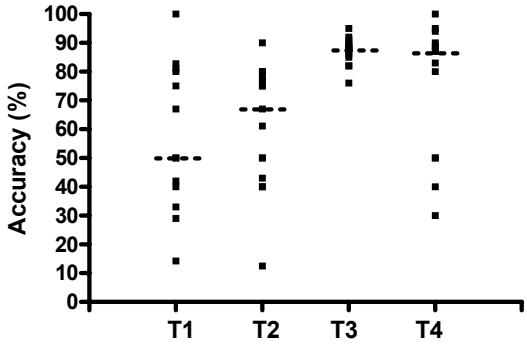

Figure 2.1. Accuracy of EUS per T stage (--- median).

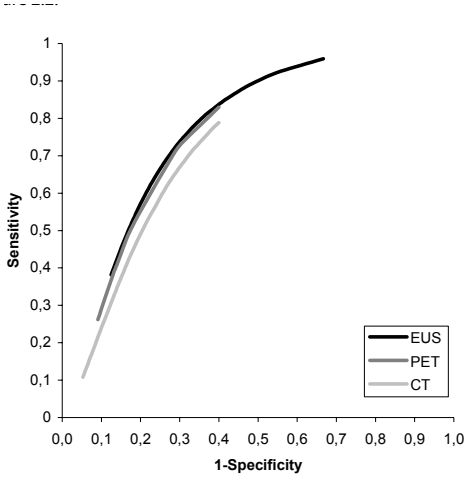

Figure 2.2. Summary receiver operating characteristic curves for EUS, PET and CT for the detection of regional lymph node metastases. The differences between EUS, PET and CT were statistically not significant.

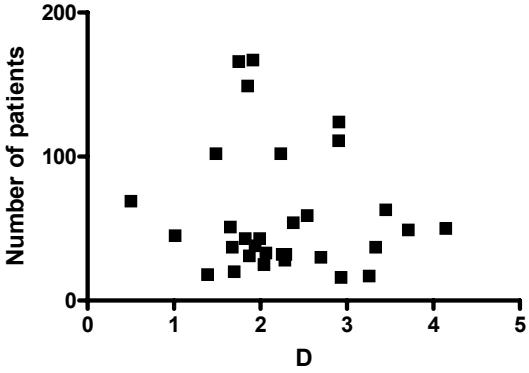

Figure 2.3. Funnel plot in which the number of patients included in studies concerning the use of EUS for the detection of regional lymph nodes were plotted against D.

Table 2.1. Characteristics of studies containing absolute numbers of TP, FN, FP, and TN test results of EUS for regional and celiac lymph node metastases.

Study	Year	Study type	Number of patients	Sensitivity (%)	Specificity (%)	Pooled sensitivity (95% C.I.)	Pooled specificity (95% C.I.)
Regional lymph node metastases						0.80 (0.75-0.84)	0.70 (0.65-0.75)
Tio, et al. (18)	1990	Not reported	111	73/77 (95)	17/34 (50)		
Ziegler, et al. (19)	1991	Prospective	37	16/25 (64)	9/12 (75)		
Rice, et al. (15)	1991	Not reported	20	7/10 (70)	7/10 (70)		
Botet, et al. (20)	1991	Prospective	50	35/36 (97)	9/14 (64)		
Grimm, et al. (23)	1993	Prospective	63	37/41 (90)	17/22 (77)		
Dittler, et al. (24)	1993	Not reported	167	85/114 (75)	37/53 (70)		
Yoshikane, et al. (60)	1994	Not reported	25	7/12 (58)	11/13 (85)		
Greenberg, et al. (25)	1994	Prospective	16	6/10 (60)	6/6 (100)		
Binmoeller, et al. (26)	1995	Prospective	38	26/29 (90)	4/9 (44)		
Hasegawa, et al.(62)	1996	Not reported	18	4/8 (50)	8/10 (80)		
Natsugoe, et al. (63)	1996	Prospective	37	4/5 (80)	28/32 (88)		
Hunerbein, et al. (28)	1996	Prospective	17	13/14 (93)	2/3 (67)		
Pham, et al. (32)	1998	Prospective	28	14/16 (88)	7/12 (58)		
Vickers, et al. (33)	1998	Prospective	49	35/36 (97)	7/13 (54)		
Bowrey, et al. (34)	1999	Not reported	30	17/19 (89)	7/11 (64)		
Salminen, et al. (37)	1999	Prospective	32	19/20 (95)	4/12 (33)		
Catalano, et al. (38)	1999	Prospective	149	75/95 (79)	34/54 (63)		
Nishimaki, et al. (57)	1999	Prospective	166	88/110 (80)	33/56 (59)		
Shinkai, et al. (68)	2000	Not reported	102	41/54 (76)	28/48 (58)		
Nesje, et al. (40)	2000	Prospective	54	36/46 (78)	6/8 (75)		
Richards, et al. (42)	2000	Retrospective	69	19/42 (45)	18/27 (67)		
Choi, et al. (67)	2000	Prospective	45	15/30 (50)	11/15 (73)		
Vazquez-Sequeiros, et al. (44)	2001	Retrospective	33	14/22 (64)	9/11 (82)		
Vazquez-Sequeiros, et al. (48)	2003	Prospective	124	68/85 (80)	32/39 (82)		
Wu, et al. (49)	2003	Not reported	31	13/19 (68)	9/12 (75)		
Rasanen, et al. (50)	2003	Prospective	32	17/19 (89)	7/13 (54)		
Heeren, et al. (51)	2004	Not reported	43	18/26 (69)	13/17 (76)		
Sihvo, et al. (52)	2004	Prospective	43	22/26 (85)	9/17 (53)		
Lowe, et al. (54)	2005	Prospective	59	38/44 (86)	10/15 (67)		
Pedrazzani, et al. (55)	2005	Retrospective	51	25/37 (68)	10/14 (71)		
DeWitt, et al. (56)	2005	Retrospective	102	48/66 (73)	28/36 (78)		

Table 2.1. continued

Study	Year	Study type	Number of patients	Sensitivity (%)	Specificity (%)	Pooled sensitivity (95% C.I.)	Pooled specificity (95% C.I.)
Celiac lymph node metastases						0.85 (0.72-0.99)	0.96 (0.92-1.00)
Binmoeller, et al. (26)	1995	Prospective	35	3/4 (75)	29/31 (94)		
Catalano, et al. (38)	1999	Prospective	149	19/23 (83)	124/126 (98)		
Eloubeidi, et al. (69)	2001	Retrospective	102	48/62 (77)	34/40 (85)		
Vazquez-Sequeiros, et al. (44)	2001	Retrospective	33	3/4 (75)	29/29 (100)		
Parmar, et al. (70)	2002	Retrospective	20	18/18 (100)	1/2 (50)		

C.I., confidence interval

Accuracy of EUS for celiac lymph node metastases was reported in only 7 articles (21, 26, 34, 38, 44, 69, 70) and sensitivity and specificity in 4 articles (38, 44, 69, 70). The accuracy varied between 66% and 100%, sensitivity between 75% and 100%, and specificity between 50% and 100%. In the meta-analysis, 5 articles containing the absolute numbers of TP, FN, FP, and TN test results of EUS for celiac lymph nodes were included (Table 2.1). The random effects pooled sensitivity and specificity of EUS for the detection of celiac lymph nodes were 0.85 (95% C.I. 0.72-0.99) and 0.96 (95% C.I. 0.92-1.00), respectively. D measured 3.89 (95% C.I. 2.67-5.11). As the number of articles was only 5, it was not possible to assess whether publication bias was present with visual inspection of the funnel plot.

During EUS, fine-needle aspiration (FNA) can be performed to obtain tissue for the cytological analysis of the presence of malignant lymph nodes. The reported results of EUS-FNA were clearly better than those of EUS alone for determining N stage (44, 69-71), with accuracies ranging from 72% to 93% (14, 38, 44, 48, 51, 53, 56). This is due to a better differentiation between reactive (non-malignant) and malignant lymph nodes (71).

A learning curve has been demonstrated for performing EUS. In a retrospective study, it has been reported that for the first 100 EUS examinations, accuracy for T stage was 58% and that for the following 131, accuracy was 83%. This study concluded that acceptable accuracy rates can only be obtained after at least 100 examinations (29). Another study came to the same conclusion, however, this study concluded that reliable results could already be obtained after at least 75 EUS examinations (72). The number of EUS investigations performed in a center per year also affects the results of esophageal cancer staging. Results of EUS performed in a low volume EUS center where <50 EUS per endoscopist per year were performed compared unfavorably with those reported from high volume EUS centers (71).

In 25-36% of patients presenting with esophageal cancer, a stenotic tumor is present preventing the EUS probe from passing the primary cancer (73). This obviously results in incomplete tumor staging with inferior EUS results (71, 74). Dilation can be performed to allow examination of the whole esophagus in these patients. Recent studies have not dem-

onstrated serious complications, i.e., perforation or bleeding, in patients having undergone dilation prior to EUS (75-77). An alternative option is to use a mini-EUS probe with a diameter of about 8 mm. It has been reported that the accuracy rates of miniprobes are similar to those of conventional EUS probes (26, 34). Finally, a non-optical wire-guided EUS probe can be used. The diameter of this probe is smaller than the diameter of a conventional EUS probe, due to the elimination of the fiberoptics and an instrument channel (78).

A limitation of EUS is that only lymph nodes in the proximity of the esophageal and gastric wall can be visualized as the EUS probe has a limited penetration depth of approximately 5 cm. As a consequence, metastases in distant lymph nodes or organs can often not be detected by EUS (46). Nevertheless, EUS is an useful investigation for the determination of T and N stage.

Computed tomography (CT)

CT of the cervical region, chest and abdomen is used to evaluate the presence of cancer in the esophageal wall, invasion into the tracheobronchial tree, aorta, or pericardium, and the presence of metastatic disease in lymph nodes, lung, liver, bones or adrenal glands (79, 80). For an optimal CT, contrast should be administered both orally and intravenously during the investigation. Oral contrast is used for a better delineation of the esophageal wall, whereas intravenous contrast is administered for a better distinction of the vascular structures and the margins of the tumor (81) and for the detection of liver metastases. Particularly, liver metastases are more readily detected after contrast enhancement (82, 83). Slice thickness should not exceed 5 mm. With a slice thickness of more than 5 mm, the chance to miss metastases is highly increased.

CT is able to detect the presence of esophageal cancer, however CT is not able to define the different layers of the esophageal wall, and thus, for example, to make a differentiation between T1 and T2 tumors (27, 84).

Tracheobronchial tree involvement on CT is suspected when the tumor displaces or compresses the trachea or bronchus (84, 85). As the trachea and bronchus are distensible air-filled structures, distortion of the normal appearance is usually easily detected on CT (85). In two studies, accuracy for tracheobronchial tree involvement was reported, ranging from 88% to 97%, respectively (80, 84). Sensitivity varied between 31% and 100% and specificity between 86% and 97% (84, 86).

Aortic invasion is detected through the contact between the esophageal tumor and the aorta. With the total circumference of the aorta being 360°, aortic invasion is considered to be present if the contact between the tumor and the aorta exceeds 90° on CT. If the contact is between 45° and 90°, the result is considered to be indeterminate (85). Another criterion for aortic invasion is the obliteration of the triangular fat space between the esophagus, spine and aorta (87). The results of CT for aortic invasion are variable with accuracies varying be-

tween 55% and 94% (80, 84), sensitivities between 6% and 100%, and specificities between 52% and 89% (84, 86).

Involvement of the pericardium is suggested when the cancer extends into the pericardium and the fat planes are obliterated at that level (88). Results of CT for pericardial involvement have been reported in one study, showing an accuracy of 97% (84).

In two prospective studies, the use of different patient positions, i.e., supine, left lateral decubitus and prone, was assessed to determine whether this could improve the detection of invasion into surrounding organs. The results of these studies are contradictory. In one study it was found that adding other positions to the supine position did not improve the prediction of aortic invasion, whereas another study claimed that the risk of overstaging declined if scanning in the prone position was added to scanning in the supine position, which is normally performed (89, 90).

CT is also able to detect lymph node metastases. Lymph nodes are considered to be malignant if the size exceeds 10 mm on CT (16, 30, 39, 82, 91). Results of CT for regional lymph nodes were reported in 24 articles (16, 19, 20, 25, 27, 30, 46, 48-52, 54, 57, 60, 67, 80, 84, 92-97) and for abdominal lymph nodes in 8 articles (70, 80, 81, 84, 86, 97-99). For regional lymph nodes, accuracy, sensitivity and specificity varied between 33% and 86% (16, 19, 20, 27, 30, 46, 48-52, 57, 60, 67, 80, 84, 92-95, 97), 22% and 84%, and 60% and 100% (16, 25, 48-52, 54, 57, 60, 67, 84, 92-94, 96, 97), respectively. It is known that the quality of CT has been improved over the years. The distribution of accuracy of CT for regional lymph nodes in the period 1984-2004 is shown in Figure 2.4. This figure surprisingly shows that the accuracy of CT for the detection of regional lymph nodes remained more or less stable over the years. We included 17 articles containing the absolute numbers of TP, FN, FP, and TN test results of CT for regional lymph nodes in the meta-analysis (Table 2.2). The random effects pooled sensitivity and specificity of CT for the detection of regional lymph nodes were 0.50 (95% C.I. 0.41-0.60) and 0.83 (95% C.I. 0.77-0.89), respectively. The value of D was 1.40 (95% C.I. 1.08-1.72). The estimated SROC curve is shown in Figure 2.2. In the meta-analysis, a significant predictor of

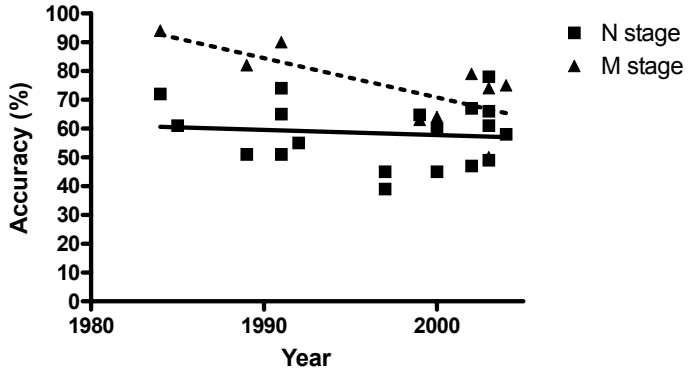

Figure 2.4. Distribution of accuracy of CT for regional lymph nodes (N stage) and distant metastases (M stage) over years (—N stage, ---M stage).

Table 2.2. Characteristics of studies containing absolute numbers of TP, FN, FP, and TN test results of CT for regional lymph node metastases, abdominal lymph node metastases and distant metastases.

Study	Year	Study type	Number of patients	Sensitivity (%)	Specificity (%)	Pooled sensitivity (95% C.I.)	Pooled specificity (95% C.I.)
Regional lymph node metastases						0.50 (0.41-0.60)	0.83 (0.77-0.89)
Quint, et al. (84)	1985	Retrospective	33	11/18 (61)	9/15 (60)		
Ziegler, et al. (19)	1991	Prospective	37	10/24 (42)	9/13 (69)		
Botet, et al. (20)	1991	Prospective	42	23/29 (79)	8/13 (62)		
Sondenaa, et al. (92)	1992	Retrospective	42	5/23 (22)	18/19 (95)		
Yoshikane, et al. (60)	1994	Not reported	25	4/12 (33)	11/13 (85)		
Greenberg, et al. (25)	1994	Prospective	16	5/10 (50)	4/6 (67)		
Flanagan, et al. (93)	1997	Retrospective	29	5/18 (28)	8/11 (73)		
Nishimaki, et al. (57)	1999	Prospective	210	81/136 (60)	55/74 (74)		
Choi, et al. (67)	2000	Prospective	48	13/32 (41)	16/16 (100)		
Wren, et al. (94)	2002	Retrospective	21	4/7 (57)	10/14 (71)		
Vazquez-Sequeiros, et al. (48)	2003	Prospective	124	40/85 (47)	36/39 (92)		
Wu, et al. (49)	2003	Not reported	41	17/22 (77)	15/19 (79)		
Yoon, et al. (96)	2003	Prospective	81	12/39 (31)	36/42 (86)		
Rasanen, et al. (50)	2003	Prospective	32	9/19 (47)	12/13 (92)		
Heeren, et al. (51)	2004	Not reported	60	17/39 (44)	19/21 (90)		
Sihvo, et al. (52)	2004	Prospective	43	11/26 (42)	14/17 (82)		
Lowe, et al. (54)	2005	Prospective	59	37/44 (84)	10/15 (67)		
Abdominal lymph node metastases						0.42 (0.29-0.54)	0.93 (0.86-1.00)
Quint, et al. (84)	1985	Retrospective	33	2/3 (67)	26/30 (87)		
Becker, et al. (81)	1986	Retrospective	50	13/23 (57)	27/27 (100)		
Watt, et al. (98)	1989	Prospective	65	11/35 (31)	26/30 (87)		
Van Overhagen, et al. (99)	1993	Prospective	86	13/27 (48)	55/59 (93)		
Parmar, et al. (70)	2002	Retrospective	20	5/18 (28)	1/2 (50)		
Distant metastases						0.52 (0.33-0.71)	0.91 (0.86-0.96)
Van Overhagen, et al. (99)	1993	Prospective	113	38/54 (70)	50/59 (85)		
Flamen, et al. (39)	2000	Prospective	74	14/34 (41)	33/40 (83)		
Wren, et al. (94)	2002	Retrospective	24	10/12 (83)	9/12 (75)		
Rasanen, et al. (50)	2003	Prospective	42	5/15 (33)	26/27 (96)		
Yoon, et al. (96)	2003	Prospective	81	1/7 (14)	70/74 (95)		
Sihvo, et al. (52)	2004	Prospective	55	6/19 (32)	35/36 (97)		
Lowe, et al. (54)	2005	Prospective	48	21/26 (81)	18/22 (82)		

C.I., confidence interval

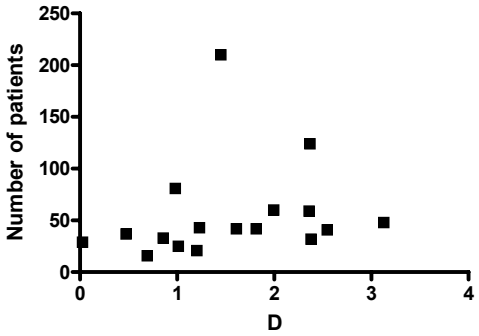

Figure 2.5. Funnel plot in which the number of patients included in studies concerning the use of CT for the detection of regional lymph nodes were plotted against D.

diagnostic performance for regional lymph nodes was the year of publication of the study. If the log odds ratio (D) of CT for regional lymph nodes was plotted against year of publication, the plot showed a statistically significant improvement of diagnostic performance over the years (p=0.031). In Figure 2.5, the funnel plot is shown, which has a symmetric shape, indicating that publication bias was not present.

For abdominal lymph nodes, accuracy varied between 35% and 85% (70, 80, 81, 84, 97, 98), sensitivity between 25% and 67%, and specificity between 58% and 100% (70, 81, 84, 86, 97-99). In the meta-analysis, 5 articles containing the absolute numbers of TP, FN, FP, and TN test results of CT for abdominal lymph nodes were included (Table 2.2). The random effects pooled sensitivity and specificity of CT for the detection of abdominal lymph nodes were 0.42 (95% C.I. 0.29-0.54) and 0.93 (95% C.I. 0.86-1.00), respectively. D measured 1.74 (95% C.I. 0.45-3.04). As the number of articles included in the meta-analysis was only 5, it was not possible to assess whether publication bias was present with visual inspection of the funnel plot.

Despite the fact that most authors use a cut-off size of 10 mm for the assessment of malignant lymph nodes on CT, only one study assessed different cut-off sizes to determine an optimal size. In this study, the correlation between findings on CT and the histopathological result were examined for different size criteria of lymph nodes, i.e., 3, 5, 10, 15 and 20 mm. It was concluded that 5 mm is already the optimal cut-off size that could differentiate between benign and malignant lymph nodes, because the sensitivities at 5 mm were substantial higher than those at other cut-off sizes, whereas the specificity was only slightly decreased (100).

Results of CT for distant metastases were reported in 13 articles (16, 20, 39, 50, 52, 54, 80, 94, 96, 97, 99, 101, 102). Accuracy varied between 45% and 94% (16, 20, 39, 50, 52, 80, 94, 97, 101, 102), sensitivity between 14% and 81%, and specificity between 11% and 97% (16, 39, 50, 52, 54, 96, 97, 99, 101, 102). The accuracy for distant metastases declined over the years (Figure 2.4). The reason for this observation is not clear, however might reflect the fact that over the years, CT was also performed in less experienced centers. In the meta-analysis, 7 articles containing the absolute numbers of TP, FN, FP, and TN test results of CT for distant metastases were included (Table 2.2). The random effects pooled sensitivity and specificity

of CT for the detection of distant metastases were 0.52 (95% C.I. 0.33-0.71) and 0.91 (95% C.I. 0.86-0.96), respectively. D has a value of 2.10 (95% C.I. 1.59-2.62). The diagnostic performance of CT was statistically significant lower than the diagnostic performance of PET, which is shown in the SROC curve (Figure 2.6). This difference between CT and PET remained when covariates were added to the model. It was not possible to assess whether publication bias was present with visual inspection of the funnel plot, as the number of articles included in the meta-analysis was only 7.

Only in two studies, specific results for liver metastases detection were reported, with accuracies of 85% (98) and 100% (84).

CT has also been suggested to be useful for the detection of growth of the esophageal tumor into the stomach. Accuracies varied between 79% (84) and 83% (80).

In a retrospective study, the quality of preoperative metastasis detection in a high volume referral center was compared with that in low volume referring regional centers. The diagnostic sensitivity of metastasis detection was higher in the high volume referral center than in referring regional centers, which could be due to both better CT scanning equipment and more experienced radiologists in the referral center (103).

CT is not able to detect metastases in normal sized lymph nodes. Furthermore, an enlarged lymph node may contain metastases, but may also be enlarged as a consequence of inflammation (67, 79, 104). The same is true for other abnormalities, for example in the liver or adrenal gland, for which it is not always clear whether these are metastases or not. In these patients, CT- or US-guided biopsy should be performed to confirm or exclude the presence of metastatic disease (105).

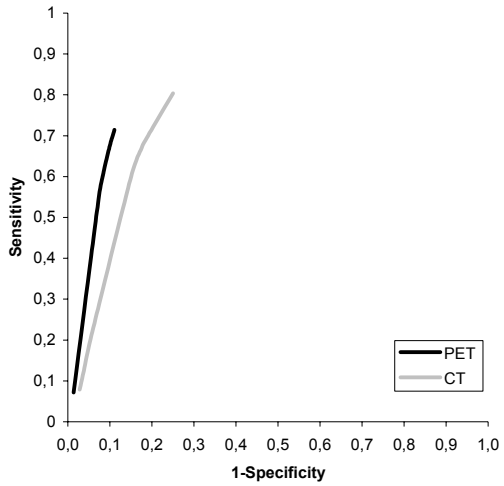

Figure 2.6. Summary receiver operating characteristic curves for PET and CT for the detection of distant metastases. The difference between PET and CT was statistically significant (p = 0.03).

Despite the above-mentioned limitations, the evidence is convincing that CT should be performed in the work-up of patients with esophageal cancer, especially for the detection of distant metastases. If a CT is performed, both oral and intravenous contrast material should be administered during scanning, and a slice thickness of 5 mm or less is advisable.

^{18}F-fluoro-2-deoxy-D-glucose positron emission tomography (FDG-PET)

The metabolism of glucose is increased in malignant cells. ^{18}F-fluoro-2-deoxy-D-glucose (FDG) is a glucose analogue that accumulates in cells with high glucose metabolism and the principle of FDG-PET is to identify this accumulation of FDG in malignancies (52, 106-113).

In 78% to 97% of patients with esophageal cancer, the primary tumor can be demonstrated with FDG-PET (50, 52, 91, 96, 106, 113-116). Early stage tumors, i.e., carcinoma *in situ* or T1 carcinoma, are mostly not detected by FDG-PET (110).

FDG-PET is also able to determine whether malignant regional lymph nodes or distant metastases are present. Accuracy for regional lymph nodes was reported in 8 articles (50-52, 67, 93, 94, 109, 114) and sensitivity and specificity in 10 articles (50-52, 54, 67, 93, 94, 96, 109, 114). Accuracy varied between 48% and 83%, sensitivity between 22% and 82% and specificity between 60% and 100%. All 10 articles also contained the absolute numbers of TP, FN, FP, and TN test results of FDG-PET for regional lymph nodes and these were included in the meta-analysis. Study characteristics are shown in Table 2.3. The random effects pooled sensitivity and specificity of FDG-PET for the detection of regional lymph nodes were 0.57 (95% C.I. 0.43-0.70) and 0.85 (95% C.I. 0.76-0.95), respectively. D measured 1.71 (95% C.I. 1.22-2.20). The estimated SROC curve is shown in Figure 2.2. The specificity of FDG-PET for N stage is higher than the sensitivity, meaning that FDG-PET is particularly useful to exclude the presence of malignant lymph nodes. It was not possible to assess whether publication bias was present, as the number of articles included in the meta-analysis was only 10.

Accuracy for M stage was reported in 10 articles (39, 50-52, 94, 97, 101, 102, 109, 114) and sensitivity and specificity also in 10 articles (39, 50-52, 54, 97, 101, 102, 109, 114). Accuracy varied between 50% and 91%, sensitivity between 35% and 88% and specificity between 87% and 98%. In 9 articles, the absolute numbers of TP, FN, FP, and TN test results of FDG-PET for distant metastases were reported and these articles were included in the meta-analysis (Table 2.3). The random effects pooled sensitivity and specificity of FDG-PET for the detection of distant metastases were 0.71 (95% C.I. 0.62-0.79) and 0.93 (95% C.I. 0.89-0.97), respectively. D had a value of 2.93 (95% C.I. 2.41-3.45). The estimated SROC curve is shown in Figure 2.6. As the number of articles included in the meta-analysis was only 9, it was not possible to assess whether publication bias was present.

FDG-PET was compared with bone scintigraphy for the detection of bone metastases. The accuracy of 93%, sensitivity of 92% and specificity of 94% of FDG-PET were slightly higher than the results of bone scintigraphy, but the differences were statistically not significant. Particularly, osteoblastic metastases had a lower metabolic activity and these metastases

Table 2.3. Characteristics of studies containing absolute numbers of TP, FN, FP, and TN test results of PET for regional lymph node metastases and distant metastases.

Study	Year	Study type	No. of patients	Sensitivity (%)	Specificity (%)	Pooled sensitivity (95% C.I.)	Pooled specificity (95% C.I.)
Regional lymph node metastases						0.57 (0.43-0.70)	0.85 (0.76-0.95)
Luketich, et al. (114)	1997	Retrospective	21	9/20 (45)	1/1 (100)		
Flanagan, et al. (93)	1997	Retrospective	29	13/18 (72)	9/11 (82)		
Lerut, et al. (109)	2000	Prospective	29	4/18 (22)	10/11 (91)		
Choi, et al. (67)	2000	Prospective	48	26/32 (81)	14/16 (88)		
Wren, et al. (94)	2002	Retrospective	21	5/7 (71)	12/14 (86)		
Yoon, et al. (96)	2003	Prospective	81	25/39 (64)	29/42 (69)		
Rasanen, et al. (50)	2003	Prospective	32	7/19 (37)	13/13 (100)		
Heeren, et al. (51)	2004	Not reported	61	22/40 (55)	15/21 (71)		
Sihvo, et al. (52)	2004	Prospective	43	9/26 (35)	17/17 (100)		
Lowe, et al. (54)	2005	Prospective	59	36/44 (82)	9/15 (60)		
Distant metastases						0.71 (0.62-0.79)	0.93 (0.89-0.97)
Luketich, et al. (114)	1997	Retrospective	35	7/8 (88)	25/27 (93)		
Lerut, et al. (109)	2000	Prospective	42	10/13 (77)	26/29 (90)		
Flamen, et al. (39)	2000	Prospective	74	25/34 (74)	36/40 (90)		
Wren, et al. (94)	2002	Retrospective	24	8/12 (67)	11/12 (92)		
Yoon, et al. (96)	2003	Prospective	81	3/7 (43)	73/74 (99)		
Rasanen, et al. (50)	2003	Prospective	42	7/15 (47)	24/27 (89)		
Sihvo, et al. (52)	2004	Prospective	55	10/19 (53)	32/36 (89)		
Heeren, et al. (51)	2004	Not reported	74	21/27 (78)	43/47 (91)		
Lowe, et al. (54)	2005	Prospective	48	21/26 (81)	20/22 (91)		

C.I., confidence interval

may be missed by FDG-PET. For osseous metastases, however, FDG-PET was superior to bone scintigraphy (111).

It has been demonstrated that in 0-20% of patients with esophageal cancer, distant metastases were detected with FDG-PET, which were not found with other investigations. In patients in whom distant metastases were detected with FDG-PET, the treatment modality was corrected from a curative to a palliative option and unnecessary surgery was precluded (39, 93, 94, 101, 106, 107, 109, 115, 117, 118).

An advantage of FDG-PET is that it is based on an altered tissue glucose metabolism and not only on size, as biochemical changes appear earlier in time than structural changes and also are more specific (93, 106). For example, FDG-PET is able to detect metastases in lymph nodes that have a normal size, but can also verify whether metastases are present in lymph nodes that are enlarged (113). Nevertheless, lesions less than 1 cm in diameter can be missed

by FDG-PET due to difficulties in resolving increased FDG uptake (109). The additional value of PET depends on the quality of other investigations that are performed in patients with esophageal cancer, i.e., EUS and CT. PET is mainly used for the detection of distant metastases that have not otherwise been detected. Therefore, if EUS and CT are of good to high quality, PET will have a lower additional value in the detection of metastases. The opposite is true if the quality of EUS or CT is somewhat lower; this will increase the diagnostic yield of PET.

Anatomic structures cannot be delineated with FDG-PET (93). Therefore, invasion of esophageal cancer into other organs cannot be visualized with FDG-PET, which is however important in determining whether esophageal resection is possible or not (107). Another disadvantage of FDG-PET is that lymph nodes adjacent to the primary esophageal cancer are difficult to discriminate from the primary tumor (119). This is due to the intense activity in the primary cancer (93) and the limited spatial resolution of PET (107, 114). FDG is not tumor specific, as an increase in glucose metabolism can also be present in areas with inflammation (67, 93, 113, 120, 121). Lesions detected by FDG-PET should therefore always be confirmed by pathologic examination or alternatively by another preoperative investigation (39, 50, 109). Combined PET-CT is a new modality that can be used to more precisely localize uptake, which is useful for determining in which structure the accumulation of the glucose analogue is present (101, 112, 121), however this needs further elucidation.

US of cervical region

US of the cervical region is able to determine whether malignant lymph nodes are present in that region. Enlarged lymph nodes are more likely to be malignant if they have a rounded shape, i.e., a short to long axis ratio more than 0.5, and if there is diffuse hypoechogenicity, intranodal necrosis, absence of an echogenic hilus and capsular rather than central vascularity (122).

The accuracy of US for malignant lymph nodes in the cervical region varies between 86% and 94% (65, 123-125). The sensitivity is lower than the specificity (55-79% versus 91- 98%, respectively) (99, 123-125).

An advantage of US is that it can be combined with FNA. US *plus* FNA has been demonstrated to be a relatively simple and safe technique which increases accuracy of staging compared to US alone (126-129). However, FNA is sometimes technically difficult if the lymph node is situated close to vessels or has a small diameter (63). Another advantage of US is that the detection of malignant lymph nodes is not only based on size, but also on morphological criteria (63). Nevertheless, US is not able to detect metastases in lymph nodes of normal size and shape and the accuracy of US largely depends on the experience of the investigator. Regardless of these limitations, US of the cervical region should be performed in all patients with esophageal cancer to determine whether malignant lymph nodes are present or not.

US abdomen

The presence of liver metastases, peritoneal metastases and malignant lymph nodes can be determined with abdominal US. The celiac axis and its branches can be used as landmarks to assess the location of lymph nodes (130). Abdominal lymph nodes are considered malignant if the size is 1 cm or more (99, 126).

Results of US abdomen have been reported in a few studies in which patients with esophageal or gastric cardia cancer were included. Accuracy for intra-abdominal lymph node metastases varied between 52% and 89%, with sensitivity and specificity of 17-74% and 93-100%, respectively (98, 99, 130). An accuracy of 83%, a sensitivity of 48% and a specificity of 97% have been reported for liver metastases detection, whereas accuracy for peritoneal metastases was reported to be 89%, with a sensitivity of 22% and specificity of 100% (98).

The experience of the investigator is again an important factor in the results obtained with abdominal US (98, 131). FNA can be performed during abdominal US to obtain tissue for cytological analysis to confirm or exclude the presence of malignancy (105).

The quality of abdominal US can be affected by respiratory movements or overlying bowel shadow (126). In addition, in obese patients, it can be difficult to evaluate the region around the celiac axis, due to interference with fat and/or gas (130). Due to these limitations, it is nowadays accepted that the diagnostic accuracy for the detection of metastases in celiac lymph nodes and the liver is better for CT than abdominal US.

Bronchoscopy

Bronchoscopy is able to determine whether the esophageal tumor invades the tracheobronchial tree (132). Several studies (132-135) have suggested that bronchoscopy with biopsy, and brush and washings cytology should be performed in patients with esophageal cancer. Particularly, an accuracy of 93% has been reported in patients with suprabifurcal esophageal cancer (134). In our opinion, bronchoscopy with biopsy, and brush and washings cytology should be performed in patients with suprabifurcal esophageal cancer to determine whether the tumor involves the tracheobronchial tree, as the incidence of tracheobronchial invasion is considerable in these patients (around 15%) (134). In patients with infrabifurcal esophageal cancer, bronchoscopy should only be performed if tracheobronchial invasion is likely based on clinical evidence or other staging investigations.

Bronchoscopy, bronchoscopic US, EUS and CT were prospectively compared in 59 patients with suprabifurcal esophageal cancer. Accuracy for tracheobronchial invasion was higher for bronchoscopic US (91%) compared to bronchoscopy (78%), EUS (85%) and CT (58%). It was concluded that bronchoscopic US is the diagnostic modality to be used in patients with tumors in the upper esophagus (136).

Chest X-ray

Abnormalities attributable to esophageal cancer can be present on a chest X-ray. Lindell *et al.* evaluated chest X-rays of 103 patients with esophageal cancer and demonstrated that abnormalities were present on 49 (48%) of these chest X-rays. The most common abnormalities were an abnormal azygo-esophageal line (20 patients), widening of the mediastinum (13 patients) and a posterior tracheal indentation and/or mass (12 patients). All these abnormalities are however not specific for esophageal cancer (137).

Chest X-ray is also able to determine whether lung metastases are present. A disadvantage of chest X-ray is that it is not useful for the detection of small lesions, and abnormalities in the posterior costophrenic angles and the peripheral parts of the lungs. Chest X-ray is also not very sensitive for evaluating the mediastinum or soft tissues of the thorax (138). For these reasons, CT is superior to chest X-ray for the detection of lung metastases and other abnormalities in the thorax and there is hardly any role for chest X-ray in the staging of esophageal cancer.

Magnetic resonance imaging (MRI)

MRI has several limitations in the staging of esophageal cancer patients. As MRI cannot differentiate between the different layers of the esophageal wall, it cannot be used to determine T stage (49). Furthermore, MRI is not able to differentiate between enlarged lymph nodes containing metastases and enlarged lymph nodes due to a benign cause, and it cannot identify the presence of tumor in lymph nodes that have a normal size (139). Most importantly, cardiac wall movement, peristalsis, and effects of blood flow and respiration result in motion artifacts on MRI precluding adequate staging of esophageal cancer (140). The above-mentioned limitations are also true for CT, with the exception of cardiovascular effects, which is the most important limitation of MRI. For this reason, MRI is dominated by CT in the staging of esophageal cancer patients.

Bone scintigraphy

Bone scintigraphy is able to determine whether bone metastases are present. In 44 patients, an accuracy of 82%, a sensitivity of 77% and a specificity of 84% for bone metastases detection were demonstrated (111). A disadvantage is that early skeletal metastatic lesions are often not detected by bone scintigraphy, as it does not detect the bone metastasis itself, but the resulting osteoblastic reaction of the involved bone (141). Clinically important metastases are rare in patients with esophageal cancer and, therefore, bone scintigraphy is only indicated if the presence of bone metastases is suspected based on symptoms or another staging investigation.

DISCUSSION

The diagnosis and staging of patients with esophageal cancer is important for the selection of the most optimal treatment modality. In Figure 2.7, we propose the optimal diagnostic and staging procedures in patients with esophageal cancer. If esophageal cancer is suspected, upper gastrointestinal endoscopy *plus* biopsies is the first investigation to be performed. There is no role for a barium swallow anymore, as the information obtained with a barium swallow can also be collected with endoscopy, which has, in addition, a higher accuracy to detect early lesions, and the ability to take biopsies and to inspect the stomach.

After the histological confirmation of a diagnosis of esophageal cancer and when the patient is fit enough to undergo a curative treatment, staging investigations should be performed to evaluate preoperative TNM stage. EUS has been demonstrated to be superior to CT in determining T stage of esophageal cancer, as only EUS is able to clearly differentiate between the 5 layers of the esophageal wall. Bronchoscopy is performed in patients with suprabifurcal esophageal cancer to determine tumor involvement into the tracheobronchial tree.

The presence of malignant regional lymph nodes can be determined with EUS, CT, and FDG-PET. Of these, EUS is the most accurate staging investigation. The differences between the three investigations were however statistically not significant in the meta-analysis (Figure

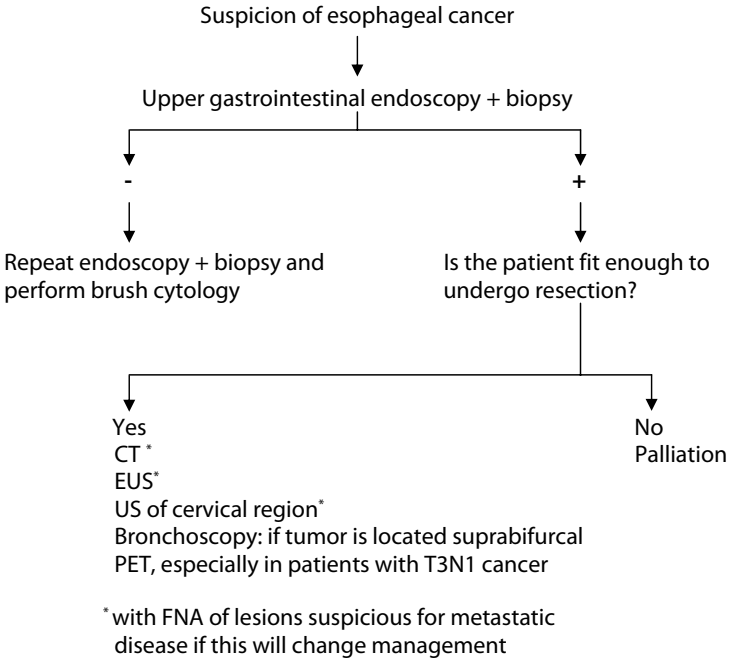

Figure 2.7. Staging of esophageal cancer.

2.3). The presence of distant metastases in celiac and supraclavicular lymph nodes, liver, lung, adrenal glands and bone should also be assessed. For malignant supraclavicular lymph nodes, US of the cervical region is most appropriate. If the presence of bone metastases is suspected, bone scintigraphy is indicated. Both CT thorax and abdomen, and PET can be performed to determine whether other distant metastases are present. It is difficult to determine how these investigations should be used during staging of patients with esophageal cancer. The random effects pooled sensitivity and specificity of CT for the detection of distant metastases was 0.52 (95% CI 0.33-0.71) and 0.91 (95% CI 0.86-0.96), respectively. For PET, these values were 0.71 (95% CI 0.62-0.79) and 0.93 (95% CI 0.89-0.97), respectively. The results found for PET were comparable to results found in a previous meta-analysis (142), in which the summary pooled sensitivity and specificity were 0.67 (95% CI 0.58-0.76) and 0.97 (95% CI 0.90-1.0), respectively. In the present meta-analysis, we found that the diagnostic performance of PET was significantly higher than that of CT (Figure 2.6). In other studies, it has been demonstrated that PET results for the detection of distant metastases were also higher compared with CT results. In a prospective study in which PET was compared with conventional noninvasive staging modalities for the detection of distant metastases, the accuracy of PET was 82%, sensitivity 74% and specificity 90%, whereas the results of CT were 64%, 41% and 83%, respectively (39). Another study in which PET was compared to CT showed that the accuracy of PET for the detection of distant metastases was 84%, sensitivity 69% and specificity 93%. Again, lower results of CT were reported, with an accuracy of 63%, sensitivity of 46% and specificity of 74% (101). The relatively average results of CT are however important to take into consideration in the interpretation of the clinical value of these studies. In contrast, in other studies in which PET and CT were compared, similar accuracies of PET and CT for the detection of distant metastases were found (50, 52, 94, 97, 102). A disadvantage of PET are the high costs, and at present it is questionable whether the costs of PET can be compensated from the cost reduction of resections that are not performed due to the finding of distant metastases with PET. Another important disadvantage of PET is that anatomic structures cannot be delineated. To overcome this problem, the use of a combined PET-CT might be useful, but the real value of this technique in the work-up of patients with esophageal cancer needs to be determined. It is still not established what the role of PET is in the work-up of patients with esophageal cancer, if EUS, CT and US of the cervical region have already been performed. The additional value of PET will probably largely depend on the quality of these remaining investigations. There may be a role for PET, especially in patients with T3N0-1 cancer to exclude the presence of metastases, which were not otherwise detected.

During EUS, CT or US, FNA can be performed to obtain tissue of suspicious lesions for cytological analysis. FNA should, however, only be performed in patients in whom the FNA result will change the treatment decision.

The results of EUS for celiac lymph node metastases were high in comparison with the results of EUS for regional lymph node metastases. An explanation for this could be that the

few studies that reported on EUS results for the detection of celiac lymph node metastases were likely to have been performed in high volume EUS centers. In contrast, studies that reported results of EUS for regional lymph node metastases were not only performed in high volume centers, but also in low volume centers. It is already known that results of EUS performed in a center where <50 EUS procedures per endoscopist per year (low volume center) are performed compared unfavorably with results reported from high volume EUS centers (71).

There are various limitations that could be present in this meta-analysis. First, only studies containing results of EUS, CT or PET for the detection of lymph node or distant metastases from which absolute numbers of TP, FN, FP, and TN test results were available or derivable were included. Several studies that contain results of EUS, CT or PET for the detection of lymph node or distant metastases did not report these absolute numbers of test results and were therefore excluded. For this reason, only a selection of published studies was included in the analysis. The percentage of excluded articles was not equal for EUS, CT and PET. For example, 7/24 (29%) articles containing results of CT for regional lymph nodes were excluded, because no absolute numbers of TP, FN, FP, and TN test results were available or derivable. These excluded articles were not only early studies on the use of CT in esophageal cancer, but were also published in later years, i.e., in the period between 2002 and 2004. The same was true for EUS for N staging; 16/47 (34%) articles were not used. No articles containing results of PET for regional lymph nodes were excluded, as in all these articles the absolute numbers of TP, FN, FP, and TN test results were available or derivable.

Second, if a decision to perform a procedure, that is considered to be the gold standard, i.e., resection or FNA, depends on the results of the test under investigation, verification bias might be present. In all articles included in our meta-analysis, verification bias will most likely be present, as the results of the staging investigations performed in patients with esophageal cancer were always used to decide whether patients should undergo a resection or not and whether FNA should be performed or not.

Third, publication bias, i.e., the selective reporting of manuscripts with more positive results, might be present. To assess this, funnel plots were constructed. Visual inspection of the plots shown in Figure 2.3 and 2.5 revealed that publication bias was not likely to be present in the meta-analysis concerning EUS and CT for the detection of regional lymph nodes. Nevertheless, the number of included studies was small for the other meta-analyses, which made it impossible to draw conclusions about the role of publication bias in these analyses.

Fourth, the time period in which articles concerning the results of an investigation were published might be an important factor as well. The early reports of results of a new investigation are often more favorably than reports published later in time if the same equipment is used in less selected study populations. In our meta-analysis, the articles concerning the use of CT for the detection of distant metastases were published between 1984 and 2004, whereas the articles concerning the use of PET were published between 1997 and 2005.

In conclusion, EUS is the investigation of choice for the determination of T and N stage. For malignant supraclavicular lymph nodes, US of the cervical region is most appropriate. CT and PET can both be used to detect the presence of distant metastases, however PET should particularly be considered in patients with a tumor that is otherwise staged as T3N0-1, to detect metastases that were not seen with other investigations.

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CHAPTER 3

Ultrasound, computed tomography or the combination for the detection of supraclavicular lymph nodes in patients with esophageal or gastric cardia cancer: a comparative study

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ABSTRACT

Background: Malignant supraclavicular lymph nodes in patients with thoracic esophageal or gastric cardia cancer are considered to be distant metastases. Both ultrasound (US) and computed tomography (CT) can be used to detect these metastases. We compared US, US *plus* fine-needle aspiration (US-FNA), CT, and the combinations US + CT, and US-FNA + CT for the detection of supraclavicular lymph node metastases in patients with esophageal or gastric cardia cancer.

Methods: From 1994 to 2004, 567 patients underwent US and CT, both including the supraclavicular region, for staging of esophageal or gastric cardia cancer. The gold standard was FNA, postoperative detection of lymph nodes in the supraclavicular region in the resected specimen, or a radiological result with ≥ 6 months of follow-up.

Results: Sensitivities of US (75%), US-FNA (72%), US + CT (80%) and US-FNA + CT (79%) were higher than sensitivity of CT alone (25%) ($p<0.001$). Specificities were high for US-FNA (100%), CT (99%), and US-FNA + CT (99%), whereas those of US alone (91%) and US + CT (91%) were lower ($p<0.001$). In 4/65 (6%) patients with true-positive malignant supraclavicular lymph nodes, CT was positive with US and/or US-FNA being negative. However, in 36/65 (55%) patients, US and/or US-FNA were positive with CT being negative.

Conclusion: US-FNA seems the preferred diagnostic modality for the detection of supraclavicular lymph node metastases in patients with esophageal or gastric cardia cancer. Sensitivity of metastases detection only slightly improves if US-FNA is combined with CT. A prospective, comparative study is however needed to confirm these results.

INTRODUCTION

Malignant supraclavicular lymph nodes in patients with thoracic esophageal cancer or gastric cardia cancer are considered to be distant metastases (1). In the presence of preoperatively detected malignant supraclavicular lymph nodes, a resection is not performed and patients will undergo a palliative treatment modality (2). Although supraclavicular lymph node metastases thus play an important role in the treatment decision and prognosis of patients with esophageal or gastric cardia cancer, the assessment of the supraclavicular lymph node status still poses a problem to clinicians (3).

There are several methods to assess the supraclavicular lymph node status. Palpation alone has however been demonstrated to be an unreliable method for the detection of these lymph nodes (3, 4). Computed tomography (CT) and ultrasound (US) of the supraclavicular region, either alone or in combination, are investigations that can be used for the assessment of the supraclavicular lymph node status (5, 6). The combination of CT and US is suspected to be more accurate than the use of either one alone (7). Fine-needle aspiration (FNA) during US can be performed to obtain tissue for the cytological analysis of the presence of metastatic supraclavicular lymph nodes. US *plus* FNA (US-FNA) has been demonstrated to contribute to more accurate esophageal and gastric cardia cancer staging than US alone (8).

Until 2000, almost all patients with esophageal or gastric cardia cancer in the Erasmus MC – University Medical Center Rotterdam underwent both US of the supraclavicular region and CT scanning including the supraclavicular region. After 2000, CT of the supraclavicular region, thorax and upper abdomen was still performed, but the use of US of the supraclavicular region declined to approximately 70% of patients.

In order to speed up the work-up of patients with esophageal or gastric cardia cancer, we wondered whether CT alone would be sensitive enough for investigating the supraclavicular region for the presence of metastases. Therefore, we retrospectively evaluated the results of US of the supraclavicular region, if indicated with FNA, and CT in our center to determine whether one of these or both investigations should be used for the detection of supraclavicular lymph node metastases in patients with esophageal or gastric cardia cancer.

PATIENTS AND METHODS

Patients

Data were obtained from a prospective database of patients with esophageal or gastric cardia cancer referred to the Erasmus MC - University Medical Center Rotterdam, The Netherlands. This database contains information on general patient characteristics, staging investigations, treatment modality and postoperative TNM stage of all patients with esophageal or gastric cardia cancer treated in our tertiary referral center (9). Information not present in the data-

base but necessary for this study was obtained from the patient notes stored in the electronic 'hospital information system'.

From January 1994 to June 2004, 1159 patients were diagnosed with and treated for esophageal or gastric cardia cancer in our center. In the majority of patients, esophageal or gastric cardia cancer was first diagnosed in a regional center and, subsequently, these patients were referred to our center. Patients often underwent staging investigations in the regional centers, but the results of these investigations were not included in the present analysis. Between January 1994 and June 2004, 567 patients underwent both US of the supraclavicular region and CT of the supraclavicular region, thorax and abdomen for staging of esophageal or gastric cardia cancer in our center and these patients were included in this study.

US of the supraclavicular region

All US examinations, including FNA of suspicious lesions, were performed by radiologists who were aware of the presence of an esophageal or gastric cardia cancer in patients. US was performed with a 7 MHz linear array transducer. Enlarged supraclavicular lymph nodes with a short axis > 7 mm and visualized on US were considered to be malignant if the node showed the following combination of criteria: a round shape, absence of an echogenic hilus, diffuse hypoechogenicity and/or intranodal necrosis (6). In case of a suspicious supraclavicular lymph node, FNA was performed if the result could change the treatment decision. If multiple suspicious lymph nodes were present, FNA was performed of the most suspicious lymph node. All specimens were cytologically examined by an experienced gastrointestinal cytologist.

In this study, both the result of US before FNA and the result of US-FNA were registered. The result of US could be positive or negative. US was considered to be negative if: a) no lymph nodes were present, or b) the lymph nodes that were present did not meet the criteria mentioned above. US-FNA could also be positive or negative. US-FNA was considered to be positive if the aspirate contained tumor cells and negative if no tumor cells were present in the aspirate. In patients in whom FNA was not representative and the procedure was not repeated, US-FNA was also considered to be negative.

CT

Between January 1994 and June 2004, four different CT scanners were used in our center. These comprised a Somatom Plus VD30 single slice consecutive CT scanner (Siemens Medical Solutions, Erlangen, Germany) from January 1994 to May 1996, a Somatom Plus 4 single slice spiral CT scanner (Siemens Medical Solutions, Forchheim, Germany) from May 1996 to April 2003, a Somatom Volume Zoom multidetector spiral CT scanner (Siemens Medical Solutions, Forchheim, Germany) from August 1999 until the end of the study period and a Somatom Sensation 16 multidetector spiral CT scanner (Siemens Medical Solutions, Forchheim, Germany) from May 2003 until the end of the study period. The scanning protocols are shown in Table 3.1. The contemporary CT reports were used in this study. CT scanning was performed

Table 3.1. Scanning protocols.

CT scanner	Scanner type	Detector collimation	Slice width	Pitch	Slice spacing	Contrast material	Injection rate
Somatom Plus VD30	Axial	10 mm	10 mm	n.a.	10 mm	120 mL, 300 mg I/mL	Drip IV
Somatom Plus 4	Spiral	8 mm	8 mm	1.4	8 mm	120 mL, 300-320 mg I/mL	2 mL/sec delay 40 sec
Volume Zoom	4 MDCT	4x2.5 mm	5 mm	1.25	5 mm	120 mL, 320 mg I/mL	2 mL/sec delay 70 sec
Sensation 16	16 MDCT	16x1.5 mm	5 mm	1.0	5 mm	120 mL, 320 mg I/mL	2 mL/sec delay 70 sec

MDCT, multidetector computed tomography; n.a., not applicable; I, iodine; IV, intravenous

with slices ≤ 10 mm ranging from the supraclavicular region to the upper abdomen, after injection of intravenous contrast medium. The patient was positioned with the arms alongside the head. The CT scan was interpreted by radiologists who were aware of the presence of an esophageal or gastric cardia cancer. The criterion of a malignant supraclavicular lymph node on CT was a short axis ≥ 10 mm (5, 10). CT was considered to be positive for the presence of malignant supraclavicular lymph nodes if it showed enlarged lymph nodes according to the above-mentioned criterion and negative if this was not the case.

Gold standard

As gold standard we defined the following criteria for the absence of metastases: negative result of FNA, postoperative detection of only benign lymph nodes in the supraclavicular region in the resected specimen, or a negative radiological finding in the relevant area with ≥ 6 months of follow-up, and for the presence of metastases: cytological confirmation of metastases in the fine-needle aspirate, postoperative detection of malignant lymph nodes in the supraclavicular region in the resected specimen, or a positive radiological finding in the relevant area with ≥ 6 months of follow-up.

Statistical analysis

Sensitivity, specificity, accuracy, positive predictive value (PPV) and negative predictive value (NPV) of US, US-FNA, CT, and the combinations US + CT and US-FNA + CT for the detection of lymph node metastases in the supraclavicular region were calculated using the data of all patients. For US + CT and US-FNA + CT, a result was considered positive for the presence of metastases if at least one of the investigations was positive, and negative if both investigations were negative. In addition, sensitivity, specificity and accuracy of CT were calculated for the subgroups of patients who were scanned with a specific CT scanner to determine whether the results were different for the various CT scanners used during the study period.

The McNemar test and Chi-square test (linear-by-linear association) were used for calculating p-values. All p-values were based on two-sided tests of significance. A p-value < 0.05 was considered as significant. SPSS (SPSS, Inc., Chicago, IL) was used for all calculations.

RESULTS

Patient and tumor characteristics

Results of 567 patients, in whom both CT and US were performed for staging of esophageal or gastric cardia cancer, were available. US was performed on the same day as CT in 146 patients (26%), on an earlier day than CT in 278 patients (49%), and later than CT in 143 patients (25%). The median interval between CT and US was 2 days (range: 0-79 days). The interval between CT and US was longer than 4 weeks in 20 patients (4%). The gold standard was a radiological result with ≥ 6 months of clinical follow-up in 402 patients, FNA in 122 patients and the postoperative detection of lymph nodes in the supraclavicular region in the resected specimen in 43 patients. In 21/122 (17%) patients, US and US-FNA were performed as two separate procedures, whereas in 101/122 (83%) patients, US followed by FNA was performed during the same procedure. Patient and tumor characteristics are shown in Table 3.2.

Table 3.2. Patient and tumor characteristics of patients with esophageal or gastric cardia cancer in whom CT and US of the supraclavicular region were performed.

Characteristic	n=567
Mean age ± SD (years)	62.1 ± 10.2
Gender (%)	
Male	433 (76)
Female	134 (24)
Histology of tumor at biopsy (%)	
Squamous cell carcinoma	220 (39)
Adenocarcinoma	322 (57)
Other	25 (4)
Location of tumor (%)	
Cervical	5 (1)
Upper 1/3 thoracic	28 (5)
Central 1/3 thoracic	102 (18)
Lower 1/3 thoracic	221 (39)
Gastroesophageal junction	211 (37)

Table 3.3. Results of US, US-FNA, CT, US + CT, and US-FNA + CT for the detection of malignant supraclavicular lymph nodes in esophageal or gastric cardia cancer patients.

	US	US-FNA	CT	US + CT	US-FNA + CT
Sensitivity (%)	49/65 (75)	47/65 (72)	16/65 (25)	52/65 (80)	51/65 (79)
Specificity (%)	458/502 (91)	502/502 (100)	500/502 (99)	457/502 (91)	500/502 (99)
PPV (%)	49/93 (53)	47/47 (100)	16/18 (89)	52/97 (54)	51/53 (96)
NPV (%)	458/474 (97)	502/520 (97)	500/549 (91)	457/470 (97)	500/514 (97)
Accuracy (%)	507/567 (89)	549/567 (97)	516/567 (91)	509/567 (90)	551/567 (97)

US, ultrasound; FNA, fine-needle aspiration; CT, computed tomography

Results of investigations

Results of US, US-FNA, CT, US + CT and US-FNA + CT are shown in Table 3.3. Sensitivities of US (75%), US-FNA (72%), US + CT (80%) and US-FNA + CT (79%) were higher than sensitivity of CT (25%) ($p<0.001$). The difference in sensitivity between US and US-FNA was caused by a negative FNA result in 2 patients in whom US was suspicious for malignant supraclavicular lymph nodes, whereas the gold standard (a second FNA performed after 1 respectively 2 weeks following a negative FNA) was also positive for a malignant lymph node. Specificities were lower for US (91%) and US + CT (91%) than for US-FNA (100%), CT (99%) and US-FNA + CT (99%) ($p<0.001$).

In the whole group of 567 patients, 65 patients (11%) had malignant supraclavicular lymph nodes according to our defined gold standard. The gold standard was a positive radiological finding in the relevant area with ≥ 6 months of follow-up in 10 patients, cytological confirmation of metastasis in 49 patients and postoperative detection of malignant lymph nodes in the supraclavicular region in the resected specimen in 6 patients.

The results of CT were compared with the results of US and US-FNA (Table 3.4). In 3/65 (5%) patients (US *versus* CT) and in 4/65 (6%) patients (US-FNA *versus* CT), respectively, with malignant supraclavicular lymph nodes according to our defined gold standard, CT detected true-positive supraclavicular lymph node metastases, where US or US-FNA were negative. In 1 patient, US was positive whereas US-FNA was negative. In the 3 patients with a positive CT result and a negative US result, a second repeat US was positive in 2 of these patients, whereas in 1 patient US was not repeated.

In 36/65 (55%) patients (US *versus* CT) and in 35/65 (54%) patients (US-FNA *versus* CT), respectively, with malignant supraclavicular lymph nodes according to our defined gold standard, US or US-FNA detected true-positive supraclavicular lymph node metastases, whereas the CT result was negative. In 1 patient, US was positive whereas US-FNA was negative, which was responsible for the difference between US *versus* CT and US-FNA *versus* CT.

In 553/567 (98%) patients, we ware able to determine what type of CT scanner had been used (Table 3.5). Linear-by-linear association testing showed no statistically significant correlation between the various scanners used on the one hand, and sensitivity ($p=0.76$), specificity ($p=0.54$) or accuracy ($p=0.78$) on the other hand.

Table 3.4. Results of CT compared with US and US-FNA in 65 of 567 patients with malignant supraclavicular lymph nodes according to our defined gold standard, with - meaning no malignant supraclavicular lymph nodes detected and + meaning malignant supraclavicular lymph nodes detected with a particular investigation.

		CT	
		-	+
US	-	13	3
	+	36	13

		CT	
		-	+
US-FNA	-	14	4
	+	35	12

Table 3.5. Results of CT for the detection of supraclavicular lymph nodes in esophageal or gastric cardia cancer patients given per CT scanner.

CT scanner	Period	Number of patients	Sensitivity (%)	Specificity (%)	Accuracy (%)
Somatom Plus VD30	January 1994 - May 1996	53	2/3 (67)	50/50 (100)	52/53 (98)
Somatom Plus 4	May 1996 - April 2003	302	8/37 (22)	263/265 (99)	271/302 (90)
Plus 4 Volume Zoom	August 1999 - end of study	163	5/19 (26)	144/144 (100)	149/163 (91)
Sensation 16	May 2003 - end of study	35	1/3 (33)	32/32 (100)	33/35 (94)

DISCUSSION

In this study, we compared US of the supraclavicular region, if indicated with FNA, CT, and the combination of these investigations for the detection of supraclavicular lymph node metastases in patients with esophageal or gastric cardia cancer. Our results showed that US and US-FNA, either alone or in combination with CT, were more sensitive than CT alone for the detection of supraclavicular lymph node metastases ($p<0.001$), whereas specificities were higher for CT and US-FNA, the latter alone or in combination with CT, than for US alone or in combination with CT ($p<0.001$). In addition, in 4/65 (6%) patients with malignant supraclavicular lymph nodes according to the gold standard, CT was positive whereas US and/or US-FNA were negative. In contrast, in 36/65 (55%) patients, CT was negative whereas US and/or US-FNA were positive.

It has been reported that the sensitivity and specificity of CT for the detection of supraclavicular lymph nodes is 57% and 98%, respectively (11). In the present study, sensitivity of CT was slightly lower (25%), whereas specificity was comparable (99%) to published results. Sensitivity of US without FNA has been reported to range from 68% to 79% and specificity from 91% to 97% (7, 12-14), which was comparable to our results (75% and 91%, respectively).

In this study, we reported the results of US and US-FNA separately (Table 3.3 and 3.4). Adding FNA to US increased the specificity from 91% to 100%. This is probably explained by the

presence of enlarged non-malignant lymph nodes in some cases, which were considered to be malignant if only US criteria for malignancy were applied. This resulted in a higher percentage of false-positive findings with US alone. FNA is a safe technique that can be used to distinguish reactive, inflammatory lymph nodes from malignant lymph nodes (5). In our opinion, FNA should always be used in patients with suspected supraclavicular lymph nodes if the result of FNA is important for the decision to perform a resection for esophageal or gastric cardia cancer or not.

CT technology has improved considerably over the years and it was expected that the results would differ for the various CT scanners used in the study period. Nevertheless, no statistically significant correlations were demonstrated between sensitivity, specificity and accuracy on the one hand and CT scanners used during the study period on the other hand. As this finding was somewhat surprising, we suspect that the number of patients in this study was too small to detect more favorable results with later generation CT scanners.

In 23 patients, the FNA specimen obtained during US was not representative. In 5 of these patients, FNA was repeated until the specimen was representative and the result of that specimen was used in the present study. In the remaining 18 patients, FNA was not repeated and we considered this FNA specimen to be truly negative. The reason that we did not exclude these patients was that at the end of the staging period the supraclavicular lymph nodes of all these patients were considered to be non-malignant in the treatment decision. Moreover, 9 patients indeed underwent an esophageal resection based on this staging result, which would not have been performed in the presence of a high suspicion of malignant supraclavicular lymph nodes.

The size of the supraclavicular lymph nodes is the most important criterion for the diagnosis of lymph node metastases by US and CT (3), however the size of lymph nodes was not the only criterion used in this study if US was performed. For US, enlarged supraclavicular lymph nodes (> 7 mm) were considered more likely to be malignant if the node displayed one or more of the following criteria: a round shape, absence of an echogenic hilus, diffuse hypoechogenicity and/or intranodal necrosis (6). These criteria were always used, as it is known that enlarged nodes can be reactive instead of being metastatic (15). The criterion for a malignant lymph node on CT was only based on size, i.e., whether their size was ≥ 10 mm (5, 10).

There are various limitations to this study. First, the study was retrospective and represented the results of daily clinical practice, indicating that there was no control over the gold standard. In patients, in whom as gold standard a radiological result with ≥ 6 months of clinical follow-up was used, no cytological and/or histological confirmation of the diagnosis was performed. Furthermore, only in 5 of 23 patients with a non-representative cytological specimen, FNA was repeated until the specimen was representative, whereas this was not done in the remaining 18 patients. This is clearly a limitation that occurs in daily clinical practice. The median interval between CT and US was 2 days (range: 0-79 days), however this was more

than 4 weeks in 4% of patients. After a delay of several weeks, metastases could have grown to a detectable size, resulting in the detection of metastases in the second investigation. Nonetheless, none of the patients with a prolonged time interval between CT and US were retrospectively found to have undetected metastases according to our gold standard. In the present study, the order in which US and CT were performed was random, i.e., US and CT were performed on the same day in 26% of patients, or, alternatively, US (49%) or CT (25%) were the initial investigation. We found however no effect of the sequence of investigations on the staging result (results not shown).

Second, the patients included in this study were a selection of all patients present in the database, indicating a selection bias. The included patients were all considered to be fit enough to undergo a resection and they all had undergone CT as well as US of the supraclavicular region in our center. Patients who had undergone CT and/or US in another hospital were excluded from this study.

Third, the criteria used for the presence of malignant supraclavicular lymph nodes were different for US and CT (see above). A minimum size for a malignant lymph node to be detectable with a particular radiological examination is required. US is able to detect smaller lymph nodes compared to CT, indicating a difference in detection threshold. This difference could be the reason for the detection of more malignant supraclavicular lymph nodes by US compared to CT. We are however not aware of any evidence from the literature that this difference in detection threshold could have resulted in more false-positive supraclavicular lymph nodes with US, particularly in cases without FNA having been performed.

Fourth, FNA was only performed when lymph nodes were suspicious for the presence of metastases. In case the lymph nodes were not suspicious, FNA was not performed and cytological specimen was not available to exclude more definitely the presence of metastatic disease. Furthermore, US-FNA, which was one of the methods under investigation, was also determined to be one of the gold standards. Nevertheless, in the absence of a surgical exploration of the neck region, this could not be avoided.

Finally, esophagectomy was not performed in all included patients. In addition, in patients in whom an esophagectomy was performed, dissection of the supraclavicular lymph nodes was not a standard procedure. Therefore, it is unknown in how many cases micrometastases in the supraclavicular lymph nodes were in fact not detected by US or CT. By extending the follow-up to at least 6 months, we hoped to have corrected most optimally for this factor.

In conclusion, the results of this study suggest that US-FNA is the preferred diagnostic modality for the detection of supraclavicular lymph node metastases in patients with esophageal or gastric cardia cancer. The sensitivity of metastases detection only slightly improves if US-FNA is combined with CT. Nevertheless, the sensitivity of US-FNA + CT was still only 79%, indicating that in more than 20% of patients metastatic supraclavicular lymph nodes were not detected. In these patients, an esophagectomy in the presence of metastatic disease could have been performed, while in fact a less invasive, palliative treatment was indicated.

However, a prospective, blinded, comparative study is needed to determine which investigation or combination of investigations is able to detect most if not all malignant supraclavicular lymph nodes in patients with esophageal or gastric cardia cancer.

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CHAPTER 4

A comparison between low-volume referring regional centers and a high-volume referral center in quality of preoperative metastasis detection in esophageal carcinoma

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ABSTRACT

Background: An inverse correlation between hospital volume and esophageal resection mortality has been reported. In this study, we compared the quality of preoperative metastasis detection between a high-volume referral center with that of low-volume referring regional centers.

Methods: In 573 patients diagnosed with esophageal cancer (1994-2003), the results of preoperative staging investigations (CT scan, ultrasound of abdomen and neck, and chest X-ray) performed in 61 regional centers were re-evaluated and/or repeated in one referral center. The gold standards were either a radiological result with ≥6 months follow-up, fine-needle aspiration or the postoperative TNM-stage.

Results: In the same group of patients, the preoperative investigations performed in regional centers detected true-positive malignant lymph nodes in 8% of patients and true-positive distant metastases in 7% of patients, whereas these percentages were 16% and 20%, respectively, in the referral center. In 72/573 (13%) patients, one or more metastases detected in the referral center had been missed in the regional centers. After allowing resectability in the presence of M1a lymph nodes, this would still have resulted in futile esophageal resections in 6% of patients. In contrast to the higher diagnostic sensitivity in the referral center, specificity was comparable between referral and regional centers.

Conclusion: This study found that, in assessing the operability of esophageal cancer, the diagnostic sensitivity of metastasis detection in a high-volume referral center was higher than that in referring regional centers. This resulted from both better CT scanning equipment and more experienced radiologists in the referral center. Should the decision to perform esophagectomy have only been based on metastasis detection in these regional centers, over 1 in 20 patients would have undergone resection in the presence of metastases.

INTRODUCTION

After diagnosing esophageal cancer by endoscopy and biopsy and with the patients' physical condition permitting esophageal resection, tumor staging is the next step (1, 2). Current preoperative investigations include endoscopic ultrasonography (EUS) (2-9), CT scanning (2, 7, 10-12), ultrasound (US) of the neck (13-15) and the abdomen (14, 16), chest X-ray (2) and bronchoscopy (12, 17-19). The preoperative TNM-staging is performed by a combination of these investigations. The T-stage describes the extent of local invasion of the tumor through the esophageal wall (20). EUS is currently the standard investigation for determining T-stage, whereas CT scanning and bronchoscopy are considered to be less sensitive and specific (21, 22). The N-stage indicates the presence of regional lymph node metastases (20). Both EUS, and to a lesser extent CT scanning, can be used in assessing the N-stage (21). The M-stage registers the presence of distant metastases (20). Esophageal carcinoma commonly disseminates to the celiac and supraclavicular lymph nodes, the liver, lung and adrenal glands (23).

The majority of diagnostic upper gastrointestinal endoscopies in The Netherlands are performed in regional centers. A regional center is a center where no specific expertise for the treatment of a specific disorder, for example esophageal cancer, is present. In regional centers, most cases of esophageal carcinomas are diagnosed, however, the total number of patients with esophageal cancer in regional centers is low, i.e., less than 10 per year. Patients often undergo preoperative staging investigations in these regional centers. Subsequently, they may be treated in the regional center or, more often, are referred to a specialized referral center with a volume of more than 100 patients with esophageal cancer per year. When patients are referred to a specialized referral center, the preoperative investigations performed in the referring regional center are often re-evaluated and/or repeated.

Recently, an inverse correlation between hospital volume and postoperative mortality from esophageal resection has been reported (24-33). This led us to assess the quality of preoperative metastasis detection in a specialized referral center versus that of regional referring centers.

PATIENTS AND METHODS

Patients

These were ascertained from a prospective database of all patients with esophageal carcinoma treated between January 1994 and October 2003 at the Erasmus MC Rotterdam, The Netherlands, a specialized referral center, which currently treats approximately 120 patients per year for esophageal cancer. This database contains data on general patient characteristics, preoperative investigations, treatment modalities and postoperative TNM-staging of these patients. Information, not present in the database, but necessary for this study, was obtained

from the patient notes stored in the electronic 'hospital information system'. A total of 1,088 patients with esophageal cancer were evaluated in the referral center between 1994 and 2003 (Figure 4.1). In 906 patients, esophageal cancer was first diagnosed in a regional center and, subsequently, these patients were referred to the referral center. In total, 61 regional centers participated in the study, which is approximately half of all regional centers in The Netherlands. These centers were mainly situated in the southern part of The Netherlands. The median number of patients referred by the different regional centers to the referral center in the period 1994-2003 was 3 per regional center (range: 1-82).

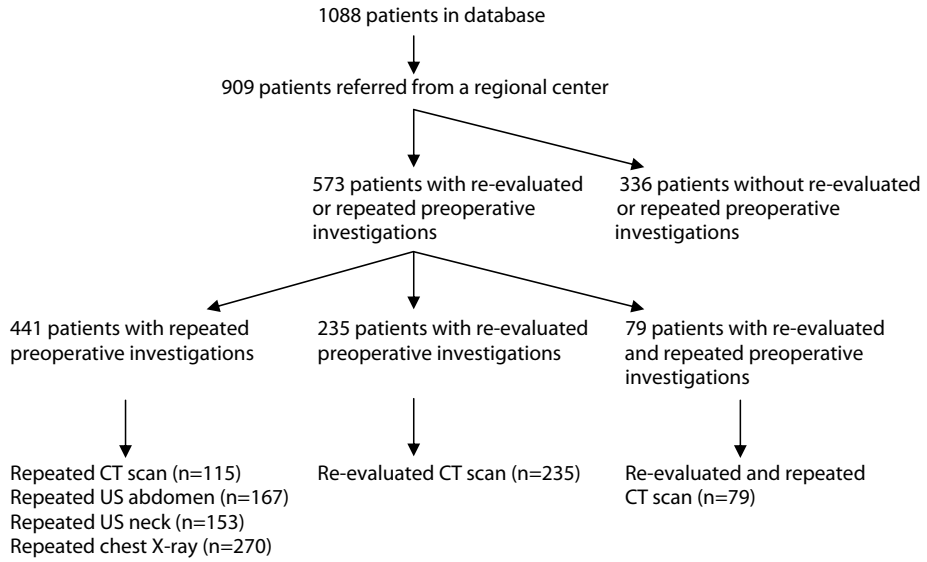

Figure 4.1. Flow diagram of the patients included in this study.

Anatomical regions investigated for metastases

This study investigated the presence of metastases in periesophageal, supraclavicular and celiac lymph nodes, liver, lung, and adrenal glands. Regional lymph node metastases were subdivided in periesophageal and celiac lymph node metastases. Distant metastases were subdivided in metastases to supraclavicular and celiac lymph nodes, liver, lung and, adrenal glands. Celiac lymph node metastases were considered as regional if the primary tumor was located in the gastric cardia, as stage M1a if the tumor was located in the distal part of the esophagus and as stage M1b when the tumor was located in the proximal part of the esophagus. Lymph nodes were considered malignant if the short axis was greater than 10 mm.

Preoperative investigations

The preoperative investigations assessed in this study were CT scanning, US scanning of the cervical region and the abdomen, and chest X-ray. EUS could not be compared, as it was practically never performed in the regional centers.

In cases where patients were undergoing preoperative staging, CT scans performed in the regional centers were re-evaluated by radiologists in the referral center. Where these CT scans were considered to be inadequate they were repeated in the referral center. This became particularly common after 1999 when a new generation of CT scanners became available in the referral center. After 2000, EUS became the predominant technique for preoperative staging in the referral center and consequently the percentage of US investigations of the cervical region and the abdomen which until 2000 were routinely repeated, declined to 10-20% after this date. The same was true for chest X-rays which were again initially routinely repeated but after 2000 the percentage declined to 50%.

The input for the comparison between regional centers and the referral center were the number of metastases correctly diagnosed by the regional centers *versus* the referral center after re-evaluated, repeated, and re-evaluated ánd repeated investigations. The final arbiters for the correct diagnosis of the presence or absence of metastases were three gold standards. These comprised: (a) for the absence of metastases, negative radiological findings in the relevant area with ≥ 6 months of follow-up, negative result of the fine-needle aspirate or the postoperative pathological TNM-stage, and (b) for the presence of metastases, positive radiological findings in the relevant area with ≥ 6 months of follow-up, histological or cytological confirmation of metastasis at the fine-needle aspirate or the postoperative pathological TNM-stage (Figure 4.2).

In 333 patients referred to the referral center, no preoperative investigations other than endoscopy with biopsy were performed in the regional center (n=207) or the performed preoperative investigations were not re-evaluated or repeated in the referral center (n=126). In the remaining 573 referred patients, preoperative investigations performed in a regional center were re-evaluated and, if necessary, repeated in the referral center (Figure 4.1).

Preoperative investigations were repeated in the referral center in 441 patients. The repeated investigations in the referral center included CT scan of thorax and abdomen (n=115), US abdomen (n=167), US neck (n=153) and chest X-ray (n=270) (Figure 4.1). In some patients, more than one investigation was repeated. The median interval between the baseline and repeated investigation was 2 weeks (range: 4 days to 10 weeks). In the majority of cases, the investigations were repeated because the quality of preoperative investigations in the regional centers was considered to be inadequate for optimal detection of local progression and metastases. We compared the results of the preoperative investigations performed in regional centers with the results of the repeated investigations in the referral center. The results of these investigations were assessed against the gold standards (see above).

In 235 patients, the CT scan performed in a regional center was re-evaluated but not re-

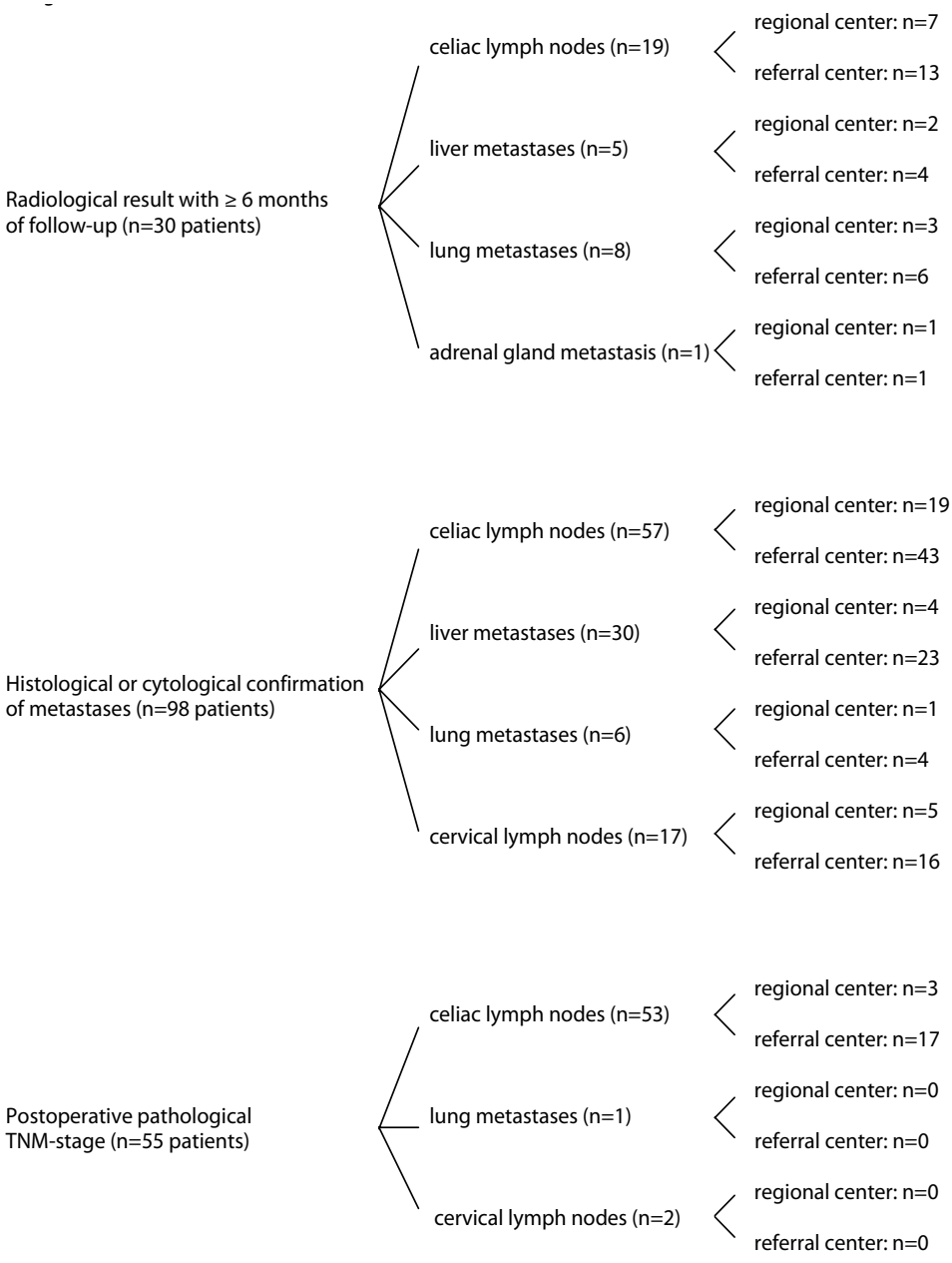

Figure 4.2. Radiologically detected metastases in the regional and referral centers in relation to the gold standard in 183 patients with metastases at gold standard (some patients had more than one metastasis).

peated in the referral center, implying that the same CT scan was examined by a radiologist in both centers (Figure 4.1). If considered adequate, the CT scan was only re-evaluated, and not repeated. This study compared the radiological conclusions from the regional center and the referral center and assessed the outcomes against the gold standards (see above).

After re-evaluation, the CT scans of 79 patients from regional centers were repeated in the referral center (Figure 4.1). In these patients, the results of the CT scans performed in the regional centers, the results of the re-evaluation of these CT scans and the results of the repeated CT scans were compared.

Statistical analyses

The diagnostic sensitivity and specificity of the preoperative investigations performed in the regional centers and of the repeated and re-evaluated preoperative investigations performed in the referral center were calculated. All results were nominal and paired. The McNemar and chi-square test were used for calculating p-values. All p-values were based on two-sided tests of significance. A p-value <0.05 was considered as significant. Binary logistic regression was performed to analyze whether a correlation existed between the sizes of the regional centers and the sensitivity or specificity of the investigations performed in the regional centers, i.e., CT scanning, US scanning of the cervical region and the abdomen, and chest X-ray. SPSS (SPSS, Inc., Chicago, IL) was used to calculate p-values and to perform binary logistic regression.

Table 4.1. Patient and tumor characteristics of all patients (n=1088), and patients with repeated (n=441), re-evaluated (n=235), repeated and re-evaluated (n=79), and without re-evaluated or repeated (n=333) investigations.

Characteristic	All patients n=1088	Repeated investigations n=441	Re-evaluated investigations n=235	Repeated and re-evaluated investigations n=79	No repeated ± re-evaluated investigations n=333
Mean age ± SD (yrs.)	63 ±10.4	62 ± 10.5	64 ± 10.2	61 ± 9.6	64 ± 10.5
Gender (%)					
Male	841 (77)	350 (79)	175 (74)	59 (75)	257 (77)
Female	247 (23)	91 (21)	60 (26)	20 (25)	76 (23)
Histology of tumor at biopsy (%)					
Squamous cell ca.	385 (35)	152 (34)	89 (38)	31 (39)	113 (34)
Adenocarcinoma	620 (57)	251 (57)	136 (58)	47 (60)	186 (56)
Other	83 (8)	38 (9)	10 (4)	1 (1)	34 (10)
Location of tumor (%)					
Cervical	10 (1)	5 (1)	3 (1)	0 (0)	2 (1)
Upper 1/3 thoracic	44 (4)	15 (3)	8 (3)	4 (5)	17 (5)
Central 1/3 thoracic	167 (15)	62 (14)	34 (15)	14 (18)	57 (17)
Lower 1/3 thoracic	422 (39)	179 (41)	94 (40)	28 (35)	121 (36)
Gastric cardia	445 (41)	180 (41)	96 (41)	33 (42)	136 (41)

RESULTS

Patient and tumor characteristics

Patient and tumor characteristics in the different subgroups are shown in Table 4.1. As can be seen from this table, no important differences in these characteristics were found between patients with repeated, re-evaluated, repeated and re-evaluated, and without repeated and/or re-evaluated examinations.

CT scan

In 115 patients, the CT scan performed in a regional center was repeated in the referral center. The gold standard was in 32 patients a radiological finding with ≥ 6 months of follow-up, in 21 fine-needle aspiration (FNA) and in 62 postoperative pathological TNM-stage.

Table 4.2. Repeated (n=115) and re-evaluated (n=235) CT-scans in patients with esophageal cancer.

Investigation	Regional center	Referral center	p-value
Repeated CT scan (n=115)			
Sensitivity (%)			
Regional lymph nodes	12/46 (26)	24/46 (52)	0.002
Distant metastases	14/32 (44)	27/32 (84)	0.001
Periesophageal lymph nodes	11/42 (26)	20/42 (48)	0.022
Celiac lymph nodes	12/29 (41)	23/29 (79)	0.001
Liver metastases	3/10 (30)	6/10 (60)	0.250
Specificity (%)			
Regional lymph nodes	65/69 (94)	68/69 (99)	0.375
Distant metastases	82/83 (99)	81/83 (98)	1.000
Periesophageal lymph nodes	71/73 (97)	72/73 (99)	1.000
Celiac lymph nodes	83/86 (96)	85/86 (99)	0.625
Liver metastases	105/105 (100)	102/105 (97)	0.083
Re-evaluated CT scan (n=235)			
Sensitivity (%)			
Regional lymph nodes	24/123 (19)	50/123 (41)	<0.001
Distant metastases	13/74 (18)	32/74 (43)	<0.001
Periesophageal lymph nodes	21/115 (18)	42/115 (36)	<0.001
Celiac lymph nodes	10/77 (13)	35/77 (45)	<0.001
Liver metastases	1/13 (8)	4/13 (31)	0.250
Specificity (%)			
Regional lymph nodes	103/112 (92)	101/112 (90)	0.804
Distant metastases	156/161 (97)	153/161 (95)	0.375
Periesophageal lymph nodes	109/120 (91)	109/120 (91)	1.000
Celiac lymph nodes	153/158 (97)	150/158 (95)	0.453
Liver metastases	216/222 (97)	216/222 (97)	1.000

Sensitivities and specificities of repeated CT scans are shown in Table 4.2. The sensitivity of CT scan for regional lymph nodes in regional centers *versus* the referral center was 26% *versus* 52% (p=0.002). The sensitivity for distant metastases was 44% in the regional centers *versus* 84% in the referral center (p=0.001). The specificities were comparable between the regional centers and the referral center. Table 4.2 also shows the sensitivities and specificities of the CT scan for periesophageal lymph node metastases, celiac lymph node metastases, and liver metastases. It was not possible to calculate the sensitivity and specificity of the CT scan for lung and adrenal gland metastases due to the low number of patients with these types of metastases.

In 235 patients, the CT scan performed in one of the regional centers was re-evaluated in the referral center. The gold standard was in 69 patients a radiological finding with ≥ 6 months of follow-up, in 32 FNA and in 134 postoperative pathological TNM-stage. The sensitivities for regional lymph nodes and distant metastases were significantly higher in the referral center than in the regional centers. The specificities were comparable (Table 4.2). Table 4.2 also shows the sensitivities and specificities of the re-evaluated CT scan for peri-esophageal lymph node metastases, celiac lymph node metastases, and liver metastases.

In 79 patients, the CT scan performed in a regional center was re-evaluated in the referral center and subsequently repeated in the referral center. The gold standard was in 23 patients a radiological finding with ≥ 6 months of follow-up, in 21 FNA and in 35 postoperative pathological TNM-stage. The sensitivity and specificity are shown in Table 4.3 and show that the highest sensitivity was found for CT scans performed and evaluated in the referral center.

Table 4.3. Sensitivities and specificities in 79 patients with a CT scan performed and evaluated in regional centers, which was re-evaluated ánd repeated in the referral center.

	CT performed and evaluated in regional center	CT performed in regional center and evaluated in referral center	CT performed and evaluated in referral center
Sensitivity (%)			
Regional lymph nodes	11/41 (27)	15/41 (37)	20/41 (49)
Distant metastases	7/25 (28)	13/25 (52)	20/25 (80)
Specificity (%)			
Regional lymph nodes	37/38 (97)	35/38 (92)	37/38 (97)
Distant metastases	53/54 (98)	49/54 (91)	51/54 (94)

Abdominal ultrasound

In 167 patients, abdominal US performed in one of the regional centers was repeated in the referral center, with FNA if indicated. The gold standard was in 38 patients a radiological finding with ≥ 6 months of follow-up, in 42 FNA and in 87 postoperative pathological TNM-stage. The sensitivities of abdominal US for celiac lymph node and liver metastases were signifi-

cantly higher in the referral center compared with the regional centers. The specificities were comparable (Table 4.4).

Ultrasound of the neck

In 153 patients, US neck performed in one of the regional centers was repeated in the referral center, with FNA if indicated. The gold standard was in 107 patients a radiological finding with ≥ 6 months of follow-up, in 35 FNA and in 11 postoperative pathological TNM-stage. The sensitivity of US neck for detecting lymph node metastases in the regional centers *versus* the referral center was 26% *versus* 84% (p=0.001), whereas the specificity was not different (Table 4.4).

Chest X-ray

In 270 patients, the chest X-ray performed in one of the regional centers was repeated in the referral center. In these patients, the gold standard was in 261 patients a radiological finding with ≥ 6 months of follow-up, in 8 FNA and in 1 postoperative pathological TNM-stage. The sensitivity of chest X-ray for detecting lung metastases in regional centers *versus* the referral center was 9% *versus* 64% (p=0.031), whereas the specificity was comparable (Table 4.4). The chest X-rays performed in the regional centers were not re-evaluated in the referral center.

Table 4.4. Repeated US abdomen (n=167), repeated US neck (n=153) and repeated chest x- ray (n=270) in patients with esophageal cancer.

Investigation	Regional center	Referral center	p-value
Repeated US abdomen (n=167)			
Sensitivity (%)			
Celiac lymph nodes	3/46 (7)	20/46 (44)	<0.001
Liver metastases	1/17 (6)	12/17 (71)	0.001
Specificity (%)			
Celiac lymph nodes	121/121 (100)	120/121 (99)	0.320
Liver metastases	150/150 (100)	150/150 (100)	1.000
Repeated US neck (n=153)			
Sensitivity (%)	5/19 (26)	16/19 (84)	0.001
Specificity (%)	134/134 (100)	134/134 (100)	1.000
Repeated chest X-ray (n=270)			
Sensitivity (%)	1/11 (9)	7/11 (64)	0.031
Specificity (%)	258/259 (99)	258/259 (99)	1.000

All investigations combined

In total, 573 patients underwent re-evaluation and/or repetition of diagnostic procedures for the staging of esophageal cancer. The gold standard detected malignant regional lymph nodes (N1) in 206 patients (36%) and distant metastases (M1) in 183 patients (32%). Both

malignant lymph nodes and distant metastases were present in 73 patients (13%). The detected distant metastases and the corresponding gold standards are shown in Figure 4.2. Investigations performed in regional centers detected true-positive malignant lymph nodes in 46/573 patients (8%) and true-positive distant metastases in 40 patients (7%). In the referral center, true-positive malignant lymph nodes were found in 91 patients (16%) and true-positive distant metastases in 112 patients (20%). In 72/573 (13%) patients, one or more distant metastases were detected in the referral center, which were not found in a regional center. In 39 of these patients only M1a celiac lymph nodes were present, which did not preclude a resection in the referral center. In the remaining 6% (33/573), other distant metastases than M1a celiac lymph nodes were present and the treatment was directed from a (curative) resection to a palliative treatment.

The binary logistic regression, which was performed to analyze whether a correlation existed between the sizes of regional centers and the sensitivity and specificity of the investigations performed in the regional centers, showed that there was no significant relationship.

DISCUSSION

This study compared the detection rate of regional malignant lymph nodes and distant metastases in the preoperative work up of patients with esophageal carcinomas between a high-volume referral center and 61 low-volume regional centers, which referred their patients to the referral center. CT scan, abdominal ultrasound, ultrasound of the neck and chest X-ray were compared. The regional centers were found to have detected positive regional malignant lymph nodes (N1) in 46 patients and distant metastases (M1) in 40 patients, whereas, within the same group of patients, the referral center found N1 lymph nodes in 91 patients and M1 metastases in 112 patients. It should be realized that endoscopic ultrasound (EUS) is nowadays accepted as the best method for nodal staging (34) and PET-scanning could be used for the detection of metastases of esophageal carcinoma (35). However, EUS was available in a very limited number of regional centers, whereas the PET scan was not used at all in the period (1994-2003) when this study was performed.

How can the differences in the detection of metastases in esophageal cancer patients between the regional centers and the referral center be explained? To our surprise, more metastases were detected on the CT scans from the regional centers when re-evaluated in the referral center than in the regional centers of origin (Table 4.2 and 4.3), indicating that the experience of the radiologist in this specific field is of great importance. In addition, it seems likely that the higher sensitivity in detecting metastases on repeated CT scans in the referral center resulted probably from better technology and/or methodology of CT scanning. There are several explanations for this: (1) The newest generation CT scanners were always used in the referral center in the study period, which were mostly not available in the regional

centers. (2) CT slices of 5 mm were always made in the referral center, whereas slices of 10 mm were made in some of the regional centers. (3) Intravenous and oral contrast were always used when performing a CT scan in the referral center, whereas CT scans without the use of intravenous and/or oral contrast were made in some of the regional centers.

The role of the difference in experience of radiologists on the one hand and that in technology and/or methodology of CT scanning on the other hand was illustrated by the sensitivities for the detection of regional lymph node metastases and distant metastases found in the 79 patients who had both re-evaluated and repeated CT scans (Table 4.3). In these patients, the lowest sensitivity was found for CT scans performed and evaluated in the regional centers whereas the sensitivity for CT scans performed in the regional centers and re-evaluated in the referral center was higher. This indicates that the experience of radiologists is important, as this was the only factor which was different between the original and re-evaluated evaluation. The sensitivity for CT scans performed and evaluated in the referral center was highest, which is likely to be explained by differences in technology and/or methodology of CT scanning, as this was the only factor which was different between this evaluation and the re-evaluated CT scans from the regional centers.

On the other hand, for both re-evaluated and repeated preoperative investigations (Table 4.2 and 4.4), there was no significant difference in specificity between the regional centers and the referral center. This contrasts the findings from preoperative investigations in other malignancies. For example, in the re-evaluation of mammograms (36) and barium enemas (37), the specificity was found to be lower for the re-evaluated investigations in comparison with the original investigations because of a tendency to over interpret the original investigations. The authors of these studies speculated that this might have been due to the fact that the second opinion radiologists were aware of the fact that these investigations had already been evaluated. The reason for the absence of this phenomenon in the present study is not clear, although, for repeated examinations, the explanation could be that in most cases the radiologist in the referral center was not aware of the results obtained in the regional center.

The median interval between the baseline and repeated investigation was 2 weeks, with a range of 4 days to 10 weeks. After a delay of 10 weeks, metastases could have grown to a detectable size on a CT scan. This could explain why, in some cases, no metastases were detected in the regional center, but were seen on repeated investigations (Table 4.2 and 4.3) in the referral center. However, none of the patients with a long time interval between the baseline and the repeated CT scan in the present study were found to have previously undetected metastases according to the gold standard.

What are possible pitfalls in the present study? Of all patients referred to the referral center, 77% (699/906) had undergone preoperative investigations in the regional center. In most cases, the radiologists in the referral center were unaware of the results from these investigations. This was particularly true for repeated CT scans without a re-evaluation. In case of

re-evaluation of a CT scan performed in a regional center, the radiologists were obviously aware of the fact that the patient had been referred from a regional center.

The patients with esophageal cancer, who were referred to the referral center, were obviously only a selection of the patients who had been diagnosed with esophageal cancer in the regional centers, as, in general, patients with metastases were not often referred to the referral center. This is likely to have resulted in the referral center of a more difficult patient group with small metastases, which were hard to detect on preoperative staging investigations.

In this study, 61 referring centers were included and only 1 referral center. In total, there are approximately 120 regional centers in The Netherlands. For the treatment of esophageal cancer, there are two large referral centers, one for the northern part and one for the southern part of The Netherlands. This explains why 61 regional centers referred to one referral center in this study. Nevertheless, as only 1 referral center was included in this study, the data of this study may not be generalizable to other centers.

Radiologists in regional centers were sometimes found to have used criteria for the presence of metastatic lymph nodes that differed from those of radiologists in the referral center. In some regional centers, lymph nodes with a short axis smaller than 10 mm were considered to be malignant, whereas in the referral center an enlarged lymph node was only classified as malignant if the short axis was greater than 10 mm. This could have resulted in a lower specificity for malignant lymph node detection in regional centers. On the other hand, whenever a preoperative investigation in the referral center showed evidence of the presence of lymph node metastases or distant metastases, FNA or a biopsy were performed to confirm the diagnosis. The only exceptions were patients in whom the results of the radiological investigations were very obvious or in whom an esophagectomy was to be performed anyway. It was not always possible to obtain tissue from a suspicious lesion. Unless the result of the preoperative investigation was highly suspicious for metastases, it was decided that, in evaluating these cases for comparison, the gold standard indicated a score of "no metastases" and these suspicious preoperative findings were therefore considered to be false-positive. In a number of cases this resulted in a lower specificity in the referral center. As there was no difference in specificity between regional centers and the referral center, it would appear that these two different approaches cancelled each other out.

Finally, what was the clinical relevance of the greater diagnostic accuracy in the referral center? An M1-stage can be subdivided into an M1a- or M1b-stage (20), depending on the location of the primary tumor. For an esophageal carcinoma located in the distal esophagus, celiac lymph nodes are M1a metastases, and these tumors are no longer considered to be unresectable (38). In 40/72 patients (7% of 573 patients) with distant metastases only detected in the referral center, these metastases were found at the celiac axis. Of these, 39 patients had a distal esophageal carcinoma, implying them still to have been resectable. In these patients, the preferred treatment would have been an esophageal resection anyhow. An argument against performing a resection in patients with M1a celiac lymph node metastases is how-

ever that the postoperative survival of patients with M1a disease has been reported to be only 13.8 months compared to 39.8 months in patients with M0 disease (39). Another argument underlining the importance of the accurate detection of celiac lymph node metastases is to allow the comparison of the results of different surgical treatment modalities, or preoperative chemotherapy and/or radiotherapy by avoiding a prognostic imbalance between the different treatment arms. In the remaining 33 patients (6% of 573 patients) with distant metastases, the metastases were staged as M1b. In these patients, a resection was withheld and a palliative treatment was instituted.

In conclusion, this study shows that the detection rate of metastases for esophageal cancer was higher in the referral center, a high-volume center, when compared with regional centers. Our results suggest that these differences could, on the one hand, be explained by the use of technically more advanced equipment, and, on the other hand, by the presence of more experienced radiologists in the referral center in the evaluation of preoperative investigations for esophageal cancer. Improving the experience of the radiologists in regional centers, for example by training courses, may reduce these differences in detecting metastases from esophageal cancer. However, another option to consider would be to concentrate staging procedures for esophageal cancer in centers with ample experience in this field. With regard to this, the regional centers, which were included in this study, treated the patients probably appropriately by referring them to the referral center, even if the regional center failed to diagnose metastases. Finally, had the decision to perform an esophagectomy in this particular group of patients only been based on preoperative investigations performed in the regional centers, 6% of patients would have undergone a non-curative resection.

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CHAPTER 5

Radiologist experience and quality of CT scans determine metastasis detection in patients with esophageal or gastric cardia cancer

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Submitted

ABSTRACT

Introduction: In a previous retrospective study, we found that metastases in patients with esophageal or gastric cardia cancer were more frequently detected on CT scans made and evaluated in a referral center compared to a non-referral center. We speculated that this was caused by the presence of more experienced radiologists and/or the use of technically more advanced equipment in the referral center. The aim of the present study was to prospectively disentangle radiologists experience from quality of CT scans of patients with esophageal or gastric cardia cancer to determine the exact role of these factors in the evaluation of CT scans.

Methods: Two radiologists of referral centers for esophageal and gastric cardia cancer ('expert radiologists') and 6 radiologists of non-referral, regional centers ('non-expert radiologists') performed 240 evaluations of 72 CT scans of patients diagnosed with esophageal or gastric cardia cancer between 1994 and 2003 in a stratified design. The gold standard was the postoperative stage, fine-needle aspiration or a radiological result with ≥ 6 months of follow-up.

Results: Expert radiologists had a nearly 3 times higher chance of making a correct diagnosis of the presence or absence of distant metastases according to the gold standard compared to non-expert radiologists. For the subgroup of CT scans with the presence of distant metastases according to the gold standard, a statistically significant correlation was found between the quality of the CT scan as judged by the radiologists and a correct diagnosis. This indicates that the quality of the CT scan was particularly important for the confirmation of the presence of distant metastases.

Discussion: Both radiologist experience and quality of CT scans play a role in metastasis detection in patients with esophageal or gastric cardia cancer. Therefore, we suggest that staging procedures for esophageal or gastric cardia cancer should be concentrated in centers with ample experience of radiologists in evaluating CT scans for this indication and the ability to produce high quality CT scans.

INTRODUCTION

Staging of patients with esophageal or gastric cardia cancer is important after a diagnosis is made in order to choose the most appropriate treatment modality (1, 2). The extent of local invasion of the tumor through the esophageal wall is described by T stage, the presence of regional lymph node metastases is indicated by N stage, with N0 indicating absence and N1 presence of lymph node metastases, whereas M stage describes the presence or absence of distant metastases, with M0 indicating absence and M1 presence of distant metastases (3). Esophageal cancer most commonly disseminates to celiac and supraclavicular lymph nodes, liver, lung and adrenal glands (4).

In the Netherlands, diagnostic upper gastrointestinal (GI) endoscopies are mostly performed in regional centers, i.e., centers without specific expertise in the treatment of upper GI malignancies, such as esophageal cancer. Following a diagnosis of esophageal or gastric cardia cancer, patients often undergo preoperative staging investigations in these regional centers. Subsequently, patients may be treated in the regional center or are referred to a specialized referral center for staging and treatment of esophageal or gastric cardia cancer. When patients are referred from a regional center to a referral center, the staging investigations performed in the referring regional center are frequently re-evaluated and/or repeated in the referral center (5).

In a previous retrospective study, we reported that metastases in patients with esophageal or gastric cardia cancer were more frequently detected on CT scans made and evaluated in a referral center compared to a regional center. We speculated that this was caused by the presence of more experienced radiologists and/or the use of technically more advanced equipment in the referral center (5). The aim of the present study was to prospectively disentangle radiologist experience from the quality of CT scans, to determine the exact role of these factors in the evaluation of CT scans of patients with esophageal or gastric cardia cancer.

METHODS

Patients

In the Erasmus MC – University Medical Center Rotterdam, The Netherlands, a database is maintained with information on patients who have been diagnosed with esophageal or gastric cardia cancer. A total of 1088 patients were included in the period January 1994 to October 2003. In 906 of these patients, the diagnosis was made in a regional center and, subsequently, these patients were referred to our referral center for further evaluation and/or treatment. In 235 patients, the preoperative CT scan performed in the regional center was re-evaluated in our referral center ('re-evaluated CT scans': 235 CT scans from regional centers available). When the quality of the CT scan was determined as sufficient, only a re-evalua-

tion of the CT scan was performed. In 79 patients, the quality of the CT scan performed in the regional center was determined as insufficient after re-evaluation, and the CT scan was therefore repeated in the referral center ('re-evaluated and repeated CT scans': 79 scans from regional centers and 79 scans from the referral center available). In 115 patients, the CT scan performed in a regional center was not re-evaluated in the referral center, but was only repeated ('repeated CT scans': 115 scans from regional centers and 115 scans from the referral center available).

Methods

Two radiologists of two different referral centers ('expert radiologists') and 6 radiologists of 6 different regional centers ('non-expert radiologists') evaluated CT scans of patients with esophageal or gastric cardia cancer. For this, we made a selection of 72 CT scans out of all CT scans performed in the 429 patients with a previously re-evaluated and/or repeated CT scan. We used the CT scans of these particular patients, because for these patients CT scans from both the referral center and the regional center were available. The selection of the 72 CT scans was stratified according to the following schedule. Twenty-six CT scans were re-evaluated CT scans (26 scans from regional centers), 28 scans were repeated CT scans (14 scans from regional centers and 14 scans from the referral center, which were performed in the same 14 patients), and 18 scans were re-evaluated and repeated CT scans (9 scans from regional centers and 9 scans from the referral center, which were performed in the same 9 patients). This was an almost similar distribution as compared to the number of re-evaluated CT scans, repeated CT scans, and re-evaluated and repeated CT scans in the period January 1994 to October 2003 in our center. We decided to include only CT scans from both the regional centers and the referral center that were performed in the same patient, as the possible differences between these CT scans then only could be attributed to the origin of the CT scans and not to the characteristics of the patients in whom the CT scan was performed. We selected 37 CT scans (51%) with distant metastases, i.e., metastases in celiac lymph nodes, liver, lung and/or adrenal glands, according to the gold standard, whereas the other 35 CT scans (49%) were without distant metastases. Celiac lymph node metastases were considered as regional if the primary tumor was located in the gastric cardia and as distant metastases if the tumor was located in the esophagus. The gold standard was either the postoperative pathological TNM stage, the result of fine-needle aspiration (FNA), or a radiological result with ≥ 6 months of follow-up.

The distribution of CT scans among the radiologists is shown in Figure 5.1. We made three groups of 24 CT scans. The two expert radiologists evaluated 48 CT scans, of which one set of 24 CT scans were evaluated by both expert radiologists, to determine the variability between the expert radiologists. Six non-expert radiologists each evaluated a set of 24 CT scans. To determine the variability between the non-expert radiologists, the set of 24 CT scans in each group was evaluated by two non-expert radiologists. In summary, in group 1 and 3, 24 CT

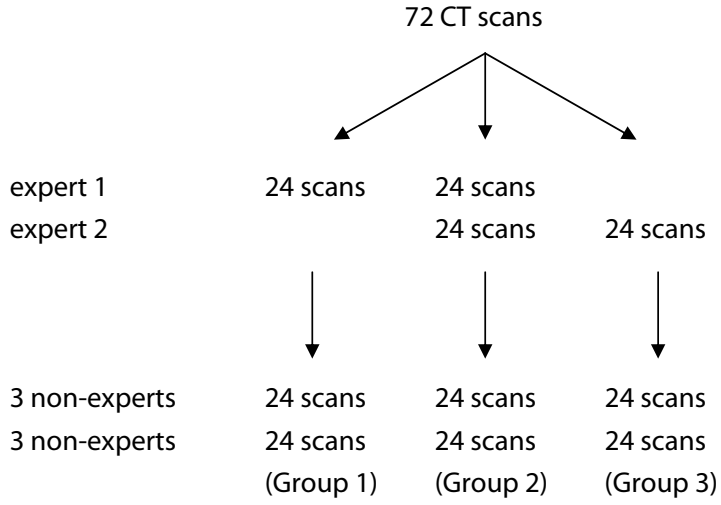

Figure 5.1. Distribution of the CT scans among the various radiologists.

scans were evaluated by 1 expert radiologist and 2 non-expert radiologists. In group 2, 24 CT scans were evaluated by 2 expert radiologists and 2 non-expert radiologists.

The distribution of CT scans among the radiologists was stratified, in such a way that each radiologist evaluated CT scans from regional centers and the referral center (Table 5.1). In addition, each radiologist evaluated two different CT scans performed in the same patient, meaning that both the CT scan from the regional center and that from the referral center performed in the same patient were evaluated by the same radiologist. In group 1, 4 CT scans from the regional center and 4 CT scans from the referral center performed in the same 4 patients were evaluated by the radiologists. In group 2, this number was 6 and in group 3, it was 5. Furthermore, each radiologist evaluated CT scans with distant metastases as well as CT scans without metastases according to the gold standard. The characteristics of the CT scans per group are shown in Table 5.1.

Each CT scan was evaluated using a form with straightforward questions on: a) the quality of the CT scan (good / moderate / poor / actually too poor to evaluate), b) whether a tumor was present (yes / no), and, if 'yes', what the primary location of the tumor was (esophagus / gastroesophageal junction / gastric cardia), and c) whether metastases were present (yes / no), and, if 'yes', what the location of the metastases was.

Statistical analyses

The results of the evaluations of the radiologists were compared with the gold standard, i.e., the postoperative pathological TNM stage, FNA or a radiological result with ≥ 6 months of follow-up. Sensitivities, specificities and accuracies for N and M stage were calculated per

Table 5.1. Characteristics of CT scans per group.

	Group 1 n=24	Group 2 n=24	Group 3 n=24	Total n=72
Origin of CT scan				
Regional center	16	17	16	49
Referral center	8	7	8	23
Number of patients with CT scan from the regional center and from the referral center	4	6	5	23
N stage				
N0	17	11	13	41
N1	7	13	11	31
M stage				
M0	12	11	12	35
M1	12	13	12	37
Gold standard				
Postoperative stage	9	8	5	22
Fine-needle aspiration	6	4	8	18
Radiological finding with ≥ 6 months of follow-up	9	12	11	32

radiologist. In addition, sensitivities and specificities were calculated for metastases per organ, i.e., metastases in regional and celiac lymph nodes, lung, liver and adrenal glands. For each group, the sensitivities, specificities and accuracies of the radiologists were compared with each other to determine whether the experience of radiologists was important in the evaluation of CT scans, as this was the only factor that was different between the radiologists per group. McNemar test was performed to determine whether the differences between the accuracies for N and M stage obtained by the radiologists were statistically significant. To determine whether the hospital where the CT scan had been made was also important, sensitivities and specificities for N and M stage were calculated for CT scans from regional centers and those from the referral center. Furthermore, multivariable conditional logistic regression analysis was performed to determine the relative importance of the experience of radiologists and origin of the CT scan, adjusting for the statistical clustering of multiple CT scans of the same patient.

To determine whether quality of CT scans was important in the evaluation, sensitivities and specificities for N and M stage were calculated for CT scans scored as good or moderate by the radiologists and for CT scans scored as poor or too poor to evaluate. These results were calculated per radiologist. In addition, multivariable conditional logistic regression analysis was repeated with the quality of the CT scans according to the opinion of each radiologist as an extra covariate in the model.

Conditional logistic regression analysis was also performed for the subgroup of CT scans without lymph node or distant metastases (specificity) and CT scans with lymph node or

Table 5.2. Results of evaluated CT scans per radiologist. All radiologists from the same group evaluated similar CT scans.

	Group 1			Group 2				Group 3		
	Expert 1 (n=24)	Non-expert 1 (n=24)	Non-expert 2 (n=22)	Expert 1 (n=21)	Expert 2 (n=20)	Non-expert 3 (n=22)	Non-expert 4 (n=23)	Expert 2 (n=22)	Non-expert 5 (n=24)	Non-expert 6 (n=24)
Sensitivity (%)										
N stage	4/7 (57)	4/7 (57)	1/6 (17)	4/13 (31)	6/11 (55)	9/13 (69)	4/13 (31)	3/9 (33)	4/11 (36)	6/11 (55)
M stage	7/12 (58)	3/12 (25)	1/11 (9)	6/12 (50)	3/10 (30)	9/13 (69)	3/12 (25)	6/10 (60)	4/12 (33)	4/12 (33)
Regional lymph nodes	4/7 (57)	4/7 (57)	1/6 (17)	4/13 (31)	6/11 (55)	9/13 (69)	4/13 (31)	3/9 (33)	4/11 (36)	6/11 (55)
Celiac lymph nodes	7/10 (70)	1/10 (10)	0/9 (0)	3/6 (50)	0/4 (0)	2/7 (29)	0/6 (0)	0/5 (0)	0/7 (0)	0/7 (0)
Lung	0/1 (0)	0/1 (0)	0/1 (0)	1/2 (50)	0/2 (0)	1/2 (50)	0/2 (0)	-	-	-
Liver	0/2 (0)	1/2 (50)	1/2 (50)	2/4 (50)	3/4 (75)	2/4 (50)	1/3 (25)	4/5 (80)	4/5 (80)	2/5 (40)
Adrenal gland	-	-	-	-	-	-	-	-	-	-
Specificity (%)										
N stage	14/17 (82)	9/17 (53)	16/16 (100)	4/8 (50)	8/9 (89)	5/9 (56)	7/10 (70)	10/13 (77)	11/13 (85)	10/13 (77)
M stage	10/12 (83)	9/12 (75)	10/11 (91)	9/9 (100)	10/10 (100)	5/9 (56)	11/11 (100)	12/12 (100)	9/12 (75)	10/12 (83)
Regional lymph nodes	14/17 (82)	9/17 (53)	16/16 (100)	4/8 (50)	8/9 (89)	5/9 (56)	7/10 (70)	10/13 (77)	11/13 (85)	10/13 (77)
Celiac lymph nodes	14/14 (100)	14/14 (100)	13/13 (100)	15/15 (100)	16/16 (100)	10/15 (67)	17/17 (100)	17/17 (100)	16/17 (94)	14/17 (82)
Lung	23/23 (100)	22/23 (96)	21/21 (100)	18/19 (95)	18/18 (100)	17/20 (85)	21/21 (100)	22/22 (100)	19/24 (79)	24/24 (100)
Liver	20/22 (91)	19/22 (86)	19/20 (95)	17/17 (100)	16/16 (100)	15/18 (83)	19/19 (100)	15/17 (88)	17/19 (90)	18/19 (95)
Adrenal gland	24/24 (100)	24/24 (100)	22/22 (100)	19/21 (91)	20/20 (100)	21/22 (96)	21/23 (91)	22/22 (100)	24/24 (100)	24/24 (100)
Accuracy (%)										
N stage	18/24 (75)	13/24 (54)	17/22 (77)	8/21 (38)	14/20 (70)	14/22 (64)	11/23 (49)	13/22 (59)	15/24 (63)	16/24 (67)
M stage	17/24 (71)	12/24 (50)	11/22 (50)	15/21 (71)	13/20 (65)	14/22 (64)	14/23 (61)	18/22 (82)	13/24 (54)	14/24 (58)

distant metastases according to the gold standard (sensitivity).

Software used for the analyses were SPSS (SPSS version 12.0, Chicago, IL) and EGRET (EGRET version 2, Cytel Software Corporation, Cambridge, MA). All p-values were based on two-sided tests. A p-value <0.05 was considered as statistically significant.

RESULTS

Experience of the radiologists

In Table 5.2, sensitivities, specificities, and accuracies are shown for each radiologist per group. The results for N stage differed between the different radiologists, both experts and non-experts. The accuracy for M stage was slightly higher for expert radiologists than for non-expert radiologists. These differences were however not statistically significant. It is important to point out that 5 of the 8 radiologists had not evaluated all CT scans as they judged the quality of some CT scans too poor to allow evaluation of the CT scan.

Conditional logistic regression analysis for N stage showed no statistically significant correlation between expert/non-expert radiologists on the one hand and a correct diagnosis of the presence or absence of lymph node metastases according to the gold standard on the other hand (adjusted odds ratio (OR): 0.94; 95% confidence interval (C.I.) 0.50-1.77) (Table 5.3). In addition, correlations were also not found for the subgroup of CT scans without lymph node metastases (specificity) and CT scans with lymph node metastases (sensitivity), indicating that radiologist experience is not important for determining N stage.

Conditional logistic regression analysis for M stage showed that expert radiologists had a nearly 3 times higher chance of making a correct diagnosis of the presence or absence of distant metastases according to the gold standard compared to non-expert radiologists (adjusted OR: 2.93; 95% C.I. 1.36-6.29) (Table 5.3). For the subgroup of CT scans without distant metastases this chance was nearly 7 times higher (adjusted OR: 6.90; 95% C.I. 1.29-37.0). This association was less pronounced for the subgroup of CT scans with distant metastases (adjusted OR: 2.21; 95% C.I. 0.89-5.52). These results indicate that the radiologist experience is important in determining M stage, and, particularly, in confirming the absence of distant metastases.

Quality of CT scans

Sensitivity for N and M stage was higher for CT scans of moderate or good quality compared to those of poor quality. In contrast, specificity for N and M stage was lower for CT scans of moderate or good quality compared with CT scans of poor quality (Table 5.4). Radiologists gave higher quality scores to CT scans from the referral center compared to those from the regional centers (Table 5.5).

Both for N and M stage, conditional logistic regression analysis showed no statistically

Table 5.3. Conditional logistic regression analyses analyzing whether a correlation is present between a correct diagnosis according to the gold standard on the one hand and the radiologist experience, quality of the CT scan and origin of the CT scan on the other hand.

Variable	Adjusted odds ratio (95% C.I.)
Radiologist experience*	
Lymph node metastases	
All CT scans	0.94 (0.50-1.77)
CT scans with metastases according to gold standard	0.68 (0.25-1.86)
CT scans without metastases according to gold standard	1.23 (0.52-2.89)
Distant metastases	
All CT scans	2.93 (1.36-6.29)
CT scans with metastases according to gold standard	2.21 (0.89-5.52)
CT scans without metastases according to gold standard	6.90 (1.29-37.0)
Quality of CT scan**	
Lymph node metastases	
All CT scans	0.93 (0.56-1.55)
CT scans with metastases according to gold standard	0.91 (0.41-2.03)
CT scans without metastases according to gold standard	1.04 (0.53-2.05)
Distant metastases	
All CT scans	1.94 (1.00-3.68)
CT scans with metastases according to gold standard	3.52 (1.36-9.08)
CT scans without metastases according to gold standard	0.78 (0.28-2.17)
Origin of the CT scan*	
Lymph node metastases	
All CT scans	1.06 (0.46-2.42)
CT scans with metastases according to gold standard	1.31 (0.37-4.62)
CT scans without metastases according to gold standard	1.22 (0.52-2.89)
Distant metastases	
All CT scans	0.85 (0.38-1.94)
CT scans with metastases according to gold standard	0.46 (0.16-1.35)
CT scans without metastases according to gold standard	2.38 (0.56-10.09)

C.I., confidence interval

* Covariates: radiologist experience, origin of CT scan

** Covariates: radiologist experience, origin of CT scan, quality of CT scan

Table 5.4. Sensitivity and specificity of CT scans judged as of good or moderate quality or of poor quality according to the opinion of each radiologist. Radiologists from the same group evaluated similar CT scans.

	Group 1			Group 2				Group 3		
	Expert 1 (n=24)	Non-expert 1 (n=24)	Non-expert 2 (n=22)	Expert 1 (n=21)	Expert 2 (n=20)	Non-expert 3 (n=22)	Non-expert 4 (n=23)*	Expert 2 (n=22)	Non-expert 5 (n=24)**	Non-expert 6 (n=24)
Quality score: good or moderate	n=16	n=17	n=16	n=14	n=17	n=9	n=15	n=14	n=14	n=22
Sensitivity (%)										
N stage	4/6 (67)	4/5 (80)	0/5 (0)	3/8 (38)	6/9 (67)	4/5 (80)	4/10 (40)	3/6 (50)	2/3 (67)	6/10 (60)
M stage	6/8 (75)	2/10 (20)	0/9 (0)	3/7 (43)	3/9 (33)	5/6 (83)	3/9 (33)	4/7 (57)	4/8 (50)	4/11 (36)
Specificity (%)										
N stage	8/10 (80)	6/12 (50)	11/11 (100)	4/6 (67)	7/8 (88)	2/4 (50)	4/5 (80)	7/8 (88)	9/11 (82)	9/12 (75)
M stage	7/8 (88)	5/7 (71)	6/7 (86)	7/7 (100)	8/8 (100)	1/3 (33)	6/6 (100)	7/7 (100)	3/6 (50)	9/11 (82)
Quality score: poor / too poor to evaluate	n=8	n=7	n=6	n=7	n=3	n=13	n=7	n=8	n=6	n=2
Sensitivity (%)										
N stage	0/1 (0)	0/2 (0)	1/1 (100)	1/5 (20)	0/2 (0)	5/8 (63)	0/2 (0)	0/3 (0)	0/4 (0)	0/1 (0)
M stage	1/4 (25)	1/2 (50)	1/2 (50)	3/5 (60)	0/1 (0)	4/7 (57)	0/2 (0)	2/3 (67)	0/4 (0)	0/1 (0)
Specificity (%)										
N stage	6/7 (86)	3/5 (60)	5/5 (100)	0/2 (0)	1/1 (100)	3/5 (60)	3/5 (60)	3/5 (60)	2/2 (100)	1/1 (100)
M stage	3/4 (75)	4/5 (80)	4/4 (100)	2/2 (100)	2/2 (100)	4/6 (67)	5/5 (100)	5/5 (100)	2/2 (100)	1/1 (100)

* 1 CT scan without information on quality

** 4 CT scans without information on quality

Table 5.5. Correlation between the origin of CT scans and the quality.

Origin	Quality			
	Good	Moderate	Poor	Too poor to evaluate
Referral center	41 (59%)	26 (30%)	8 (13%)	0 (0%)
Regional center	28 (41%)	60 (70%)	52 (87%)	20 (100%)

Linear-by-linear association test: $p < 0.001$

significant correlation between quality of the CT scans as judged by the radiologists and a correct diagnosis according to the gold standard (adjusted OR: 0.93; 95% C.I. 0.56-1.55 and adjusted OR: 1.94; 95% C.I. 1.00-3.68, respectively) (Table 5.3). For the subgroup of CT scans with distant metastases, it was however found that the chance to confirm the presence of distant metastases was 3.52 times higher for a one point higher quality score compared with a lower quality score (for example good *versus* moderate quality or moderate *versus* poor quality). This indicates that the quality of the CT scan is a factor to consider in the confirmation of the presence of distant metastases.

Origin of CT scan

In addition to the quality scores given by the radiologists, we also looked at the correlation between origin of the CT scan and findings on the CT scan. No correlations were however found between the findings on CT scans on the one hand and the hospital where the CT scan had been performed on the other hand (Table 5.6).

Conditional logistic regression analysis for N and M stage also showed no statistically significant correlation between the origin of the CT scan and a correct diagnosis according to the gold standard (Table 5.3), indicating that the origin of the CT scan is probably not important in detecting metastases on CT scans of patients with esophageal or gastric cardia cancer.

DISCUSSION

In a previous study, we retrospectively compared the results of CT scan evaluation in patients with esophageal or gastric cardia cancer in regional centers with those in the referral center (5). In that study, we showed that in the referral center more distant metastases were detected in the same patients than in regional centers. We speculated that this difference between regional centers and the referral center was explained by the fact that radiologists in the referral center were more experienced in evaluating CT scans of patients with esophageal or gastric cardia cancer and/or the use of technically more advanced equipment in the referral center.

Table 5.6. Sensitivity and specificity of CT scans from the regional center and the referral center. Radiologists from the same group evaluated similar CT scans.

	Group 1			Group 2				Group 3		
	Expert 1 (n=24)	Non-expert 1 (n=24)	Non-expert 2 (n=22)	Expert 1 (n=21)	Expert 2 (n=20)	Non-expert 3 (n=22)	Non-expert 4 (n=23)	Expert 2 (n=22)	Non-expert 5 (n=24)	Non-expert 6 (n=24)
Regional center	n=16	n=16	n=14	n=14	n=13	n=15	n=16	n=14	n=16	n=16
Sensitivity (%)										
N stage	2/4 (50)	2/4 (50)	1/3 (33)	3/9 (33)	4/7 (57)	6/9 (67)	3/9 (33)	2/7 (29)	2/9 (22)	5/9 (56)
M stage	3/7 (43)	2/7 (29)	1/6 (17)	2/8 (25)	1/6 (17)	5/9 (56)	2/8 (25)	4/7 (57)	3/9 (33)	2/9 (22)
Specificity (%)										
N stage	11/12 (92)	5/12 (42)	11/11 (100)	2/5 (40)	5/6 (83)	4/6 (67)	5/7 (71)	6/7 (86)	5/7 (71)	5/7 (71)
M stage	8/9 (89)	7/9 (78)	8/8 (100)	6/6 (100)	7/7 (100)	4/6 (67)	8/8 (100)	7/7 (100)	6/7 (86)	7/7 (100)
Referral center	n=8	n=8	n=8	n=7	n=7	n=7	n=7	n=8	n=8	n=8
Sensitivity (%)										
N stage	2/3 (67)	2/3 (67)	0/3 (0)	1/4 (25)	2/4 (50)	3/4 (75)	1/4 (25)	1/2 (50)	2/2 (100)	1/2 (50)
M stage	4/5 (80)	1/5 (20)	0/5 (0)	4/4 (100)	2/4 (50)	4/4 (100)	1/4 (25)	2/3 (67)	1/3 (33)	2/3 (67)
Specificity (%)										
N stage	3/5 (60)	4/5 (80)	5/5 (100)	2/3 (67)	3/3 (100)	1/3 (33)	2/3 (67)	4/6 (67)	6/6 (100)	5/6 (83)
M stage	2/3 (67)	2/3 (67)	2/3 (67)	3/3 (100)	3/3 (100)	1/3 (33)	3/3 (100)	5/5 (100)	3/5 (60)	3/5 (60)

In this prospective study, two expert radiologists and six non-expert radiologists performed 240 evaluations of 72 CT scans of patients diagnosed with esophageal or gastric cardia cancer to determine whether experience of radiologists and/or quality of the CT scans were indeed factors involved in the quality of CT scan evaluation. Our findings showed that expert radiologists had a nearly 3 times higher chance to make a correct diagnosis of the presence or absence of distant metastases according to the gold standard compared to non-expert radiologists, which indicates that radiologist experience is an important factor for determining M stage (Table 5.3). For the subgroup of CT scans with distant metastases according to the gold standard (sensitivity), a statistically significant correlation was found between the radiologists' opinion on the quality of a CT scan and a correct diagnosis according to the gold standard, which indicates that, in addition to expertise, the quality of the CT scan also plays a role in the confirmation of the presence of distant metastases. Thus, we prospectively confirmed that the experience of radiologists and quality of the CT scans are both factors to consider in the evaluation of CT scans of patients with esophageal or gastric cardia cancer.

Sensitivities, specificities and accuracies for N and M stage differed between radiologists in the present study. In the literature, accuracies, sensitivities and specificities of CT for N stage have also been reported in a wide range, i.e., from 33% to 86%, 22% to 84% and 60 to 100%, respectively (6-29). Varying results were also found for M stage, with accuracies, sensitivities and specificities reported in the range from 45% to 94%, 32% to 81% and 11% to 97%, respectively (6, 8, 10, 19, 24, 26, 27, 29-32). The differences found in our study were statistically not significant (Table 5.2). This could be due to various reasons. First, it could be that the number of CT scans that were evaluated by the radiologists in this study was in fact too low to detect statistically significant differences between the radiologists. Alternatively, it could also be that differences between expert and non-expert radiologists were indeed small, which makes them clinically irrelevant.

It seems likely that the finding that expert radiologists were more likely to make a correct diagnosis of the presence or absence of distant metastases than non-expert radiologists is due to differences in experience of the radiologists. It may, however, also be due to differences in evaluation practices between expert and non-expert radiologists. For example, it may be that expert radiologists are less inclined to report the presence of distant metastases compared to non-expert radiologists. This will on the one hand lead to fewer false-positive results (higher specificity), but on the other hand also to more false-negative results (lower sensitivity) for expert radiologists. Nevertheless, the opposite may also be true, with expert radiologists more frequently reporting the presence of distant metastases compared to non-expert radiologists, resulting in more false-positive results (lower specificity), but fewer false-negative results (higher sensitivity) for expert radiologists. The results of this study suggest that obvious differences in evaluation practices were not present. For the subgroup of CT scans without distant metastases (specificity), and to a lesser extent for the subgroup of CT scans with distant metastases (sensitivity), the adjusted OR for radiologist experience

was above 1 (Table 5.3), which indicates that expert radiologists were more likely to make a correct diagnosis than non-expert radiologists for both subgroups of CT scans.

We also determined whether the quality of CT scans was important for the detection of lymph node and distant metastases. For this, the radiologists gave their opinion on the quality of the CT scans. Remarkably, the number of CT scans of good or moderate quality according to the opinion of the radiologists ranged from 9 to 22 (Table 5.4), which shows that judging the quality of CT scans is a subjective matter, in which some radiologists were more inclined to give lower quality scores than other radiologists.

More metastases were detected on CT scans of better quality (adjusted OR: 3.52; 95% C.I. 1.36-9.08) (Table 5.3). This suggests that distant metastases in patients with esophageal or gastric cardia cancer were not always visible or were not easily detected on CT scans of poor quality. No statistically significant correlation was however found for the subgroup of CT scans without distant metastases according to the gold standard (adjusted OR: 0.78; 95% C.I. 0.28-2.17) (Table 5.3), which may indicate that the quality of CT scans is less important in the confirmation of the absence of distant metastases. Our results suggest that quality of the CT scans is specifically important for the detection of distant metastases, which is highly desirable as patients with distant metastases should undergo a palliative treatment and not a surgical resection.

In addition, conditional logistic regression analysis was performed to determine whether a correlation was present between the origin of the CT scan (regional/referral center) and a correct diagnosis of the presence or absence of lymph node or distant metastases according to the gold standard. In the referral center, the newest generation CT scanners were always used during the study period, which were in most cases not available in the regional centers. In addition, intravenous and oral contrast were always administered when a CT scan was performed in the referral center, whereas CT scans without the use of intravenous and/or oral contrast were made in some of the regional centers. The analyses showed however no statistically significant correlations between the origin of the CT scan and a correct diagnosis on the presence or absence of lymph node or distant metastases (Table 5.3). Nevertheless, a correlation was found between the origin of the CT scan and the quality according to the opinion of the radiologists, with higher quality scores for CT scans from the referral center (Table 5.5).

There are several limitations to this study. First, this study was not performed in daily clinical practice. The radiologists who evaluated CT scans in this study were all aware of the fact that these CT scans were made in patients with esophageal or gastric cardia cancer, but had no information on the results of other staging investigations performed in the patients. In clinical practice, radiologists are not always blinded to the results of other investigations. Furthermore, 51% of CT scans were performed in patients who had distant metastases according to the gold standard, whereas the other CT scans were of patients without distant metastases. This distribution is not alike clinical practice in our center, where fewer patients have distant

metastases detected. We decided however for this distribution, because the number of CT scans with distant metastases would otherwise be too small to draw conclusions.

Second, not all radiologists evaluated all available CT scans as they judged the quality of some CT scans too poor to allow a conclusion to be made. We proposed that the CT scans, that were not evaluated, were specifically those for which it was more difficult to determine whether lymph node or distant metastases were present or not. To determine whether this was indeed the case, we also evaluated CT scans that were evaluated by all radiologists in each separate group. For these CT scans, sensitivities, specificities and accuracies were calculated per radiologist and these results were compared with the data shown in Table 5.2. We found that the sensitivities, specificities and accuracies of CT scans that were evaluated by all radiologists of each group were higher compared to the results shown in Table 5.2, meaning that better results were obtained after deleting the CT scans that were not evaluated by all radiologists. This suggests that CT scans that were not evaluated by radiologists were indeed CT scans for which it was more difficult to determine whether lymph node or distant metastases were present or not.

Finally, some CT scans were incomplete, meaning that not the complete thorax and abdomen were present on the CT scans. Particularly, the lung and liver could not be fully evaluated in some cases. There are two possible explanations for these incomplete CT scans. First, slides might have been lost over the years. Second, the 'missing' slides were indeed not made and the CT scans were incomplete due to the protocol that was used in the center. We assume that the last reason was most likely, as the 'missing' slides were always slides above the highest part of the body that was scanned or below the lowest part of the body that was scanned. Nevertheless, it is important to stress that the complete thorax and abdomen should be scanned in patients undergoing CT scanning for staging of esophageal or gastric cardia cancer. By doing this, determination of the presence or absence of metastases is optimal.

In conclusion, both experience of radiologists and quality of CT scans are important factors in the evaluation of CT scans performed in patients with esophageal or gastric cardia cancer. The results from this study suggest that staging procedures for esophageal or gastric cardia cancer should be concentrated in centers with ample experience of radiologists in evaluating CT scans for this indication and the ability to produce high quality CT scans, which optimally will allow the detection of metastases from esophageal or gastric cardia cancer.

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CHAPTER 6

Staging of esophageal carcinoma in a low-volume EUS center compared with reported results from high-volume centers

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ABSTRACT

Background: It is well known that a learning curve exists for performing endoscopic ultrasonography (EUS). The aim was to determine whether the number of EUS investigations performed in a center affects the results of esophageal cancer staging.

Methods: We compared EUS in the evaluation of T stage and the presence of regional and celiac lymph nodes in a low-volume center where <50 EUS/endoscopist/year were performed with reported results from 7 high-volume EUS centers. From 1994 to 2003, 244 patients underwent EUS, without specific measures to pass a stenotic tumor or fine-needle aspiration (FNA), and with postoperative TNM stage as the criterion standard in the low-volume EUS center. In the high-volume centers, 670 EUS investigations for esophageal cancer were performed, if needed, with dilation, and with postoperative TNM stage and/or FNA as the criterion standard.

Results: In the low-volume center, results of EUS for T3 staging in patients in whom passage of the EUS probe was possible were almost comparable for sensitivity (85% vs 88%-94%) but lower for specificity (57% vs 75%-90%), whereas both sensitivity (58% vs 75%-90%) and specificity (87% vs 94%-97%) for T1 or T2 stage were lower than those reported in the high-volume centers. In the low-volume center, sensitivities of EUS for regional (45% vs 63%-89%) and celiac (19% vs 72%-83%) lymph nodes were lower, whereas specificities (75% vs 63%-82% and 99% vs 85%-100%, respectively) were comparable with those from high-volume centers. Results in the low-volume EUS center were worse if the EUS probe could not pass the stricture, which occurred in almost 30% of patients.

Conclusion: The results of EUS performed in a low-volume EUS center compared unfavorably with those reported from high-volume EUS centers. The results of this study suggest that preoperative staging by EUS should be performed by experienced and dedicated EUS endoscopists to optimize staging of esophageal cancer.

INTRODUCTION

Esophageal carcinoma is currently in sixth place of estimated cancer deaths worldwide (1). The prognosis of patients with esophageal cancer is dismal (2). The reason for this is that more than 50% of patients already have lymph-node metastases, distant metastases, or locally infiltrating carcinoma at the time of presentation (2). Therefore, it is important to determine the depth of infiltration of the cancer into the different layers of the esophageal wall (T stage) and the presence of lymph nodes (N1) or metastases (M1) to optimize the selection of patients for a curative resection. Endoscopic ultrasonography (EUS) is considered to be an important investigation for the evaluation of local invasion of the tumor through the esophageal wall and the presence of regional and celiac lymph nodes (3).

It is known that a learning curve exists for the quality of performing EUS (4, 5). After having performed 75 to 100 examinations, acceptable results can be obtained. However, it is not known whether the number of EUS investigations performed per year affects the results of esophageal cancer staging. The Erasmus MC - University Medical Center Rotterdam, the Netherlands, is a high-volume center for esophageal cancer referrals (>90 cases/year), but a low-volume center for EUS when it comes to individual endoscopists, with each endoscopist involved in EUS staging performing less than 50 EUS staging procedures per year. In this study, we evaluated the 10-year experience in this low-volume center for EUS for the preoperative evaluation of the T, N and M stages of esophageal carcinoma and compared this with reported results from high-volume EUS centers.

PATIENTS AND METHODS

Database

Data were obtained from a database that contains information on EUS findings of 761 patients with esophageal or gastric cardia cancer, which is present in the Erasmus MC – University Medical Center Rotterdam. These EUS investigations were performed as part of the diagnostic evaluation to determine resectability of these cancers.

Patients and methods

Between January 1994 and October 2003, 761 patients underwent EUS in the Erasmus MC – University Medical Center Rotterdam. More than 95% of procedures were performed with a mechanical radial echoendoscope (Olympus GIF-UM20; Olympus America, Inc, Melville, NY). The T stage was subdivided in T1 to T4 stages, with a T1 carcinoma infiltrating into the mucosa (T1m) or the submucosa (T1sm), a T2 into the muscularis propria, a T3 through the muscularis propria, and a T4 infiltrated into surrounding organs or vessels (6). The differentiation of benign from possible malignant lymph nodes depended on size, shape, and echo

Table 6.1. Level of experience in the high-volume centers: volumes from the literature.

Name	Reference	Number of EUS papers	Time period	Number of patients reported on:						Total number of patients
				Esophagus/ stomach	Pancreas/ bile duct	Mediastinum	Small bowel	Rectum	Other/not specified	
Fockens P	4	7	1996-2004	463	0	0	0	0	0	463
van den Brande JH	4	1	1996	231	0	0	0	0	0	231
Tytgat GN	4	16	1986-2004	650	43	0	0	20	0	713
Reed CE	7	13	1996-2005	532	0	663	0	0	0	1195
Mishra G	7	8	1999-2005	178	332	167	0	0	0	677
Hawes RH	7	63	1992-2004	874	932	1409	0	6	628	3843
Vazquez-Sequeiros E	8,9	15	2001-2005	241	231	0	0	0	1154	1626
Norton ID	8	14	2001-2005	241	343	0	34	0	1115	1733
Wiersema MJ	8, 9	57	1992-2005	369	726	0	34	102	4532	5763
Zinsmeister AR	9	4	2001-2005	167	120	0	34	0	0	321
Catalano MF	10, 11	14	1994-2004	359	301	88	0	0	34	782
Sivak MV Jr	10, 11	26	1989-2004	502	205	60	0	45	317	1129
Van Dam J	10	15	1994-2004	342	3	0	0	0	138	483
Alcocer E	11	3	1998-2000	219	140	0	0	0	0	359
Eloubeidi MA	12	33	2001-2005	470	961	114	0	0	748	2293
Wallace MB	12	37	2000-2005	611	276	424	0	0	743	2054
Hoffman BJ	12	44	1995-2005	673	646	532	0	0	1115	2966

pattern. Lymph nodes were considered to be malignant if 3 or more of the following features were present: a size greater than 5 mm, a sharp demarcation of the borders, a round shape and a central echo pattern, which was homogeneous and echopoor (7-9). In the included patients in the low-volume EUS center, fine-needle aspiration (FNA) or measures to fully stage a stenotic tumor, such as dilation or use of a blind ultrasonic probe, were not performed. A resection without neoadjuvant chemotherapy and/or radiation therapy was performed in 244 of 761 patients who had undergone EUS. In these patients, resection of the greater part of the esophagus and the upper part of the stomach, including the tumor and the regional and celiac lymph nodes, was performed. All specimens were histologically examined by an experienced gastrointestinal pathologist and the postoperative TNM stage was determined. The pathologist had no information on the preoperative results of the EUS. In this study, the TNM stage, as determined by EUS, was compared with the postoperative TNM stage, which was considered to be the criterion standard.

Literature review

A PubMed MEDLINE literature search was performed to identify articles relating to the use of EUS in patients with esophageal or gastric cardia cancer. Search terms used were combinations of EUS, endoscopic ultrasonography, staging, accuracy, esophageal cancer, esophagus, gastric cardia, cancer, and carcinoma. Articles included in this study contained information on the accuracy of the T, N and/or M stages as determined by EUS that were performed in a center with expertise in the use of EUS.

Seven relevant articles were selected from 7 high-volume centers, i.e., 5 articles containing information on T stage as determined by EUS (4, 8-11), 6 articles with information on N and/or M stages as determined by EUS (7-12), and 3 articles with information on N and/or M stages as determined by EUS-FNA (8, 9, 12). In total, 670 patients in the high-volume centers underwent EUS for staging of esophageal cancer, with dilation if indicated. The criterion standard in these articles was the postoperative TNM stage and/or the result of FNA.

Information used from these articles included accuracy of the T, N and M stages, and sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of the N and M stages if given. Outcome measures that were not present in an article, were, if possible, calculated from results in that particular article.

The level of experience in these centers was checked for the first, the second and the last author in MEDLINE (Table 6.1). For this, we (a) checked the total number of articles on EUS that were published by these authors, (b) checked the time period in which these articles were published, and (c) created a subdivision for the number of patients that had been evaluated for each organ system, i.e., esophagus/stomach, mediastinum, small bowel, pancreas/bile duct and rectum (Table 6.1).

We also contacted the authors of the papers to get precise case volumes (Table 6.2). An e-mail was sent to 1 EUS endoscopist of each included center to ask for the following: (1)

Table 6.2. Level of experience in the high-volume centers: real volumes from the responding centers.

	1994	1995	1996	1997	1998	1999	2000	2001	2002	2003	Total
University Hospitals of Cleveland, Cleveland, Ohio											
EUS procedures	150	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	700	5000
EUS procedures for esophageal cancer	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	300
Number of endoscopists	2	2	2	4	4	4	4	4	5	5	
Academic Medical Center, Amsterdam, The Netherlands											
EUS procedures	700	700	700	700	700	700	700	750	800	850	7300
Number of endoscopists	2	2	2	3	3	3	3	3	3	3	
Mayo Clinic Rochester, Rochester, Minn											
EUS procedures	136	165	369	535	725	1187	1653	1822	1632	1608	9832
EUS procedures for esophageal cancer	26	17	47	75	88	151	280	262	248	257	1451
Number of endoscopists	2	3	3	3	4	4	5	5	4	6	

the total EUS procedures/year in the period 1994 to 2003, (2) the total EUS procedures for esophageal cancer/year in the period 1994 to 2003, (3) the number of endoscopists who performed EUS in the period 1994 to 2003 (per year), and (4) if possible, the number of EUS procedures/endoscopist/year in the period 1994 to 2003. Two weeks after the first e-mail, a reminder e-mail was sent to the authors who had not yet sent us the required data.

Statistical analyses

Sensitivity, specificity, accuracy, PPV and NPV of EUS for the presence of regional and celiac lymph-node metastasis were calculated. For the T stage, sensitivity, specificity, accuracy and kappa-value (κ value) were calculated. The κ value was used for describing the measure of agreement between the T stage determined by EUS and the postoperative T stage. A κ value <0.40 was considered poor; between 0.40 and 0.60, moderate or fair; between 0.60 and 0.80, good; and between 0.80 and 1, close to perfect (13).

The chi-square test was used for calculating p-values. All p-values were based on 2-sided tests of significance. A p-value <0.05 was considered significant. SPSS (SPSS Inc., Chicago, Ill) was used for all calculations.

RESULTS

Patient and tumor characteristics in the low-volume center

A total of 244 patients underwent EUS followed by esophageal resection without neoadjuvant chemo- or radiotherapy. EUS procedures had been performed by 4 senior and 5 junior endoscopists in the low-volume center. The endoscopists performed <50 EUS investigations per person per year, mainly for staging of carcinoma of the esophagus or the gastric cardia, and for benign disorders of the esophagus or stomach (Table 6.3).

If the junior faculty was supervised by a senior endoscopist, the procedure was counted for the senior endoscopist; if not supervised the procedure was counted for the junior endoscopist. The junior faculty was trained at the Department of Gastroenterology and Hepatology, Erasmus MC Rotterdam. No differences were observed in performance over time or among the 9 endoscopists.

Table 6.3. Level of experience in the low-volume center.

Endoscopist	Time period	Esophageal/gastric cardia carcinoma	Benign disorders of esophagus and gastric cardia	Pancreas	Total
#1	1994-2003	245	47	6	298
#2	1994-2002	192	39	3	234
#3	2000-2003	106	20	7	133
#4	1997-1999	55	11	0	66
#5	2000-2001	46	10	0	56
#6	1994-1996	38	8	0	46
#7	2001-2003	38	9	5	52
#8	1998-1999	34	7	0	41
#9	2001-2002	7	1	0	8
Total		761	152	21	934

As can be seen in Table 6.3, the 9 endoscopists performed 934 EUS procedures, 761 for staging of esophageal and gastric cardia cancers, 152 for benign disorders of the esophagus and gastric cardia and 21 for pancreatic disorders. Staging of pancreatic disorders was only performed during the last 2 years of the study period. In the period 1994 to 2003, staging of rectal disorders was not performed by the Department of Gastroenterology and Hepatology, but by the Department of Surgery, Erasmus MC Rotterdam.

Patient and tumor characteristics are shown in Table 6.4. The distribution of patients over subsequent years is shown in Figure 6.1.

Level of experience in high-volume centers

In total, 3 of 7 contacted centers sent us data. In Table 6.2, the total number of EUS procedures/year, the number of EUS procedures for esophageal cancer/year, and the number

Table 6.4. Patient and tumor characteristics of patients who underwent EUS and resection of a carcinoma of the esophagus or gastroesophageal junction without neoadjuvant therapy (N=244).

Variable	N=244
Mean age ± SD (years)	64 ± 10.3
Sex (%)	
Male	202 (83)
Female	42 (17)
Histology of tumor at biopsy (%)	
Squamous-cell carcinoma	23 (10)
Adenocarcinoma	213 (87)
Other	8 (3)
Location of tumor (%)	
Cervical	-
Upper 1/3 thoracal	-
Central 1/3 thoracal	10 (4)
Lower 1/3 thoracal	96 (39)
Gastroesophageal junction	138 (57)

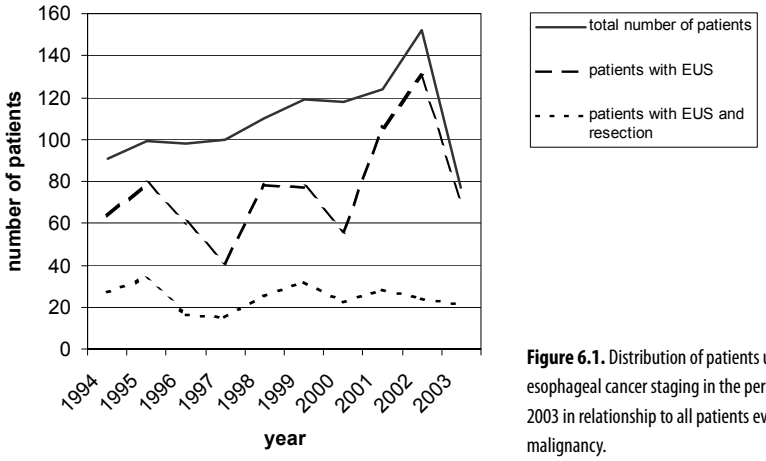

Figure 6.1. Distribution of patients undergoing EUS for esophageal cancer staging in the period 1994 to October 2003 in relationship to all patients evaluated for this malignancy.

of EUS endoscopists/year are shown, because these were the data that were sent by the 3 centers. The data showed that the total number of EUS procedures per endoscopist is higher in the high-volume centers compared with the low-volume center. In the low-volume center, each endoscopist involved in EUS staging performed fewer than 50 EUS staging procedures per year, whereas in the high-volume centers, this number was higher than 50 per year, indicating more experience with EUS in the high-volume centers.

Table 6.5. Accuracy of EUS for determining preoperative T stage in esophageal carcinoma divided in results of 173 patients with esophageal carcinoma in the low-volume center in whom passage of the EUS probe was possible, results of 71 patients in the low-volume center in whom passage of the EUS probe was impossible, and results of high-volume centers.

	Low-volume center (EUS probe passage)	Low-volume center (No EUS probe passage)	High-volume centers
Sensitivity			
T3 vs other T stages	85% (75/88)	79% (49/62)	88%-94%
T4 vs other T stages	0% (0/2)	0% (0/3)	67%-95%
T3-4 vs T1-2	87% (78/90)	83% (54/65)	94%-97%
T1-2 vs T3-4	58% (48/83)	17% (1/6)	75%-90%
Specificity			
T3 vs other T stages	57% (48/85)	11% (1/9)	75%-90%
T4 vs other T stages	99% (170/171)	97% (66/68)	95%-99%
T3-4 vs T1-2	58% (48/83)	17% (1/6)	75%-90%
T1-2 vs T3-4	87% (78/90)	83% (54/65)	94%-97%
Accuracy			
Overall	54% (94/173)	69% (49/71)	68%-89%
T1	21% (9/43)	-	33%-100%
T2	25% (10/40)	0% (0/6)	12.5%-84%
T3	85% (75/88)	79% (49/62)	75%-94%
T4	0% (0/2)	0% (0/3)	50%-100%
κ value (95% CI)	0.23 (0.14-0.33)	-0.09 (-0.29-0.11)	0.58 (0.47-0.69) to 0.83 (0.77-0.89)

CI, confidence interval

T stage

In all 244 patients in the low-volume center, the T stage was determined by EUS. In 71% of patients (173/244), the EUS probe could pass the malignant structure. A pathological T stage was as follows: in 43 patients, T1 carcinoma; in 40, T2 carcinoma; in 88, T3 carcinoma; and in 2, T4 carcinoma. In 29% of patients (71/244), the EUS probe could not pass the tumor. A pathological T stage in these patients was as follows: in 6 patients, T2 carcinoma; in 62, T3 carcinoma; and in 3, T4 carcinoma. The results of EUS in the low-volume center for determining preoperative T stage are shown in Table 6.5. The reported EUS results of high-volume centers regarding T stage (4, 8-11) are also shown in Table 6.5.

In the low-volume center, results of EUS for T3 stage were almost comparable for sensitivity and were lower for specificity, whereas accuracy was not different from high-volume centers. In contrast, accuracies for determining T1, T2 and T4 stages were lower in the low-volume EUS center than in the high-volume centers. A similar pattern was found for sensitivities and overall κ values. The specificity for determining T1 and T2 stages was lower in the low-volume EUS

center than in the high-volume centers, whereas the specificity for determining the T4 stage was comparable between the low-volume center and the high-volume centers. The results of T staging were worse in patients, in whom the EUS probe could not pass the tumor (Table 6.5).

N and M stages

In 236 of 244 patients in the low-volume center, both N (regional lymph nodes) and M (celiac lymph nodes) stage were determined by EUS. In 72% of patients (171/236), N and M stages were determined with passage of the EUS probe, and in 28% of patients (65/236), passage of the EUS probe was not possible. In patients in whom passage of the EUS probe was possible, 94 regional and 16 celiac lymph-node metastases were histologically detected in the resected specimen. In patients in whom passage of the EUS probe was not possible, 44 regional and 9 celiac lymph-node metastases were histologically detected in the resected tissues. The results of EUS for determining preoperative N and M stages in the low-volume center are shown in Table 6.6. The reported results of high-volume centers with regard to the determination of N and M stages by EUS (7-12) and confirmed by the postoperative pathological results are also shown in Table 6.6. The results of high-volume centers with regard to N and/or M stages and confirmed by EUS-FNA (8, 9, 12) are shown in Table 6.7.

In the low-volume center, sensitivity, NPV and accuracy of EUS for regional lymph nodes were lower compared with high-volume centers. Specificity and PPV for regional lymph nodes were comparable with those in high-volume centers (Table 6.6). Sensitivity and PPV

Table 6.6. Accuracy of EUS for determining preoperative N and M stages in esophageal carcinoma divided in results of 171 patients with esophageal carcinoma in the low-volume center in whom passage of the EUS probe was possible, results of 65 patients in the low-volume center in whom passage of the EUS probe was impossible, and results of high-volume centers.

	Low-volume center (EUS probe passage)	Low-volume center (No EUS probe passage)	High-volume centers
Regional lymph nodes			
Sensitivity	45% (42/94)	32% (14/44)	63%-89%
Specificity	75% (58/77)	91% (19/21)	63%-82%
PPV	69% (42/61)	88% (14/16)	53%-91%
NPV	53% (58/110)	39% (19/49)	63%-87%
Accuracy	64% (110/171)	51% (33/65)	70%-84%
Celiac lymph nodes			
Sensitivity	19% (3/16)	11% (1/9)	72%-83%
Specificity	99% (154/155)	100% (56/56)	85%-100%
PPV	75% (3/4)	100% (1/1)	89%-96%
NPV	92% (154/167)	88% (56/64)	71%-100%
Accuracy	92% (157/171)	88% (57/65)	81%-97%

PPV, positive predictive value; NPV, negative predictive value

for celiac lymph nodes were lower in the low-volume EUS center, whereas specificity, NPV and accuracy for celiac lymph nodes were comparable with those from high-volume centers (Table 6.6). The results of detecting regional and celiac lymph nodes in the low-volume EUS center compared even more unfavorably if EUS results of tumors that could not be passed by the EUS probe were compared with those from high-volume centers (Table 6.6).

There was a median of 4 weeks between an EUS and a resection (range: 0.5-11 weeks). Therefore, we examined EUS results of patients with 5 to 11 weeks between an EUS and a resection separately from those of patients with 0 to 4 weeks between an EUS and a resection. As can be seen from Table 6.8, results for sensitivity and specificity of T, N and M stages were not statistically significantly different between these 2 time periods.

Table 6.7. EUS-guided FNA for detecting regional and celiac lymph nodes in high-volume centers.

	Number of patients	Sensitivity	Specificity	PPV	NPV	Accuracy
Regional lymph nodes						
Vazquez-Sequeiros, et al (8), 2001	31	93%	100%	33%	100%	93%
Vazquez-Sequeiros, et al (9), 2003	76	83%	93%	95%	76%	87%
Celiac axis						
Vazquez-Sequeiros, at al (8), 2001	14	93%	-	0%	100%	93%
Eloubeidi, et al (12), 2001	51	98%	100%	100%	83%	98%

PPV, positive predictive value; NPV, negative predictive value

Table 6.8. Results in patients with 0 to 4 weeks and with 5 to 11 weeks between EUS and resection.

	0-4 weeks (probe passage)	0-4 weeks (no probe passage)	5-11 weeks (probe passage)	5-11 weeks (no probe passage)
Sensitivity				
T3 vs other T stages	86% (47/55)	74% (31/42)	85% (28/33)	90% (18/20)
T4 vs other T stages	0% (0/1)	0% (0/3)	0% (0/1)	-
T3-4 vs T1-2	88% (49/56)	80% (36/45)	85% (29/34)	90% (18/20)
T1-2 vs T3-4	53% (27/51)	20% (1/5)	66% (21/32)	0% (0/1)
Regional lymph nodes	39% (23/59)	30% (9/30)	54% (19/35)	36% (5/14)
Celiac lymph nodes	30% (3/10)	13% (1/8)	0% (0/6)	0% (0/1)
Specificity				
T3 vs. other T-stages	52% (27/52)	13% (1/8)	64% (21/33)	0% (0/1)
T4 vs. other T-stages	99% (105/106)	96% (45/47)	100% (65/65)	100% (21/21)
T3-4 vs. T1-2	53% (27/51)	20% (1/5)	66% (21/32)	0% (0/1)
T1-2 vs. T3-4	88% (49/56)	80% (36/45)	85% (29/34)	90% (18/20)
Regional lymph nodes	83% (38/46)	88% (14/16)	65% (20/31)	100% (5/5)
Celiac lymph nodes	99% (94/95)	100% (38/38)	100% (60/60)	100% (18/18)

p = not significant

DISCUSSION

In this study, EUS without FNA, and without dilation in case of a stenotic tumor, and performed in a tertiary referral center but not by dedicated EUS endoscopists, was compared with reported results from high-volume EUS centers. Our findings demonstrate that the results of the low-volume EUS center compared unfavorably with those reported by high-volume centers.

In the low-volume EUS center, the overall accuracy of T3 staging was 83%, which was comparable with those in high-volume centers, whereas accuracies for other T stages (T1, 21%; T2, 25%; and T4, 0%) were much lower. The reason that T3 staging was comparable between low-volume and high-volume EUS centers could be that a T3-stage esophageal cancer is the most commonly observed stage. Increased experience with this tumor stage could make it easier for an endoscopic ultrasonographist to recognize whether a tumor is growing through the muscularis propria (T3 stage) or not (T1 or T2 stages). Overstaging occurred in 63 of 89 patients (71%) with a T1- or T2-stage carcinoma whereas understaging was observed in 23 of 150 patients (15%) with a T3 stage and in all 5 (100%) patients with a T4-stage carcinoma. Overstaging of T stage has been reported to be due to the presence of nonmalignant peritumorous inflammation (14) or by overinflating of the EUS transducer balloon. Overinflation may push malignant lesions deeper into layers of the esophagus, leading to pseudoinvasion (15). On the other hand, understaging of the T stage could be caused by microinvasion of the carcinoma in the esophageal wall (14), which, at the time of performing the EUS, is undetectable. The most likely explanation for understaging a T4-stage tumor in our series of patients was, however, the low number of patients with advanced esophageal cancer. This is caused by selection bias in our series, which mainly contains patients who were considered operable. Since T4 disease is generally considered a contraindication for surgery when detected before surgery, these patients were often not referred to our hospital.

In the low-volume EUS center, sensitivities for detecting regional and celiac lymph nodes (45% and 19%, respectively) were also lower, whereas specificities were comparable (75% and 99%, respectively) with those in high-volume EUS centers. Overstaging and understaging in detecting malignant lymph nodes were often observed in the low-volume EUS center. Overstaging occurred in 21 of 98 regional lymph nodes (21%) and in 1 of 211 celiac lymph nodes (<1%), whereas understaging was seen in 82 of 138 regional lymph nodes (59%) and in 21 of 25 celiac lymph nodes (84%). Lymph nodes were only morphologically considered to be malignant. It is well known, however, that cytology obtained by FNA is better able to detect small metastatic lymph-node involvement (16). This could be an explanation for understaging of malignant lymph nodes by EUS. Another reason for understaging could be that patients with celiac lymph nodes are often considered to be unresectable. False-positive celiac lymph nodes have, therefore, undesirable consequences for patients, and this could be a reason why an endoscopist is careful to report the presence of "positive" celiac lymph

nodes, particularly if FNA is not available. It is known that reactive lymph nodes and malignant lymph nodes are often difficult to distinguish (16). As a consequence of this, overstaging of lymph nodes by EUS may also occur.

This study had several limitations because of the design. The term "high-volume center" was partly based on a review of articles relating to the use of EUS in the centers included in this study. Nevertheless, it is possible that the number of patients in articles is not equal to the real number of patients in that center. A reason for this could be that only patients who met the study criteria were included in the study and not all patients with EUS leading to underestimation of the number of patients. Another reason is that patients may be included in more than 1 study, which could have led to overestimation of the number of patients in a center. Therefore, we also contacted the authors of the papers to get more precise case volumes. Because only 3 of 7 centers responded, it was not possible to give the real volumes of EUS procedures/year and the number of EUS endoscopists/year for all centers. Nevertheless, the data of the 3 responding centers clearly show that the level of experience in performing EUS is higher in the high-volume centers.

Only 2 endoscopists in the low-volume center performed EUS procedures during almost the entire study period (1994-2003), whereas the other 7 endoscopists performed EUS procedures during 1 to 3 years of the study period. The sensitivities and specificities of EUS of the 2 endoscopists who performed EUS for almost the entire period did not differ from those of the other 7 endoscopists, who performed EUS procedures for a shorter period. The reason for this is unclear; however, it seems likely that the main explanation for the comparable sensitivities and specificities of EUS is that the 2 "more experienced" endoscopists in the low-volume center did not have a specific interest in performing EUS procedures.

There are several explanations for the differences in results between the low-volume EUS center and the high-volume centers. First, the quality of an EUS examination and its conclusions are highly dependent on the experience of the endoscopist. It has been shown that with increasing expertise in performing EUS, the endoscopist is more accurate in determining the presence and the extent of local invasion of the tumor through the esophageal wall as well as the presence of lymph node metastases (4, 5). As can be seen from Tables 6.1, 6.2 and 6.3, the level of experience in performing EUS was clearly lower in the low-volume EUS center as compared with the high-volume centers.

Second, the median time period between an EUS and an esophageal resection was relatively long in some patients in this study, i.e., up to 11 weeks. A delay of more than 5 weeks between an EUS and a resection may increase the risk of understaging by EUS. The results of patients with a period of 5 to 11 weeks and those of patients with 0 to 4 weeks between an EUS and a resection were however not significantly different (Table 6.8). The time between an EUS and a resection in articles from high-volume EUS centers was only reported in 1 of these studies (10).

Third, the capacity to visualize abnormalities could depend on the type of EUS devices that were used in a center (17). This could be a factor in explaining the difference in EUS results among various centers. In addition, it seems likely that experienced centers use technically more advanced equipment than low-volume EUS centers.

Fourth, FNA was not performed in the low-volume EUS center when a lymph node was suspicious for malignancy. In the high-volume EUS centers included in this study (8, 9, 12), FNA was often performed when a lymph node was visualized, and it was questionable whether this contained malignancy (Table 6.7). These results were not used for the comparison between the low-volume EUS center and the high-volume centers. However, if one compares the results of EUS alone (Table 6.6) with the results of EUS with FNA (Table 6.7), than the results of EUS-FNA were clearly better.

Fifth, in 29% of patients (71/244) in the low-volume EUS center, a stenotic esophageal carcinoma was present, which could not be passed by the EUS probe. In these patients, dilation was not performed in the low-volume EUS center and staging, therefore, was incomplete. This could have resulted in an underestimation of T, N and M stages. For that reason, we separately analyzed patients in whom passage of the EUS probe was possible or not. Our results showed that, in patients in whom passage of the EUS probe was possible, the EUS results were more accurate compared with patients in whom passage of the EUS probe was not possible (Table 6.5 and 6.6). In contrast, in most high-volume EUS centers, dilation was performed in patients with malignant strictures if this was indicated (7-9, 11, 12). Alternatively, in 2 studies, patients with stenotic malignant strictures were excluded from evaluation (4, 10).

Sixth, in the low-volume EUS center, lymph nodes were considered malignant if 3 or more of the following criteria were present: a size larger than 5 mm, a sharp demarcation of the borders, a round shape, and a central echo pattern that was homogeneous and echo poor. These criteria were also used in some of the high-volume EUS centers (7-9). However, in other high-volume centers lymph nodes were only considered to be malignant if the size was larger than 10 mm rather than 5 mm (10-12). High-volume EUS centers in which lymph nodes larger than 10 mm were considered malignant had higher sensitivities in comparison with centers in which lymph nodes larger than 5 mm were considered malignant. As a result of this, it seems likely that subjectivity of EUS criteria also could lead to differences in results among different studies.

Seventh, publication bias may be present, meaning that favorable results of EUS staging for esophageal cancer are more likely to be reported. The presence of selection bias is already known for EUS staging of rectal cancer (18) and could also be present for esophageal carcinoma.

Finally, in this study, we only included patients who underwent preoperative EUS followed by an esophageal resection without neoadjuvant therapy. These patients were a selection of all patients present in the database, indicating the possibility of verification bias. The patients included in this study had a relatively lower, i.e., more favorable, TNM stage as determined

by EUS, compared with the other patients. These patients also had no distant metastases, as detected by other preoperative investigations, i.e., CT and ultrasound of the neck and the abdomen. As was shown, particularly, accuracy for T1- and T2-stage esophageal carcinomas was low compared with patients with a T3-stage carcinoma (Table 6.5). Therefore, the presence of relatively more T1- and T2-stage esophageal carcinomas and fewer T3-stage carcinomas in this group of patients could have led to more unfavorable overall results in this study compared with high-volume EUS centers. It should be realized, however, that verification bias is also possible in high-volume EUS centers. In the high-volume EUS centers, different exclusion criteria were used with regard to stenotic carcinomas and/or the criterion standard, which also could have led to differences in severity of disease among the various high-volume centers.

In conclusion, the results of EUS, without preceding dilation of malignant strictures and without FNA, performed in a low-volume EUS center compared unfavorably with those obtained in high-volume EUS centers. Our results suggest that preoperative staging by EUS, preferably with FNA and with dilation of stenotic tumors if indicated, should be centralized and performed by dedicated and experienced endoscopists to optimize staging of esophageal cancer. We presently have adapted this policy in such a way that all EUS staging procedures in our center are now performed by a few dedicated EUS endoscopists with considerable annual experience.

ACKNOWLEDGMENTS

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CHAPTER 7

Publication bias does not play a role in the reporting of EUS staging results in upper gastrointestinal cancer

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ABSTRACT

Background: An overestimation of EUS results in rectal cancer staging has recently been reported, which was found to be caused by the selective reporting of more positive results. In this study, we assessed whether publication bias was also present in the reporting of EUS staging results in upper gastrointestinal (GI) cancer.

Methods: A Medline literature search was performed. Articles containing information on the accuracy of EUS for T and/or N staging of esophageal, gastric and pancreatic cancer and published in the English literature were included. Excluded were articles published in abstract form only, case reports, and reviews. In addition, EUS results of patients with preoperative radiation and/or chemotherapy were also excluded. Results of EUS were plotted against numbers of patients, year of publication, journal type and impact factor.

Results: The plots of the numbers of patients against accuracies for T and N stage and the statistical analyses showed no evidence for publication bias of upper GI cancer. The reported accuracy of EUS for T stage of esophageal, gastric and pancreatic cancer declined slightly over the years, with only esophageal cancer being statistically significant (p=0.01). No statistically significant correlations were found for N stage of all three types of cancer. In addition, no correlations were found between EUS results and journal type or impact factor, respectively.

Conclusion: No evidence was found for the selective reporting of more positive EUS results of esophageal, gastric and pancreatic cancer staging, which suggests that publication bias was not present.

INTRODUCTION

The prognosis of upper gastrointestinal (GI) tract cancer is poor with 5-year survival rates of 8-15% for esophageal cancer, 20-22% for gastric cancer and only 4% for pancreatic cancer (1). The reason for this is that many patients have already locally infiltrating cancer, lymph node metastases or distant metastases at the time of presentation.

Preoperative investigations which are commonly performed for staging of esophageal cancer include endoscopic ultrasonography (EUS) (2), computed tomography (CT) (3), ultrasound (US) of neck and abdomen (4), chest X-ray (5), and bronchoscopy (6). EUS is considered to be the most important modality for the evaluation of local invasion of tumor into the esophageal wall (T stage) and the presence of regional lymph nodes (N stage) (7). In the literature, accuracy for T stage of esophageal cancer ranges from 70% to 90%, whereas accuracy for N stage has been reported to vary between 65% and 80% (8, 9). EUS, CT (10), US abdomen (11), magnetic resonance imaging (MRI) (12), and laparoscopy (13) can be used for the staging of gastric cancer. The accuracy of EUS for T stage of gastric cancer has been reported to vary between 60% and 90% and for N stage between 50% and 80% (14). For the diagnosis and staging of pancreatic cancer, a combination of EUS, CT, US abdomen (15), endoscopic retrograde cholangiopancreaticography (ERCP) (16), MRI and angiography (17) is often performed. EUS has been reported to be the most accurate investigation for staging of pancreatic cancers (18), with an accuracy for T stage of 78-94% and accuracy for N stage of 64-82% (19, 20).

For rectal cancer, it has recently been reported that accuracy of EUS in the literature is overestimated due to publication bias, i.e., the selective reporting of manuscripts with more positive results (21). It is unknown whether publication bias is also present for EUS staging of esophageal, gastric and pancreatic cancer. We therefore assessed whether biases were present in the reporting of EUS results in upper GI cancer.

METHODS

Selection of articles

A Medline literature search was performed to identify articles relating to the use of EUS in patients with upper GI cancer. Search terms to identify articles relating to the use of EUS in patients with esophageal cancer were combinations of 'endoscopic ultrasonography', 'EUS', 'esophagus', 'oesophagus', 'cancer', 'neoplasm' and 'carcinoma'. For the identification of articles relating to gastric cancer, the search terms were combinations of 'endoscopic ultrasonography', 'EUS', 'gastric', 'stomach', 'cancer', 'neoplasm', and 'carcinoma'. For pancreatic cancer, combinations of 'endoscopic ultrasonography', 'EUS', 'pancreatic', 'pancreas', 'cancer', 'neoplasm', 'tumor' and 'carcinoma' were used. Abstracts obtained from these searches were

evaluated. Articles containing information on overall accuracy of EUS for T and/or N staging of esophageal, gastric and/or pancreatic cancer and published in the English literature before February 2006 were included. Excluded were articles published in abstract form only, case reports, and reviews. In addition, EUS results of patients with preoperative radiation and/or chemotherapy were also excluded, as it is well known that accuracy of EUS decreases as a result of post-inflammatory changes caused by radiation and/or chemotherapy (22, 23). In this study, pancreatic cancer was defined as pancreatic adenocarcinoma. Articles that reported on other types of pancreatic cancer, for example neuroendocrine tumors, cystic neoplasms, and ampullary cancer were not included, as the incidence and clinical behavior of these tumors are clearly different from pancreatic adenocarcinoma. However, if EUS results of pancreatic adenocarcinoma and other types of pancreatic cancer were reported separately in a combined article, we included pancreatic adenocarcinoma results, if these met the inclusion criteria, whereas the results of other types of pancreatic cancer were excluded. The references of included articles and reviews, found with the literature searches, were also examined for additional articles that met the inclusion criteria of this study.

Information obtained from the articles were, if present, accuracy of EUS for T and N staging of esophageal, gastric and pancreatic cancer, sensitivity and specificity of EUS for N stage, year of publication of a particular article, and number of included patients in the study. In addition, the type and impact factor of a journal were obtained from ISI Web of Knowledge. Journals were subdivided into gastroenterological, surgical, radiological, and oncological journals. The impact factor of a journal was calculated as cites to recent articles divided by the number of recent articles in that journal. Impact factors were obtained from the ISI Web of Knowledge edition corresponding with the year of publication of that particular article, when available.

Statistical analyses

The numbers of patients with esophageal, gastric and pancreatic cancer, respectively, were plotted against accuracies of EUS for T and N stage, resulting in funnel plots. A funnel plot is an epidemiologic method for assessing publication bias. The idea is that studies with the largest numbers of patients will estimate the accuracy of EUS for T and N staging most accurate, whereas studies with fewer patients will have a more variable result, with both lower and higher accuracies compared to accuracies of larger studies. If this is the case, the plot will have a symmetric, inverted funnel shape. If publication bias is present, a majority of studies with high accuracies of EUS for T or N staging has been published, whereas studies with small numbers of patients reporting low accuracies of EUS are limited available and the left base of the plot will disappear (24). Funnel plots, which were made in this study, were first assessed visually. It is known, however, that it may be difficult to determine in this way whether publication bias is present or not (24). In order to correct for this, Mann-Whitney U-test and

Spearman's rank correlation test were performed to determine whether a statistically significant correlation was present between results of EUS and numbers of patients.

Accuracies of EUS for T and N stage of esophageal, gastric and pancreatic cancer, respectively, were also plotted against impact factor of the journal, year of publication, and type of journal. Slopes and p-values were calculated for the correlations between accuracies of EUS and impact factor or year of publication, respectively. To determine whether a correlation was present between results of EUS and type of journal, the Kruskal-Wallis test was performed.

The same plots were made for sensitivity and specificity of EUS for N staging. As sensitivity and specificity of EUS for T staging can only be calculated for T1, T2, T3 and T4 stage separately and not for overall T stage, and sensitivity and specificity for T staging were only reported in a few articles, we included these results not in the analysis of this study.

If articles contained information on the accuracy of EUS for N staging, but sensitivity and specificity were not reported, these were calculated if possible. Plots were made between numbers of patients and reported and calculated sensitivities and specificities of EUS for N stage. Mann-Whitney U-test was performed to determine whether the EUS results were different between articles that reported sensitivity and specificity compared with articles that did not.

All calculated p-values were based on two-sided tests of significance. A p-value <0.05 was considered as significant. GraphPad Prism 4 was used to make plots and to calculate slopes and corresponding p-values. SPSS (SPSS, Inc., Chicago, IL) was used to perform statistical tests and to calculate p-values.

RESULTS

Esophageal cancer

Included articles

The Medline literature search for the identification of articles relating to the use of EUS in patients with esophageal cancer gave 582 hits on our search terms. In total, 54 articles met the inclusion and exclusion criteria (25-78). Of these, 45 articles were included after assessing the abstracts (26, 31-33, 35-38, 40-71, 73-77). In the references of the included articles and reviews found with our literature search, 9 additional articles (25, 27-30, 34, 39, 72, 78) were detected. The characteristics of the included articles are shown in Table 7.1. In 12 studies (25, 27, 28, 41, 48, 51, 54, 62, 65, 70, 74, 75), the number of patients in whom T stage was determined by EUS was not similar to the number of patients in whom N stage was determined. Therefore, we reported these results separately.

In total, EUS determined T stage in 2050 patients and N stage in 2571 patients. The median number of patients with EUS for T staging was 38 patients (range: 10-167) per article. For N

Table 7.1. Characteristics of articles containing information on the accuracy of EUS for T and/or N stage of esophageal cancer.

Reference	Year	Journal	Journal type*	Impact factor	# patients T stage	Accuracy T stage (%)	# patients N stage	Accuracy N stage (%)
(25)	1989	Gastroenterology	4	5.919	66	89	74	80
(26)	1990	Surgery	2	1.856	33	90.1	-	-
(27)	1990	Hepatogastroenterology	6	0.573	102	89.2	111	81
(28)	1991	J Thorac Cardiovasc Surg	2	2.593	22	59	20	70
(29)	1991	Radiology	3	3.307	50	92	50	88
(30)	1991	Gut	4	2.991	37	89	37	69
(31)	1992	Gastrointest Endosc	4	3.313	44	82	44	70
(32)	1993	Endoscopy	6	1.284	167	86	167	73
(33)	1993	Endoscopy	6	1.284	63	85.7	63	86
(34)	1993	Endoscopy	6	1.284	41	76	-	-
(35)	1994	Gastrointest Endosc	4	3.564	-	-	100	84
(36)	1994	Arch Surg	2	2.402	-	-	34	82
(37)	1994	Am J Gastroenterol	4	1.856	-	-	25	72
(38)	1994	Surgery	2	2.038	20	85	-	-
(39)	1995	Gastrointest Endosc	4	2.295	38	89	38	79
(40)	1996	World J Surg	2	2.077	-	-	74	87
(41)	1996	Surg Endosc	2	1.809	19	84	17	88
(42)	1996	Endoscopy	6	1.794	-	-	37	86.5
(43)	1996	Gastrointest Endosc	4	4.494	71	70	-	-
(44)	1996	Gastrointest Endosc	4	4.494	-	-	18	67
(45)	1996	J Surg Oncol	5	0.634	-	-	74	87.8
(46)	1996	Australas Radiol	3	-	15	87	15	73
(47)	1997	J Thorac Cardiovasc Surg	2	3.068	-	-	21	65
(48)	1997	Surg Laparosc Endosc	2	0.955	40	90	23	87
(49)	1998	Gastrointest Endosc	4	3.531	10	90	10	78
(50)	1998	Aust N Z J Surg	2	0.536	28	61	28	75
(51)	1998	Ann R Coll Surg Engl	2	0.827	50	92	49	86
(52)	1999	Ann Thorac Surg	2	2.022	-	-	166	73
(53)	1999	J Gastrointest Surg	6	2.064	17	94	17	94
(54)	1999	Gastrointest Endosc	4	3.225	145	89	149	73
(55)	1999	Endoscopy	6	1.726	30	56.7	30	63.3
(56)	1999	Scand J Gastroenterol	4	2.336	32	65.6	32	71.9
(57)	1999	Dis Esophagus	4	0.424	10	90	10	90
(58)	2000	J Clin Oncol	1	8.773	42	64	-	-
(59)	2000	Dig Surg	6	0.810	68	79	68	79

Table 7.1. continued

Reference	Year	Journal	Journal type*	Impact factor	# patients T stage	Accuracy T stage (%)	# patients N stage	Accuracy N stage (%)
(60)	2000	Gut	4	5.386	-	-	102	67.6
(61)	2000	J Nucl Med	3	3.617	-	-	45	58
(62)	2000	Scand J Gastroenterol	4	1.842	53	70	54	78
(63)	2000	Ann R Coll Surg Engl	2	0.439	69	80	69	54
(64)	2001	Am J Surg	2	2.131	22	87	22	82
(65)	2001	Gastrointest Endosc	4	2.776	37	84	33	70
(66)	2002	Gut	4	6.323	32	81.3	-	-
(67)	2002	Digestion	4	1.672	76	72	76	76
(68)	2003	Ann Surg Oncol	5	3.574	32	63	32	75
(69)	2003	Br J Surg	2	3.772	29	75.9	29	85.7
(70)	2003	Gastroenterology	4	12.718	29	86	124	81
(71)	2003	Endoscopy	6	3.227	18	83	18	83
(72)	2003	World J Gastroenterol	4	3.318	31	84	31	71
(73)	2004	J Gastrointest Surg	6	2.064	43	63	43	72
(74)	2004	Endoscopy	6	4.034	110	73	96	80
(75)	2004	J Nucl Med	3	5.362	42	67	43	72
(76)	2005	J Surg Oncol	5	1.779	51	52.9	51	68.6
(77)	2005	Dis Esophagus	4	0.936	102	72	102	75
(78)	2005	Mol Imaging Biol	-	-	14	71	-	-

* Journal type: (1) oncological, (2) surgical, (3) radiological, (4) gastroenterological, (5) oncological/surgical, (6) surgical/gastroenterological, (7) radiological/gastroenterological

staging, the median was 43 patients (range: 10-167) per article. Accuracy of EUS for T staging was reported in 43 articles and for N staging in 47 articles. Median accuracy of EUS for T staging was 83% (range: 53-94%). For N staging, median accuracy was 76% (range: 54-94%). In 28 articles, sensitivity and specificity of EUS for N staging were reported (25, 27, 28, 32, 33, 35-37, 40, 42, 44, 47, 49, 51, 52, 54, 57, 60, 61, 65, 68-70, 72, 73, 75-77). This showed that median sensitivity of EUS was 77% (range: 37-100%), whereas median specificity was 74% (range: 50-90%).

Numbers of included patients in articles versus results of EUS

In Figure 7.1, numbers of esophageal cancer patients were plotted against results of EUS. Plotting the numbers of patients against accuracies of EUS for T and N staging suggested that publication bias was not present (Figure 7.1A+B). This was confirmed by a Spearman's rank correlation test for T and N staging of r= -0.087 (p=0.58) and r= -0.037 (p=0.81), respectively. In articles with fewer than 40 included patients, median accuracies for T and N staging

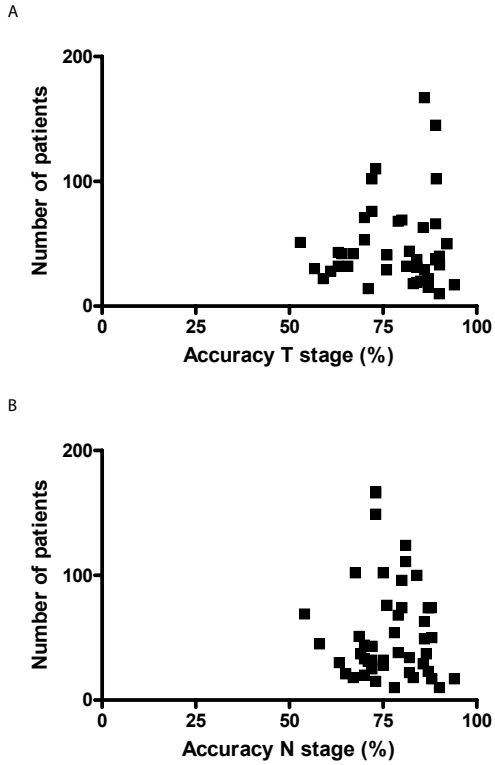

Figure 7.1. Numbers of included esophageal cancer patients in articles *versus* reported results of EUS, with (A) accuracy for T stage, and (B) accuracy for N stage. Publication bias was not found in the reporting of the accuracy of EUS for T stage (Mann-Whitney U-test: p = 0.59, Spearman's rank correlation test: r = -0.087, p = 0.58) (A) and N stage (Mann-Whitney U-test: p = 0.98, Spearman's rank correlation test: r = -0.037, p = 0.81) (B).

were 84% (range: 57-94%) and 75% (range: 63-94%), respectively, which were comparable to articles with more than 40 included patients, in which median accuracies were 79% (range: 53-92%) (p=0.59) and 77% (range: 54-88%) (p=0.98), respectively, indicating that publication bias was not present. The number of 40 patients was chosen, as the number of articles with fewer than 40 included patients was roughly equal to the number of articles with more than 40 included patients. The presence of publication bias was also not found for sensitivity and specificity of EUS for N staging (not shown). In 19 articles, accuracy of EUS for N stage was reported without data on sensitivity and specificity (29-31, 39, 41, 45, 46, 48, 50, 53, 55, 56, 59, 62-64, 67, 71, 74). Sensitivity and specificity could however be calculated from data in 9 of these articles (29-31, 39, 41, 50, 56, 62, 63). Figure 7.2 compares the distribution of the calculated and reported sensitivities and specificities of EUS for N stage. As is shown in Figure 7.2, specificity (Figure 7.2B) was lower in articles that had no reported specificity ("calculated") compared with articles that had reported this (p=0.03).

Results of EUS versus year of publication

In Figure 7.3, results of EUS were plotted against year of publication. The plot of accuracy for T stage against year of publication showed a slope of –1.00 (p=0.01), which indicates a

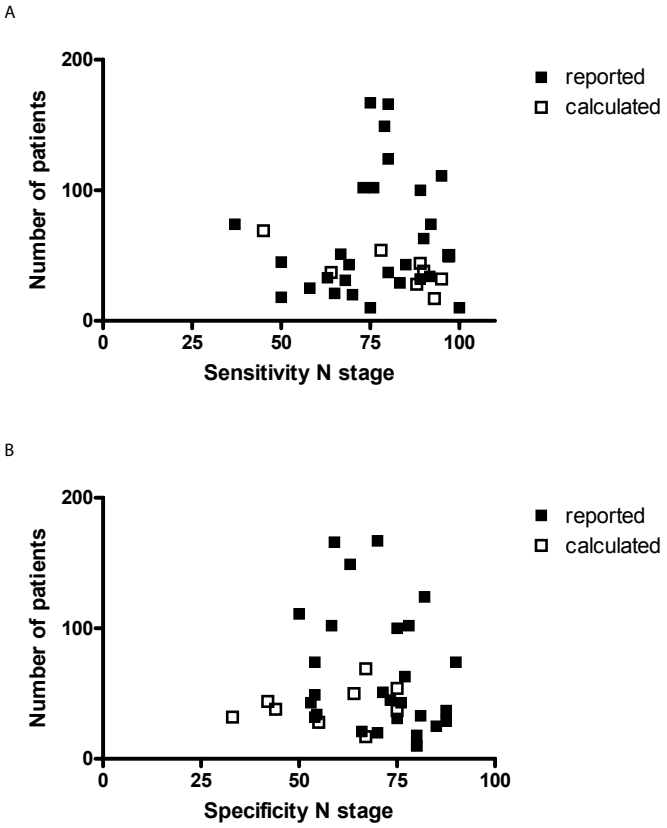

Figure 7.2. Numbers of included esophageal cancer patients in articles *versus* reported and calculated results of EUS, with (A) sensitivity for N stage, and (B) specificity for N stage. Sensitivity was comparable between articles that had no reported sensitivity ("calculated") and articles that had reported this (Mann-Whitney U-test: $p = 0.23$) (A). Specificity was lower in articles that had no reported specificity compared with articles that had reported this (Mann-Whitney U-test: $p = 0.03$) (B).

statistically significant decline in accuracy of EUS for T stage of esophageal cancer over the years (Figure 7.3A). Plots of accuracy (Figure 7.3B) and sensitivity for N stage also showed a slight decline over the years, but these correlations were statistically not significant (p=0.30 and p=0.46, respectively). Plotting specificity for N stage against year of publication showed a slight, but statistically not significant increase over the years (p=0.40).

Results of EUS versus impact factor of journal

No statistically significant correlations were found between impact factor of the journal and accuracy of EUS for T or N stage, respectively (p=0.84 and p=0.58, respectively) (Figure 7.4A+B). In addition, no correlations were present in the plots of sensitivity and specificity for N stage against impact factor (p=0.64 and p=0.57, respectively) (not shown).

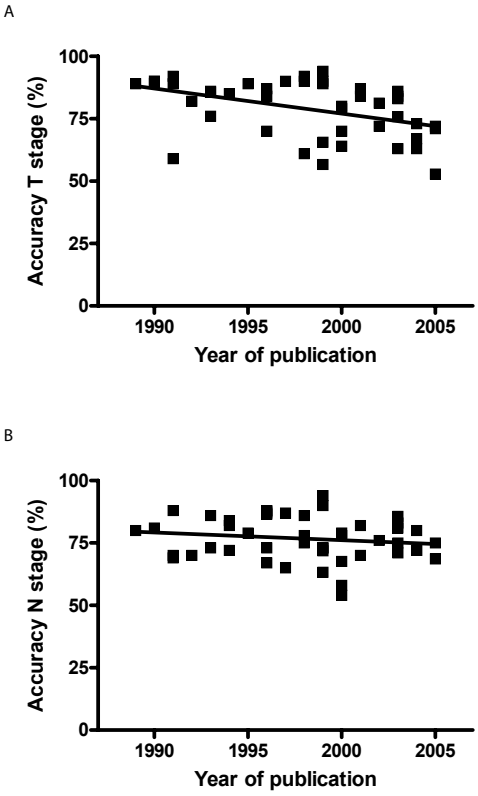

Figure 7.3. Results of EUS in patients with esophageal cancer *versus* year of publication, with (A) accuracy for T stage, and (B) accuracy for N stage. Accuracy of EUS for T stage declined over the years (Slope = -1.00 ± 0.33, p = 0.01) (A). The correlation between accuracy for N stage and year of publication was statistically not significant (Slope = -0.31 ± 0.30, p = 0.30) (B).

Results of EUS versus type of journal

In Figure 7.5, results of EUS were plotted against type of journal. Median accuracy of EUS for T staging was lowest in oncological (64%) (n=1) and oncological/surgical journals (58%) (n=2), whereas median accuracies were higher in surgical (85%) (n=10), radiological (80%) (n=2), gastroenterological (84%) (n=16), and surgical/gastroenterological journals (81%) (n=10) (Figure 7.5A). These differences were statistically not significant (p=0.25).

Median accuracies of EUS for N staging were also comparable for different journal types (p=0.53) (Figure 7.5B). Plots of sensitivity and specificity for N stage against type of journal are not shown, but the statistical analyses revealed statistically no significant correlations (p=0.35 and p=0.57, respectively).

Gastric cancer

Included articles

The Medline search terms used for the identification of articles relating to the use of EUS in patients with gastric cancer gave 533 hits. In total, 43 articles met the inclusion and exclusion

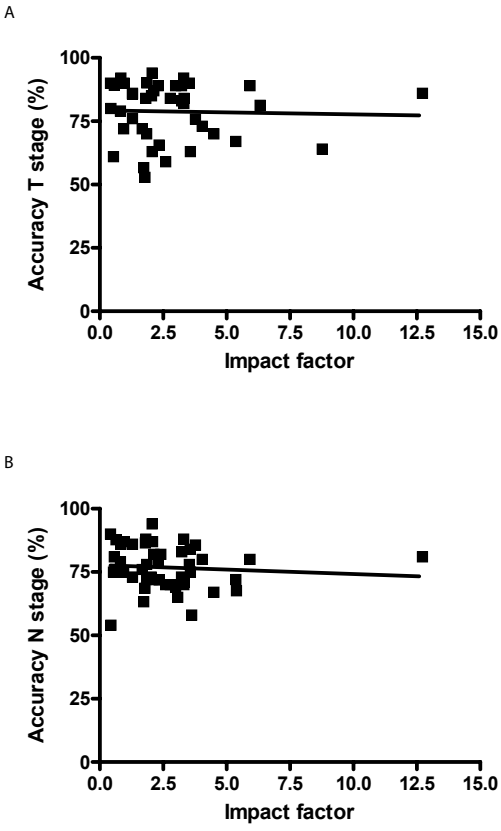

Figure 7.4. Results of EUS in patients with esophageal cancer *versus* impact factor of journal, with (A) accuracy for T stage, and (B) accuracy for N stage. No statistically significant correlations were found between impact factor of the journal and accuracy of EUS for T and N stage, respectively (Slope = -0.16 ± 0.77, p = 0.84 and slope = -0.36 ± 0.65, p = 0.58, respectively).

criteria (10, 31, 33, 38, 41, 49, 66, 67, 79-113). Thirty-eight of these articles were included after assessment of the abstracts (10, 31, 33, 38, 41, 49, 66, 67, 79, 82-95, 97-102, 104-110, 112-114). The other 5 articles (80, 81, 96, 103, 111) were detected after assessment of the references of the included articles and reviews. The characteristics of the included articles relating to the use of EUS in gastric cancer patients are shown in Table 7.2.

In total, T stage was determined in 3560 gastric cancer patients and N stage in 2618 patients. The median number of patients with EUS for T staging was 59 patients (range: 7-1109) per article. For N staging, the median was 58 patients (range: 20-254) per article. In 37 articles, accuracy of EUS for T staging was reported, whereas accuracy of EUS for N staging was reported in 35 articles. Median accuracies of EUS for T and N staging were 80% (range: 55-92%) and 74% (range: 63-90%), respectively. Sensitivity and specificity of EUS for N staging were reported in 23 articles (33, 49, 80, 81, 83-85, 89, 93, 94, 97-99, 101, 102, 104-107, 109, 111-113). Median sensitivity was 68% (range: 0- 97%), whereas median specificity was 86% (range: 47-100%).

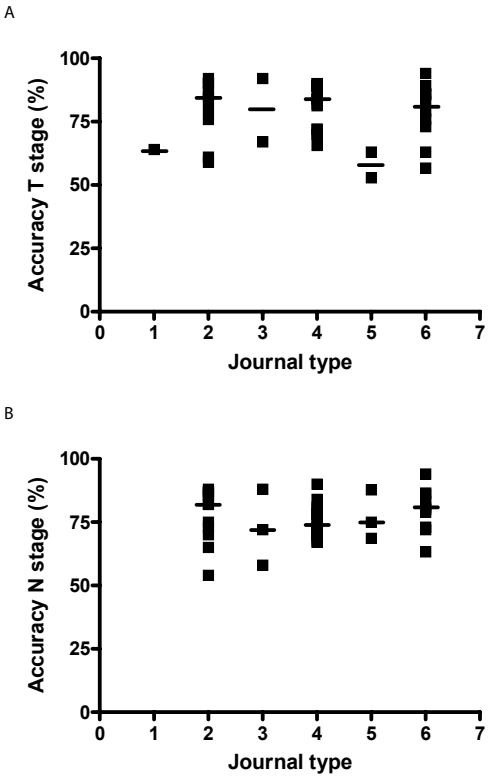

Figure 7.5. Results of EUS in patients with esophageal cancer *versus* type of journal ((1) oncological, (2) surgical, (3) radiological, (4) gastroenterological, (5) oncological/surgical, (6) surgical/gastroenterological, (7) radiological/gastroenterological), with (A) accuracy for T stage, and (B) accuracy for N stage. Median accuracies of EUS for T and N staging were comparable for different journal types (Kruskal-Wallis test: p = 0.25 and p = 0.53, respectively). (– median)

Numbers of included patients in articles versus results of EUS

In Figure 7.6, numbers of gastric cancer patients were plotted against accuracies of EUS for T and N stage. Visual inspection of these plots suggested that publication bias was not present. This was confirmed by a Spearman's rank correlation test for T and N staging of r=0.114 (p=0.50) and r= 0.019 (p=0.92), respectively. Median accuracies for T and N staging were 79% (range: 55-92%) and 78% (range: 63-90%), respectively, in articles with fewer than 60 included patients, which were again comparable to articles with more than 60 included patients, in which median accuracies for T and N staging were 81% (range: 63-89%) (p=0.86) and 73% (range: 64-90%) (p=0.35). Publication bias was also not found for sensitivity and specificity of EUS for N staging (not shown). As sensitivity and specificity of EUS for N stage could only be calculated for 2 of the 12 articles that had only reported accuracy for N stage, it was not possible to compare the distribution of the calculated and reported sensitivities and specificities of EUS for N stage.

Results of EUS versus year of publication

The accuracy of EUS for T stage slightly decreased over the years, whereas accuracy for N stage slightly increased, but these correlations were statistically not significant (p=0.17 and

Table 7.2. Characteristics of articles containing information on the accuracy of EUS for T and/or N stage of gastric cancer.

Reference	Year	Journal	Journal type*	Impact factor	# patients T stage	Accuracy T stage (%)	# patients N stage	Accuracy N stage (%)
(79)	1989	Hepatogastroenterology	6	0.573	68	83.8	72	68.1
(80)	1989	Radiology	3	3.307	76	83	80	66
(81)	1990	Gastrointest Endosc	4	3.313	79	83	84	73
(10)	1991	Radiology	3	3.307	50	92	50	78
(82)	1991	Gut	4	2.991	74	81.1	-	-
(31)	1992	Gastrointest Endosc	4	3.313	41	71	41	75
(83)	1992	Radiology	3	3.307	-	-	83	83.1
(84)	1993	Endoscopy	6	1.284	254	83	254	66
(85)	1993	Surgery	2	1.991	35	91	32	69
(33)	1993	Endoscopy	6	1.284	147	78	148	83.1
(86)	1993	J Clin Oncol	1	7.533	43	86	43	63
(87)	1993	Gut	4	2.858	108	86	108	74
(38)	1994	Surgery	2	2.038	7	71	-	-
(88)	1996	Abdom Imaging	7	0.733	29	79	29	79
(41)	1996	Surg Endosc	2	2.103	60	65	54	73
(89)	1996	Hepatogastroenterology	6	1.104	65	89	65	68
(90)	1996	J Formos Med Assoc	-	0.186	69	71	-	-
(91)	1997	Br J Radiol	3	0.811	-	-	149	81
(92)	1997	Br J Radiol	3	0.811	59	61	59	69
(93)	1997	Endoscopy	6	1.380	-	-	58	90
(49)	1998	Gastrointest Endosc	4	3.531	22	82	20	80
(94)	1998	Gastrointest Endosc	4	3.531	-	-	46	80
(95)	1998	Clin Imaging	3	0.311	119	70	119	65
(96)	1998	Endoscopy	6	1.634	1109	78.4	-	-
(97)	1999	Eur J Surg Oncol	5	1.098	29	55.2	29	72.4
(98)	1999	Cancer	1	3.632	-	-	182	90
(99)	1999	Am J Gastroenterol	4	2.945	-	-	31	65
(100)	1999	J Med Invest	-	-	46	71.7	-	-
(101)	2000	Surg Endosc	2	2.056	116	78	116	77
(102)	2000	Hepatogastroenterology	6	0.905	74	85	74	72
(103)	2000	Tumori	1	0.485	79	76	-	-
(104)	2002	J Clin Gastroenterol	4	1.357	57	88	57	79
(66)	2002	Gut	4	6.323	33	66.7	-	-
(67)	2002	Digestion	4	1.672	41	63	41	83

Table 7.2. continued

Reference	Year	Journal	Journal type*	Impact factor	# patients T stage	Accuracy T stage (%)	# patients N stage	Accuracy N stage (%)
(105)	2003	World J Gastroenterol	4	3.318	35	80	35	68.6
(106)	2004	Endoscopy	6	4.034	88	63	64	67
(107)	2004	Gastrointest Endosc	4	3.483	45	71	45	80
(108)	2004	Gastrointest Endosc	4	3.483	48	87.5	48	79.1
(109)	2004	Radiology	3	5.076	51	86	50	90
(110)	2004	Surg Endosc	2	1.962	49	88	-	-
(111)	2004	ANZ J Surg	2	0.742	112	83	112	64.2
(112)	2006	World J Gastroenterol	4	3.318	41	68.3	41	66
(113)	2006	Surg Endosc	2	1.746	102	80.4	99	77.7

* Journal type: (1) oncological, (2) surgical, (3) radiological, (4) gastroenterological, (5) oncological/surgical, (6) surgical/gastroenterological, (7) radiological/gastroenterological

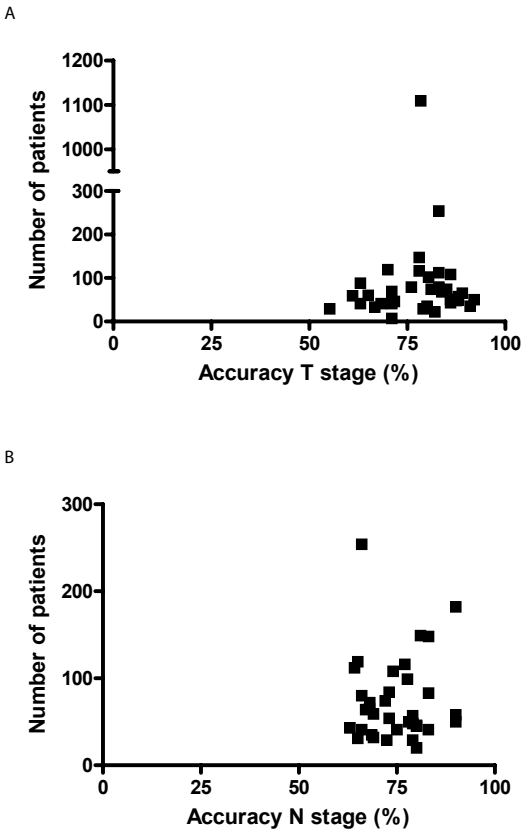

Figure 7.6. Numbers of included gastric cancer patients in articles *versus* results of EUS, with (A) accuracy for T stage, and (B) accuracy for N stage. Publication bias was not found in the reporting of the accuracy of EUS for T stage (Mann-Whitney U-test: $p = 0.86$, Spearman's rank correlation test: $r = 0.114$, $p = 0.50$) (A) and N stage (Mann-Whitney U-test: $p = 0.35$, Spearman's rank correlation test: $r = 0.019$, $p = 0.92$) (B).

0.44, respectively) (Figure 7.7A+B). In addition, no statistically significant correlations were found in the plots of sensitivity and specificity for N stage against year of publication (p=1.00 and p=0.07, respectively) (not shown).

Results of EUS versus impact factor of journal

The plots of accuracy of EUS for T and N stage against impact factor showed a slight increase in accuracy of EUS with an increase in impact factor, but these correlations were statistically not significant (p=0.58 and p=0.74, respectively). Also no correlations were present in the plots of sensitivity and specificity for N stage against impact factor (p=0.85 and p=1.00, respectively) (not shown).

Results of EUS versus type of journal

Accuracies of EUS for T and N staging were comparable for different journal types (p=0.76 and p=0.95, respectively). The statistical analyses revealed also no statistically significant correlations between the sensitivity and specificity for N stage and the journal type (p=0.49 and p=0.47, respectively) (not shown).

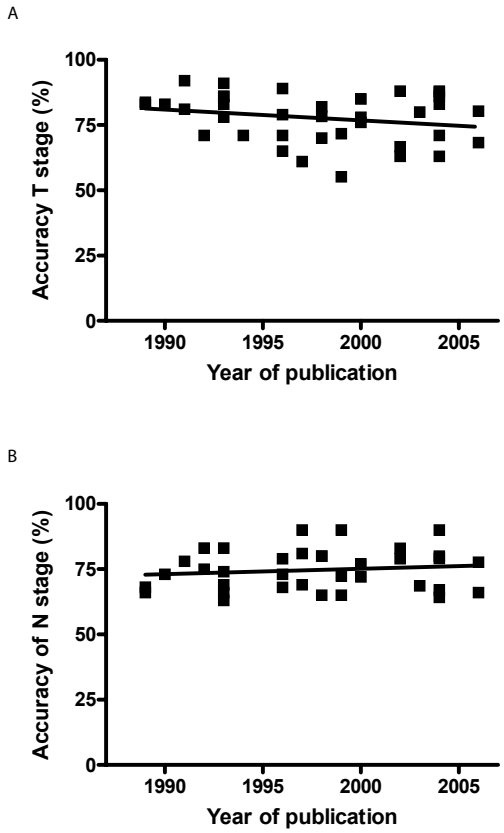

Figure 7.7. Results of EUS in patients with gastric cancer *versus* year of publication, with (A) accuracy for T stage, and (B) accuracy for N stage. No statistically significant correlations were found between year of publication and accuracy of EUS for T and N stage, respectively (Slope = -0.42 ± 0.30, p = 0.17 and slope = 0.21 ± 0.27, p = 0.44, respectively).

Pancreatic cancer

Included articles

For the identification of articles relating to the use of EUS in patients with pancreatic cancer, our search terms gave 770 hits. In total, only 11 articles met the inclusion and exclusion criteria (15, 66, 115-123). Eight of these articles were included after assessment of the abstract (15, 66, 118-123), whereas the other 3 articles were found in the references of the included articles and reviews (115-117). In Table 7.3, the characteristics of the included articles relating to the use of EUS in patients with pancreatic cancer are shown. EUS determined T stage of pancreatic cancer in 324 patients and N stage in 377 patients. The median number of patients with EUS for T staging was 36 patients (range: 16-77) per article, whereas the median for N staging was 37 patients (range: 16-65). Median accuracies of EUS for T (n=8 articles) and N staging (n=10) were 79% (range: 69-93%) and 69% (range: 50-88%), respectively. In 7 articles, sensitivity and specificity of EUS for N staging were reported (15, 115, 117-121). In these articles, median sensitivity was 63% (range: 33-92%), whereas median specificity was also 63% (range: 26-100%).

Table 7.3. Characteristics of articles containing information on the accuracy of EUS for T and/or N stage of pancreatic cancer.

Reference	Year	Journal	Journal type*	Impact factor	# patients T stage	Accuracy T stage (%)	# patients N stage	Accuracy N stage (%)
(115)	1990	Radiology	3	3.307	36	92	35	74
(15)	1993	Endoscopy	6	1.284	-	-	38	74
(116)	1993	Endoscopy	6	1.284	-	-	29	66
(117)	1994	Radiology	3	3.800	16	75	16	50
(118)	1996	Gastrointest Endosc	4	4.494	61	83.6	55	69.1
(119)	1999	Gastrointest Endosc	4	3.225	26	73	26	69
(120)	2000	Scand J Gastroenterol	4	1.842	-	-	41	53
(121)	2000	Gastrointest Endosc	4	2.820	77	69	65	54
(66)	2002	Gut	4	6.323	36	72.2	-	-
(122)	2004	Pancreatology	4	1.445	27	88.9	27	85.2
(123)	2005	Surg Endosc	2	1.746	45	93.1	45	87.5

* Journal type: (1) oncological, (2) surgical, (3) radiological, (4) gastroenterological, (5) oncological/surgical, (6) surgical/gastroenterological, (7) radiological/gastroenterological

Numbers of included patients in articles versus results of EUS

Visual inspection of the plots in which the number of pancreatic cancer patients was plotted against accuracy of EUS for T or N staging, respectively, suggested that the left base of the plot had disappeared (Figure 7.8A+B). Nevertheless, the Spearman's rank correlation test did not show a statistically significant correlation between number of patients and accuracy for

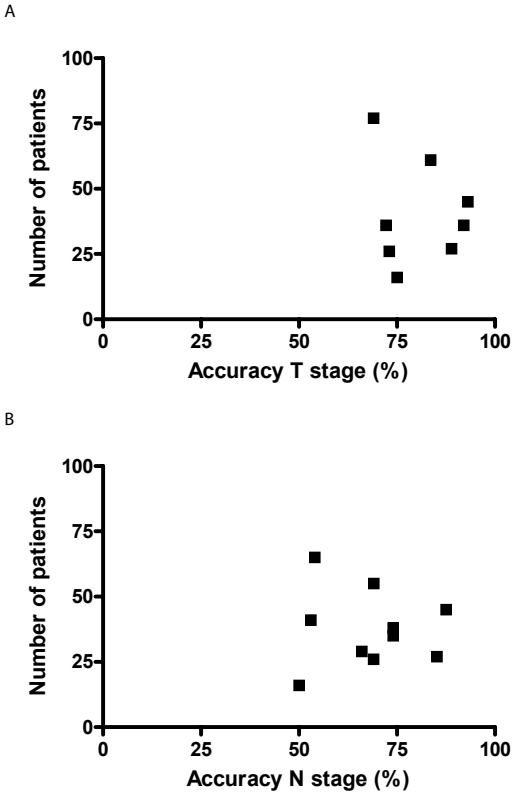

Figure 7.8. Numbers of included pancreatic cancer patients in articles *versus* results of EUS, with (A) accuracy for T stage, and (B) accuracy for N stage. Publication bias was not found in the reporting of the accuracy of EUS for T stage (Mann-Whitney U-test: p = 0.88, Spearman's rank correlation test: r= -0.060, p=0.89) (A) and N stage (Mann-Whitney U-test: p = 0.83, Spearman's rank correlation test: r = 0.146, p = 0.69) (B).

T or N stage, respectively (r= -0.060, p=0.89 and r=0.146, p=0.69, respectively), meaning that there was no indication that publication bias was present. Median accuracies for T and N staging were 75% (range: 72-92%) and 72% (range: 50-85%), respectively, in articles with fewer than 40 included patients, which were again comparable to articles with more than 40 included patients, in which median accuracies for T and N staging were 84% (range: 69-93%) (p=0.88) and 62% (range: 53-88%) (p=0.83). These latter two p-values also showed that there was no indication that publication bias was present. The presence of publication bias was also not found for sensitivity and specificity of EUS for N staging of pancreatic cancer (not shown). In 3 articles (116, 122, 123), accuracy of EUS for N stage was reported without data on sensitivity and specificity. As it was not possible to calculate sensitivity and specificity from these articles, calculated and reported results could not be compared.

Results of EUS versus year of publication

Accuracy of EUS for T stage remained equal over the years (p=0.98) (Figure 7.9A). The plot of accuracy of EUS for N stage showed a slight increase in accuracy over the years, but the correlation between accuracy and year of publication was statistically not significant (p=0.37)

(Figure 7.9B). In addition, no statistically significant correlation was found for sensitivity and specificity of EUS for N stage (p=0.56 and p=0.73, respectively) (not shown).

Results of EUS versus impact factor of journal

No statistically significant correlations were present between impact factor of the journal and accuracy for T stage (p=0.20), accuracy for N stage (p=0.31), sensitivity for N stage (p=0.71) or specificity for N stage (p=0.30), respectively (not shown).

Results of EUS versus type of journal

Accuracies of EUS for T and N staging were comparable for different journal types (p=0.18 and p=0.44, respectively). The statistical analyses revealed also no statistically significant correlation between journal type and sensitivity or specificity for N stage, respectively (p=0.77 and p=0.30, respectively) (not shown).

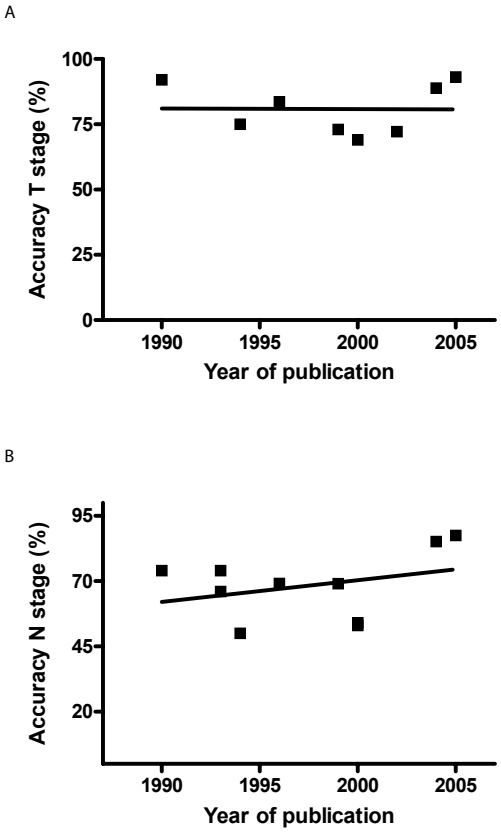

Figure 7.9. Results of EUS in patients with pancreatic cancer *versus* year of publication, with (A) accuracy for T stage, and (B) accuracy for N stage. No statistically significant correlations were found between year of publication and accuracy of EUS for T and N stage, respectively (Slope = -0.02 ± 0.77, p = 0.98 and slope = 0.83 ± 0.87, p = 0.37, respectively).

DISCUSSION

In this study, we showed that the reporting of EUS staging in upper GI cancer is probably not influenced by publication bias, as was indicated by the fact that no overrepresentation of more positive EUS results for esophageal, gastric and pancreatic cancer staging in the literature was found (Figure 7.1, 7.6, 7.8). We observed however that the accuracy of EUS for T stage of esophageal cancer declined over the years (p=0.01), whereas a statistically significant correlation was not found for gastric and pancreatic cancer. For all three types of cancer, no correlation was present between results of EUS and type of journal or impact factor, respectively.

The reporting of better results shortly after the introduction of a new technique has also been reported for the use of CT for staging of esophageal cancer. In the late 1980's and early 1990's, the accuracy of CT for assessing tumor extent (T stage) was reported to vary between 80 and 90% (124-126). The last few years, however, it is well established that CT is not sensitive enough for determining T stage of esophageal cancer. In fact, EUS has now become the standard investigation for the evaluation of T stage and CT is considered to be particularly useful for the detection of distant metastases (127).

The observed decline in accuracy of EUS for T stage of esophageal cancer over the years may be explained by two phenomena. After the introduction of EUS for esophageal cancer, excellent results may have been reported by so-called expert centers. In subsequent years, more widespread use of EUS resulted in reports with lower, but likely more realistic, accuracies for T stage evaluation in normal daily practice, especially since EUS is widely recognized to be very operator-dependent (128). We have however not found evidence for this explanation in other studies on diagnostic modalities. Another possibility is that EUS accuracies vary for different T stages of esophageal cancer. It has been reported that accuracy increases with higher T stage (129, 130). In the initial reports, mostly results of patients with T3 and T4 esophageal cancer were reported. In more recent years, patients with T3 or T4 esophageal cancer more frequently have been subjected to regimens with preoperative radiation and/or chemotherapy followed by esophageal resection (77, 131, 132) and these patients are usually not included in studies in which EUS results are compared with postoperative TNM stage. As a consequence, the presence of relatively more T1 and T2 stage esophageal cancers and fewer T3 and T4 stage cancers could have led to less favorable EUS results in the last few years. For gastric cancer, the accuracy of EUS for T stage also declined over the years, but this correlation was statistically not significant (p=0.17). Also for gastric cancer, the decline in T stage could probably be explained by the same observations discussed above. The accuracy for T stage of pancreatic cancer remained unchanged over the years (p=0.98). The reason for this latter observation is not clear, but it is important to emphasize that only 8 articles with results on accuracy of EUS for T stage were found.

In contrast to T stage, no statistically significant decline in accuracy for N stage of esophageal cancer was found over the years (Figure 7.3B). An explanation for this could be that fine needle aspiration (FNA) was more frequently used in recent years. The use of FNA to obtain tissue for the cytological analysis of the presence of metastatic lymph nodes has been reported in articles published since 1999. It has clearly been shown that results of EUS-FNA are better than results of EUS alone for N staging of esophageal cancers (65, 133, 134). Particularly, EUS-FNA is better able to distinguish between reactive lymph nodes and malignant lymph nodes compared to EUS alone (134). The importance of FNA in determining the accuracy of EUS for esophageal cancer staging is suggested by the slight, but statistically not significant increase in specificity of EUS for N stage over the years. For gastric and pancreatic cancer, the accuracy of EUS for N stage slightly increased over the years, but this was statistically not significant. What are possible explanations for this observation? First, the use of FNA could have led to better results for N stage in later years. Nevertheless, in none of the articles containing data on accuracy for N stage of gastric or pancreatic cancer, it was reported that FNA had been used for suspicious lymph nodes. Second, the development of higher quality EUS probes could have resulted in a better accuracy for N stage of gastric and pancreatic cancer. Nevertheless, this seems not very likely, as the accuracy for T stage had not increased over the years. Third, it could be that over the years, centers that have reported on accuracy of EUS for N stage of gastric and pancreatic cancer may have overcome their learning curve, however we found no evidence for this in the literature.

This study showed no statistically significant correlations between EUS results and numbers of included patients (Figure 7.1, 7.6, 7.8), which indicates that publication bias was not present in the reporting of results of EUS for upper GI cancer. An inverse correlation was however found between numbers of included patients and accuracy of EUS for rectal cancer (21), indicating the presence of publication bias for EUS in this malignancy. We were somewhat surprised by this difference and revised the literature on publication bias for EUS in rectal cancer patients. It appeared that the report on publication bias in rectal cancer had some methodological flaws that might, at least partly, explain the results and conclusions in that study. First, the conclusion of publication bias for T stage in rectal cancer was obviously based on the presence of two outline points in the graph, representing a study of 422 patients with an accuracy of EUS for T stage of 63% (135) and a study of 545 patients with an accuracy of 69% (136). In the 38 other studies, accuracies for T stage varied between 72% and 100% with a maximum of 356 patients per study. For N stage, the 2 outline points represented a study of 356 patients with an accuracy of 66% (137) and a study of 545 patients with an accuracy of 64% (136), with the other 25 studies showing accuracies for N stage between 54% and 86% with a maximum of 164 patients per study. Second, of the 3 studies with more than 300 patients included (135-137), two were multicenter studies with patients obtained from 75 and 2 centers, respectively (135, 137). Therefore, the number of patients per center was probably much lower and these centers apart would not have represented the studies with the largest

numbers of patients. Third, although the number of patients in articles with EUS for rectal cancer staging was suggested to be high, N stage was only histologically assessed in 238/545 (44%) patients and 263/356 (74%) patients, respectively (136, 137). We suppose that these are the real numbers of patients that should have been used in the analyses for N stage. As a consequence of this, the plot of the accuracy for N stage would have been more flat. Finally, in one of these studies (136), not only patients with rectal cancer were included (n=397), but also patients with villous adenomas (n=148). This last group clearly represents patients with a pre-malignant stage or at most early cancer, but certainly not advanced rectal cancer.

There are some limitations to our study. First, we used search terms to identify articles reporting on accuracy of EUS for T and N stage. All abstracts obtained by this literature search were assessed. We did however not evaluate the articles of which the abstracts revealed that it was highly unlikely that they contained information on accuracy of EUS. Therefore, there is a small risk that articles, which met the criteria used for this study, were excluded from evaluation. Furthermore, it is possible that articles with results on accuracy of EUS did not match with the search terms. In order to correct for this, all references of included articles and reviews were examined to find additional articles that met the inclusion criteria.

Second, articles included in this study were published between 1989 and 2006. Impact factors of journals were mostly obtained from the ISI Web of Knowledge edition of the year of publication of these articles. Nevertheless, it was not for all articles shown in Table 7.1-7.3 possible to obtain the impact factor in the corresponding edition of ISI Web of Knowledge. For these articles, the editions closest to that particular year were examined.

Third, the majority of articles with results of EUS in patients with esophageal cancer included patients with squamous cell carcinoma and adenocarcinoma. Nevertheless, in six studies, only patients with esophageal squamous cell carcinoma or adenocarcinoma were included (42, 56, 60, 61, 68, 73). As there is no evidence that histology of tumor could have influenced the results of EUS, all articles that met the inclusion criteria were evaluated, irrespective of tumor histology.

Fourth, most articles with results of EUS in esophageal cancer patients reported accuracies of EUS for T and/or N stage. In only seven articles (31, 39, 54, 57, 65, 133, 138), however, information was given on accuracies of EUS for celiac axis lymph nodes (M stage). These accuracies were not included in our analyses, as these results would probably not have changed the message of this study. We also found articles that reported results on resectability (119, 139, 140) and vascular involvement of pancreatic cancer (15, 116, 123, 141-145). Again, these results were not included in our analyses, as this was beyond the scope of this article and, in addition, the number of articles was small.

Fifth, in ten studies it was reported that dilation was used in patients with a stricture due to esophageal cancer (32, 39, 54, 57, 59, 65, 70, 71, 77, 78). For gastric and pancreatic cancer, none of the articles reported on the use of dilation in patients with a stricture. In several articles reporting on the results of EUS for upper GI cancer, patients who had a stenosing cancer

were excluded, patients were included without performing dilation or a miniprobe was used. Nevertheless, in some articles, no mention was made whether patients with a stricture due to cancer were included. It is known that in patients in whom a stricture was present due to esophageal cancer, EUS results are inferior compared with patients in whom the complete esophagus could be examined (134). Nevertheless, all articles that met the inclusion criteria, irrespective whether dilation was performed or not, were included, as in a subanalysis no evidence was found for publication bias in these different subgroups (results not shown).

Sixth, in some studies on gastric cancer, the N stage was divided into N0 (no malignant lymph nodes) and N1 stage (malignant lymph nodes), whereas in others it was divided into N0, N1 and N2, with in the latter also the number of lymph nodes involved. Although we supposed that accuracies would be higher for the division N0-1 compared with N0-2, we found these accuracies to be equal for the two classifications (results not shown), suggesting that the use of two different classifications did not influence the results of this study.

Seventh, we found only 8 articles with results of EUS for T stage of pancreatic cancer and 10 articles with results for N stage. Plotting accuracy for T and N stage against number of pancreatic cancer patients suggested that the left base of the plot had disappeared. Nevertheless, no statistically significant correlations were found. A reason for this discrepancy could be that the number of included articles was too small to demonstrate the presence of publication bias. The number of included articles would have been higher if other types of pancreatic cancer would have been included in this study. As several features of these tumors are different from pancreatic adenocarcinoma, we decided not to include these types of pancreatic cancer in the analyses.

In conclusion, we found no evidence that the reporting on EUS staging in esophageal, gastric and pancreatic cancer patients is influenced by publication bias, which means that the results of EUS staging for upper GI cancer were not overestimated in the literature.

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CHAPTER 8

Strategies to detect distant metastases in patients with esophageal or gastric cardia cancer: a diagnostic decision analysis

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Submitted

ABSTRACT

Background: Computed tomography (CT) is presently the standard procedure to detect metastases in patients with esophageal or gastric cardia cancer. We aimed to determine the additional diagnostic value of alternative staging investigations.

Methods: We included 569 esophageal or gastric cardia cancer patients who had undergone CT neck/thorax/abdomen, and ultrasound (US) abdomen, US neck, and/or chest X-ray for staging esophageal or gastric cardia cancer. We compared three strategies for each organ: CT alone, CT *plus* an investigation if CT was negative for metastases (1 positive scenario), and CT *plus* an investigation if CT was positive, requiring that both were positive for a positive result (2 positive scenario). Sensitivity and specificity were first determined at an organ level, and then at a patient level, considering that the detection of distant metastases is a contraindication to surgery. Costs, life expectancy and quality adjusted life years (QALYs) were based on data from the literature.

Results: CT showed sensitivities for detecting metastases in celiac lymph nodes, liver and lung of 69%, 73%, and 90%, respectively, which was higher than the sensitivities of US abdomen (44% for celiac lymph nodes and 65% for liver metastases), EUS (38% for celiac lymph nodes) and chest X-ray (68% for lung metastases). US neck showed a far higher sensitivity for supraclavicular lymph nodes than CT (85% *versus* 28%). At a patient level, sensitivity for detecting distant metastases was 66% and specificity was 95% if only CT was performed. A higher sensitivity (86%) was achieved when US neck was added to CT (1 positive scenario), at the same specificity (95%). This strategy resulted in lower costs compared to CT only, at an almost similar (quality adjusted) life expectancy. Slightly higher specificities (97-99%) were achieved by requiring confirmation of liver and/or lung metastases found on CT by US abdomen or chest X-ray, respectively (2 positive scenario). In addition, these strategies only had slightly higher QALYs, but substantial higher costs.

Conclusion: The combination of CT and US neck was most cost-effective in staging patients with esophageal or gastric cardia cancer. Combining this with US abdomen, EUS and chest X-ray for metastases detection had only limited additional value to guide treatment choice in these patients.

INTRODUCTION

Patients with esophageal or gastric cardia cancer have a dismal prognosis, due to the presence of locally advanced cancer, lymph node metastases or distant metastases at the time of presentation in more than 50% of patients (1). Investigations that can be used for staging esophageal or gastric cardia cancer include endoscopic ultrasonography (EUS) (2), computed tomography (CT) of neck, thorax and abdomen (3), ultrasound (US) of the neck (4) and abdomen (5), chest X-ray (6) and bronchoscopy (7). The TNM stage of patients with esophageal or gastric cardia cancer is established by a combination of these investigations. The TNM stage system is subdivided into T stage describing the extent of local invasion of the tumor through the esophageal wall, N stage indicating whether metastases are present in regional lymph nodes and M stage describing the presence of distant metastases (8).

For most organs in which metastases from esophageal or gastric cardia cancer can be found, usually more than one investigation is used to detect these metastases, however, in almost all patients CT neck/thorax/abdomen is a standard investigation. It is however not clear whether US abdomen, EUS, US neck and chest X-ray are also necessary for assessing the presence of metastases in these patients.

In this study, we aimed to determine the diagnostic value of US abdomen, EUS, US neck and chest X-ray, in addition to CT, in patients with esophageal or gastric cardia cancer. We particularly evaluated these diagnostic procedures at an organ level and at a patient level for the detection of metastases. The assumption was that the finding of distant metastases in patients with esophageal or gastric cardia cancer makes them unsuitable candidates for a curative surgical treatment.

PATIENTS AND METHODS

Patients

We used a prospectively collected database with data on 1088 patients with esophageal or gastric cardia cancer diagnosed and treated between January 1994 and October 2003 at the Erasmus MC – University Medical Center Rotterdam, The Netherlands. Data that were collected included general patient characteristics, and results of staging investigations, treatment modalities and postoperative TNM stage of these patients. Additional information, which was not present in the database but necessary for this study, was obtained from the electronic hospital information system.

We assessed which preoperative investigations had been performed in the 1088 patients. In 906/1088 (83%) patients, esophageal or gastric cardia cancer was first diagnosed in a regional center and, subsequently, these patients were referred to our referral center. Patients often underwent preoperative staging investigations in these regional centers, however the results

of these investigations were not included in our analyses. We identified 569 esophageal or gastric cardia cancer patients who had undergone CT neck/thorax/abdomen and at least one other investigation, i.e., US abdomen, US neck and/or chest X-ray, in our center (Figure 8.1).

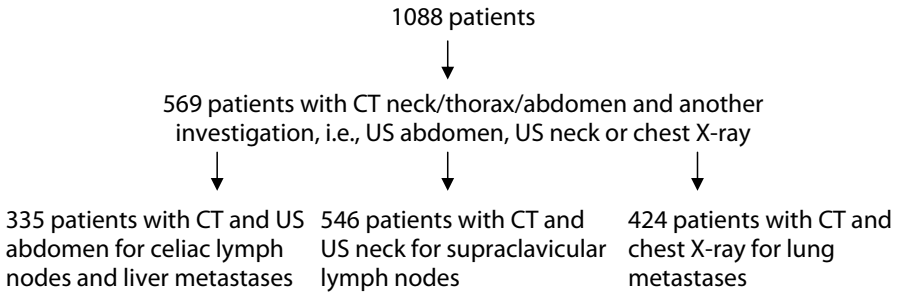

Figure 8.1. Flow diagram of inclusion of patients.

Staging investigations

The organs to which esophageal or gastric cardia cancers most frequently metastasize, i.e., liver, celiac lymph nodes, supraclavicular lymph nodes and lung, were first evaluated separately ('organ level'). Specifically, we assessed whether both CT neck/thorax/abdomen and US abdomen, if indicated with fine-needle aspiration (FNA), should be performed to determine whether liver metastases are present using the data of 335 patients who had undergone both these investigations. For the detection of celiac lymph nodes, we analyzed 143 patients who had undergone CT, US abdomen, and EUS. The presence of malignant supraclavicular lymph nodes was studied in 546 patients, who had undergone CT neck/thorax/abdomen and US neck, if indicated with FNA. Finally, in order to determine whether both CT and chest X-ray should be performed for detecting lung metastases, 424 patients who had undergone both these investigations were analyzed (Figure 8.1). The result of the investigations, i.e., the presence or absence of metastases, was registered and compared with the gold standard, which was the postoperative pathological TNM stage, the result of FNA, or a radiological finding in the relevant organ with ≥6 months of follow-up.

Celiac lymph node metastases were considered as regional (N1) when the primary tumor was located in the gastric cardia, as stage M1a when the tumor was located in the distal part of the esophagus and as stage M1b when the tumor was located in the mid or proximal part of the esophagus (9). Since esophageal cancers with M1a celiac lymph node metastases are in many centers no longer considered to be unresectable (10), only M1b celiac lymph nodes were considered to be distant metastases in the part of the study concerning patient level. Malignant supraclavicular lymph nodes were considered as N1 if the tumor was located in the proximal part of the esophagus and as M1 if the tumor was located in the mid or distal part of the esophagus or in the gastric cardia (9).

The treatment modality of patients with esophageal or gastric cardia cancer largely depends on the presence or absence of metastatic disease in any organ. Therefore, combinations of staging procedures were considered ('patient level'). Staging information was complete in 264 patients, meaning that these patients had undergone all investigations, i.e., CT neck/thorax/abdomen, US abdomen, US neck and chest X-ray. In 305 patients, any one or more of these investigations were not performed. At the organ level, the results of EUS for the detection of celiac lymph nodes were inferior compared to CT and US abdomen (see Results). For that reason, EUS was considered to be irrelevant for the detection of distant metastases, and was not included in the part of the analyses concerning patient level.

Statistical analyses

Sensitivities and specificities of CT neck/thorax/abdomen, US abdomen, EUS, US neck, and chest X-ray were calculated for the detection of metastases in the various organs. The McNemar test was performed to determine whether the differences between sensitivities of pairs of tests and specificities of pairs of tests were statistically significant. Furthermore, the numbers of false positive and false negative results were assessed for CT neck/thorax/abdomen, US abdomen, EUS, US neck and chest X-ray alone, and for the various combined results of CT and US abdomen, EUS, US neck and chest X-ray. The combined results were calculated twice. First, the result was considered positive for metastases if at least one of two investigations for a particular organ was positive and negative if both investigations were negative (1 positive scenario). This is a strategy that uses the additional diagnostic information of the second investigation as an extra check for a negative CT. If the CT is positive, the result of another investigation is irrelevant in this strategy, because the final result will remain positive irrespective of the result of the other investigation. Second, the result was considered positive if both CT and another investigation were positive and negative if at least one of the investigations was negative (2 positive scenario). This is a strategy that uses additional diagnostic investigations to confirm a positive CT finding. If the CT is negative, the performance of another investigation is unnecessary using this strategy, because the final result will remain negative irrespective of the result of the other investigation. For celiac lymph nodes, the number of false positive and false negative results was also calculated for the combination of CT neck/thorax/abdomen, US abdomen and EUS. We calculated accuracy rates and 95% confidence intervals using exact methods.

For the part of the analyses related to treatment modality at the patient level, we assessed whether distant metastases (M1b) were present in liver, lung, celiac lymph nodes and supraclavicular lymph nodes and, consequently, whether an esophageal resection should have been performed or not on the basis of the staging investigations. The assumption was that an esophageal resection should be withdrawn if distant metastases were present in an organ. Similar to the analyses at the organ level, three staging strategies were possible for each

organ: CT only, another investigation if CT was negative (1 positive scenario), or another confirmatory investigation if CT was positive (2 positive scenario).

We plotted sensitivity against 1-specificity in a receiver operating characteristic (ROC) curve as a visual index of the accuracy of combinations of staging investigations. Sensitivity is the proportion of patients who are correctly identified as having distant metastases (true positive results), and 1-specificity is the proportion of patients in whom the gold standard is negative for distant metastases, but who are incorrectly identified as positive by the staging investigations (false positive results). ROC curves were made for the detection of distant metastases (M1b) with CT neck/thorax/abdomen and the combination of CT and another investigation (both the 2 positive and 1 positive scenario) in an organ, whereas in the other organs we only included the CT result. For example, to assess whether both CT neck/thorax/abdomen and US abdomen should be performed to determine whether liver metastases were present, we compared three different strategies: 1) combination of CT and US abdomen in the 2 positive scenario for the liver and CT for the other organs, 2) combination of CT and US abdomen in the 1 positive scenario for the liver and CT for the other organs, 3) CT for all organs.

Sensitivities and specificities for the detection of distant metastases at the patient level were calculated for each combination of investigations. The combinations of investigations consisted of the various combinations of CT, 1 positive scenario and 2 positive scenario for distant metastases in the liver, celiac lymph nodes, supraclavicular lymph nodes and lung. In total, 81 different combinations were possible (3 strategies for 4 organs).

Of the 569 patients, 264 patients had undergone all investigations. An exploratory analysis was performed in which missing values were imputed for the 305 patients with one or more missing values by the expectation maximization (EM) method as implemented in SPSS software (version 12, SPSS Inc, Chicago, Ill). This was repeated 5 times to incorporate uncertainties in the imputation process. Sensitivities and specificities for the detection of distant metastases were calculated for each combination of investigations using the 5 completed data sets. All p-values were based on two-sided tests of significance. A p-value <0.05 was considered as statistically significant.

Cost-effectiveness analysis

Costs, life expectancies and quality-adjusted life years (QALYs) were compared between the different combinations of investigations. For the assumption that all patients had regional disease (surgery in all patients), costs, life expectancy and QALYs were also determined. For costs, the extra costs of a resection over palliative treatment were estimated to be approximately 50,000 dollar. The costs for the performance of extra investigations were negligible compared to the extra costs of resection, i.e., US: $100, chest X-ray: $60 and CT: $750, and these costs were therefore not taken into account. Life expectancy and QALYs were taken from a previous study (11). Life expectancy was assumed to be 2.41 and 1.00 year for local/regional disease with and without resection, respectively, and 0.42 and 0.37 year for distant

disease with and without resection, respectively. QALYs were estimated to be 1.45 and 0.70 for local/regional disease, and 0.17 and 0.19 for distant disease, with and without resection, respectively. A cost-effectiveness plane was constructed in which the differences in costs between strategies (Δ costs) were plotted against the differences in QALY (Δ QALY). Costs were expressed per 1,000 $ (k$) for easier interpretation.

RESULTS

In Table 8.1, patient and tumor characteristics are shown for the 569 patients who had undergone both CT neck/thorax/abdomen and at least one other investigation, i.e., US abdomen, US neck and/or chest X-ray, and for the 264 patients who had undergone all investigations. Chi-square testing revealed that the differences between the two groups were statistically not significant.

Table 8.1. Patient and tumor characteristics of 569 patients who had undergone CT neck/thorax/abdomen and at least one other investigation, i.e., US abdomen, US neck and/or chest X-ray, and 264 patients who had undergone all these investigations for esophageal or gastric cardia cancer staging.

Variable	N=569	N=264
Mean age ± standard deviation (years)	61.9 ± 10.2	61.2 ± 10.4
Sex (%)		
Male	436 (77)	207 (78)
Female	133 (23)	57 (22)
Histology of tumor at biopsy (%)		
Squamous cell carcinoma	227 (40)	116 (44)
Adenocarcinoma	304 (53)	132 (50)
Other	38 (7)	16 (6)
Location of tumor (%)		
Cervical	5 (1)	4 (2)
Upper 1/3 thoracic	30 (5)	11 (4)
Central 1/3 thoracic	101 (18)	53 (20)
Lower 1/3 thoracic	219 (38)	96 (36)
Gastroesophageal junction	214 (38)	100 (38)
Distant metastases according to gold standard (%)		
M0	473 (83)	214 (81)
M1	96 (17)	50 (19)

p = not significant

Organ level

In Table 8.2, the gold standard diagnoses are shown per organ. Positive gold standard diagnoses were confirmed with FNA or resection in the majority of cases (92/135 (68%)), whereas in 43 of 135 (32%) cases the presence of metastases was not histologically confirmed.

Sensitivity for liver metastases was higher for CT neck/thorax/abdomen than for US abdomen, but this was statistically not significant (73% *versus* 65%) (p=0.63). Specificity was lower for CT than for US abdomen (97% *versus* 99%) (p=0.004) (Table 8.3). Sensitivity for celiac lymph node metastases was higher for CT (69%) than for US abdomen (44%) and EUS (38%) (CT *versus* US abdomen: p=0.08 and CT *versus* EUS: p=0.03), but specificity was highest for US abdomen (100%) compared to CT (92%) (p=0.01) and EUS (94%) (p=0.03). Sensitivity for supraclavicular lymph node metastases was much higher for US neck than for CT neck/thorax/abdomen (85% *versus* 28%) (p<0.001), whereas specificity for both was 99% (p=1.00). Sensitivity for lung metastases was slightly higher for CT than for chest X-ray, but this was statistically not significant (90% *versus* 68%) (p=0.29). Specificity for both was 99% (p=0.13).

Accuracies for combinations of staging investigations all exceeded 80% (Table 8.4). If only CT was performed for liver metastases, the number of false positive results was 10 and the number of false negative results 7. The addition of US abdomen (1 positive scenario) resulted in a decline in the number of false negative results to 6, with a similar number of false positive results. This combination was therefore considered to be better than CT alone. For celiac lymph nodes, the combination of CT *plus* US abdomen (1 positive scenario) resulted in fewer false negative results in comparison with the performance of CT alone (6 *versus* 10), with both having 9 false positive results. If only CT was performed for supraclavicular lymph nodes, the number of false negative results was 42. With US neck or the combination of CT and US neck (1 positive scenario) less false negative results were obtained (9 and 8, respectively). The total number of false positive and false negative results was highly comparable for the (combinations of) investigations for lung metastases. Overall, the number of false positive results was high for the combination of CT neck/thorax/abdomen and another investigation in the 1 positive scenario. In contrast, the number of false negative results was high for the combination of CT and another investigation in the 2 positive scenario (Table 8.4).

Patient level

In the ROC curve, sensitivity and specificity of CT and the combinations of CT and US abdomen (2 positive and 1 positive scenarios) were roughly equal for liver metastases, which was in line with the results at the organ level. Adding US abdomen (2 positive and 1 positive scenario) to CT neck/thorax/abdomen did not result in a difference in sensitivity and specificity for celiac lymph nodes, when for the other organs only the result of CT was included. For supraclavicular lymph nodes, the combination of CT and US neck (1 positive scenario) resulted in a better overall sensitivity compared with CT and the combination of CT and US neck (2 positive scenario), whereas specificities were comparable. For lung metastases, sensi-

Table 8.2. Gold standards in patients with esophageal or gastric cardia cancer.

Organ	Gold standard		
	FNA	Postoperative stage	Radiological finding with ≥ 6 months of follow-up
Liver (n=335)			
Positive (n=26)	15	0	11
Negative (n=309)	22	8	279
Celiac lymph nodes (n=143)			
Positive (n=32)	6	15	11
Negative (n=111)	3	74	34
Supraclavicular lymph nodes (n=546)			
Positive (n=58)	44	6	8
Negative (n=488)	68	35	385
Lung (n=424)			
Positive (n=19)	5	1	13
Negative (n=405)	7	0	398

FNA, fine needle aspiration

Table 8.3. Sensitivities and specificities of preoperative investigations for the detection of metastases in patients with esophageal or gastric cardia cancer.

	Sensitivity	Specificity
Liver metastases (n=335)		
CT	19/26 (73%)	299/309 (97%)
US abdomen	17/26 (65%)	308/309 (99%)
Celiac lymph nodes (n=143)		
CT	22/32 (69%)	102/111 (92%)
US abdomen	14/32 (44%)	111/111 (100%)
EUS	12/32 (38%)	104/111 (94%)
Supraclavicular lymph nodes (n=546)		
CT	16/58 (28%)	484/488 (99%)
US neck	49/58 (85%)	484/488 (99%)
Lung metastases (n=424)		
CT	17/19 (90%)	399/405 (99%)
Chest X-ray	13/19 (68%)	404/405 (99%)

CT, computed tomography; US, ultrasound; EUS, endoscopic ultrasonography

Table 8.4. The number of false positive and false negative results and the accuracy rates *plus* 95% confidence intervals for CT neck/thorax/abdomen, US abdomen, EUS, US neck and chest X-ray only and the combinations of CT neck/thorax/abdomen and the other investigations in patients with esophageal or gastric cardia cancer.

	False positive: false negative	Accuracy rate	95% confidence interval
Liver (n=335, 26 metastases)			
CT	10:7	0.95	0.92-0.97
US abdomen	1:9	0.97	0.95-0.99
CT+US abdomen: 1 positive	10:6	0.95	0.92-0.97
CT+US abdomen: 2 positive	1:10	0.97	0.94-0.98
Celiac lymph nodes (n=143, 32 metastases)			
CT	9:10	0.87	0.80-0.92
US abdomen	0:18	0.87	0.81-0.92
EUS	7:20	0.81	0.74-0.87
CT+EUS: 1 positive	11:6	0.88	0.82-0.93
CT+EUS: 2 positive	5:24	0.80	0.72-0.86
CT+US abdomen: 1 positive	9:6	0.90	0.83-0.94
CT+US abdomen: 2 positive	0:22	0.85	0.78-0.90
CT+US abdomen+EUS: ≥ 1 positive	11:5	0.89	0.82-0.93
CT+US abdomen+EUS: ≥ 2 positive	5:13	0.87	0.81-0.92
CT+US abdomen+EUS: 3 positive	0:30	0.79	0.71-0.85
Supraclavicular lymph nodes (n=546, 58 metastases)			
CT	4:42	0.92	0.89-0.94
US neck	4:9	0.98	0.96-0.99
CT+US neck: 1 positive	7:8	0.97	0.96-0.98
CT+US neck: 2 positive	1:43	0.92	0.89-0.94
Lung (n=424, 19 metastases)			
CT	6:2	0.98	0.96-0.99
Chest X-ray	1:6	0.98	0.97-0.99
CT+chest X-ray: 1 positive	7:0	0.98	0.97-0.99
CT+chest X-ray: 2 positive	0:8	0.98	0.96-0.99

CT, computed tomography; US, ultrasound; EUS, endoscopic ultrasonography

tivities and specificities were roughly equal across the strategies.

Sensitivity for detecting distant metastases was 66% and specificity was 95% if only CT was performed for all organs (Table 8.5). The highest sensitivity, which could be obtained with 12 different combinations of staging investigations, was 86%. For 6 of these 12 combinations the specificity was 94.4%, whereas for 6 other combinations the specificity was slightly higher (94.9%). The combination of investigations to obtain a sensitivity of 86% and

Table 8.5. Sensitivities and specificities for the detection of distant metastases with combinations of investigations in patients with esophageal or gastric cardia cancer who had undergone all staging investigations (n=264) and the average sensitivity and specificity of the 5 completed data sets (n=569).

Supraclavicular lymph nodes	Celiac lymph nodes	Liver	Lung	n=264		n=569	
				Sensitivity (%)	Specificity (%)	Sensitivity (%)	Specificity (%)
CT	CT	CT	CT	66 (33/50)	95 (204/214)	68 (65/96)	96 (454/473)[1]
1 positive	CT	CT	CT	86 (43/50)	95 (203/214)	84 (81/96)	96 (453/473)[2]
1 positive	CT	2 positive	CT	82 (41/50)	97 (208/214)	81 (78/96)	98 (463/473)[3]
1 positive	CT	2 positive	2 positive	78 (39/50)	99 (211/214)	74 (71/96)	99 (469/473)[4]

CT, computed tomography

[1] 569/569 values (100%) were present before imputation of missing values

[2] 1115/1138 values (98%) were present before imputation of missing values

[3] 1450/1707 values (85%) were present before imputation of missing values

[4] 1874/2276 values (82%) were present before imputation of missing values

a specificity of 94.9% with the lowest number of investigations was the combination of CT neck and US neck for the detection of supraclavicular lymph nodes (1 positive scenario), and CT thorax/abdomen only for the detection of metastases in celiac lymph nodes, liver and lung. A slightly higher specificity of 97% was achieved by the addition of US abdomen for liver metastases, but only in the 2 positive scenario. When chest X-ray (2 positive scenario) for the detection of lung metastases was added, the specificity further increased to 99%. Sensitivity however declined with increasing specificity, meaning that more patients would have undergone a curative treatment option in the presence of distant metastases (more false negative results).

The average results obtained from the data with imputation of missing values (n=569) were roughly equal compared to the results obtained from the complete data of patients who had undergone all staging investigations (n=264 patients) (Table 8.5).

Costs were lowest for the combination of CT neck and US neck for supraclavicular lymph nodes (1 positive scenario) and CT thorax/abdomen only for the other organs (average costs per patient: 39,8 k$) (Table 8.6). A decline in sensitivity, which occurred with the addition of US abdomen for liver metastases and chest X-ray for lung metastases, resulted in more false negative results and, consequently, more patients with surgery in the presence of distant metastases. This resulted in substantially higher costs related to an operation, and slightly higher life expectancy and QALYs (Table 8.6). The cost-effectiveness ratios of these alternative strategies were unfavorable, at 95 k$ and 113 k$ per QALY gained (Table 8.6, Figure 8.2).

Table 8.6. Costs, life expectancies and quality adjusted life years (QALYs) for patients with esophageal or gastric cardia cancer who had undergone all staging investigations (n=264).

Supraclavicular lymph nodes	Celiac lymph nodes	Liver	Lung	Number of patients with operation (%)	Costs per patient (k$)	Life expectancy per patient (year)	QALY per patient	Δ Costs / Δ QALY (k$ per QALY)
CT	CT	CT	CT	221/264 (84)	41,9	1.973	1.178	Dominated
1 positive	CT	CT	CT	210/264 (80)	39,8	1.966	1.176	Reference
1 positive	CT	2 positive	CT	217/264 (82)	41,1	1.993	1.190	94,7
1 positive	CT	2 positive	2 positive	222/264 (84)	42,0	2.010	1.198	113,3
Surgery in all patients				264/264 (100)	50,0	2.033	1.204	365,3

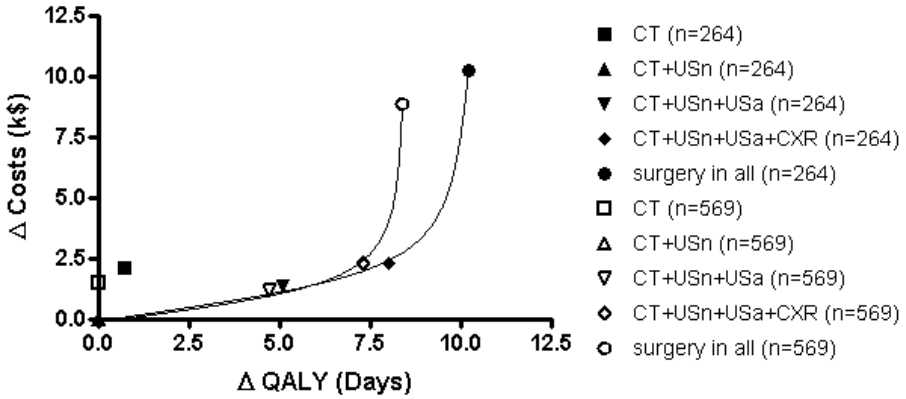

Figure 8.2. Marginal cost-effectiveness plane with the combination of CT neck and US neck for the detection of supraclavicular lymph nodes (1 positive scenario), and CT thorax/abdomen only for the detection of metastases in celiac lymph nodes, liver and lung as reference strategy calculated in patients with esophageal or gastric cardia cancer who had undergone all staging investigations (n=264) and using the completed dataset (n=569).
QALY, quality adjusted life year; CT, computed tomography; USn, ultrasound neck; USa, ultrasound abdomen; CXR, chest X-ray

DISCUSSION

In this study, we assessed which traditional staging investigations should be performed in patients with esophageal or gastric cardia cancer to determine whether distant metastases were present and, consequently, whether a curative treatment, i.e., an esophageal resection, could be performed. Our findings demonstrate that the highest sensitivity for the detection of distant metastases was obtained with the combination of CT neck and US neck for the detection of supraclavicular lymph nodes (1 positive scenario), and with CT thorax/abdomen only for the detection of metastases in celiac lymph nodes, liver and lung. For a slightly higher specificity (less false positives) US abdomen and chest X-ray could be added, but only

in the 2 positive scenario. A higher specificity resulted however in a decline in sensitivity and consequently in more resections being performed in the presence of distant metastases.

The choice for the optimal combination of investigations highly depends on the number of patients with a false positive (no curative treatment option in the absence of distant metastases) or a false negative (a curative treatment option in the presence of distant metastases) staging result one is willing to accept. With the combination of CT neck/thorax/abdomen and US neck, the highest sensitivity for the detection of distant metastases was obtained and the number of patients undergoing a resection in the presence of distant metastases was lowest. A higher specificity could be achieved by the addition of US abdomen to CT neck/thorax/abdomen for the detection of liver metastases and chest X-ray for the detection of lung metastases, but only using the 2 positive scenario. The higher specificity that was obtained with this scenario resulted from the lower number of false positive results, which was also seen in the analyses concerning the number of false positive and false negative results at the organ level (Table 8.4). Using the 2 positive scenario, the number of false negative results became however higher, with more patients undergoing a resection in the presence of distant metastases. Hence, requiring 2 staging procedures to be positive is probably clinically not a valuable strategy.

A combination of investigations with a high sensitivity for the detection of distant metastases, but a lower specificity, would result in relatively low costs, but the average life expectancy and average QALYs would also be relatively low (Table 8.6). This is due to the substantially lower QALYs for patients with local/regional disease who would not undergo a resection (false positive staging result) compared with patients with local/regional disease undergoing a resection. It is also possible to use a combination of investigations with a higher specificity, but the consequence of this would be that the sensitivity becomes lower, resulting in more patients undergoing a resection in the presence of distant metastases and more costs related to the procedure. In cost-effectiveness analyses, a ratio of approximately 50 k$ per QALY is generally considered as acceptable for a clinical strategy compared to a reference strategy (12). The ratios of the alternatives were all far above this threshold in the present study (Table 8.6) and, therefore, no combination of investigations was more cost-effective than the combination of CT neck and US neck for the detection of supraclavicular lymph node metastases (1 positive scenario) and CT thorax/abdomen for the other regions.

On the basis of the results at the organ level, we concluded that the performance of US abdomen, US neck and chest X-ray, respectively, in combination with CT neck/thorax/abdomen resulted in a higher accuracy over the performance of CT alone. The addition of EUS had no additional value over the performance of CT in combination with US abdomen for the detection of malignant celiac lymph nodes and, for that reason, EUS was not included in the part of the analysis concerning treatment modality. It is important to stress that the sensitivity of EUS for the detection of celiac lymph nodes was lower in our study compared to the literature (38% *versus* 75-100%, respectively), whereas specificity was comparable (94%

versus 50-100%, respectively) (13-16). The difference in sensitivity can be explained by the fact that in the early years of this study FNA was not performed during EUS in our center when a celiac lymph node was detected which was suspicious for malignancy. In addition, dilation was often not performed in patients with a stenotic tumor. The few studies that have reported on sensitivities and specificities of EUS for celiac lymph nodes have mainly been performed in centers with a high volume of EUS procedures and a large expertise. Recently, we demonstrated that results of EUS performed in a center where <50 EUS procedures per endoscopist per year are performed compare unfavorably with those reported from high volume EUS centers (17). Therefore, we assume that the additional value of EUS for the detection of celiac lymph nodes was underestimated in our study, due to the lower results of EUS in our center compared to the literature. To assess whether this was indeed the case, we determined whether better EUS results would have changed the results of our study. For this, we calculated the median sensitivity and specificity of EUS from the literature. These were 80% and 92%, respectively. In the dataset of 264 patients who had undergone CT neck/thorax/abdomen, US abdomen, US neck and chest X-ray, we included fictitious results of EUS, in such a way that a sensitivity of 80% and a specificity of 92% for EUS were achieved. Thereafter, sensitivities and specificities for the detection of distant metastases at the patient level were calculated for each possible combination of investigations. This showed that EUS had only limited additional value for the detection of distant metastases at the patient level. An explanation for this could be that only 3/264 (1%) patients had M1b celiac lymph nodes according to the gold standard. Two of these patients also had supraclavicular lymph nodes that were detected by both CT and US neck, and these patients would not have undergone a resection anyhow, irrespective of the finding of M1b celiac lymph nodes by EUS or another investigation, such as CT or US abdomen.

There are some limitations to our study. First, patients in this study were a selection of patients diagnosed with esophageal or gastric cardia cancer. This study was performed in a referral center and not all patients in whom distant metastases were detected in regional centers were referred to our center. In addition, only preoperative staging investigations that were performed in our center were included in this study, as it is known that the diagnostic sensitivity for metastases detection is higher in a high volume referral center in comparison with referring regional centers (18). Furthermore, only patients who had undergone CT neck/thorax/abdomen and one or more other investigations, i.e., US abdomen, US neck and/or chest X-ray, in our center were included. Nevertheless, no statistically significant differences were found between the whole group of patients (n=569) and the group of patients who had undergone all investigations (n=264), indicating that these two groups of patients were comparable.

Second, if we compared the sensitivity and specificity of CT neck/thorax/abdomen, US abdomen, US neck, chest X-ray and EUS in our study with the results reported in the literature (13-16, 19-30), we found that the sensitivity of EUS for the detection of celiac lymph nodes

(38%) was substantially lower in our study compared to the literature (75-100%), as mentioned above. The other sensitivities and specificities as shown in Table 8.3 were largely comparable to the results from the literature. Nevertheless, in other centers, the optimal strategy to stage patients with esophageal or gastric cardia cancer is not automatically the combination of CT and US neck, as was found in our center. The reason for this is that sensitivities and specificities of combinations of investigations are largely depended on the quality of the staging investigations, where the experience of the person who performed the investigation and the equipment used determine the quality.

Third, positron emission tomography (PET) scan was not used in the patients who were included in this study. Nevertheless, PET can also be used to detect the presence of distant metastases and it needs to be determined what the exact role of PET is in the staging of esophageal or gastric cardia cancer.

In conclusion, the combination of CT neck and US neck for the detection of supraclavicular lymph nodes and CT thorax/abdomen for the detection of metastases in celiac lymph nodes, liver and lung is a cost-effective strategy for the detection of distant metastases in patients with esophageal or gastric cardia cancer. US abdomen, EUS and chest X-ray have only limited additional value in the detection of distant metastases in these patients. These staging investigations should only be performed for specific indications in patients with esophageal or gastric cardia cancer, since the treatment decision is in most of these patients not improved if these investigations are added to the staging logarithm.

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CHAPTER 9

The role of socio-economic status in the decision making on diagnosis and treatment of esophageal cancer in The Netherlands

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ABSTRACT

Background: In the United States (USA), a correlation has been demonstrated between socio-economic status (SES) of patients on the one hand, and tumor histology, stage of the disease and treatment modality of various cancer types on the other hand. It is unknown whether such correlations are also involved in patients with esophageal cancer in The Netherlands.

Methods: Between 1994 and 2003, 888 esophageal cancer patients were included in a prospective database with findings on the diagnostic work-up and treatment of esophageal cancer. Socio-economic status of patients was defined as the average net yearly income.

Results: Linear-by-linear association testing revealed that esophageal adenocarcinoma was more frequently observed in patients with higher SES and squamous cell carcinoma in patients with lower SES (p=0.02). Multivariable logistic regression analysis showed no correlation between SES and staging procedures and preoperative TNM stage. The adjusted odds ratio (OR) for stent placement was 0.82 (95% C.I. 0.71-0.95), indicating that with an increase in SES by 1200 euro, the likelihood that a stent was placed declined by 18%. Patients with a higher SES more frequently underwent resection or were treated with chemotherapy (OR: 1.15; 95% C.I. 1.01-1.32 and OR: 1.16; 95% C.I. 1.02-1.32, respectively).

Conclusion: Socio-economic factors are involved in esophageal cancer in The Netherlands, as patients with a higher SES are more likely to have an adenocarcinoma and patients with a lower SES a squamous cell carcinoma. Moreover, the correlations between SES and different treatment modalities suggest that both patient and doctor determinants contribute to the decision on the most optimal treatment modality in patients with esophageal cancer.

INTRODUCTION

Esophageal carcinoma is currently on the sixth place of estimated cancer deaths worldwide (1). Patients with esophageal cancer have a dismal prognosis, as more than 50% of patients have already locally advanced carcinoma, lymph node metastases, or distant metastases at the time of presentation (2).

In the United States (USA), a correlation between socio-economic status (SES) of patients and the histology of esophageal cancer has been demonstrated. Patients with a higher SES had a higher incidence of esophageal adenocarcinoma, whereas squamous cell carcinoma was more frequently found in patients with a lower SES (3).

It has also been reported that patients with a lower SES were less likely to have localized cancer at diagnosis, compared with patients with a higher SES in the USA. This correlation was found for various cancers, that is, carcinomas of the breast (4, 5), uterine cervix (5) and esophagus (6).

Finally, for breast cancer (4, 5) differences in the use of specific treatment modalities were present for SES in the USA. Patients with a higher SES were more likely to undergo a more appropriate treatment modality compared to patients with a lower SES, meaning that patients with a lower SES were at risk to receive unsatisfactory health care.

It is unknown whether in European countries a correlation is present between SES of patients with esophageal cancer on the one hand, and tumor histology, staging approach, preoperative TNM stage and treatment modality on the other hand. In the present study we investigate these correlations in The Netherlands.

PATIENTS AND METHODS

Patients and database

In the Erasmus MC Rotterdam, The Netherlands, a prospective database is 2-weekly updated with information on patients who have been diagnosed with and treated for esophageal or gastric cardia cancer from January 1994 until now. The database contains information on general characteristics, preoperative investigations and treatment modalities employed in these patients. In this study, we analyzed findings from patients collected in the database between January 1994 and October 2003. In total, 1088 patients with esophageal or gastric cardia cancer were seen in this period. SES could be determined in 1078 patients. Of these, 888 patients had squamous cell carcinoma or adenocarcinoma of the esophagus. In the remaining 190 patients, gastric cardia carcinoma (n=107) or esophageal cancer with another histology (n=83) was found and these patients were excluded from the analysis. Information, not present in the database, but necessary for this study, was obtained from the electronic 'hospital information system' which contains additional clinical information on these patients.

From the electronic 'hospital information system', we retrospectively collected information on whether a cancer located at the gastroesophageal junction was in fact an esophageal or a gastric cardia cancer. Other information retrospectively obtained from the electronic 'hospital information system' included information on chest X-rays (performed or not, and if yes the result), bronchoscopies (performed or not, and if yes the result) and CT scan results. Furthermore, the preoperative TNM stage was retrospectively determined using the results of the preoperative investigations performed.

Socio-economic status

We defined SES of patients as the average net yearly income of income receivers with 52 weeks of income. The Central Office of Statistics in The Netherlands (CBS, The Netherlands) collects information on net yearly income, which is collected on a zip code level. Each zip code area represents approximately 4,000 inhabitants. The database contains zip codes of patients and SES of patients was determined by means of these zip codes. Information on net yearly income was used from 1999. The use of information on SES with zip codes has been reported in other studies as well (7-10).

The SES varied between €11,800 and €22,100. For this study, we divided SES into 3 equal parts, that is, group 1: < €14,600 (N=295), group 2: €14,600 - €15,800 (N=291) and group 3: > €15,800 (N=302). In The Netherlands, the mean net yearly income was 15,900 euro in 2000 (11).

Tumor histology

Tumor histology was determined by means of investigation of biopsy specimens from the esophageal tumor, which were obtained by endoscopy and examined by an experienced gastrointestinal pathologist. Patients were subdivided into those with esophageal squamous cell carcinoma or adenocarcinoma. Esophageal adenocarcinoma was present if the carcinoma was found in Barrett's esophagus, or, in the absence of Barrett's esophagus, if more than 50% of the adenocarcinoma was found in the esophagus.

Staging approach

Preoperative investigations, which are commonly performed in patients with esophageal carcinoma, include chest X-ray (12), endoscopic ultrasonography (EUS) (13), CT scan (14), ultrasound (US) of neck (15) and abdomen (16) and bronchoscopy (17) in case of a carcinoma at or above the level of the carina. Patients who were included in this study were predominantly diagnosed in regional centers. After diagnosis, presumably curable patients are referred to our center where they undergo (repeat) preoperative staging investigations. For all patients included in this study, only preoperative investigations performed in our center were taken into consideration.

Preoperative TNM stage

The preoperative TNM stage was determined as a result of the preoperative staging investigations. The T stage describes the depth of infiltration of the cancer into the different layers of the esophageal wall. T stage was subdivided into T1 to T4, with a T1-carcinoma representing infiltration into the mucosa (T1m) or submucosa (T1sm), a T2 infiltrating into the muscularis propria, a T3 extending through the muscularis propria and a T4 infiltrating into surrounding organs or vessels. The N stage indicates the absence (N0) or presence (N1) of regional lymph node metastases and the M stage describes the absence (M0) or presence (M1) of distant metastases, with M1 stage being subdivided into an M1a- and M1b-stage (18). When an item of the TNM-staging system was not available, this was staged as unknown. For example, if T stage was unknown, T stage was considered as Tx.

Treatment modality

Treatment modalities, which were performed in the patients with esophageal carcinoma, were an esophageal resection, stent placement, chemotherapy, radiation therapy, a combination of chemotherapy and resection, or a combination of chemotherapy, radiation therapy and resection. For each patient, it was determined whether esophageal resection, chemotherapy, radiation therapy or stent placement had been performed.

Statistical analyses

Linear-by-linear association testing (chi-square testing) was used to determine a correlation between SES and tumor histology, extent of preoperative investigations, TNM stage and treatment modality.

For preoperative investigations, multivariable logistic regression was performed to correct for confounders. The included covariates were age, gender, tumor histology, comorbidity, tumor location and SES divided by 1,200. The SES was divided by 1,200 as the possible effect per euro was expected to be small. The number 1,200 includes the difference between the lowest and highest income of group 2 (€14,600 - €15,800). The number 1,200 is, however, not a universal number used in multivariable logistic regression analysis. If the difference between the lowest and highest income of group 2 had been, for example, 1,400, we would have divided SES by 1,400. Comorbidity comprised all other disorders of patients that required medical treatment, such as cardiac or lung diseases. Tumor location was divided into five groups, that is, cervical, upper 1/3, middle 1/3 and lower 1/3 thoracic esophagus and gastroesophageal junction.

For N and M stages, we also performed multivariable logistic regression. M stage was subdivided into M0 and M1 stage, with M1 stage containing both M1a and M1b stages. The included covariates were age, gender, tumor histology, comorbidity, tumor location, tumor stage, preoperative investigations and SES divided by 1,200. Multivariable logistic regression

was not performed for T stage, as T stage was subdivided into four groups, that is, T1-T4, and for multivariable logistic regression the dependent variable should be dichotomous.

To correct for confounders in the possible correlation between SES and treatment modality, multivariable logistic regression was performed. We included the covariates age, gender, tumor histology, comorbidity, tumor location, tumor stage (TNM stage), preoperative investigations and SES divided by 1,200.

Software used for analysis was SPSS (SPSS, Chicago, IL). All p-values were based on two-sided tests of significance. A p-value <0.05 was considered as statistically significant.

RESULTS

Patient and tumor characteristics

Patient and tumor characteristics of the 888 patients with esophageal carcinoma who were included in this study are shown in Table 9.1.

Table 9.1. Patient and tumor characteristics of patients with esophageal carcinoma (n=888).

Characteristic	
Mean age ± SD (yrs.)	62.7 ± 10.1
Gender (%)	
Male	678 (76)
Female	210 (24)
Histology of tumor (%)	
Squamous cell carcinoma	388 (44)
Adenocarcinoma	500 (56)
Location of tumor (%)	
Cervical	10 (1)
Upper 1/3 thoracic	43 (5)
Middle 1/3 thoracic	158 (18)
Lower 1/3 thoracic	406 (46)
Gastroesophageal junction	271 (30)

Tumor histology

Table 9.2 shows the number of patients with squamous cell carcinoma or adenocarcinoma per income group. We found a lower percentage of esophageal squamous cell carcinoma patients with increasing income. In contrast, the percentage of adenocarcinoma cases increased with higher SES (p=0.02).

Table 9.2. Number of patients with esophageal squamous cell carcinoma (SCC) or adenocarcinoma (AC) per income group.

Histology	Socio-economic status in Euro		
	< 14,600 (N=295)	14,600 – 15,800 (N=291)	> 15,800 (N=302)
SCC (%)	147 (50)	119 (41)	122 (40)
AC (%)	148 (50)	172 (59)	180 (60)

Linear-by-linear association test: p=0.021

Staging approach

The numbers of patients who underwent EUS, CT scan, US neck, US abdomen, chest X-ray or bronchoscopy per income group are shown in Table 9.3. The linear-by-linear association test was only statistically significant for bronchoscopy (p=0.04), demonstrating that patients with a lower SES underwent more often a bronchoscopy. P-values for EUS (p=0.92), CT scan (p=0.14), US neck (p=0.44), US abdomen (p=0.34) and chest X-ray (p=0.48) were not statistically significant.

Table 9.4 shows the results of the multivariable logistic regression analyses. This table shows that the adjusted odds ratios (ORs) of the preoperative investigations were not statistically significant. The reason that bronchoscopy was not statistically significant in multivariable logistic regression analyses, while it was statistically significant in the linear-by-linear association test, was that bronchoscopy was more often performed in patients with squamous cell carcinoma compared to patients with adenocarcinoma (data not shown).

Table 9.3. Numbers of patients with EUS, CT scan, ultrasound neck, ultrasound abdomen, chest X-ray or bronchoscopy per income group.

Investigation	Socio-economic status in Euro			p-value*
	< 14,600 (N=295)	14,600 – 15,800 (N=291)	> 15,800 (N=302)	
EUS (%)	199 (68)	203 (70)	205 (68)	0.915
CT scan (%)	175 (59)	169 (58)	161 (53)	0.138
Ultrasound neck (%)	263 (89)	253 (87)	263 (87)	0.444
Ultrasound abdomen (%)	188 (64)	178 (61)	181 (60)	0.341
Chest X-ray (%)	211 (72)	202 (69)	208 (69)	0.481
Bronchoscopy (%)	84 (29)	59 (20)	64 (21)	0.036

*Linear-by-linear association test. CT, computed tomography; EUS, endoscopic ultrasonography

Preoperative TNM stage

T, N and M stages per income group are shown in Table 9.5. T stage was unknown in 284 patients, and in these patients T stage was considered as Tx (Table 9.5). The linear-by-linear association test was not significant for T (p=0.97), N (p=0.68) and M stage (p=0.46).

In Table 9.6, the results of the multivariable logistic regression analyses are shown. It was found that the adjusted odds ratios of N (OR: 0.91; 95% C.I. 0.81-1.03) and M stage (OR: 0.93; 95% C.I. 0.81-1.07) were not statistically significant.

Table 9.4. Multivariable logistic regression to determine whether a correlation existed between SES and preoperative investigations in patients with esophageal carcinoma.

Investigation	OR	95% confidence interval	p-value
EUS	0.997	0.887-1.120	0.955
CT scan	0.960	0.861-1.071	0.466
Ultrasound neck	0.997	0.845-1.175	0.968
Ultrasound abdomen	0.957	0.858-1.068	0.434
Chest X-ray	0.968	0.862-1.088	0.590
Bronchoscopy	0.951	0.828-1.092	0.473

Covariates: age, gender, tumor histology, comorbidity, tumor location and SES/1,200. CT, computed tomography; EUS, endoscopic ultrasonography; OR, odds ratio; SES, socio-economic status

Table 9.5. T, N and M stages per income group.

Stage	Socio-economic status in Euro			p-value*
	< 14,600 (N=295)	14,600 – 15,800 (N=291)	> 15,800 (N=302)	
T stage				0.972
T1 (%)	7 (2)	7 (2)	6 (2)	
T2 (%)	28 (10)	31 (11)	25 (8)	
T3 (%)	136 (46)	144 (49)	151 (50)	
T4 (%)	29 (10)	19 (7)	21 (7)	
Tx (%)	95 (32)	90 (31)	99 (33)	
N stage				0.680
N0 (%)	166 (56)	167 (57)	175 (58)	
N1 (%)	129 (44)	124 (43)	127 (42)	
M stage				0.459
M0 (%)	225 (76)	235 (81)	238 (79)	
M1a (%)	29 (10)	26 (9)	27 (9)	
M1b (%)	41 (14)	30 (10)	37 (12)	

*Linear-by-linear association test

Table 9.6. Multivariable logistic regression to determine whether a correlation existed between SES and preoperative N and M stage in patients with esophageal carcinoma.

Stage	OR	95% confidence interval	p-value
N	0.913	0.811-1.029	0.137
M	0.932	0.813-1.068	0.310

Covariates: age, gender, tumor histology, comorbidity, tumor location, tumor stage, preoperative investigations and SES/1,200. OR, odds ratio; SES, socio-economic status

Treatment modality

The numbers of patients who underwent resection, stent placement, chemotherapy or radiation therapy per income group are shown in Table 9.7. In 40 patients, no treatment was given. In the remaining 848 patients, more than one treatment modality has been employed in a subgroup of patients. The linear-by-linear association test was statistically significant for resection (p=0.001), showing that more resections were performed in patients with a higher SES. For stent placement, the linear-by-linear association test was also statistically significant (p=0.001). The negative correlation between SES and stent placement shows that fewer stent placements were performed in patients with a higher SES.

The results of the multivariable logistic regression analyses are shown in Table 9.8. It was found that the adjusted OR for stent placement was still statistically significant with a value of 0.82 (95% C.I. 0.71-0.95), meaning that with an increase in SES by 1200 euro, the likelihood that a stent was placed declined by 18%. Furthermore, the adjusted ORs for resection and chemotherapy were also just statistically significant (OR: 1.15; 95% C.I. 1.01-1.31 and OR: 1.16; 95% C.I. 1.02-1.32, respectively), showing that resection and chemotherapy were more often performed with increasing SES. No correlation was found between SES and radiation therapy (OR: 1.04; 95% C.I. 0.90-1.22).

Table 9.7. Numbers of patients with esophageal resection, stent placement, chemotherapy or radiation therapy.

Treatment	Socio-economic status in Euro			p-value*
	< 14,600 (N=289)	14,600 – 15,800 (N=280)	> 15,800 (N=291)	
Resection (%)	154 (52)	176 (61)	197 (65)	0.001
Stent placement (%)	86 (29)	61 (21)	55 (18)	0.001
Chemotherapy (%)	117 (40)	123 (42)	132 (44)	0.317
Radiation therapy (%)	43 (15)	56 (19)	47 (16)	0.753

*Linear-by-linear association test

Table 9.8. Multivariable logistic regression to determine whether a correlation existed between SES and treatment modality in patients with esophageal carcinoma.

Treatment	OR	95% confidence interval	p-value
Resection (%)	1.152	1.008-1.317	0.038
Stent placement (%)	0.822	0.712-0.949	0.008
Chemotherapy (%)	1.155	1.015-1.315	0.029
Radiation therapy (%)	1.043	0.895-1.215	0.592

Covariates: age, gender, tumor histology, comorbidity, tumor location, tumor stage, preoperative investigations and SES/1,200. OR, odds ratio; SES, socio-economic status

DISCUSSION

In this study, a statistically significant correlation was demonstrated between SES, defined as average net yearly income of income receivers with 52 weeks of income, and histology of an esophageal carcinoma. The incidence of squamous cell carcinoma declined and the incidence of adenocarcinoma increased with increasing SES. Our analyses demonstrated no correlation between SES and extent of staging procedures and between SES and preoperative TNM stage. A statistically significant negative correlation was however present between SES and stent placement, whereas a statistically significant positive correlation was present between SES and undergoing resection and between SES and undergoing chemotherapy. No correlation was found between SES and undergoing radiation therapy.

Well-known risk factors for esophageal squamous cell carcinoma include smoking and alcohol consumption (3, 19, 20). Gastroesophageal reflux disease and obesity are identified risk factors for esophageal adenocarcinoma (19, 20). In the USA, adenocarcinoma is more often found in patients with a higher SES, whereas squamous cell carcinoma is more common among patients with a lower SES (3). This previously observed correlation between SES and tumor histology was also found in the present study performed in The Netherlands. Although we had no information on risk factors in the patients with esophageal cancer in this study, our results suggest that the higher prevalence of squamous cell cancer in the lower SES patients is due to more common smoking habits and alcohol consumption in these patients, whereas in patients with a higher income risk factors for GERD are more prominent. This is in line with findings on smoking and alcohol consumption in the literature (21, 22).

In The Netherlands, general practitioners are the gatekeepers of the health care system, meaning that patients usually first consult the general practitioner for symptoms before being referred to a hospital (23). In general, it is true that there is a low threshold and there are no economical barriers for patients to consult a general practitioner. In the present study, no statistically significant correlation was found between SES and performing preoperative staging investigations and between SES and TNM stage. This is likely to be explained by the fact that health insurance covers almost all people in The Netherlands, resulting in a similar access to health care faculties for all income groups.

In the USA, differences in the use of treatment modalities for esophageal cancer have been reported for race. Non-Caucasian patients had a higher risk of receiving a less than optimal treatment compared with Caucasian patients, that is, non-Caucasian patients were less likely to receive an esophagectomy and more likely to receive chemotherapy and/or radiation therapy (24). Factors that have been previously reported to be important in the differences in treatment modalities for both race and SES in the USA included differences in attitudes toward invasive procedures, disease severity, access to care (24), differences in undergoing staging procedures (25), and issues related to health insurance (26).

The treatment preferences and attitudes toward invasive procedures of patients in the USA could be important explanations for the differences in use of treatment modalities in the USA. It is possible that treatment preferences and attitudes toward invasive procedures were also factors of importance in The Netherlands. In the present study, stent placement was more often performed in patients with a lower SES and esophageal resection and the administration of chemotherapy were more common in patients with a higher SES. This might well suggest that patients in a higher income class are more eager to explore all therapeutic options, even experimental, to overcome the malignant disease they are suffering from. This is however speculative and we have no firm evidence to confirm this option. Furthermore, doctor contributions might also be important in the decision making on the most optimal treatment modality in patients, as it can be suspected that doctors are more willing to discuss all treatment options with patients if they are in the same income class which often represents the same educational level.

In the USA, patients with a higher SES were more likely to have a localized cancer stage at diagnosis, compared with patients with a lower SES (6). Patient with locally advanced carcinoma or distant metastases will not receive an esophageal resection and more often undergo treatment with chemotherapy and/or radiation therapy, which likely explains the differences in treatment modalities between different income classes in the USA. In the present study, no differences in preoperative TNM stage were found and as a consequence, disease stage is probably not important in the correlation between SES and treatment modality in The Netherlands.

In the USA, non-Caucasian patients were more often understaged, that is, underwent fewer preoperative staging investigations, in comparison with Caucasian patients (25). In the present study, no correlation was found between SES and performing preoperative investigations and, as a consequence, this factor could not be an explanation for the correlations found between SES and treatment modality.

It has been reported that the health insurance status of a patient has an effect on the use of treatment modalities. For non-small-cell lung carcinoma, it has been shown that patients with private insurance were more likely to undergo a lung resection compared with patients without private insurance (27). In The Netherlands, almost all (>99%) inhabitants have a health insurance, resulting in similar health care services for all income groups. For that reason, differences in health insurance cannot explain the correlation between SES and treatment modality in The Netherlands.

What are other possible explanations for the observed differences on the role that SES plays in the diagnosis and treatment of esophageal carcinoma patients between the USA and The Netherlands? First, almost all patients in this study were Caucasian. In the USA, the patients had different ethnic backgrounds and it has been demonstrated that differences in performing preoperative staging investigations, TNM stage and use of treatment modalities

were not only present for SES, but also for race (5, 24, 25, 28-31). As a consequence, race might be a more important factor compared to SES.

Second, people who are unemployed usually receive welfare in The Netherlands. As a consequence, the contrast between low and high income patients is probably smaller in The Netherlands in comparison with the USA. Therefore, the contrast between poor and rich was probably too small in this study to demonstrate the presence of differences in performing preoperative staging investigations and TNM stage.

Third, differences are present in health insurance and access to care. The majority of lower SES patients in The Netherlands have health insurance, which they receive from the Dutch National Health Service, whereas patients with higher SES pay health insurance themselves. As a consequence, almost all people in The Netherlands have health insurance, which means that access to care is equal, and similar health care services are available for all income groups. In the USA, not all patients have similar health care insurance and service, which could be responsible for the differences between the USA and The Netherlands.

There are several limitations to this study. First, in the present database with esophageal cancer patients, no direct measures of SES were available. Nevertheless, the zip code of nearly all patients was present in the database. The Central Office of Statistics (CBS, The Netherlands) has designed a measure of SES by zip code representing the median net yearly income of an average of 4,000 inhabitants. This information was used to determine the SES of individual patients. A disadvantage of this method is that an aggregate measure of SES was used for the SES of each individual patient. Another disadvantage could be that SES was relatively roughly determined, as it was estimated on the SES of an average of 4,000 inhabitants, because there was no measure at the individual level available. Nevertheless, it has been demonstrated that health differences could be slightly more prominent when a more accurate measure of SES is used (32), suggesting that the differences could be underestimated in this study. In our opinion, it is unlikely that using a more accurate measure of SES would have changed the pattern of correlations.

Second, in the zip code area, the population is heterogeneous for economic characteristics, that is, not all persons in that particular zip code area will have the same SES. In the present study, the assumption was made that SES was homogeneous within the zip code area. As a consequence, all persons in one zip code area had an equal SES. Nevertheless, it could be possible that the SES of a patient was higher or lower than the average SES of the corresponding zip code area.

Third, in this study, only 888 patients were included who had esophageal squamous cell carcinoma or adenocarcinoma. This is a relatively low number of patients to determine whether correlations existed between SES and characteristics of esophageal cancer.

Fourth, the patients who were included in this study were a selection of all patients with esophageal carcinoma in the southern part of The Netherlands. Usually, esophageal carcinoma is diagnosed in regional centers, that is, centers with fewer than 10 patients per year.

After diagnosis, patients often undergo preoperative staging investigations in these centers. Subsequently, they may be treated in the regional center or, more often, are referred to our center with a volume of more than 100 patients with esophageal cancer per year (33). Patients in whom distant metastases were present according to the preoperative investigations performed in the regional centers were however only sporadically referred to our center, which resulted in a relatively low number of patients with distant metastases in this study (Table 9.5). Furthermore, it is unknown whether other factors, such as SES or education level, played a role in the referring pattern of patients to our center.

In conclusion, a significant correlation was found between SES of patients with esophageal cancer and tumor histology. The negative correlation between SES and stent placement and the positive correlation between SES and resection and SES and chemotherapy suggest that patients in a higher income class more often do an utmost effort to overcome their disease. Furthermore, doctor contributions may be important in the decision making on treatment modality.

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CHAPTER 10

Summary and conclusions

SUMMARY

If esophageal or gastric cardia cancer is diagnosed by upper gastrointestinal endoscopy and biopsy and the physical condition of the patient permits a resection, staging investigations will be performed to determine the depth of invasion (T stage), and the presence of regional lymph node metastases (N stage) and distant metastases (M stage). The performance of staging investigations in patients with esophageal or gastric cardia cancer is required to select the most optimal treatment modality for these patients. Upper gastrointestinal endoscopy, barium contrast swallow, endoscopic ultrasonography (EUS), computed tomography (CT), positron emission tomography (PET), ultrasound (US) of neck and abdomen, bronchoscopy, chest X-ray, magnetic resonance imaging (MRI), and bone scintigraphy are staging investigations which can be performed to assess the extent of esophageal or gastric cardia cancer. It is questionable whether all investigations mentioned above should be performed in patients with esophageal or gastric cardia cancer or whether it is more effective to perform only a selection. The aim of the work described in this thesis was to assess which preoperative staging investigations should be performed in patients with esophageal or gastric cardia cancer to determine the preoperative TNM stage. In addition, we evaluated which determinants play a role in the performance and evaluation of staging investigations.

In **chapter 2**, the preoperative investigations that can be performed in patients with esophageal or gastric cardia cancer were discussed, with regard to the advantages, limitations and results, and a meta-analysis was performed. On the basis of these data, it was suggested that for assessing the depth of tumor invasion (T stage) and the presence of lymph node metastases (N stage), EUS is the investigation of choice. In patients with suprabifurcal cancer, bronchoscopy should be performed to determine whether the tumor invades the trachea or bronchus. Ultrasound of the cervical region is the most appropriate investigation for the detection of malignant supraclavicular lymph nodes. For the detection of distant metastases (M stage), CT and PET are possible options. Based on what is presently known on its performance, PET should particularly be considered in patients with a tumor that is otherwise staged as T3N0-1. In these patients, PET can be used to detect metastases that were not seen with other investigations.

Malignant lymph nodes in the supraclavicular region are considered to be distant metastases in patients with thoracic esophageal cancer or gastric cardia cancer. US of the supraclavicular region as well as CT can be performed to detect these metastases. In **chapter 3**, US of the supraclavicular region, if indicated with fine-needle aspiration (FNA), CT, and the combination of these investigations for the detection of supraclavicular lymph node metastases were compared. The aim of this study was to investigate whether one of these or both investigations should be performed for the detection of malignant supraclavicular lymph nodes in patients with esophageal or gastric cardia cancer. In total, 567 patients were included who were diagnosed with esophageal or gastric cardia cancer between January

1994 and June 2004 and who underwent both CT and US of the supraclavicular region. This study demonstrated that US-FNA, alone or in combination with CT of the supraclavicular region, is superior to US, CT or the combination of US and CT for the detection of malignant supraclavicular lymph nodes. For that reason, US-FNA is the preferred diagnostic modality for the detection of supraclavicular metastases in patients with esophageal or gastric cardia cancer. The sensitivity of metastases detection only slightly improves if US-FNA is combined with CT.

It has been reported that an inverse correlation exists between hospital volume and esophageal resection mortality. In **chapter 4**, it was investigated whether a correlation also was present between the volume of staging procedures performed in a center and the number of metastases detected from esophageal or gastric cardia cancer. Between January 1994 and October 2003, 1088 patients with esophageal or gastric cardia cancer were evaluated in the Erasmus MC Rotterdam, which is a referral center for patients with esophageal or gastric cardia cancer. In 906 patients, the diagnosis of esophageal or gastric cardia cancer was first made in a regional center and, subsequently, these patients were referred to the referral center. In 573 patients, preoperative staging investigations (CT, US of abdomen and neck, and chest X-ray) performed in 61 regional centers were re-evaluated and/or repeated in the referral center. A comparison was made between the quality of preoperative metastasis detection in the high volume referral center and that of low volume referring regional centers. It was found that more metastases were detected in the high volume referral center compared with the referring regional centers. In addition, over 1 in 20 patients would have undergone a resection in the presence of distant metastases, if the decision to perform a resection was only based on the results obtained in the regional centers. The presence of both technically more advanced CT equipment and more experienced radiologists in the high volume referral center likely explained these better results.

In the study reported in **chapter 5**, 2 radiologists from referral centers ('expert radiologists') and 6 radiologists from regional centers ('non-expert radiologists') made 240 evaluations of 72 CT scans performed in patients diagnosed with esophageal or gastric cardia cancer between 1994 and 2003. The aim of the study was to determine prospectively whether equipment and experience were indeed factors that contribute to the detection of metastases on CT scans. The results of this study showed that both the experience of radiologists and the quality of CT scans played a role in the detection of metastases on CT scans of patients with esophageal or gastric cardia cancer. These results suggest that CT scans of patients with esophageal or gastric cardia cancer should be performed in centers with experienced radiologists and the ability to produce high quality CT scans to optimize the staging process of patients with esophageal or gastric cardia cancer.

The presence of a learning curve for performing EUS has been reported and it has been demonstrated that acceptable results are obtained after the performance of at least 75-100 EUS examinations. In **chapter 6**, a comparison was made between the results of EUS for

the preoperative evaluation of the depth of tumor invasion (T stage) and the presence of malignant regional lymph nodes (N stage) of esophageal or gastric cardia cancer from the endoscopy unit of the Erasmus MC Rotterdam and reported results from high volume EUS centers. The aim of this study was to assess whether the number of endoscopic EUS examinations performed per endoscopist per year affected the results of staging of esophageal or gastric cardia cancer. Between 1994 and 2003, EUS, without measures to pass a stenotic tumor or FNA, was performed in 244 patients who had subsequently undergone a resection. In the 7 high volume centers, which had reported their experience in the literature, 670 EUS investigations for esophageal cancer were performed. In most of these centers, dilation was performed if needed. The results of EUS performed in the low volume EUS center, where <50 EUS procedures per endoscopist per year were performed, were lower compared to the results reported from high volume EUS centers. The results of this study suggest that the experience of endoscopists is an important factor in performing EUS examinations. Therefore, it is advisable that only experienced and dedicated EUS endoscopists should perform EUS to optimize staging of esophageal and gastric cardia cancer.

Recently, it has been reported that EUS results for staging of rectal cancer were overestimated in the literature due to the selective reporting of studies with more positive results, i.e., publication bias. In **chapter 7**, it was investigated whether publication bias was also present in the reporting of EUS staging results in patients with esophageal, gastric or pancreatic cancer, i.e., upper gastrointestinal (GI) cancer. A Medline literature search was performed to search for all articles containing information on the results of EUS for T and N staging of upper GI cancer. Plots were made between results of EUS and numbers of patients, year of publication, journal type and impact factor, respectively. In this study, no evidence was found that publication bias was present in the reporting on EUS staging in patients with upper GI cancer, which indicates that results of EUS for T and N staging of esophageal, gastric and pancreatic cancer are probably not overestimated in the literature. Nevertheless, the accuracy of EUS for T stage of esophageal cancer significantly declined over the years. This could be due to two reasons: 1) the more widespread use of EUS, which had resulted in the use of EUS in less experienced centers and 2) the presence of relatively more T1 and T2 stage esophageal tumors and fewer T3 and T4 stage tumors in the last few years which is a result of the more frequent application of preoperative radiation and/or chemotherapy regimens in patients with T3 or T4 esophageal cancer in the last few years. No correlations were found between EUS results and journal type or impact factor, respectively.

There are several preoperative investigations that can be used in the staging of patients with esophageal or gastric cardia cancer. CT is nowadays considered to be a standard procedure for the detection of metastases. It is however not clear whether US abdomen, EUS, US neck and chest X-ray are also necessary for assessing the presence of metastases. In **chapter 8**, it was determined whether all these investigations are indeed indicated in patients with esophageal or gastric cardia cancer or whether it is more effective to perform only one or a

small selection of preoperative investigations for the regions in which distant metastases can be present. In total, 569 esophageal or gastric cardia cancer patients had undergone CT and one or more other investigations, i.e., US abdomen, US neck and/or chest X-ray. In 335 patients, both CT and US abdomen for liver metastases were performed, while CT and US neck for supraclavicular lymph nodes were performed in 546 patients. CT and chest X-ray for lung metastases were performed in 424 patients, while CT, US abdomen and EUS for celiac lymph nodes were performed in 143 patients. Results of these investigations were compared with the gold standard based on surgery, FNA or a radiological result with follow-up. The combined result of CT with US abdomen, EUS, US neck or chest X-ray, respectively, was calculated twice. First, the result was considered positive for the presence of metastases if at least one of the investigations was positive and negative if both investigations were negative (1 positive scenario). Second, the result was considered positive if both CT and another investigation were positive and negative if at least one of the investigations was negative (2 positive scenario). At an organ level, sensitivity of CT was higher than that of US abdomen, EUS and chest X-ray for detecting metastases in celiac lymph nodes, liver and lung. The sensitivity of US neck, if indicated with FNA, for supraclavicular lymph nodes was higher than that of CT. At a patient level, the sensitivity for detecting distant metastases was 66% and specificity was 95% in the situation that only CT was performed. A higher sensitivity (86%) was achieved when US (1 positive scenario) was added for the detection of supraclavicular nodes, at the same specificity (95%). A slightly higher specificity of 97% was achieved by the addition of US abdomen for liver metastases, when the assumption was made that both CT and US abdomen had to be positive for a positive result (2 positive scenario). When chest X-ray (2 positive scenario) for the detection of lung metastases was added, the specificity further increased to 99%. Sensitivity however declined with increasing specificity, which may clinically not be desirable. When costs, life-expectancy and quality of life issues were considered, the combination of CT and US neck was most optimal. US abdomen, EUS and chest X-ray had only limited additional value to support the treatment choice in patients with esophageal or gastric cardia cancer.

In the United States, a correlation has been demonstrated between socio-economic status (SES) of patients on the one hand, and tumor histology, stage of the disease and treatment modality of various cancer types on the other hand. In **chapter 9**, it was determined whether correlations between SES and tumor histology, staging approach, preoperative TNM stage and treatment modality were also present in esophageal cancer patients in The Netherlands. Between January 1994 and October 2003, 888 patients diagnosed with esophageal cancer were included in a prospective database. This database contained information on patient characteristics, preoperative staging investigations, TNM stage and treatment. SES was defined as the average net yearly income. The results of this study showed that a correlation was present between SES and tumor histology, with the presence of statistically significant more squamous cell carcinoma in patients with lower SES and more esophageal adenocarcinoma in patients with higher SES. Using multivariable logistic regression analysis, no correlation

was found between SES and staging procedures or preoperative TNM stage, respectively. For treatment however, the adjusted odds ratio (OR) for stent placement was 0.82 (95% confidence interval (C.I.) 0.71-0.95), which indicates that the likelihood that a stent was placed declined by 18% with an increase in SES by 1200 euro. In addition, patients with a higher SES more frequently underwent resection or were treated with chemotherapy (OR: 1.15; 95% C.I. 1.01-1.32 and OR: 1.16; 95% C.I. 1.02-1.32, respectively). No correlation was found between SES and radiation therapy (OR: 1.04; 95% C.I. 0.90-1.22). The correlations between SES and stent placement, resection and chemotherapy in patients with esophageal cancer suggest that both patient and doctor determinants are important in the decision process of the most optimal treatment modality in these patients.

CONCLUSIONS

Staging is important in patients with esophageal or gastric cardia cancer for the selection of the most optimal treatment modality. Nowadays, a variety of staging investigations are available and it questionable whether all these investigations should be performed in patients with esophageal or gastric cardia cancer. From this thesis, it can be concluded that the investigations that should be performed in patients with esophageal or gastric cardia cancer are EUS, CT of the supraclavicular region, thorax and abdomen, and US of the supraclavicular region.

EUS should be performed to determine the extent of tumor growth through the esophageal wall (T stage) and the presence of regional lymph node metastases (N stage). EUS should however be performed in a center with experienced and dedicated EUS endoscopists to optimize the results of the EUS examinations.

CT is indicated to determine whether metastases are present in the supraclavicular region, thorax and abdomen. It was shown in this thesis that the experience of radiologists is an important factor in the evaluation of CT scans of patients with esophageal or gastric cardia cancer. In addition, high quality CT scans should be made to further optimize the detection of metastases.

US of the supraclavicular region is able to detect the presence of malignant supraclavicular lymph nodes and should always be performed in patients with esophageal or gastric cardia cancer, as CT alone is not sufficient enough to detect these metastases. If a suspicious lesion is detected in the supraclavicular region, FNA should be performed to obtain tissue of that lesion for cytological analysis. However, FNA should only be performed in patients in whom the treatment decision will be changed by the FNA result.

There may also be a role for bronchoscopy and PET. Bronchoscopy can be performed in patients with suprabifurcal esophageal cancer to investigate whether the tumor invades the trachea or bronchus, which precludes resection. The role of PET seems to be limited to

patients in whom metastases are not otherwise detected, especially in those with a T3N0-1 tumor as determined with other staging investigations.

Further research is needed to prospectively assess whether staging investigations, for example US abdomen or chest X-ray, can be omitted in patients with esophageal or gastric cardia cancer without negative consequences. Furthermore, the exact role of PET in the staging of esophageal or gastric cardia cancer should be determined, particularly in cases where a good to high quality CT, EUS and US of the supraclavicular region have been performed. In addition, it needs to be determined whether the high costs of performing PET are compensated for by the expected cost reduction of a reduced number of resections that are performed due to the finding of distant metastases with PET, i.e., whether the performance of PET is indeed cost-effective.

Samenvatting en conclusies

SAMENVATTING

Wanneer een tumor in de slokdarm of cardia door middel van gastroscopie is gediagnosticeerd en de conditie van de patiënt een resectie toelaat, dient de tumor gestadiëerd te worden. Hierbij wordt de doorgroei van de tumor in de wand van de slokdarm of cardia bepaald (T stadium) en wordt vastgesteld of er kwaadaardige lymfeklieren (N stadium) of uitzaaiingen (M stadium) aanwezig zijn. Het uitvoeren van stadiëringsonderzoeken bij patiënten met slokdarmkanker of cardiacarcinoom is noodzakelijk om de optimale behandeling voor deze patiënten vast te kunnen stellen. De onderzoeken die verricht kunnen worden om de uitbreiding van een slokdarmtumor of cardiacarcinoom vast te stellen, zijn een gastroscopie, endo-echografie, CT scan, PET scan, echografie van de halsregio en buik, bronchoscopie, thoraxfoto, MRI en een botscan.

Het is de vraag of alle onderzoeken die hierboven zijn genoemd, uitgevoerd moeten worden bij patiënten met slokdarmkanker of cardiacarcinoom of dat het afdoende is om een selectie van deze onderzoeken uit te voeren. Het doel van het werk beschreven in dit proefschrift was om te bepalen welke onderzoeken obligaat zijn bij patiënten met slokdarmkanker of cardiacarcinoom om de mate van uitbreiding van de tumor, weergegeven door middel van het TNM stadium, vast te stellen. Tevens werd onderzocht welke factoren een rol spelen bij het uitvoeren en evalueren van de stadiëringsonderzoeken.

In **hoofdstuk 2** werden de resultaten en de voor- en nadelen besproken van de onderzoeken die uitgevoerd kunnen worden bij patiënten met slokdarmkanker of cardiacarcinoom. Tevens werd een meta-analyse verricht, waarbij studies die resultaten van stadiëringsonderzoeken bevatten werden samengevoegd om één nauwkeurigere uitkomst te krijgen. Deze gegevens suggereren dat de endo-echografie het onderzoek van keuze is voor het bepalen van de doorgroei van de tumor in de wand van de slokdarm of cardia (T stadium) en voor het vaststellen van de aanwezigheid van kwaadaardige lymfeklieren (N stadium). Bij patiënten met een slokdarmtumor die zich boven de splitsing van de trachea bevindt, dient een bronchoscopie te worden verricht om te bepalen of de tumor in de trachea- of bronchuswand groeit. De echografie van de hals is het meest geschikte onderzoek om kwaadaardige lymfeklieren in de hals op te sporen. Voor het opsporen van overige uitzaaiingen (M stadium) kunnen een CT scan en een PET scan worden gebruikt. Op basis van wat er op dit moment bekend is over deze onderzoeken, kan worden gesteld dat de PET scan vooral overwogen dient te worden bij patiënten met een tumor die aan de hand van de overige onderzoeken is vastgesteld als een T3N0-1 tumor. Bij deze patiënten kan de PET scan worden gebruikt om uitzaaiingen te detecteren die niet met andere onderzoeken zijn gevonden.

Kwaadaardige lymfeklieren in de hals worden beschouwd als uitzaaiingen (M stadium) bij patiënten met slokdarmkanker of cardiacarcinoom. Zowel een echografie van de hals als een CT scan kunnen worden gebruikt om deze uitzaaiingen op te sporen. In **hoofdstuk 3** werden de echografie van de hals, eventueel in combinatie met dunne naald aspiratie (FNA)

om materiaal uit eventuele afwijkingen te verkrijgen voor cytologisch onderzoek, de CT scan en de combinatie van deze onderzoeken vergeleken voor het opsporen van kwaadaardige lymfeklieren in de halsregio. Het doel van deze studie was om te onderzoeken of één of beide onderzoeken uitgevoerd moeten worden bij patiënten met slokdarmkanker of cardiacarcinoom om kwaadaardige lymfeklieren in de halsregio op te sporen. Voor deze studie werden de gegevens van 567 patiënten geanalyseerd. Bij deze patiënten werd tussen januari 1994 en juni 2004 de diagnose slokdarmkanker of cardiacarcinoom gesteld en deze personen hadden zowel een CT scan als een echografie van de halsregio ondergaan. De studie liet zien dat echografie *plus* FNA, alleen of in combinatie met een CT scan van de halsregio, superieur is aan een echografie van de hals, een CT scan of de combinatie van een echografie en een CT scan voor het opsporen van kwaadaardige lymfeklieren in de halsregio. Daarom is de echografie *plus* FNA het onderzoek van keuze voor het opsporen van lymfeklieren in de halsregio bij patiënten met slokdarmkanker of cardiacarcinoom. De sensitiviteit voor het opsporen van uitzaaiingen nam slechts gering toe wanneer naast de echografie *plus* FNA van de hals een CT scan van dit gebied wordt verricht.

Het is bekend dat er een verband bestaat tussen het aantal slokdarmkankeroperaties dat in een ziekenhuis wordt uitgevoerd en het risico van overlijden van patiënten ten gevolge van de operatie, waarbij het overlijdensrisico gemiddeld lager is in ziekenhuizen waar een groter aantal operaties wordt uitgevoerd. In de studie beschreven in **hoofdstuk 4** werd onderzocht of er ook een verband bestaat tussen het aantal patiënten met slokdarmkanker of cardiacarcinoom dat wordt onderzocht in een ziekenhuis door middel van stadiëringsonderzoeken en het aantal uitzaaiingen dat wordt opgespoord. Tussen januari 1994 en oktober 2003 werden 1088 patiënten met slokdarmkanker of cardiacarcinoom geëvalueerd in het Erasmus MC Rotterdam, wat een verwijzingscentrum is voor patiënten met slokdarmkanker of cardiacarcinoom. Bij 906 patiënten werd de diagnose slokdarmkanker of cardiacarcinoom in eerste instantie in een regionaal ziekenhuis gesteld en vervolgens werden deze patiënten verwezen naar het verwijzingscentrum. Bij 573 patiënten werden de stadiëringsonderzoeken (CT scan, echografie van de buik of hals, en/of thoraxfoto) die in een regionaal ziekenhuizen waren verricht, herbeoordeeld of herhaald in het verwijzingscentrum. De kwaliteit van het opsporen van uitzaaiingen werd vergeleken tussen het hoog-volume verwijzingscentrum en de laag-volume regionale ziekenhuizen. Er werd gevonden dat in het hoog-volume verwijzingscentrum meer uitzaaiingen werden opgespoord dan in de verwijzende regionale ziekenhuizen. Met andere woorden, wanneer de beslissing om een operatie uit te voeren alleen gebaseerd zou zijn op de resultaten die in de regionale ziekenhuizen waren verkregen, zou meer dan 1 op de 20 patiënten een operatie hebben ondergaan in de aanwezigheid van uitzaaiingen, terwijl de aanwezigheid van uitzaaiingen juist een contra-indicatie is voor het verrichten van een operatie. Deze betere resultaten worden waarschijnlijk verklaard door de aanwezigheid van zowel betere CT apparatuur als meer ervaren radiologen in het hoog-volume verwijzingscentrum.

In de studie beschreven in **hoofdstuk 5** beoordeelden 2 radiologen van verwijzingscentra ('expert radiologen') en 6 radiologen van regionale ziekenhuizen ('niet-expert radiologen') 72 CT scans van patiënten bij wie tussen 1994 en 2003 de diagnose slokdarmkanker of cardiacarcinoom werd gesteld. De expert radiologen beoordeelden elk 48 CT scans en de niet-expert radiologen 24 CT scans, waardoor in totaal 240 beoordelingen werden verricht. Het doel van deze studie was om te bepalen of de kwaliteit van de CT scans en de ervaring van de radiologen inderdaad factoren zijn die een rol spelen bij het detecteren van uitzaaiingen op CT scans. De resultaten van deze studie toonden aan dat zowel de ervaring van de radiologen als de kwaliteit van de CT scans een rol spelen bij het opsporen van uitzaaiingen op CT scans van patiënten met slokdarmkanker of cardiacarcinoom. Deze resultaten duiden erop dat het stadiëren van patiënten met slokdarmkanker of cardiacarcinoom plaats zou moeten vinden in centra die de mogelijkheid hebben om kwalitatief goede CT scans te maken en waar ervaren radiologen werken. Het proces van stadiëring zou op deze manier geoptimaliseerd kunnen worden.

Het is reeds eerder vastgesteld dat voor het uitvoeren van endo-echografie een leercurve aanwezig is en dat acceptabele resultaten slechts na het uitvoeren van tenminste 75-100 endo-echografieën kunnen worden verkregen. In **hoofdstuk 6** werden de resultaten van endo-echografie die verkregen waren in het Erasmus MC Rotterdam vergeleken met gegevens van centra die een groter aantal endo-echografieën verrichten. De gegevens van deze centra waren afkomstig uit de literatuur. Het doel van de studie was om te bepalen of het aantal endo-echografieën dat per endoscopist per jaar wordt uitgevoerd invloed heeft op de resultaten van de endo-echografie bij patiënten met slokdarmkanker of cardiacarcinoom. Tussen 1994 en 2003 werd bij 244 patiënten een endo-echografie verricht en vervolgens ondergingen deze patiënten een operatie. Bij een aantal patiënten was een zodanige vernauwing van de slokdarm aanwezig ter plaatse van de tumor dat de endo-echografie probe de tumor niet kon passeren. Hoewel het recentelijk is vastgesteld dat het mogelijk is om de vernauwing op te rekken (dilatatie), was dat bij deze patiënten niet gebeurd. Er was tevens geen FNA verricht bij deze patiënten. Dit had te maken met het feit dat het uitvoeren van FNA en dilatatie nog niet gebruikelijk was ten tijde van het verrichten van deze endo-echografieën. Zeven hoog-volume centra rapporteerden hun ervaringen in de literatuur. In totaal werden in deze centra 670 endo-echografieën voor slokdarmkanker uitgevoerd. In de meeste centra werd dilatatie uitgevoerd wanneer dit nodig was. In deze studie werd gevonden dat de resultaten van endo-echografie uitgevoerd in het laag-volume endo-echografie centrum, waar <50 endo-echografieën per endoscopist per jaar werden uitgevoerd, slechter waren in vergelijking met de resultaten van de hoog-volume centra. De resultaten van deze studie duiden erop dat bij het verkrijgen van zo betrouwbaar mogelijke endo-echografie resultaten de ervaring van de endoscopist een belangrijke factor is. Daarom is het te adviseren dat alleen ervaren endoscopisten endo-echografieën verrichten om het proces van stadiëring van slokdarmkanker en cardiacarcinoom te optimaliseren.

Het is aangetoond dat de resultaten van endo-echografie voor de stadiëring van endeldarmkanker worden overschat in de literatuur als gevolg van het selectief rapporteren van studies met positieve resultaten. Dit wordt publicatiebias genoemd. In de studie beschreven in **hoofdstuk 7** werd onderzocht of publicatiebias ook aanwezig is bij het rapporteren van de resultaten van endo-echografie bij patiënten met kanker in de slokdarm, maag of alvleesklier. De beschikbare literatuur, die aanwezig is in Medline, werd hiervoor geanalyseerd. Alle artikelen die informatie bevatten over de resultaten van endo-echografie voor het vaststellen van het T en/of N stadium van tumoren in de slokdarm, maag of alvleesklier werden geëvalueerd. Er werden vervolgens grafieken gemaakt waarin de resultaten van endo-echografie werden uitgezet tegen het aantal patiënten, het jaar van publicatie van de artikelen, het soort tijdschrift en de impact factor van het tijdschrift. De impact factor is een maat om het relatieve belang van een wetenschappelijk tijdschrift aan te geven. In deze studie werden geen aanwijzingen gevonden dat publicatiebias aanwezig is bij het rapporteren van de resultaten van endo-echografie bij patiënten met een tumor in de slokdarm, maag of alvleesklier. Dit duidt erop dat de resultaten van endo-echografie voor het T en N stadium van tumoren in de slokdarm, maag of alvleesklier waarschijnlijk niet overschat zijn in de literatuur. De mate waarin het T stadium goed werd vastgesteld ('accuracy') door middel van endo-echografie nam echter af in de periode tussen 1989 en 2005. Hier zijn twee redenen voor te geven: 1) in de loop van de tijd zijn steeds meer ziekenhuizen endo-echografie gaan verrichten, waarbij endo-echografie ook in minder ervaren centra in gebruik is genomen en 2) door de jaren heen is het aantal slokdarmtumoren dat in beperkte mate in de slokdarmwand is gegroeid (T1 en T2 stadium) toegenomen en het aantal tumoren dat in meer uitgebreide mate in de wand is gegroeid (T3 en T4 stadium) afgenomen. Dit wordt waarschijnlijk veroorzaakt doordat patiënten met een T3 of T4 slokdarmtumor in de laatste jaren vaker met chemotherapie en/of bestraling werden behandeld. De resultaten van endo-echografie bij patiënten met een T1 of T2 slokdarmtumor zijn over het algemeen slechter dan de resultaten bij patiënten met een T3 of T4 slokdarmtumor. Er werd geen verband gevonden tussen de resultaten van endo-echografie en het soort tijdschrift respectievelijk de impact factor.

Er zijn verschillende onderzoeken die verricht kunnen worden bij het stadiëren van patiënten met slokdarmkanker of cardiacarcinoom. De CT scan is thans het standaard onderzoek voor het opsporen van uitzaaiingen. Het is echter niet duidelijk of daarnaast het verrichten van een echografie van de buik, endo-echografie, echografie van de halsregio en thoraxfoto noodzakelijk is voor het opsporen van uitzaaiingen. In **hoofdstuk 8** werd bepaald of deze onderzoeken inderdaad verricht moeten worden bij patiënten met slokdarmkanker of cardiacarcinoom of dat het effectiever is om één onderzoek of een (beperkte) selectie van onderzoeken te verrichten voor de regio's waarin uitzaaiingen aanwezig kunnen zijn. In totaal werden 569 patiënten met slokdarmkanker of cardiacarcinoom geanalyseerd. Deze patiënten hadden een CT scan en één of meer andere onderzoeken, zoals een echografie van de buik, echografie van de hals en/of een thoraxfoto, ondergaan. Bij 335 patiënten was zowel

een CT scan als een echografie van de buik verricht voor het opsporen van uitzaaiingen in de lever. Een CT scan en een echografie van de halsregio voor het opsporen van kwaadaardige lymfeklieren in de hals waren verricht bij 546 patiënten. Een CT scan en een thoraxfoto voor het opsporen van uitzaaiingen in de longen waren verricht bij 424 patiënten. Een CT scan, echografie van de buik en endo-echografie voor het opsporen van kwaadaardige lymfeklieren in de bovenbuik, te weten de coeliacusklieren, waren verricht bij 143 patiënten. De resultaten van deze onderzoeken werden vergeleken met de gouden standaard welke gebaseerd was op de uitslag van de operatie, FNA of een onderzoeksresultaat *plus* follow-up van tenminste een half jaar. Voor het opsporen van uitzaaiingen in een regio kan één onderzoek worden verricht (bijvoorbeeld alleen een CT scan of alleen een echografie van de buik voor het opsporen van uitzaaiingen in de lever), maar het is ook mogelijk om twee onderzoeken te verrichten (bijvoorbeeld zowel een CT scan als een echografie van de buik). Het gecombineerde resultaat van de CT scan met respectievelijk de echografie van de buik, endo-echografie, echografie van de halsregio en thoraxfoto werd twee keer berekend. Ten eerste werd het gecombineerde resultaat als positief beschouwd voor de aanwezigheid van uitzaaiingen wanneer tenminste één van de onderzoeken positief was en negatief wanneer beide onderzoeken negatief waren (scenario met 1 positief onderzoek). Ten tweede werd het gecombineerde resultaat als positief beschouwd wanneer zowel de CT scan als het andere onderzoek positief waren en negatief wanneer tenminste één van de onderzoeken negatief was (scenario met 2 positieve onderzoeken). Op orgaanniveau was de sensitiviteit van de CT scan voor het opsporen van uitzaaiingen in de coeliacusklieren, lever en longen hoger dan de sensitiviteit van de echografie van de buik, endo-echografie en thoraxfoto. De sensitiviteit van de echografie van de halsregio, eventueel in combinatie met FNA, voor het opsporen van kwaadaardige lymfeklieren in de halsregio was hoger dan de sensitiviteit van de CT scan. Op patiëntniveau was de sensitiviteit voor het opsporen van uitzaaiingen 66% en de specificiteit 95% wanneer alleen een CT scan zou zijn verricht. Een hogere sensitiviteit (86%) werd verkregen wanneer een echografie van de halsregio voor het opsporen van kwaadaardige lymfeklieren in de halsregio werd toegevoegd aan de CT scan, waarbij de specificiteit gelijk bleef (95%). Een iets hogere specificiteit (97%) werd verkregen door het toevoegen van een echografie van de buik voor het opsporen van uitzaaiingen in de lever. Dit was echter alleen het geval wanneer de aanname was dat zowel de CT scan als de echografie van de buik positief moesten zijn voor de aanwezigheid van uitzaaiingen om het resultaat als positief te kunnen beschouwen (scenario met 2 positieve onderzoeken). Wanneer de thoraxfoto voor het opsporen van uitzaaiingen in de longen werd toegevoegd, nam de specificiteit verder toe tot 99%. Ook hierbij gold dat dit alleen het geval was wanneer de aanname was dat zowel de CT scan als de thoraxfoto positief moesten zijn voor de aanwezigheid van uitzaaiingen om het resultaat als positief te kunnen beschouwen (scenario met 2 positieve onderzoeken). Belangrijk was echter dat de sensitiviteit afnam met de toename van de specificiteit. Een lagere sensitiviteit betekent in de praktijk dat meer patiënten een operatie ondergaan in de aanwe-

zigheid van uitzaaiingen, wat klinisch niet gewenst is. Wanneer rekening werd gehouden met de kosten van de operatie, de levensverwachting van de patiënten en de kwaliteit van leven kwam naar voren dat de combinatie van de CT scan en de echografie van de halsregio de optimale strategie is om patiënten te stadiëren. De echografie van de buik, endo-echografie en thoraxfoto hadden een beperkte toegevoegde waarde bij het vaststellen van de optimale behandeling van patiënten met slokdarmkanker of cardiacarcinoom.

In de Verenigde Staten is eerder een verband gevonden tussen de sociaal-economische klasse van patiënten met verschillende soorten tumoren en de histologie, de uitgebreidheid en de behandeling van de tumoren. In de studie beschreven in **hoofdstuk 9** werd onderzocht of er ook een verband bestaat tussen de sociaal-economische klasse van patiënten met slokdarmkanker in Nederland en de histologie, de stadiëringsonderzoeken die werden verricht, de uitgebreidheid en de behandeling. Tussen januari 1994 en oktober 2003 werd bij 888 patiënten de diagnose slokdarmkanker gesteld. De gegevens van deze patiënten werden verzameld in een prospectieve database. Deze database bevat informatie over kenmerken van de patiënten (geslacht, leeftijd), de uitgebreidheid van de tumor en de behandeling. De sociaal-economische klasse van de patiënten werd gedefinieerd als het gemiddelde netto jaarlijkse inkomen. De resultaten van deze studie toonden aan dat er een verband bestaat tussen de sociaal-economische klasse van patiënten en de histologie van de tumor, waarbij patiënten in een lagere sociaal-economische klasse vaker een plaveiselcelcarcinoom hadden en patiënten in een hogere sociaal-economische klasse vaker een adenocarcinoom. Er werd geen verband gevonden tussen de sociaal-economische klasse van patiënten en de onderzoeken die werden verricht respectievelijk de uitgebreidheid van de tumor. De behandeling van patiënten met slokdarmkanker kan bestaan uit het plaatsen van een stent, het verrichten van een operatie, of het toedienen van chemotherapie of bestralingen. Patiënten in een lagere sociaal-economische klasse werden vaker behandeld door middel van het plaatsen van een stent. Patiënten in een hogere sociaal-economische klasse ondergingen daarentegen vaker een operatie of een behandeling met chemotherapie. Er werd geen verband gevonden tussen de sociaal-economische klasse van patiënten en een behandeling met bestraling. De associaties tussen de sociaal-economische klasse en de behandeling met stentplaatsing, operatie of chemotherapie bij patiënten met slokdarmkanker in Nederland duiden er waarschijnlijk op dat zowel patiënt- als artsfactoren een rol spelen bij het vaststellen van de soort behandeling die patiënten krijgen, aangezien de toegang tot medische zorg in Nederland voor elke inkomensgroep gelijk is.

CONCLUSIES

Stadiëring is belangrijk bij patiënten met slokdarmkanker of cardiacarcinoom om de optimale behandeling voor deze groep patiënten te selecteren. Op dit moment zijn er vele stadi-

eringsonderzoeken beschikbaar en het is de vraag of al deze onderzoeken verricht moeten worden bij patiënten met slokdarmkanker of cardiacarcinoom. De studies beschreven in dit proefschrift tonen aan dat meestal kan worden volstaan met een selectie van de verschillende onderzoeken. De onderzoeken die wel bij elke patiënt met slokdarmkanker of cardiacarcinoom verricht zouden moeten worden, zijn een endo-echografie, een CT scan van de halsregio, borst- en buikholte en een echografie van de halsregio.

Een endo-echografie zou verricht moeten worden om de doorgroei van de tumor in de wand van de slokdarm of cardia te bepalen (T stadium) en om vast te stellen of er kwaadaardige lymfeklieren aanwezig zijn (N stadium). De endo-echografie dient echter wel te worden verricht in centra met ervaren endoscopisten om zo de resultaten van de endo-echografie te optimaliseren.

De CT scan is geïndiceerd om te bepalen of er uitzaaiingen aanwezig zijn in de halsregio, borst- en buikholte. In dit proefschrift is beschreven dat de ervaring van radiologen een belangrijke factor is bij het evalueren van CT scans van patiënten met slokdarmkanker of cardiacarcinoom. Tevens dient een CT scan kwalitatief goed te zijn om het opsporen van uitzaaiingen verder te optimaliseren.

De echografie van de hals kan worden gebruikt om kwaadaardige lymfeklieren in de halsregio op te sporen. Dit onderzoek dient bij elke patiënt met slokdarmkanker of cardiacarcinoom te worden verricht, omdat een CT scan alleen niet voldoende sensitief is om deze uitzaaiingen op te sporen. Wanneer een lymfeklier suspect is voor de aanwezigheid van een uitzaaiing, dient FNA te worden uitgevoerd om materiaal te verkrijgen voor cytologisch onderzoek. Het is belangrijk dat FNA alleen wordt verricht als de uitslag hiervan de behandelingskeuze kan veranderen.

Er zou wellicht een beperkte rol voor de bronchoscopie en PET scan kunnen zijn. Een bronchoscopie kan worden verricht bij patiënten die een slokdarmtumor hebben boven de splitsing van de trachea om vast te stellen of de slokdarmtumor in de bronchus- of tracheawand groeit, wat een contra-indicatie is voor een operatie. De PET scan zou een plaats kunnen hebben bij patiënten bij wie geen uitzaaiingen zijn gevonden met andere onderzoeken, waarbij het dan vooral gaat om patiënten met een T3N0-1 tumor.

De studies zoals beschreven in dit proefschrift zijn voornamelijk retrospectief uitgevoerd, wat inhoudt dat gebruik is gemaakt van data van patiënten die in het verleden zijn gediagnosticeerd, onderzocht en behandeld. Deze data zijn weliswaar prospectief verzameld, maar een nieuwe prospectieve studie is nodig om te beoordelen of stadiëringsonderzoeken inderdaad selectief kunnen worden verricht bij patiënten met slokdarmkanker of cardiacarcinoom zonder negatieve gevolgen voor de patiënten. Verder dient de exacte rol van de PET scan bij de stadiëring van patiënten met slokdarmkanker of cardiacarcinoom te worden bepaald. Tenslotte dient onderzocht te worden of de mogelijke voordelen van de PET scan opwegen tegen de (momenteel nog) hoge kosten van het uitvoeren van een PET scan.

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Curriculum Vitae

CURRICULUM VITAE

De auteur van dit proefschrift werd geboren op 18 januari 1982 te Naaldwijk. Na het behalen van haar V.W.O. diploma aan de Interconfessionele Scholengemeenschap het Westland, te Naaldwijk in 2000, werd in datzelfde jaar gestart met de studie Geneeskunde aan de Erasmus Universiteit te Rotterdam. Het afstudeeronderzoek behorende bij het 4e jaar van de studie Geneeskunde, werd, onder begeleiding van Dr. P.D. Siersema, verricht op de afdeling Maag-, Darm- en Leverziekten (hoofd Prof.dr. E.J. Kuipers) van het Erasmus MC te Rotterdam. Het doctoraalexamen werd behaald op 20 juli 2004. Vanaf september 2004 werkte zij als wetenschappelijk onderzoeker op de afdeling Maag-, Darm- en Leverziekten van het Erasmus MC aan haar promotieonderzoek. Tijdens deze periode werden onder dagelijkse begeleiding van Dr. P.D. Siersema de onderzoeken verricht zoals deze beschreven zijn in dit proefschrift (promotor: Prof.dr. E.J. Kuipers). Op 22 januari 2007 zal zij starten met haar co-schappen. Na haar co-schappen wil zij zich specialiseren in maag-, darm- en leverziekten.