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Current views

Preoperative staging of esophageal and gastric carcinoma

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INTRODUCTION

Preoperative staging is of paramount importance for a patient with cancer of the upper GI tract. Because the outcome of esophageal and gastric cancer is strongly related to stage, an effort has been made during the last years with respect to preoperative staging before considering application of treatment aimed at curing the disease, prolonging survival, or palliating symptoms. Esophagectomy is accompanied by the highest mortality reported for any electively performed surgical procedure. The poor performance status of most patients and the difficulty of the operative procedure are responsible for an in-hospital mortality rate that, at the beginning of 1980's, was almost 30%,[1] although this figure seems to be rather better today.

The aim of this review is to describe the available methodology for preoperative staging of esophageal and gastric carcinoma and to provide the reader with guidelines based on the current scientific data.

1. PREOPERATIVE STAGING OF ESOPHAGEAL CARCINOMA

Staging of esophageal carcinoma is based on the TNM system, which focuses on and defines the anatomical extent of disease. It must be emphasized that squamous cell carcinoma and adenocarcinoma of the esophagus are staged similarly. Moreover, symptoms such as dysphagia, and results of various laboratory tests including biomarkers, are invalid in assessing the preoperative stage of the disease.

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According to the TNM system of classification of esophageal cancer the term "T" indicates the invasion of the primary tumor, "N" indicates the spread of carcinoma to specified regional lymph nodes and "M" indicates distant metastases to either lymph nodes outside specified regional nodes or to organs not involved directly in the primary tumor, such as liver, lung, etc.

According to the American Joint Committee on Cancer (AJCC) and the International Union Against Cancer (IUAC) the length of tumor, the extent of involved circumference and the degree of luminal compromise are not important factors in staging. Any regional lymph node metastasis is considered N1 and more distant nodal metastases are considered to represent distant metastases (M1). Table 1 shows the classification of esophageal cancer according to the TNM system.

1.1. Methods for staging of esophageal carcinoma

Methods for staging of esophageal carcinoma can be classified into two groups (Table 2). The first group consists of the most useful methods available in the routine clinical setting, and the second consists of methods not widely available. Some of these later methods are currently under intense clinical investigation.

1.1.2. Initial methods of staging

Initial methods of staging of esophageal cancer include a thorough physical examination, blood tests, chest x-rays, as well as modern techniques involving primarily computed topography and endoscopic ultrasonography.

The "Practice Guidelines" of the American College of Gastroenterology recommends the following strategy for patients who have been diagnosed as having esophageal cancer: *"Computed tomography of the chest and the abdomen should be the initial tests for staging. If there is no evidence of metastatic disease, endosonography should be performed to achieve the most accurate regional staging".*[2]

Table 1. Staging classification of esophageal cancer

Primary Tumor Groupings (T)	Regional Lymph Nodes (N) (*)	Distant Metastasis (M)	Stage
TX: Primary tumor cannot be assessed	NX: Regional lymph nodes cannot be assessed	MX: Presence of distant metastasis cannot be assessed	Stage 0: Tis N0M0
T0: No evidence of primary tumor	N0: No regional lymph node metastasis	M0: No distant metastasis	Stage 1: T1N0M0
Tis: Carcinoma in situ	N1: Regional lymph node metastasis	M1: Distant metastasis	Stage IIA: T1N0M0; T3N0M0
T1: Tumor invades lamina propria or submucosa (#)			Stage IIB: T1N1M0; T2N1M0
T2: Tumor invades muscularis propria			Stage III: T3N1M0; T4, any N,M0
T3 Tumor invades adventitia T4: Tumor invades adjacent structures			Stage IV: Any T, any N, M1

(*) For the cervical esophagus, the cervical nodes are considered regional; for the intrathoracic esophagus the mediastinal and perigastric lymph nodes are considered regional

(#) T1 has been subdivided into T1m, (confined to the submucosa) ant T1sm cancer invading the submucosa)

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Table 2. Methods for staging of esophageal carcinoma

a) Initial tests for staging

- Physical examination
- Blood tests
- Chest x-rays
- Barium shallow
- Computed tomography (chest-abdomen)
- Ultrasonography (endoscopic)

a) Tests not widely used on clinical practice

- Magnetic Resonance Imaging
- Laparoscopy
- Thoracoscopy
- Bronchoscopy
- Positron emission tomography
- Reverse Transciptase-Polymerase Chain Reaction

Physical examination

Physical examination focuses mainly on sites prone to metastases such as liver and supraclavicular lymph nodes.

Blood tests

Blood tests (i.e. liver function tests) can provide useful information concerning possible liver metastases.

Chest x-rays

Chest x-rays can identify pulmonary and mediastinal metastases.

Computed Tomography

Computed tomography (CT) remains one of the most useful and widely used modern method for preoperative staging of patients with esophageal carcinoma. On CT examination lymph nodes greater than 10mm, are considered to be metastatic. CT can detect pulmonary or hepatic metastases and provide information concerning the tumor extent, adherence in adjacent structures, and detect infiltrated lymph nodes. CT can also accurately detect the circumferential or eccentric thickness of the esophageal wall at the site of the tumor. Despite the high degree of CT specificity concerning the thickness of the esophageal wall, the overall specificity for detecting spread to contiguous structures is low (40%) becoming even lower (25%) for nodal infiltration.[3] However, the diagnostic significance of lymph node enlargement becomes less important if one considers that the detection of enlarged lymph nodes does not necessarily mean the presence of metastasis.

CT is also valuable in detecting mediastinal metastases (>90%) which represents an absolute contraindication for operation.[4] Additional patient positions do not improve computed tomographic prediction of local irresectability.

Endoscopic ultrasonography

Endoscopic ultrasonography (EUS) must be used if there are no signs of distant metastases at CT of the chest and abdomen. Depth of invasion of tumor corresponds well with certain abnormalities on endoscopic wall-layer ultrasonography (Table 3). Enlarged lymph nodes on EUS are considered to be malignant if their diameter exeeds the size of 10mm and if they are hypoechoic, rounded, and sharply demarcated from the surrounding fat. It must be emphasized, however, that benign lymph nodes may sometimes be greater than 10mm. EUS has the advantage of providing the endoscopist with the ability to perform fine needle aspiration from the tumor, thus improving the diagnostic ability of the procedure. However the major problem of the method lies in its inability to pass through a stenotic area.

EUS was able to detect the depth of infiltration («T») in 36 out of 40 patients with esophageal carcinoma (90%), compared with 50% by computed topography.[5] In the same study the lymph node involvement («N») was correctly classified by EUS in 20 out of 23 patients (87%) compared with 39% by CT. In another study,[6] the overall accuracy, specificity and sensitivity of EUS were 87%, 90% and 37% respectively. The accuracy of detecting lymph node metastases was 80%.

Although EUS is mainly used for the detection of regional lymph node metastases, it could also be useful for the evaluation of metastatic celiac axis lymph nodes. In a recent study,[7] the sensitivity and specificity of EUS for the diagnosis of celiac axis lymph node metastases was 83% and 98%, respectively, while the corresponding features for diagnosis of mediastinal lymph node metastases were 79% and 63%, respectively. EUS has also been used with promising results for the detection of cervical lymph node metastases.[8]

The clinical significance of preoperative diagnosis of invaded peri- and para- esophageal lymph nodes is low.

Table 3. Depth of invasion (T) compared with endoscopic ultrasound wall-layer abnormality

Depth of invasion (T)	Endoscopic ultrasonography abnormality
T1m, mucosa	1 and 2
T1sm, submucosa	3
T2, muscularis propria	4
T3, adventitia	5
T4, adjacent organ	Adjacent organ

(Am J Gastroenterol 1999; 94:20-40)

The resection of the specimen is not lying on where lymph nodes of the mediastinal are involved or not, but rather on where the tumor is invading mediastinal vital structures such as trachea, bronchi, pericardium e.t.c. If lymph nodes are invaded the resection is considered as palliative and this type of therapy is still considered as ideal for palliation if technically possible. When lymph nodes are negative the resection is considered as curative. However, even in this case there is only a 40-50% survival rate at 5 years. Therefore the accurate diagnosis of invasion of small mediastinal lymph nodes in cases of esophageal "resectable" cancer is of academic interest in terms of surgical (operative) strategy. However it makes little difference in terms of prognosis.

1.1.3. Tests not widely used in clinical practice

Magnetic resonance imaging (MRI)

MRI compared to CT appears to be less reliable and not add significantly in the staging of patients with esophageal cancer. It is well known that staging the depth of tumor invasion on the basis of wall thickness carries a significant risk of interpretation errors. MRI can visualize the gross features of tumor growth pattern, tumor ulceration and adjacent lymph node involvement.

T1 and T2 are considered to be the case if the wall thickness ranges between 6 and 15 mm and T3 if the wall thickness is greater than 16 mm. (A wall thickness of 5mm is considered to be the upper normal limit). MRI cannot distinguish T1 from T2. Diagnosis of T4 disease is based on loss of flat planes and mass effect.

Recent reports concerning the real value of MRI challenge the previous ones. In a relevant study,[9] the depth of mural invasion visualized with MRI correlated well with that determined by pathology. However, the stage determined with MRI was higher in 3% and lower in 3% of the cases studied.

MRI must be further explored as far as its role in the preoperative staging of patients with esophageal cancer is concerned.

Bronchoscopy

Bronchoscopy can be used to detect local infiltration of the trachea or bronchi by advanced cancers in the proximal esophagus. In a relevant study,[10] the overall accuracy of bronchoscopy plus multiple brush cytology and biopsy sampling in proving or excluding airway invasion on patients with otherwise operable conditions, was 95.8%. In the same study the results of bronchoscopy and CT were found to be discordant in 40% of patients

and the specificity and positive predictive value were higher for bronchoscopy than for CT.

Bronchoscopy also allows the identification of patients who are candidates for operation despite the presence of tracheobronchial tree compression. Compression of the tracheobronchial tree does not necessarily mean infiltration by esophageal carcinoma. It has been shown that if the compression is slight and the mobility of the tracheobronchial tree is normal, a radical esophagectomy is possible in 91% of patients.[11]

Laparascopy-Thoracoscopy

Laparascopy is used in some cases to document small liver and intraperitoneal metastases, before aggressive surgery is undertaken. It could also be useful in the assessment of thoracic lymph nodes involvement. Thoracoscopic lymph node staging was found to be accurate in detecting the presence of thoracic lymph nodes in 93% of patients, while laparoscopic lymph node staging accurately detected lymph node metastases in 94%.[12] In a recent study,[13] it was found that staging of esophageal cancer by means of thoracoscopy/laparascopy had a higher specificity and accuracy than CT and EUS, especially for N1 disease in the chest. Compared with final resection pathology, the sensitivity, specificity and positive predictive value of staging for N1 disease in the chest was 62.5, 100.0 and 100.0 % by thoracoscopy; 75.0, 75.6, and 23.1% by CT and 0.0, 97.1, and 0.0% by EUS, respectively. In another study,[14] satisfactory thoracoscopic lymph node staging was achieved in 44 out of 49 patients (95%).

Positron Emission Tomography (PET)

Continuing advances in PET imaging have resulted in an improved ability to evaluate thoracic malignancies. PET provides accurate and non-invasive detection and staging of thoracic malignancies.

PET has been used mainly for the detection of lymph node metastases.[15] The (18)F-FDG PET was superior to CT in detecting metastases in the mediastinum and the upper abdomen, PET being able to detect 85% of the metastatic lymph nodes in the mediastinum and the upper abdomen. PET has also been shown to be superior of CT in detecting the primary tumor in patients with esophageal cancer (96% vs 62% respectively).[16] In the same study it was found that the diagnostic accuracy of PET was 88% compared with 65% of CT.

PET, if it becomes widely available, will probably dramatically change the rate of ill-advised surgery for esophageal cancer.

Reverse-Transcriptase-Polymerase Chain Reaction (RT-PCR)

It is well established that histologic examination of lymph nodes misses micrometastases in up to 20% of lymph nodes evaluated. Moreover it has been shown that most patients with esophagogastric malignancies have micrometastases in rib marrow at the time of diagnosis.[17] RT-PCR has recently been used on patients with esophageal carcinoma in order to identify micrometastases on lymph nodes which present negative on the conventional histology.[18] The method detects Carcinoembryonic Antigen Messenger ribonucleic acid (mRNA) on lymph nodes. The presence of CEA mRNA is evidence of micrometastatic disease. Initial follow-up suggests that a positive RT-PCR with negative histologic findings may have poor prognostic implications. However, further studies will be needed to confirm the clinical implications of this novel method.

2. PREOPERATIVE STAGING OF GASTRIC CARCINOMA

Pathological staging of gastric cancer is based on the extent of the disease at laparatomy and/or the histological examination of the excised specimen. For the classification of gastric carcinoma the TNM system (as described for esophageal cancer) has been almost universally adopted. The TNM stage grouping is shown in figure 1.

However, a new classification based on recommendations proposed by the International Union Against Cancer (UICC), has recently appeared in the literature. In this new (5^{th}) edition, the description of nodal staging has been changed from the anatomic sites of lymph nodes to the number of metastatic ones. According to this classification, pN1 corresponds to metastases in 1 to 6 lymph nodes, pN2 corresponds to metastases in 7 to 15 lymph nodes and pN3 corresponds to metastases in 16 or more lymph nodes. Two recently published studies[19,20] found this new method of nodal classification to be both reliable and practical. Moreover, the new nodal staging was closely correlated with the depth of invasion. The 5-year survival rates after gastrectomy decreased significantly by increasing the extent of pN classification. The new classification also showed more homogeneous survival at the same time than the older one.[19] In both studies it was found that the new classification was a significant prognostic determinant for gastric cancer, that can be used with confidence in clinical practice.

Very recently, one more classification based on the

classical Dukes' classification modified by the number of positive lymph nodes (Dukes' A, B, Ca and Cb) appeared in the literature.[21] According to the results of this study, the Dukes' classification was well correlated with both tumor progression and patient survival. Further studies are needed in order to confirm or to reject the findings of this interesting study.

2.1. Methods for staging of gastric cancer

As in the case of esophageal carcinoma, the methodology of preoperative gastric cancer staging includes a complete physical examination, chest x-ray and blood tests including tumor markers (CEA, CA 19-9 and Ca 72-4). Preoperative laparascopy and modern imaging techniques are widely used nowadays. The available data concerning these diagnostic modalities are analyzed subsequently.

2.1.1. Computed Tomography

Computed tomography (CT) represents one of the most useful and widely used examinations performed on patients with gastric carcinoma. However, much controversy still exist as to the value of this method on preoperative staging of patients with gastric carcinoma, because of its inability to identify correctly lymph node metastases, invasion of adjacent organs, or peritoneal metastases. The sensitivity, specificity and accuracy of preoperative CT in determining the perigastric tumor spreads was reported to be 33%, 97% and 73% in pancreatic invasion, 36%, 97% and 70% in level III lymph node involvement, and 89%, 98% and 96% in liver metastasis.[22] Peritoneal dissemination was not detected in 27% of patients and stage IV disease was not diagnosed in 45% of patients.[22] Recently applied modifications of CT examination such as water filling of the stomach resulted in optimization of visualization of the gastric wall on contrast-enhanced CT.[23,24] Using this method it was found that the overall accuracy of tumor staging ranged between 66-77%, overstaging and understaging being 17-25% and 3-8.5% respectively. The overall accuracy for N staging ranged between 46% and 51%.[23] Similar results were reported in another study.[24]

Spiral CT scanners have a number of potential advantages over conventional ones, including the absence of respiratory misregistration, and optimization of intravenous contrast enhancement. In one study[25] sensitivity of helical CT for early gastric cancer was 26% and for the advanced 100%. However, three lesions were misdiagnosed as gastric cancer. Differentiation between T2 and T3 cancer and between T1/T2 and T3/T4 (extraserosal invasion) was possible in 73% and 83% respectively. Overall T-staging was correct in 66%. Diagnosis of serosal invasion was not markedly improved by helical CT.[25] In another study[26] spiral CT remained poor at identifying lymph node metastases to both N1 and N2 lymph nodes with sensitivity ranging from 24 to 43%. However, spiral CT correctly detected 13 of 17 cases of invasion of either the colon or the mesocolon (76%) and 50% of cases with invasion of the pancreas.[26]

Other modifications of CT examination include triphasic spiral CT,[27] water filling of the stomach plus drug-induced hypotonia,[28] and spiral CT using the "breathholding" technique.[29] Using the first method, the authors were able to detect the cancer in 98% of cases and to correctly identify the T stage in 82% of patients.[26] Using the second method the authors described their results as promising in evaluating the depth of tumor invasion and for differentiating intestinal from diffuse gastric cancer.[27] Using the third technique gastric cancer was detected in 39 of 40 cases (97.5%) while location of the tumor was correctly assessed in all cases.[28] In 79.4% of cases CT was accordant with pathological staging. In the same study infiltrated lymph nodes were detected in 70% of patients.

The available data support the assumption that pancreatic involvement, extended lymph node metastasis and peritoneal dissemination are sometimes overlooked on conventional CT examination on patients with advanced gastric cancer. The newly introduced methods (helical CT and other technical modifications) have increased substantially the sensitivity and accuracy of the method in staging patients with gastric carcinoma.

2.1.2. Ultrasonography (endoscopic, hydrosonography, laparoscopic)

EUS is a valuable tool for the preoperative evaluation and staging of patients with early or advanced gastric cancer. According to the majority of relevant publications, EUS is considered to be the most accurate method for diagnosing and assessing the local staging of gastric cancer.[30] However, some technical problems remain such as how to differentiate between cancer invasion and ulcer fibrosis, how to detect microinvasion, and how to recognize malignant lymph nodes. The sensitivity of EUS for evaluating metastatic lymph nodes is still problematic. The ability of EUS to accurately predict the depth of tumor invasion (T stage) and involvement of lymph nodes (N stage) was 70% and 65%, respectively.[31] The differentiation of early gastric cancer from advanced gastric cancer showed a concordance rate of 89%, hyperestimation rate of 89% and underestimation rate of 3%. The accuracy of EUS in predicting the stage T1 to T3 was

91%.[30] EUS displays a tendency to overestimate T stage and underestimate N stage.

Hydrosonography is a new modality aiming to improve the diagnostic ability of conventional ultrasound examination. It does not require intraluminal access.[32] The available data support the assumption that this method comes close to endosonography for staging of gastric tumors.

The laparoscopic ultrasonography is also a new method aiming to combine the strengths of both laparascopy and endoscopic ultrasonography. In a relevant study,[33] it was found that T and N staging by laparascopic ultrasonography was comparable to published results for EUS and overall TNM staging was better. Laparoscopic ultrasonography may provide the optimal preoperative staging for gastric cancer.

Recently the value of miniaturized ultrasound catheter probes (miniprobes) was tested on patients with gastric cancer.[34] The overall accuracy of the method in the assessment of tumor infiltration depth was 82%. It must be emphasized however that the value of miniprobe scanning in the assessment of advanced tumors is limited because of the small imaging depth of probe (approximately 3cm). The sensitivity and specificity for detection of lymph node involvement were 73% and 89% respectively.[34]

3.3.3. Laparoscopy

Laparoscopy has recently emerged as a staging modality that is more sensitive and specific in staging of gastrointestinal malignancies than preoperative imaging modalities. Consequently, patients with disease that is amenable to resection are better identified and others with locally advanced disease are spared unnecessary laparotomies.[35] Since laparoscopic techniques may be associated with low morbidity (the rate of recurrence at the port site is very low) and rapid recovery,[36] palliative procedures are being developed for patients with advanced gastrointestinal malignancies.

Laparoscopy was compared with ultrasonography and CT in detecting intra-abdominal spread of malignancy. The method was found to be more sensitive in detecting hepatic, nodal and peritoneal metastases than CT and ultrasonography.[37] Laparoscopy has also been used preoperatively, immediately before an eventual surgical exploration. The procedure detected 21 unsuspected M+ cases out of 100.[38] In this study laparoscopic staging altered clinical staging in a significant proportion of patients (58%). The results of the previous study were recently confirmed by another study.[39] In 40% of patients, the information provided by extended diagnostic laparoscopy led to a modification of the therapeutic strategy in spite of earlier comprehensive diagnostic work-up including CT and EUS. According to earlier reports[40] laparoscopy should also be used in the assessment of patients with adenocarcinoma of the esophagogastric region before performing excisional surgery.

It seems that the application of laparoscopy could result in avoidance of unnecessary surgical exploration in M+ cases. It represents the most reliable and economic tool for the detection of locally advanced tumors in the light of neoadjuvant treatment.

2.1.3. Lavage cytology

Peritoneal lavage cytology is widely performed during surgery for gastric carcinoma. Although the reported results could be one of the most accurate prognostic factors, the cancer stage is currently determined independently of the results of lavage cytology. However, it has recently been shown that positive cytology findings are indicative of a poor prognosis and that the prognostic difference between positive and negative cytology findings are approximately a one-stage difference in the Japanese stage grouping.[41] Lavage cytology should thus be included in the preoperative staging of gastric carcinoma.

Based on the available data, the following recommendations for the preoperative staging of gastric carcinoma can be supported. Before surgical exploration the patient must be submitted for 1) chest x-ray, 2) blood tests (including serum determination of CEA, CA 19-9 and CA-50), 3) Helical computed tomography, 4) Endoscopic ultrasonography and 5) Laparoscopic exploration of the abdomen either immediately before surgery or some days before. Using these procedures we will be able to accurately determine the stage of the disease with obvious implications for the quality of the remaining life of the patient.

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