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Surgical Staging of Gastric Cancer

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INTRODUCTION

Gastric cancer is the fifth most common cancer and third leading cause of cancer deaths worldwide, with half of these occurring in Eastern Asia [1]. There are two major classification systems currently used, the Japanese classification and the system developed jointly by the American Joint Committee on Cancer **(AJCC)** and the Union for International Cancer Control **(UICC).** The Japanese classification system has been criticized for being to elaborate and difficult to use. The AJCC/UICC system is the system used mainly throughout the West, and is used by the NCCN guidelines; and will be the system used in this section.

There have been many advances in the clinical staging of gastric cancer over the last several decades. This chapter is divided into six sections. Five of the sections will cover the modalities used in the staging of gastric cancer (1. computed tomography, 2. positron emission tomography, 3. endoscopic ultrasound, 4. diagnostic laparoscopy +/- peritoneal cytology, and the 5. extent of lymphadenectomy in the staging of gastric cancers), and the last section will summarize the algorithm used in our institution for the staging of gastric cancer and how it helps direct our therapy for patients.

COMPUTED TOMOGRAPHY

Precise preoperative staging is important in the work up gastric adenocarcinoma since some patients will benefit from immediate surgical resection for a cure; some will require neoadjuvant therapy for down staging prior to surgical resection, and to avoid unnecessary laparotomy in patients who are not candidates for curative surgery. With the increasing use of endoscopic mucosal resection for early stage cancers and neoadjuvant therapy for later stage cancers, accurately diagnosing a patient's stage is crucial to ensure that each patient undergoes the appropriate therapy for their pathologic stage of disease.

Computed Tomography **(CT)** is an essential component of the workup of gastric adenocarcinoma. The NCCN guidelines recommend CT scan of the chest; abdomen and pelvis with oral and IV contrast as the initial staging investigation after histologic diagnosis of gastric adenocarcinoma. It allows evaluation of the primary tumor, regional and distant metastasis. Of these, its primary utility is in evaluating for distant metastatic spread, especially to the liver. The diagnosis of nodal metastases by CT scanning remains a challenge due to a lack of reliable CT criteria. They are usually diagnosed based on size, with nodal size criteria being inversely proportional to the likelihood of nodal involvement [2].

The primary tumor may often not be visible on computed tomography, especially without dedicated gastric protocols. A study from Korea by Kim *et al.* [2] showed a 98% detection rate for gastric cancer using volumetric CT imaging with MPR and virtual endoscopy. They injected 20 mg of scopolamine intramuscularly to relax the bowel wall and reduce bowel peristalsis, the patient then ingested 8 g of effervescent granules in 10 mL of water just prior to CT. A non-contrasted scan was then performed with the patient in the supine position after a scout film was performed to ensure gastric distention. Next a contrasted scan was performed in the supine position after 150 mL of iopromide was injected. The patient was then scanned in the supine position 72 seconds after the initiation of the contrast injection. Patients were instructed to hold their breath during the scans. Four-detector row CT scanners with a high-speed mode were used. They also were also able to diagnose 96% of T1 lesions with volumetric CT versus 69% with standard axial imaging alone, with an overall accuracy of 84% versus 77% respectively.

POSITRON EMISSION TOMOGRAPHY

In the absence of distant metastatic disease on Contrast Enhance Computed Tomography **(CECT)**, the NCCN guidelines recommend obtaining fluorine-18 Fluoro-2-Deoxyglucose Positron Emission Tomography/Computed Tomography **(FDG-PET/CT)** [3]. This is useful because the ability of CECT to predict regional nodal metastasis is poor and is dependent on the size of the lymph nodes [4]. FDG-PET has a better sensitivity and specificity for detecting lymph nodes, especially those <3cm [5].

FDG-PET/CT has a number of limitations. Approximately 20% of gastric cancers have poor FDG uptake [6]. Stahl *et al.* [7] reported 60% sensitivity for detecting locally advanced gastric carcinoma with FDG-PET, with worse sensitivity being associated with non-intestinal type when compared to tumors with the intestinal growth type. They found that FDG-PET was more sensitive for the detection of proximal compared to distal gastric tumors, 74% versus 41% respectively [7]. Another study showed that mucinous tumors had a sensitivity of less than 60% when compared to those without mucin [8], and non-intestinal type tumors seem to be more strongly associated with mucinous tumors [7].

The sensitivity of FDG-PET/CT for gastric adenocarcinoma is poor for the diagnosis of primary tumors or metastatic lymph nodes, but does have a much better specificity than CECT [7-9]. A possible reason for advanced or poorly differentiated tumors being less FDG-avid is that there often large areas of necrosis with lower concentrations of cancer cells in the primary tumor [5]. When a Standardized Uptake Value **(SUV)** of 15 is used, specificity is reported to be as high as 90% [9]. So a negative FDG-PET/CT does not rule out a primary tumor or the possibility of metastatic lymph nodes. However, when an FDG-PET/CT is positive the sensitivity of the scan for metastatic lymph nodes is similar to that of a CECT, and its specificity is superior [9]. Like CECT, FDG-PET/CT is influenced by the size of the lesion, with larger lesions increasing the sensitivity of the scan; but even with tumors ≤ 3cm FDG-PET CT has an acceptable speficity [2,9,5].

There are several factors that influence the accuracy of FDG-PET/CT in its ability to detect gastric adenocarcinomas. As previously mentioned the type of cancer cells, mucin status, and size of the tumor all affect the ability of the tumor to be identified by FDG-PET/CT [2,6-9,5]. The primary method for FDG uptake into cell is via Glucose Transporter-1 **(GLUT-1)**, and this transporter has been reported to be decreased in mucin-containing cells [10]. Another limitation of FDG-PET/CT is the normal metabolic activity of the stomach and its dense blood flow. This can have a significant influence on the ability of this modality to accurately detect an underlying malignancy giving a false-positive result [7], but having the patient drink 500 mL of water for gastric distention significantly improves this method for detecting and localizing gastric tumors [11]. The location of the tumor in the stomach also affects the sensitivity of this modality, with proximal tumors being found to have a higher detection rate than distal gastric cancers [12].

Due to these limitations, FDG-PET/CT has no role as a screening tool for the detection of primary gastric cancers [13]. However, with locally advanced gastric carcinomas being more frequently evaluated for neoadjuvant therapy for down-sizing to help facilitate an R0 resection, appropriate pre- and post-therapy staging are essential. FDG-PET/CT has a better positive predictive value for metastatic lymph nodes than for CECT scanning [5,6]. FDG-PET/CT can be useful in this context in particular if the tumor is non-mucinous intestinal type, which is associated with proximal gastric tumors; the more common type of tumor found in Western cultures. In the intestinal type of early gastric cancers, FDG-avid tumors have a high probability of regional lymph node involvement [14], which may be associated with the aggressiveness of tumors that express the

GLUT-1 transporter. It has been advocated that in these patients FDG-PET/CT is of benefit to help guide an adequate lymph node dissection [14]. FDG-PET/CT can be utilized in 80% of patients since their tumors will over express GLUT-1. Around 30-40% of gastric carcinomas respond to current chemotherapeutic regimens [13,15]. Advanced stage gastric carcinomas may also benefit from an FDG-PET/CT because of the high specificity associated with positive nodes on the imaging modality. In these patients, FDG-PET/CT will help to assess response to chemotherapy as well as guide the surgeon in planning an adequate lymph node dissection in patients eligible for surgical resection [14]. The benefit of following post-treatment response with FDG-PET/CT over CECT is that metabolic activity has been shown to change immediately following the first dose of chemotherapy [13,15], while a decrease in tumor size is a more delayed response [16].

ENDOSCOPIC ULTRASONOGRAPHY

Endoscopic Ultrasonography **(EUS)** is considered as the most accurate method to assess and accurately determine the T- and N-stage for gastric cancer when compared to both Computed Tomography **(CT)** and intraoperative assessment [2,17,18]. The accuracy of T stage diagnosis on EUS has been reported between 71-92% [18-20], with the accuracy of N stage diagnosis between 50-90% [21,22]. EUS has greater accuracy in the diagnosis of T stage compared to N stage, but both have excellent results [18-21], and this has been verified with correlation of pre-resection T and N staging with post-resection staging [23,24].

T-staging by EUS may be difficult because of thickening of the gastric wall due to tumor microinvasion, peritumoral inflammation, a markedly protruding lesion, oblique scanning, and the absence of the serosal layer in certain regions of the stomach (lesser curvature, posterior wall of the fundus, and the anterior wall of the antrum) [25,26]. The biggest difficulty is the distinction between early stage gastric cancers (T1a and T1b) because of their small size [26], as well as between T2 and T3 gastric cancers because of the often thin or absent serosal layer in areas of the stomach [27]. The problem of inappropriate T staging is a serious one since it can result in an more or less aggressive treatment course for the patient. The distinction between T1a and T1b is a very important one (see table 1) since T1a can be treated with endoscopic mucosal resection since metastasis is extremely rare when the tumor is confined to the mucosa (<5%) [28,29].

Table 1: (AJCC TNM classification).

Primary Tumor (T)
TX Primary tumor cannot be assessed
T0 No evidence of primary tumor
Tis Carcinoma in situ: intraepithelial tumor without invasion of the lamina propria
T1 Tumor invades lamina propria, muscularis mucosae orsubmucosa
T1a Tumor invades lamina propria or muscularis mucosae
T1b Tumor invades submucosa
T2 Tumor invades muscularispropria
T3 Tumor penetrates subserosal connective tissue without invasion of visceral peritoneum or adjacent structures
T4 Tumor invades serosa (visceral peritoneum) or adjacent structures
T4a Tumor invades serosa (visceral peritoneum)
T4b Tumor invades adjacent structures
Regional Lymph Nodes (N)
NX Regional lymph node(s) cannot be assessed
N0 No regional lymph node metastasis§
N1 Metastasis in 1 - 2 regional lymph nodes
N2 Metastasis in 3 - 6 regional lymph nodes
N3 Metastasis in seven or more regional lymph nodes
N3a Metastasis in 7 - 15 regional lymph nodes
N3b Metastasis in 16 or more regional lymph nodes
Distant Metastasis (M)
M0 No distant metastasis
M1 Distant metastasis
Histologic Grade (G)
GX Grade cannot be assessed
G1 Well differentiated
G2 Moderately differentiated
G3 Poorly differentiated
G4 Undifferentiated

Anatomic Stage/Prognostic Groups

Stage 0	Tis	N0	M0
Stage IA	T1	N0	M0
Stage IB	T2	N0	M0
	T1	N1	M0
Stage IIA	T3	No	M0
	T2	N1	M0
	T1	N2	M0
Stage IIB	T4a	N0	M0
	T3	N1	M0
	T2	N2	M0
	T1	N3	M0
Stage IIIA	T4a	N1	M0
	T3	N2	M0
	T2	N3	M0
Stage IIIB	T4b	N0	M0
	T4b	N1	M0
	T4a	N2	M0
	T3	N3	M0
Stage IIIC	T4b	N2	M0
	T4b	N3	M0
	T4a	N3	M0
Stage IV	Any T	Any N	M1

Nodal staging by EUS also has limitations. The transducer only permits visualization of tissue to a depth of only 5-6 cm, so distant lymph nodes cannot be evaluated [25]. The distinction between malignant and inflammatory lymph nodes cannot be made by EUS, but EUS-guided fine-needle aspiration has been demonstrated as a useful tool in determining this distinction [25,30,31]. Size > 10 mm, rounded structure, sharp demarcation of borders, and hypoechoic structure have been shown as features more prominent in metastatic lymph nodes [32-34]. The T stage of the disease has also been shown to influence the accuracy of N staging by EUS, increasing accuracy of the N stage with increasing T stages [35]. In T1/2 stage N0 stage can be assumed to be accurate if no malignant nodes are seen, while in T3/4 stages if nodes are visualized then they tend to be malignant [35].

STAGING LAPAROSCOPY AND PERITONEAL CYTOLOGY

The NCCN guidelines recently added staging laparoscopy for all patients with T1b or higher tumors prior to initiation of therapy with a 2B recommendation. Laparoscopy is not indicated in the setting of a palliative resection. The purpose of staging laparoscopy is two-fold - to detect macroscopic distant metastatic disease not apparent on CT and PET; and secondly, to identify those patients with microscopic peritoneal spread. Therefore, in the absence of finding macroscopic distant disease at laparoscopy, washings for peritoneal cytology must be performed. Positive peritoneal cytology is classified as distant metastatic disease. The basis for this recommendation is retrospective series demonstrating lack of benefit of gastric resection in the setting of positive peritoneal cytology [36]. Despite appropriate preoperative staging, up to 40% of patients can harbor occult intra-abdominal metastases at the time of surgery when diagnostic laparoscopy is not performed [37-41]. Burke *et al.* [37] performed laparoscopic exploration on 110 patients and accurately staged 94% of patient with a sensitivity of 84% and specificity of 100%. The prevalence of metastatic disease was 37% in their study showing the importance of diagnostic laparoscopy. Sarela *et al.* [40] performed diagnostic laparoscopy on 657 patients and detected M1 disease in 31% of patients. 151 (23%) patients had visibly detectable disease on laparoscopy, the remaining 506 patients underwent immediate laparotomy. Another 25 (5%) patients had evidence of M1 disease only after laparotomy, and another 16 (3%) patients had M1 disease diagnosed on final pathology. Another study from Memorial Sloan Kettering Cancer Center [42] showed the benefit of adding peritoneal cytology. 127 patients underwent diagnostic laparoscopy with peritoneal cytology by instilling 50 to 100 mL of normal saline in the right and left upper quadrants as well as the pelvis, then after gentle agitation the washings were collected. The specimens were centrifuged, filtered, and stained by the Papanicolau technique. 76 (60%) patients had no evidence of M1 disease at laparoscopy and 51 (40%) of patients had evidence of gross M1 disease. Of the 76 patients without evidence of metastatic disease peritoneal cytology was performed and 3 (4%) of patients had positive cytology.

Even with the clear benefits of SL and peritoneal cytology, Karanicolas *et al.* [43] using the Surveillance, Epidemiology and End Results **(SEER)** population-based cancer registry showed that only 8% of patients out of more than 6,000 undergoing surgery for gastric cancer had a SL, though they do state that the rate of SL doubled between 1998 and 2005; their study population was patients aged 65 or older diagnosed with gastric adenocarcinoma between 1998 and 2005. This is similar to the rate reported by Coburn et al [44] from Canada using the Ontario Cancer Registry 3,666 patients were identified to have been diagnosed with gastric adenocarcinoma from April 1, 2000 to March 31, 2005. Of the 3,666 patient identified, 8.8% of patients underwent diagnostic laparoscopy. Some have argued against SL because they believe that most of these patients are going to require resection for obstruction or dysphagia [45], but studies have shown that only 2-12% of patients end up requiring palliative surgery [37,46].

Radiographic features with increased risk for M1 disease are intra-abdominal lymph nodes ≥ 8-10 millimeters seen on CT scanning [2,6,8,18,47-50] or T3/T4 primary tumors [2,8]. Other features with increased risk of M1 disease are tumors located at the gastroesophageal junction or tumors involving the whole stomach [37].

More detailed molecular examination of peritoneal washings, including immunohistochemistry and nucleic acid analysis may help increase the sensitivity of staging laparoscopy. While cytology positive for metastatic disease portends a much worse prognosis some have identified it as an independent predictor for worse survival [51,52] and others have shown it as a significant predictor of poorer overall survival, but not an independent risk factor [53,54]. Some have argued that due to the false-negative rate that the procedure as a prognostic factor is limited [55], and while its role has been largely adopted efforts to decrease the false-negative rate are underway. There are several different methods to evaluate the cytology sample and these include immunohistochemistry or quantitative reverse transcriptase-polymerase chain reaction for expression of carcinoembryonic antigen messenger RNA **(mRNA)** or trypsinogen mRNA. All of these methods may have improved yield in identifying positive cytology over conventional cytology with a Papanicolaou test, but their results for defining patient prognosis vary and are still investigational [51,56,57]. What is uniform amongst all of these methods is that positive cytology portends a worse prognosis and should be treated as Stage IV disease.

For those patients treated with neoadjuvant chemotherapy, there is limited retrospective data advocating for repeat staging laparoscopy prior to attempted curative resection. Cardona *et al.* [58] found that 7% of patients without evidence of M1 disease before chemotherapy progressed to M1 disease while undergoing neoadjuvant chemotherapy. In the majority of cases, this M1 disease was visible at staging laparoscopy, rather than being only detectable by peritoneal cytology. Thus, laparoscopy at the time of planned resection may be useful to select out those patients with progressive disease.

EXTENT OF LYMPHADENECTOMY

Nodal status was originally defined by the distance of a nodal metastasis from the primary tumor. N1 disease was defined as metastatic lymph nodes within 3 cm of the primary tumor, and N2 disease as more than 3 cm from the primary tumor. Compliance with this staging system was low, so in 1997 the UICC [59] and AJCC [60] redefined the nodal status based on the number of metastatic lymph nodes found rather than on their location. The Japanese system, more commonly used in the East, still relies on node location rather then number for node staging. In the West, the NCCN guidelines require a minimum of 15 nodes to be examined to allow accurate regional staging. This new staging system with the importance based on number rather than location of lymph nodes has been studied and validated as a more accurate predictor of survival [61,62]. While a minimum of 15 nodes should be examined, increased survival has been shown with increasing number of lymph nodes resected [63]. This survival benefit with increased lymph node resection is likely due to several reasons with two of them being not only just better locoregional control, but also it helps to prevent stage migration or inappropriately under staging of the disease when too few lymph nodes are examined.

Nodal involvement is one of the most important prognostic factors in gastric adenocarcinoma [64] with nodal metastasis seen in up to one-fifth of tumors invading the submucosa **(T1b)** [65] and this rate increases to >50% if there is invasion beyond the submucosa [64]. While retrieval of ≥ 15 lymph nodes is recommended [63,66], one large Western study has shown that this occurs in only about one-third of resections for gastric cancers [67]. And when less than 10 nodes are examined on final pathology the final staging of gastric cancer cannot be confidently performed since stage migration occurs [63,68]. When a D2 resection is performed, one study reported that the median number of nodes removed was 22 [69] and another that 100% of patients have > 16 nodes removed [70].

There is much debate in the west about performing a D1 versus a D2 resection, while in the East the D2 and sometimes a D3 resection is considered the standard of care. A D1 resection is removal of the perigastric nodes directly attached along the lesser curvature and greater curvature of the stomach (stations 1-6, N1 level). A D2 dissection will include the removal of nodes along the left gastric artery, common hepatic artery, celiac trunk, splenic hilum, and splenic artery (stations 7-11, N2 level). And D3 dissections include the removal of lymph nodes along the hepatoduodenal ligament and the root of the mesentery (stations 12-14, N3 level) (see Table 2). It has been argued that surgery alone can be curative with extended lympadenctomies [71].

Table 2: (Definition of D1-D4 dissections).

D1 (stations 1-6, N1 level):
1: Right cardia lymph nodes
2: Left cardia lymph nodes
3: Lymph nodes along the lesser curvature
4: Lymph nodes along the greater curvature
4sa: Lymph nodes along the short gastric vessels
4sb: Lymph nodes along the left gastroepiploic vessels
4d: Lymph nodes along the right gastroepiploic vessels
5: Suprapyloric lymph nodes
6: Infrapyloric lymph nodes
D2 (stations 7-11, N2 level)
7: Left gastric artery
8: Common hepatic artery
9: Celiac trunk
10: Splenic hilum
11: Splenic artery
D3 (stations 12-14, N3 level)
12: Lymph nodes in the hepatoduodenal ligament
13: Lymph nodes on the posterior surface of the head of the pancreas
14: Lymph nodes at the root of the mesentery
14A: lLymph nodes along the superior mesenteric artery
14V: Lymph nodes along the superior mesenteric vein
D4 (stations 15-16, N4 level)
15: Para-aortic
16: Paracolic region

Data from the east has shown improved outcomes with regard to recurrence and survival with a more extensive lymphadenectomy [72-74]. In Europe two randomized control trials were undertaken to determine the benefit of a D2 resection over D1 if any existed. Their 5-year data showed a significantly increased morbidity and mortality associated with the D2 resection when compared to a D1 resection with no decrease in cancer related survival [75-77], and this was again shown at 11 years [78]. These studies included distal pancreatectomy and splenectomy in their D2 resections, and this was found to be the cause of the higher morbidity in the D2 arm rather than due to the lymphadenectomy itself [78]. However, the 15-year follow-up of the Dutch trial found that D2 lymphadenectomy was associated with lower locoregional recurrence and fewer gastric cancer-related deaths than D1 [79]. While the UK [75,77] and Dutch [76,78,79] trials were well designed, they have been criticized for including learning periods for the surgeons, low volume hospitals of D2 surgery, relatively large numbers of surgeons and pathologists involved, and that distal pancreatectomy and splenectomy were routinely performed in their D2 resections.

In the East, the management of gastric adenocarcinoma is centralized, with gastric resections only performed by high volume surgeons and hospitals. There have been reports of favorable outcome in the west with D2 resections [80-82], but the 15-year follow-up of the Dutch trial is the only randomized prospective trial to show any improved survival to date [79]. At high volume gastric cancer centers in the West, surgeons have shown that D2 resections can be safely performed without the need for distal pancreatectomy or splenectomy with similarly acceptable morbidity and mortality seen in the East after appropriate training [70,83,84].

Surgeons in Taiwan have also reported on D1 versus D3 dissection [72,73]. They showed an increased morbidity with the D3 resection to include increased blood loss, operation time, and hospital stay; but the 30-day hospital mortality was the same [73]. They also showed decreased recurrence of gastric cancer after D3 compared to D1, but this difference was not statistically significant [72]. These morbidity and mortality rates of more extensive lymphadenectomy are consistent with those reported from Japan [74] and Korea [85]. The East has also reported improved survival with extended lymph node dissections compared to the west and while the disease does vary widely between the eastern and western countries [62,86,87], stage migration alone cannot explain this as one western study did show that at lymph node counts greater than 17 there is likely a therapeutic benefit [63].

While D2 lymphadenectomy remains the standard of care in the east, some have advocated for the addition of a Para-Aortic Lymph Node Dissection **(PAND)** due to the incidence of microscopic metastases in the para-aortic region being as high as 10-30% [88,89]. Sasako *et al.* [14] showed in a randomized controlled trial of D2 lymphadenectomy versus D2 lymphadenectomy plus PAND that there was no improvement in overall recurrence-free survival, as well as no reduction in the rate of the recurrence of cancer in the lymph nodes at 5-years with the addition of PAND. While there was no statistically significant increase in surgical related major complications (anastomatic leak, pancreatic fistula, abdominal abscess, pneumonia) there was very significant increase in minor complications with the addition of PAND versus D2 lymphadenectomy alone (20% versus 9.1% respectively). Therefore, the current data do not support the addition of PAND to D2 lymphadenectomy.

Currently, the NCCN guidelines now recommend resection of the perigastric lymph nodes (D1) and those along the named vessels of the celiac axis (D2), with a goal of examining at least 15 or greater lymph nodes [3]. A D2 resection is recommended because it provides a more accurate pathologic staging and better regional disease control with acceptable morbidity and mortality when performed by an experienced surgeon without the addition of distal pancreatosplenectomy at a high-volume institution [90,91].

CONCLUSION

Appropriate workup and staging is essential to optimize patient outcome (Figure 1). At our institution all of our patients are presented at a multidisciplinary tumor board and initially screened with a CT of the chest, abdomen, and pelvis with both PO and IV contrast (see Figure 1). If no evidence of systemic disease is discovered on CT then we obtain an FDG-PET/CT scan. If FDG-PET/CT is negative then we proceed with EUS. Patients with T1a N0 or T1b N0 tumors on EUS have their tumor removed either by Endoscopic Mucosal Resection **(EMR)** or by surgical resection. Tumors that are ≥T2 or have any positive nodes undergo a diagnostic laparoscopy with peritoneal cytology as a separate procedure prior to any planned oncologic therapy.

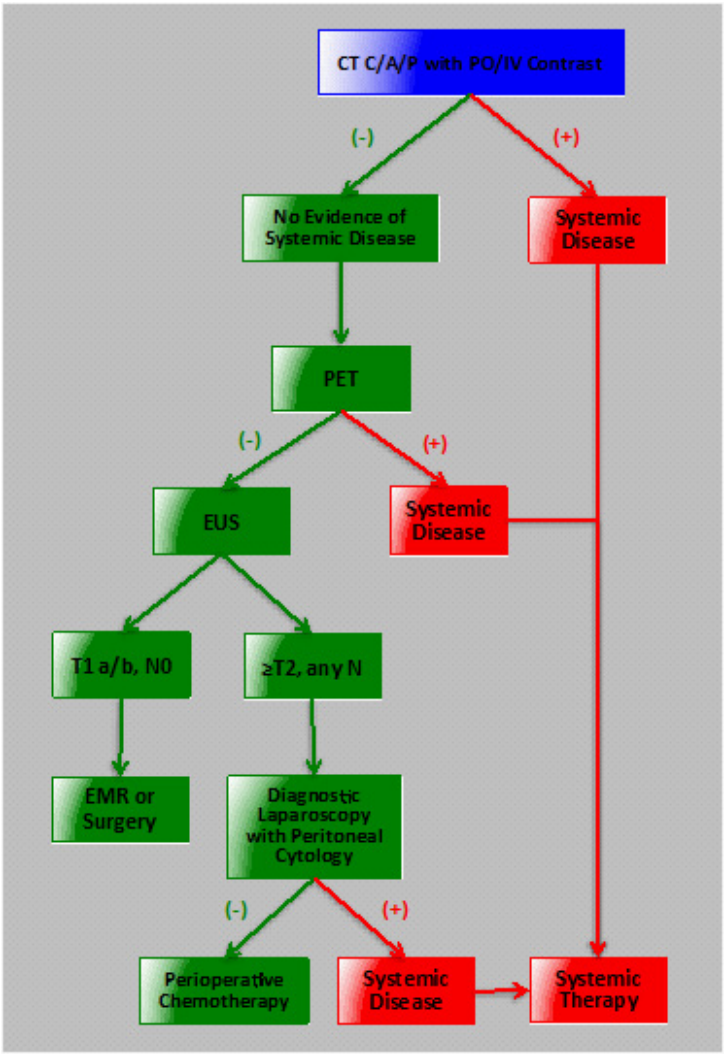

Figure 1: Algorithm for work-up of gastric adenocarcinoma.

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