Clinical features, diagnosis, and staging of gastric cancer

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INTRODUCTION

Most patients with gastric cancer in the United States are symptomatic and already have advanced, incurable disease at the time of presentation. Despite advances in medicine, approximately 50 percent have disease that extends beyond locoregional confines at the time of presentation, and only one-half of those who appear to have locoregional tumor involvement can undergo potentially curative resection. Surgically curable early gastric cancers are usually asymptomatic and are only infrequently detected outside of screening programs. Screening is not widely performed, except in countries that have a very high incidence, such as Japan, Korea, Venezuela, and Chile. (See "Gastric cancer screening".)

The common presenting symptoms of and diagnostic approaches to gastric cancer will be reviewed here. Epidemiology, issues related to screening for high-risk patients, and treatment of gastric cancer are discussed separately. (See "Epidemiology of gastric cancer" and "Gastric cancer screening" and "Adjuvant and neoadjuvant treatment of gastric cancer" and "Surgical management of invasive gastric cancer" and "Initial systemic therapy for metastatic esophageal and gastric cancer".)

CLINICAL FEATURES

Signs and symptoms — Most patients with gastric cancer are symptomatic. Weight loss and persistent abdominal pain are the most common symptoms at initial diagnosis (table 1) [1]. Approximately 25 percent of patients with gastric cancer have a history of gastric ulcer. (See "Peptic ulcer disease: Clinical manifestations and diagnosis", section on 'Clinical manifestations'.)

- Weight loss usually results from insufficient caloric intake, rather than increased catabolism, and may be attributable to anorexia, nausea, abdominal pain, early satiety, and/or dysphagia.

- When present, abdominal pain tends to be epigastric, vague, and mild early in the disease but more severe and constant as the disease progresses.

- Dysphagia is a common presenting symptom in patients with cancers arising in the proximal stomach (figure 1) or at the esophagogastric junction (EGJ). A pseudoachalasia syndrome may occur as the result of involvement of Auerbach's plexus due to local extension or to malignant obstruction near the gastroesophageal junction [2]. (See "Achalasia: Pathogenesis, clinical manifestations, and diagnosis", section on 'Differential diagnosis'.)

- Nausea or early satiety may result from the tumor mass. In cases of an aggressive form of diffuse-type gastric cancer called linitis plastica (image 1), these symptoms arise from the inability of the stomach to distend. Patients may also present with gastric outlet obstruction from an advanced distal tumor.

- Occult gastrointestinal bleeding, with or without iron deficiency anemia, is not uncommon, while overt bleeding (ie, melena or hematemesis) is seen in fewer than 20 percent of cases. The presence of a palpable abdominal mass, although uncommon, is the most common physical finding and generally indicates long-standing, advanced disease [1].

- Patients may also present with signs or symptoms of distant metastatic disease. The most common sites of metastatic disease are the liver, the peritoneal surfaces, and the nonregional or distant lymph nodes. Less commonly, ovary, central nervous system (brain or leptomeningeal), bone, intrathoracic (pleural or parenchymal), or soft tissue metastases can occur:

- In patients with lymphatic spread, the physical examination may reveal a left supraclavicular lymph node (Virchow's node [3], which is the most common physical examination finding of metastatic disease), a periumbilical nodule (Sister Mary Joseph's node [4]), or a left axillary node (Irish node).

- Peritoneal spread can present with an enlarged ovary (Krukenberg tumor [5]) or a mass in the cul-de-sac on rectal examination (Blumer's shelf [6]). While there are patients with ovarian metastases without other peritoneal disease, these are usually a harbinger of later development of visible peritoneal disease.

- Ascites can also be the first indication of peritoneal carcinomatosis.

- A palpable liver mass can indicate metastases, although metastatic disease to the liver is often multifocal or diffuse. Liver involvement is often, but not always, associated with an elevation in the serum alkaline phosphatase concentration.

- Jaundice or clinical evidence of liver failure, if seen, suggests advanced metastatic disease [7]. However, jaundice is also occasionally seen with locally advanced distal tumors, and these patients typically also have gastric outlet obstruction.

- More rarely, patients with gastric cancer may present with complications that result from direct extension of the gastric cancer through the gastric wall. As an example, feculent emesis or passage of recently ingested material in the stool can be seen with malignant gastrocolic fistula, although this is quite rare. More commonly, colonic obstruction may occur.

Paraneoplastic manifestations — Systemic manifestations of gastric cancer related to paraneoplastic phenomena are rarely seen at initial presentation. Dermatologic findings may include the sudden appearance of diffuse seborrheic keratoses (sign of Leser-Trélat) [8] or acanthosis nigricans [9], which is characterized by velvety and darkly pigmented patches on skin folds. Neither finding is specific for gastric cancer, and they may be associated with other gastrointestinal malignancies or simply a benign process. (See "Cutaneous manifestations of internal malignancy", section on 'Hyperkeratotic and proliferative dermatoses'.)

Other paraneoplastic abnormalities that can occur in gastric cancer include a microangiopathic hemolytic anemia [10], membranous nephropathy [11], and

hypercoagulable states (Trousseau's syndrome) [12]. Like with most advanced gastrointestinal malignancies, gastric cancer patients can develop pulmonary emboli. Polyarteritis nodosa has been reported as the single manifestation of an early and surgically curable gastric cancer [13]. (See "Membranous nephropathy: Pathogenesis and etiology" and "Risk and prevention of venous thromboembolism in adults with cancer" and "Clinical manifestations and diagnosis of polyarteritis nodosa in adults".)

IMAGING FINDINGS

Cross-sectional imaging — For patients with a suspected gastric cancer, contrast-enhanced computed tomography (CT) imaging provides information about the primary tumor, and it can also visualize low-volume ascites, peritoneal metastases, liver metastases, and perigastric and distant nodal disease. The CT appearance of a proximal gastric cancer can be illustrated by the figure (image 2). The CT appearance of a distal tumor is provided separately (image 3). (See 'Computed tomography scan in all patients' below.)

Barium studies — Barium studies can identify both malignant gastric ulcers and infiltrating lesions (image 4), and some early gastric cancers may also be seen. However, false-negative barium studies can occur in as much as 50 percent of cases [14]. This is a particular problem in early gastric cancer, where the sensitivity of barium studies may be as low as 14 percent [15]. (See "Early gastric cancer: Clinical features, diagnosis, and staging".)

Given the widespread availability of upper endoscopy and contrast-enhanced CT scans, it is extremely rare in our experience to see a patient whose tumor was initially suspected based on a barium study.

The one scenario in which a barium study may be superior to upper endoscopy for diagnostic evaluation is in patients with linitis plastica. The decreased distensibility of the stiff, "leather-flask" appearing stomach is more obvious on barium study, and the endoscopic appearance may be relatively normal. However, clinical staging and histologic confirmation require endoscopic evaluation, typically endoscopic ultrasound (EUS). (See 'Endoscopic ultrasound' below.)

DIAGNOSIS

- **When to suspect the diagnosis** – The diagnosis of gastric cancer may be suspected in patients with abdominal pain or weight loss and a history of gastric ulcer, or because of findings on upper endoscopy or radiographic imaging (eg, abdominal computed tomography [CT] or barium studies). However, histologic examination of gastric tumor tissue is required to establish the diagnosis; this is almost always acquired with endoscopic biopsies.

- **Endoscopic appearance** – Tissue diagnosis and anatomic localization of the primary tumor are best obtained by upper gastrointestinal endoscopy. The early use of upper endoscopy in patients presenting with gastrointestinal complaints may be associated with a higher rate of detection of early gastric cancers. (See "Surgical management of invasive gastric cancer", section on 'Early diagnosis of gastric cancer'.)

  The typical appearance of gastric cancer is a friable, ulcerated mass (picture 1A-B). In patients with a gastric ulcer, the presence of folds surrounding the ulcer crater that are nodular, clubbed, fused, or stop short of the ulcer margin, and the presence of overhanging, irregular, or thickened ulcer margins are also suggestive of a malignant ulcer. (See "Peptic ulcer disease: Clinical manifestations and diagnosis", section on 'Malignant appearing ulcers'.)

  The gastric mucosa may appear normal in patients with linitis plastica, a particularly aggressive form of diffuse-type gastric cancer. Tumors with extensive submucosal spread (the linitis plastica appearance (image 1)) can be difficult endoscopically; in fact, this is responsible for the vast majority of gastric cancers for which upper endoscopy is nondiagnostic. These tumors tend to infiltrate the submucosa and muscularis propria extensively, and there may be no superficial mucosal findings. Poor distensibility of the stomach may be the only finding on endoscopic evaluation.

- **Biopsy technique** – During endoscopy, any suspicious-appearing gastric ulceration should be biopsied. Since up to 5 percent of malignant ulcers appear benign grossly, it is imperative that all such lesions be evaluated with biopsy and histologic assessment [16].

We obtain biopsies using jumbo forceps and sampling the edges of the ulcer. A single biopsy has a 70 percent sensitivity for diagnosing an existing gastric cancer, while performing seven biopsies from the ulcer margin and base increases the sensitivity to greater than 98 percent [16]. While it is clear that any suspicious-appearing lesion requires biopsy, it may be even more important to take numerous biopsies from smaller, benign-appearing gastric ulcers, especially in patients at high risk for gastric cancer, since the diagnosis of early gastric cancer offers the greatest opportunity for surgical cure and long-term survival. (See "Early gastric cancer: Clinical features, diagnosis, and staging" and "Peptic ulcer disease: Clinical manifestations and diagnosis", section on 'Selected benign appearing ulcers'.)

Because these tumors tend to infiltrate the submucosa and muscularis propria, superficial mucosal biopsies may be falsely negative. For this reason, the combination of strip and bite biopsy techniques should be used when there is suspicion of a diffuse type of gastric cancer [17]. Jumbo biopsies are also employed when this is suspected. (See 'Barium studies' above.)

If bleeding with biopsy is of concern to the endoscopist, it is reasonable to brush the ulcer base, since the risk of bleeding from this technique is negligible. Brush cytology increases the sensitivity of a single biopsy, but the extent to which it enhances diagnostic yield when seven biopsies are obtained remains unknown [18].

STAGING EVALUATION

Patients with documented gastric cancer should undergo a complete staging evaluation in order to guide therapy and more reliably predict outcome. Careful staging allows the clinician to select the most appropriate therapy, minimizes unnecessary surgery, and maximizes the likelihood of benefit from the selected treatment.

Staging systems — There are two major classification systems in use for gastric cancer. The more elaborate Japanese classification is based on refined anatomic location, particularly of the lymph node stations [19]. The other and more widely used staging system, developed jointly by the American Joint Committee on Cancer (AJCC) and the Union for International Cancer Control (UICC), is the classification most often used in the Western hemisphere and is now commonly used in Asian countries, including Japan, as well.

TNM staging criteria — The staging schema of the AJCC/UICC is based on tumor, node, metastasis (TNM) classifications.

The most recent revision of the AJCC/UICC TNM staging classification (eighth edition, 2017) includes separate prognostic stage groups for clinical and pathologic staging, including pathologic staging following a course of neoadjuvant therapy (yp stage) (table 2) [20]. This change is a reflection of the dramatically changed landscape of the use of neoadjuvant therapy for gastric cancer in this country, as well as around the world over the past 15 years (figure 2) [21]. The stratification in overall survival according to pathologic stage in the absence of neoadjuvant therapy and following neoadjuvant therapy, respectively, is depicted in the figures (figure 3 and figure 4) [20,22].

A notable omission is the lack of classification for a ypT0N0 tumor in this system. A modification to the postneoadjuvant pathologic staging system has been proposed, but is not in widespread use [23].

One of the most important changes from the earlier 2010 classification is a redefinition of the boundary between esophageal and gastric cancers. Tumors involving the esophagogastric junction (EGJ) with the tumor epicenter no more than 2 cm into the proximal stomach are staged as esophageal rather than gastric cancers (table 3). In contrast, EGJ tumors with their epicenter located more than 2 cm into the proximal stomach are staged as stomach cancers. (See "Clinical manifestations, diagnosis, and staging of esophageal cancer", section on 'TNM staging criteria' and "Neoadjuvant and adjuvant therapy for locally advanced resectable esophagogastric junction and gastric cardia adenocarcinoma", section on 'AJCC classification' and "Neoadjuvant and adjuvant therapy for locally advanced resectable esophagogastric junction and gastric cardia adenocarcinoma", section on 'Siewert classification'.)

The regional nodes for tumors involving different parts of the stomach are depicted in the figure (figure 5). Involvement of other intra-abdominal nodal groups (ie, pancreatoduodenal, retropancreatic, peripancreatic, superior mesenteric, middle colic, para-aortic, and retroperitoneal) is classified as distant metastasis [20].

Treatment implications of clinical staging — Although prognosis is most accurately determined by the surgical pathology after tumor resection, the clinical stage directs the initial approach to therapy:

- **Patients who appear to have locoregional disease** (stage I to III (table 2)) after preoperative testing are potentially curable; all patients with a primary tumor that is considered to invade through the submucosa (T2 or higher) or with a high suspicion of nodal involvement on pretreatment staging studies should be referred for multidisciplinary evaluation to identify the best treatment strategy (ie, upfront surgery versus initial chemotherapy or chemoradiotherapy). Adjuvant and neoadjuvant treatment for gastric and esophagogastric junction cancer and surgical management of gastric cancer, including criteria for surgical resectability, are discussed in detail separately. (See "Adjuvant and neoadjuvant treatment of gastric cancer" and "Surgical management of invasive gastric cancer", section on 'Adjuvant and neoadjuvant therapy' and "Neoadjuvant and adjuvant therapy for locally advanced resectable esophagogastric junction and gastric cardia adenocarcinoma".)

- **Patients with locally advanced unresectable, or advanced stage IV disease** are usually referred for palliative therapy depending on their symptoms and functional status. Multiple studies indicate both longer survival and better quality of life with systemic treatment (see "Initial systemic therapy for metastatic esophageal and gastric cancer"). Invasion of a major vascular structure, such as the aorta, or disease encasement or occlusion of the hepatic artery or celiac axis/proximal splenic artery is widely considered to represent locally advanced, unresectable disease. In approximately 5 percent of primary gastric cancers, a broad region of the gastric wall, or even the entire stomach, is extensively infiltrated by malignancy, resulting in a rigid, thickened stomach, termed linitis plastica (image 1). Linitis plastica has an extremely poor prognosis, and many surgeons consider the presence of linitis plastica to be a contraindication to potentially curative resection, even in the absence of other indicators of unresectability. At some institutions, these patients may be considered candidates for extended neoadjuvant therapy. We typically will administer four to six months of chemotherapy and, if no evidence of progression, will follow with chemoradiotherapy. If after the completion of this, there is no evidence of distant disease, resection is considered. (See "Surgical management of invasive gastric cancer", section on 'Linitis plastica'.)

Evaluation — The goal of the staging evaluation is to initially stratify patients into two clinical groups in order to guide management: those with locoregional, potentially resectable (stage I to III (table 2)) disease and those with either locally advanced, unresectable or metastatic (stage IV) disease. (See 'Treatment implications of clinical

staging' above.)

Suggested approach — The ultimate choice of staging modality is dependent on the clinical scenario and local expertise. Our suggested approach, which is generally consistent with guidelines from the National Comprehensive Cancer Network (NCCN) [24] and the European Society for Medical Oncology (ESMO) [25], is provided in the algorithm (algorithm 1) and summarized as follows:

- Computed tomography (CT) scans of the chest, abdomen, and pelvis are indicated in all patients with gastric cancer to evaluate for metastatic disease (M stage). Abdominal CT scans should not be relied on for assessing tumor depth (T stage), the presence or absence of lymph node involvement (N stage), or the presence of peritoneal metastases, although they can alert the clinician that further assessment may be necessary. (See 'Additional tests in selected patients' below.)

  While thickening of the wall of the stomach may be related to tumors, it should be considered cautiously. The degree of distension of the stomach has a dramatic impact on wall thickness in general. There are other causes of gastric wall thickening besides gastric adenocarcinoma, both benign and malignant, that one should be aware of but are beyond the scope of this topic review.

  Suspicious intrathoracic findings, visceral (hepatic) lesions, omental or peritoneal masses, or retroperitoneal lymph nodes require biopsy confirmation. Indeterminate hepatic lesions may be further evaluated with magnetic resonance imaging (MRI) or ultrasound if indicated. Paracentesis should be performed when ascites is detected, and the fluid should be sent for cytology and standard chemical analysis. CT imaging may also reveal bone metastases in some patients with advanced disease. In patients who present with bone pain, evaluation with a bone scan may be considered. (See "Evaluation of adults with ascites", section on 'Determining the cause of the ascites' and 'Computed tomography scan in all patients' below.)

- For most patients with gastric cancer who have no radiographic evidence of metastatic (M1) disease, we recommend endoscopic ultrasound (EUS) for assessment of T and N stage. (See 'Endoscopic ultrasound' below.)

- For most patients with clinical stage ≥T2N0 disease and a radiographic staging evaluation that is negative for metastatic disease, we perform integrated positron

emission tomography (PET)/CT to screen for distant metastases. As with CT, suspicious lesions may warrant biopsy. (See '18-fluorodeoxyglucose positron emission tomography scan' below.)

- For most patients, we recommend pretreatment staging laparoscopy to detect occult peritoneal dissemination in any medically fit patient who appears to have more than a T1a lesion on EUS, who has no histologic confirmation of stage IV disease, and who would not otherwise require palliative gastrectomy because of symptoms. (See 'Staging laparoscopy' below.)

- Serum tumor markers (including carcinoembryonic antigen [CEA] and the glycoprotein cancer antigen 125 [CA 125]) are of limited utility, and we do not routinely assay for them preoperatively, unless a patient is undergoing neoadjuvant therapy. (See 'Serologic markers' below.)

- For certain patients, such as those with an obstructing or significantly bleeding distal gastric cancer with no evidence of metastases by CT scan, it may be reasonable to directly proceed to surgery without further testing.

Computed tomography scan in all patients — All patients in whom a gastric cancer is suspected or histologically confirmed should undergo cross-sectional imaging of the chest, abdomen, and pelvis, typically with a contrast-enhanced (typically oral plus IV) CT scan. CT is widely available, is noninvasive, and is well suited to evaluating widely metastatic disease, especially hepatic or adnexal metastases, ascites, or distant nodal spread. Patients who have CT-defined visceral metastatic disease can avoid unnecessary surgery, although biopsy confirmation is recommended because of the risk of false-positive findings.

However, peritoneal metastases and hematogenous metastases smaller than 5 mm are frequently missed by CT, even using modern CT techniques [26]. In 20 to 30 percent of patients with a negative CT, intraperitoneal disease (including positive peritoneal washings) will be found at either staging laparoscopy or at open exploration [27-29].

Another limitation of CT is its inability to accurately assess the depth of primary tumor invasion (particularly with small tumors) and the presence of lymph node involvement. CT accurately assesses the T stage of the primary tumor in only approximately 50 to 70 percent of cases, typically for more advanced cases (image 5) [30-36]. More often, the

tumor is understaged because the depth of invasion is underestimated; however, overstaging also occurs.

The classification of nodal status is usually based on lymph node size, and the sensitivity of CT for detecting regional nodal metastases is limited for involved nodes that are smaller than 0.8 cm [30,35]. Furthermore, false-positive findings may be attributed to inflammatory lymphadenopathy. In series of patients undergoing staging CT for gastric cancer or gastric and esophageal cancer, sensitivity and specificity rates for regional nodal metastases range from 65 to 97 percent and from 49 to 90 percent, respectively [37-41].

Additional tests in selected patients

Endoscopic ultrasound — EUS is the most reliable nonsurgical method available for evaluating the depth of invasion of primary gastric cancers. EUS is recommended by both the NCCN and ESMO for pretreatment evaluation of all patients with gastric cancer who have no radiographic evidence of metastatic (M1) disease and have otherwise potentially operable disease [24,25]. (See 'Suggested approach' above.)

Accurate assessment of T and N stage (table 2) is important for treatment selection. As examples, in patients with early gastric cancer, accurate assessment of submucosal invasion is essential before considering the option of endoscopic mucosal resection. Neoadjuvant chemotherapy or chemoradiotherapy may be recommended for patients with a primary tumor that is considered to invade into the muscularis propria (T2 or higher) or with a high suspicion of nodal involvement on pretreatment staging studies. (See "Adjuvant and neoadjuvant treatment of gastric cancer", section on 'Initially locally unresectable nonmetastatic disease' and "Adjuvant and neoadjuvant treatment of gastric cancer", section on 'Is there a role for neoadjuvant chemoradiotherapy' and "Neoadjuvant and adjuvant therapy for locally advanced resectable esophagogastric junction and gastric cardia adenocarcinoma", section on 'Patients not yet resected'.)

In a systematic review of studies comparing EUS staging versus histopathology, the sensitivity and specificity rates for distinguishing T1 from T2 cancers with EUS were 85 and 90 percent, respectively [42]. The sensitivity and specificity rates for distinguishing T1/2 from T3/4 tumors were 86 and 90 percent, respectively. For metastatic involvement of lymph nodes, the sensitivity and specificity rates were 83 and 67 percent, respectively. There was significant between-study heterogeneity that could not be easily explained. However, as with any technical endeavor, there is a degree of variability in operator

expertise, which could at least partially explain these findings. We have found an increasing number of patients presenting already having had an EUS. Without knowing the experience level of the endoscopist, it is vital to consider the entire patient's situation. For example, if a patient is reported as having a T1 tumor, which may be amenable for upfront surgery or endoscopic mucosal dissection, yet presented with a GI bleed, this clinical dissonance should be further evaluated. Furthermore, an analysis of positive and negative likelihood ratios revealed that EUS diagnostic performance was favorable for neither exclusion nor confirmation of nodal positivity. Thus, EUS alone cannot be considered optimal for distinguishing positive from negative lymph node status.

EUS is better than CT at assessing tumor depth (T stage) and perhaps lymph node involvement (N stage), particularly if fine-needle aspiration (FNA) is also performed. In comparative studies of preoperative staging, EUS generally provides a more accurate prediction of T stage than does CT [43-46], although newer CT techniques (such as three-dimensional, multidetector row CT) and MRI may achieve similar results in terms of diagnostic accuracy in T staging [41,47,48]. In contrast, accuracy for nodal staging is only slightly greater for EUS as compared with CT [43,49-54]. EUS-guided FNA of suspicious nodes and regional areas adds to the accuracy of nodal staging [55]. (See "Endoscopic ultrasound-guided fine needle aspiration in the gastrointestinal tract".)

EUS is a relatively low-risk procedure, although it is more invasive than CT. One review quoted a risk of serious complications of 0.3 percent, most of which occurred in the setting of obstructing esophageal tumors [56]. (See "Endoscopic ultrasound for evaluating patients with esophageal cancer".)

18-fluorodeoxyglucose positron emission tomography scan — The role of 18-fluorodeoxyglucose (FDG)-PET in the staging evaluation of gastric cancer continues to evolve. We have become more selective in our use of PET imaging. Previously, we used it liberally in any patient with ≥T2N0 disease despite a negative CT. With the current high quality of contrast-enhanced CT imaging, we have found decreasing yield with the expanded use of PET. This is particularly true for diffuse type tumors where significant numbers of patients have tumors that are not FDG avid. Further, for patients with signet ring cell histology, the peritoneum is the most common site of metastatic disease; a site which we find better assessed by laparoscopy with washings [57]. Generally we reserve PET-CT for those patients who have equivocal findings on CT imaging or patients with clinical indications of possible metastatic disease and otherwise negative imaging. This

practice is consistent with NCCN and ESMO guidelines [24,25].

FDG-PET is more sensitive than CT for the detection of distant metastases, and FDG-PET/CT is positive in 6 to 16 percent of cases in most reports (image 6) [58-62]. In one representative prospective study, integrated PET/CT identified otherwise radiographically occult metastatic lesions in approximately 10 percent of patients with locally advanced gastric cancer (≥T3 or ≥N1 disease (table 2)) [59]. However, others note a lower detection rate for detecting distant metastatic disease (3 percent), with limited sensitivity (33 percent), a high number of incidental findings, and significant overlap with findings at staging laparoscopy [63].

From the standpoint of locoregional staging, integrated PET/CT imaging can be useful to confirm malignant involvement of CT-detected lymphadenopathy [64]. However, this usually does not impact the decision to proceed to surgery.

FDG-PET has some important limitations:

- The sensitivity of PET scanning for peritoneal carcinomatosis is only approximately 50 percent [65]. It is therefore not an adequate replacement for staging laparoscopy. (See 'Staging laparoscopy' below.)

- PET/CT is only helpful if the tumor is FDG avid (image 1). A negative PET is therefore not helpful, since even large tumors with a diameter of several centimeters can be falsely negative if the tumor cells have a fairly low metabolic activity or are not FDG avid. Notably, many diffuse-type gastric cancers (signet ring carcinomas) are not FDG avid [58,63,66-69].

Staging laparoscopy — Our practice is to use pretreatment staging laparoscopy to detect occult peritoneal dissemination in any medically fit patient who appears to have more than a T1a lesion on EUS, who has no histologic confirmation of stage IV disease, and who would not otherwise require palliative gastrectomy because of symptoms. Diagnostic laparoscopy should also be undertaken in any patient who is being considered for neoadjuvant therapy. Our approach is consistent with NCCN guidelines [24] but differs slightly from ESMO guidelines (which suggest diagnostic laparoscopy, with or without peritoneal washings, for all stage IB to III tumors that are considered potentially resectable) [25].

Other experts disagree, suggesting that only patients with EUS stage T3/4 disease should undergo diagnostic staging laparoscopy because of the greater yield found than in patients with earlier stage disease [29]. However, we believe that there is sufficient difficulty in the distinction between T2 and T3 lesions on EUS to warrant making decisions for or against staging laparoscopy based on EUS differentiation between T2 and T3 stages. (See "Diagnostic staging laparoscopy for digestive system cancers", section on 'Esophagogastric junction and gastric cancer'.)

Laparoscopy, while more invasive than CT or EUS, has the advantage of directly visualizing the liver surface and the peritoneum and can be used to examine local lymph nodes. Between 20 and 30 percent of patients who have disease that is beyond T1 stage on EUS will be found to have peritoneal metastases despite having a negative CT scan [27-29,70,71]. The risk of finding occult peritoneal dissemination is even higher for certain subsets of patients, including those with advanced (T4) primary tumors or a linitis plastica appearance [72]. In such cases, performance of a diagnostic laparoscopy frequently alters management (typically by avoiding unnecessary laparotomy) and may do so in up to one-half of patients [72,73]. As noted previously, the sensitivity of PET scans for the detection of peritoneal carcinomatosis is only approximately 50 percent. (See "Adjuvant and neoadjuvant treatment of gastric cancer" and '18-fluorodeoxyglucose positron emission tomography scan' above and "Surgical management of invasive gastric cancer", section on 'Linitis plastica'.)

Another advantage of laparoscopy is the opportunity to perform peritoneal cytology or washings in patients who have no visible evidence of peritoneal spread. In most (but not all [74]) series, this is a poor prognostic sign, even in the absence of overt peritoneal dissemination, and predicts for early peritoneal relapse [75-77]. The vast majority of patients who are found to have peritoneal disease on laparoscopy will never require laparotomy or resection. The preference for laparoscopy over exploratory laparotomy to assess the peritoneal cavity cannot be overstated due to the substantially lower morbidity of laparoscopy. However, at some institutions (including our own), for patients with a positive peritoneal cytology in the absence of other evidence of intra-abdominal disease, a more nuanced approach is used. (See "Surgical management of invasive gastric cancer", section on 'Significance of positive peritoneal cytology'.)

Diagnostic laparoscopy is especially important for patients who are being considered for neoadjuvant therapy trials. At our institution, we routinely obtain peritoneal washings

during laparoscopy in patients who lack visible peritoneal disease. We refer patients with a positive cytology in the absence of other evidence of metastatic disease for neoadjuvant approaches with more intensive chemotherapy than is used in the typical neoadjuvant setting. If at the completion of this, they remain free of visible disease, they would undergo chemoradiotherapy. They would then undergo staging laparoscopy with repeat washings and, if free of metastatic disease, would be considered for resection. (See "Surgical management of invasive gastric cancer", section on 'Neoadjuvant chemotherapy and chemoradiotherapy'.)

Serologic markers — Serum tumor markers (including CEA and CA 125) are of limited utility in selected patients. Low rates of sensitivity and specificity prevent the use of any of these serologic markers as diagnostic tests for gastric cancer.

- **CEA, CA 125, CA 19-9, and CA 72-4** – Serum levels of CEA, CA 125, carbohydrate antigen 19-9 (CA 19-9; also called cancer antigen 19-9), and cancer antigen 72-4 (CA 72-4) may be elevated in patients with gastric cancer [78-82]. However, we do not routinely assay for them preoperatively, unless a patient is undergoing neoadjuvant therapy on trial. In a minority of patients, a drop in an elevated level of CEA and/or CA 125 may correlate with response to preoperative therapy, but clinical decisions are almost never made based on tumor marker changes alone. Likewise, in many [83-93] (but not all [81,94]) studies, preoperative elevations in serum tumor markers are an independent indicator of adverse prognosis. However, no serologic finding should be used to exclude a patient from surgical consideration. Recommendations for preoperative evaluation and staging of gastric cancer from the NCCN [24] do not include assay of any tumor marker.

- **Alpha-fetoprotein** – Some gastric cancers are associated with elevated serum levels of alpha-fetoprotein (AFP); they are referred to as AFP-producing gastric cancers [95-98]. A subset, hepatoid adenocarcinoma of the stomach, has a histologic appearance that is similar to that of hepatocellular cancer. Regardless of morphology, AFP-producing gastric cancers are aggressive and associated with a poor prognosis.

- **Pepsinogen** – Increases in serum pepsinogen II or decreases in the pepsinogen I to pepsinogen II ratio have been used in population screening programs to identify patients at increased risk for gastric cancer, but they are insufficiently sensitive or specific to establish a diagnosis in an individual patient. (See "Gastritis: Etiology and

diagnosis".)

REFERRAL FOR GENETIC TESTING

Although most gastric cancers are sporadic, aggregation within families occurs in approximately 10 percent of cases. Truly hereditary (familial) gastric cancer accounts for 1 to 3 percent of the global burden of gastric cancer and comprises at least three major syndromes: hereditary diffuse gastric cancer (HDGC), gastric adenocarcinoma and proximal polyposis of the stomach (GAPPS), and familial intestinal gastric cancer (FIGC). The risk of developing gastric cancer is high in these families, but only HDGC is genetically explained (table 4) [99]. Guidelines from the International Gastric Cancer Linkage Consortium (IGCLC) and others recommend referral for genetic counseling and DNA testing for cadherin 1 (*CDH1*) mutations and large rearrangements in patients with diffuse gastric cancer who have one or more of the following [100,101] (see "Hereditary diffuse gastric cancer", section on 'Criteria for genetic testing'):

- Family history of two gastric cancers, at any age, with at least one confirmed diffuse gastric cancer
- Diffuse gastric cancer diagnosed at age <40 years, regardless of family history
- Personal or family history of diffuse gastric cancer and lobular breast cancer, with at least one diagnosed at <50 years of age

In addition, families in whom testing could be considered include the following:

- Bilateral lobular breast cancer or family history (first- or second-degree relative) of two or more cases of lobular breast cancer <50
- A personal or family history (first- or second-degree relative) of cleft lip/palate in a patient with diffuse gastric cancer
- An individual with in situ signet ring cells and/or pagetoid spread of signet ring cells on a gastric biopsy

IGCLC guidelines are currently under revision, and publication of these are expected sometime in 2020.

ISSUES RELATED TO HELICOBACTER PYLORI INFECTION

Infection with *Helicobacter pylori* is a major risk factor for gastric cancer. Individuals with gastric cancer should be screened for *H. pylori* infection and treated if positive. At least in the setting of early gastric cancer, *H. pylori* infection is associated with the development of metachronous gastric cancers, and eradication decreases the risk of developing metachronous gastric cancer after endoscopic treatment. (See "Early gastric cancer: Management and prognosis", section on 'Eradicate H. pylori infection'.)

SOCIETY GUIDELINE LINKS

Links to society and government-sponsored guidelines from selected countries and regions around the world are provided separately. (See "Society guideline links: Gastric cancer".)

INFORMATION FOR PATIENTS

UpToDate offers two types of patient education materials, "The Basics" and "Beyond the Basics." The Basics patient education pieces are written in plain language, at the 5th to 6th grade reading level, and they answer the four or five key questions a patient might have about a given condition. These articles are best for patients who want a general overview and who prefer short, easy-to-read materials. Beyond the Basics patient education pieces are longer, more sophisticated, and more detailed. These articles are written at the 10th to 12th grade reading level and are best for patients who want in-depth information and are comfortable with some medical jargon.

Here are the patient education articles that are relevant to this topic. We encourage you to print or e-mail these topics to your patients. (You can also locate patient education articles on a variety of subjects by searching on "patient info" and the keyword(s) of interest.)

- Basics topics (see "Patient education: Stomach cancer (The Basics)" and "Patient education: Upper endoscopy (The Basics)")
- Beyond the Basics topic (see "Patient education: Upper endoscopy (Beyond the Basics)")

SUMMARY AND RECOMMENDATIONS

- **Clinical features and diagnosis**
  - Most patients with gastric cancer are symptomatic, with weight loss and abdominal pain being the most common symptoms. (See 'Clinical features' above.)
  - The diagnosis of gastric cancer may be suspected because of findings on upper endoscopy or radiographic studies, but histologic examination of tumor tissue (usually acquired endoscopically) is required to establish the diagnosis. (See 'Diagnosis' above.)
- **Staging and the staging workup**
  - The most commonly used staging schema for gastric cancer is that of the American Joint Committee on Cancer (AJCC)/Union for International Cancer Control (UICC), which is based on tumor, node, metastasis (TNM) classifications (table 2). Tumors involving the esophagogastric junction (EGJ) with the tumor epicenter no more than 2 cm into the proximal stomach are staged as esophageal rather than gastric cancers, while EGJ tumors with their epicenter located more than 2 cm into the proximal stomach are staged as stomach cancers, as are all cardia cancers not involving the EGJ. (See 'TNM staging criteria' above.)
  - Patients with documented gastric cancer should undergo a complete staging evaluation prior to surgical exploration in order to guide therapy and more reliably predict outcome. Our suggested approach is outlined in the algorithm (algorithm 1) and summarized as follows (see 'Evaluation' above):
    - CT scan of the chest, abdomen, and pelvis is indicated in all patients to look for metastatic disease (M stage); it should not be relied on for assessing tumor depth (T stage), lymph node involvement (N stage), or the definitive presence of peritoneal metastases. Suspicious visceral lesions, omental masses, or retroperitoneal lymph nodes require biopsy confirmation. Paracentesis should be performed when ascites is detected, and the fluid should be sent for cytology and standard chemical analysis. (See 'Computed tomography scan in all patients' above.)

- Endoscopic ultrasound (EUS) is better than CT at assessing T stage and perhaps N stage, particularly if fine-needle aspiration (FNA) is also performed. An accurate assessment of T and N stage is important for treatment selection, particularly when selecting patients for neoadjuvant therapy rather than initial surgery. Consistent with guidelines from the NCCN and ESMO, we perform EUS for patients who have otherwise no evidence of metastatic (M1) disease. (See 'Endoscopic ultrasound' above.)

- The role of 18-fluorodeoxyglucose (FDG)-PET in the staging evaluation of gastric cancer continues to evolve. Diffuse type tumors are frequently not FDG avid, and for patients with signet ring cell histology, the peritoneum is the most common site of metastatic disease, and this is better assessed by laparoscopy with washings. In general, we reserve PET-CT for those patients with non-diffuse-type tumors who have equivocal findings on CT imaging or in those with clinical suspicion of possible metastatic disease with otherwise negative imaging. As with CT, suspicious lesions warrant biopsy. (See '18-fluorodeoxyglucose positron emission tomography scan' above.)

- Serum tumor markers (including carcinoembryonic antigen [CEA] and the glycoprotein cancer antigen 125 [CA 125]) are of limited utility, and we do not routinely assay for them, unless a patient is undergoing neoadjuvant therapy on trial. (See 'Serologic markers' above.)

- Although others disagree, we advise preoperative staging laparoscopy for any medically fit patient who appears to have more than a T1a lesion on EUS, no histologic confirmation of stage IV disease, and would not otherwise require palliative gastrectomy. Diagnostic laparoscopy should also be undertaken in any patient who is being considered for neoadjuvant therapy. We routinely obtain peritoneal washings during laparoscopy in the absence of visible peritoneal disease. (See 'Staging laparoscopy' above.)

- For certain patients, such as those with an obstructing or significantly bleeding distal gastric cancer with no evidence of metastases by CT scan, it may be reasonable to directly proceed to surgery without further testing.

- **Genetic issues**

- Gastric cancers are sporadic, though familial aggregation occurs in approximately 10 percent of cases. Truly hereditary (familial) gastric cancer accounts for 1 to 3 percent of the global burden of gastric cancer and comprises at least three major syndromes: hereditary diffuse gastric cancer (HDGC), gastric adenocarcinoma and proximal polyposis of the stomach (GAPPS), and familial intestinal gastric cancer (FIGC). Only HDGC has a defined genetic basis (table 4).

- Referral for genetic counseling and testing for cadherin *1 (CDH1*) mutations and large rearrangements is recommended for individuals with diffuse gastric cancer who meet one or more of the following criteria (see 'Referral for genetic testing' above):

  - Family history of two gastric cancers, at any age, with at least one confirmed diffuse gastric cancer.

  - Diffuse gastric cancer diagnosed at age <40 years, regardless of family history.

  - Personal or family history of diffuse gastric cancer and lobular breast cancer, with at least one diagnosed at <50 years of age.

- ***H. Pylori*** – Individuals with gastric cancer and *H. pylori* should be screened for *H. pylori* infection and treated if positive. (See 'Issues related to helicobacter pylori infection' above.)

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