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Contents

Gastric and Small Bowel Tumors

L. Mark Knab and Anthony Yang

Abstract

The incidence of gastric adenocarcinoma has decreased in the United States over the past 70 years although it continues to have a poor prognosis. While radical resection was initially the primary treatment for adenocarcinoma of the stomach, systemic chemotherapy and radiation have been shown to play a role in prolonging survival in most patient populations. This chapter explores the evidence that guides treatment for gastric cancer today. It also discusses the treatment for gastrointestinal stromal tumors (GIST), and small bowel tumors. In addition to systemic therapies, this chapter explores the surgical management of gastric and small bowel tumors including the extent of the gastric lymph node dissection.

Keywords

Gastric adenocarcinoma · Gastrointestinal stromal tumors (GIST) · Small bowel tumors · Lymph node dissection

1 Gastric Adenocarcinoma

The incidence of gastric cancer in the United States (US) has decreased substantially over the past several decades. While it was once a leading cause of cancer-related death in the United States, it now ranks 13th among major causes. Gastric cancer remains the second leading cause of cancer-related death worldwide and its incidence varies dramatically with geography. It occurs with the highest

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rates in East Asia and the lowest rates in North America. Part of this discrepancy is believed to be due to the decreased use of salted, pickled, and smoked foods and increased use of refrigeration in developed countries.

The decrease in gastric cancer rates in the US unfortunately has not correlated with an improvement in 5-year survival. The 5-year survival rate for all races with gastric cancer from the period of 2001–2007 was 27 % [1]. Unlike countries with screening policies in place for gastric cancer, most of the patients that present in the US are in advanced stage. A study from the National Cancer Data Base (NCDB) demonstrated that 55 % of patients with gastric cancer presented with locally advanced or metastatic disease [2]. The 5-year survival rates have been shown to be directly related to stage upon presentation. The survival rate for stage IA disease was 78 %, for stage IB it was 58 %, for stage II, 34 %, for stage IIIA, 20 %, for stage IIIB, 8 %, and for stage IV it was 7 %.

1.1 Classification

Gastric adenocarcinoma can be divided into two histologic subtypes: intestinal (or glandular) and diffuse [3]. The intestinal subtype has been associated with atrophic gastritis and diets high in nitrates [4]. It is also associated with elderly patients and generally arises in the distal stomach. The diffuse subtype most commonly occurs in the cardia of the stomach and in younger patients. It has no identifiable precursor, and cancer cells infiltrate the tissue diffusely. This results in a thickened stomach without a discrete mass or ulceration which is typically seen in the intestinal subtype.

1.2 Risk Factors

Multiple epidemiologic studies worldwide have demonstrated a strong association between gastric cancer and H. pylori infection [5]. Serologic studies have shown that individuals who are infected with H. pylori are three to six times more likely to develop gastric cancer compared with those who do not have H. pylori [6]. The exact mechanism is unclear given that a large proportion of the entire world's population is thought to be infected with H. pylori, yet only a small fraction will eventually develop gastric adenocarcinoma. H. pylori infection results in a chronic state of inflammation which can potentiate environmental and/or genetic factors that can result in cancer [7]. There is also a genetic predisposition for gastric cancer, and individuals with first-degree relatives that have gastric cancer have a higher risk of developing the disease [8].

It is thought that certain environmental factors exert a teratogenic effect on the stomach and increase the risk of gastric cancer. Gastric specimens from operations and autopsies have been associated with areas of atrophic gastritis and intestinal metaplasia. It is thought that environmental factors such as nitrates and nitrose compounds found in smoked, pickled, and salted foods potentiate the effect of chronic gastritis, leading to metaplasia and eventually carcinoma [9].

1.3 Clinical Evaluation

In the United States, due to the low incidence of gastric adenocarcinoma, it is not cost effective to use screening programs. Because of this, the majority of cases are diagnosed after they are locally advanced or metastatic. Early stage gastric cancer generally does not result in symptoms and it is often only after the cancer has progressed that patients will present with symptoms such as fatigue, weight loss, early satiety, vomiting, and hematemesis. Physical findings such as jaundice, ascites, or a palpable mass are generally indicative of incurable disease. Other physical findings consistent with advanced disease include periumbilical metastases (Sister Mary Joseph nodule), supraclavicular lymphadenopathy (Virchow node), and a palpable mass in the rectovesical or rectouterine space from dropped metastases (Blumer shelf).

The primary diagnostic tool is now upper gastrointestinal endoscopy which allows for direct visualization of the stomach and biopsies to confirm the diagnosis. It is recommended that at least four biopsies be taken of the area in suspicion to prevent false negative results [10]. Imaging studies should be obtained for staging purposes, including a CT chest, abdomen, and pelvis. The overall accuracy of CT in staging tumors is about 70 % for advanced tumors and 44 % for early lesions [11]. The sensitivity of CT for detecting N1 and N2 disease is 24–43 %, and the specificity approaches 100 % [12]. While CT needs to be done for metastatic workup, locoregional staging is ideally performed with endoscopic ultrasound (EUS). EUS is able to assess the depth of tumor invasion through the gastric wall (T stage) as well as evaluate regional nodes (N stage). The overall accuracy of EUS for evaluating the extent of tumor infiltration ranges from 67 to 92 % [13].

1.4 Staging

There are two main systems in place for staging gastric cancer. There is the Japanese classification which is an elaborate staging scheme based on the anatomic location of the tumor and including specific lymph node stations. The second staging system developed by the American Joint Committee on Cancer (AJCC) and the International Union Against Cancer (UICC) is widely used in Western countries, and uses the tumor-node-metastasis (TNM) system commonly used in other cancer types. This system stages tumors according to depth of tumor invasion into the gastric wall (Figs. 1 and 2), lymph node involvement, and the presence of distant metastases (Tables 1 and 2).

1.5 Surgical Management

Management of gastric adenocarcinoma has shifted over the years from surgery alone to multimodality therapy including surgery in combination with chemotherapy or chemoradiotherapy. NCCN guidelines recommend surgery alone or

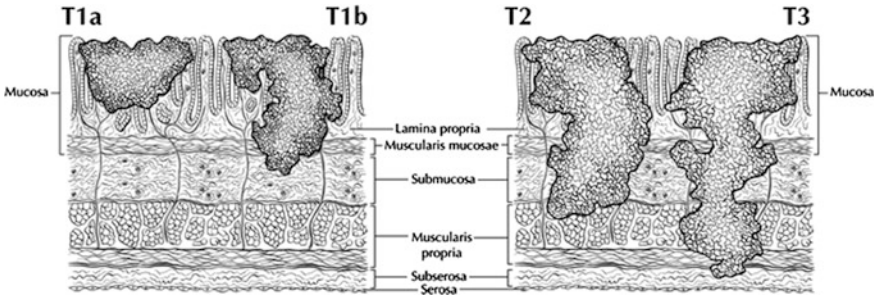

Fig. 1 American Joint Committee on Cancer staging T1–T3 diagram. T1a is defined as tumor that invades the lamina propria and T1b invades the submucosa. T2 is defined as a tumor that invades the muscularis propria, and T3 extends into the subserosal tissue

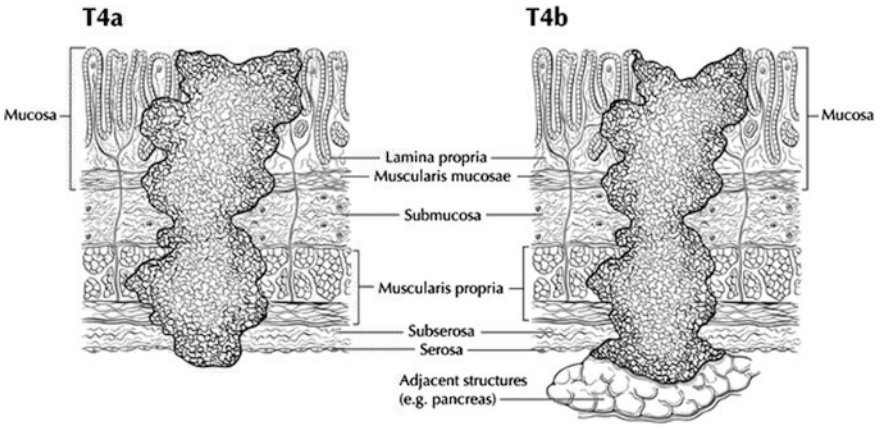

Fig. 2 American Joint Committee on Cancer staging T4 diagram. T4a is defined as a tumor that invades the serosa without invasion of adjacent structures, while T4b is a tumor that invades adjacent structures

endoscopic mucosal resection (EMR) for Tis or T1a lesions. Surgery alone is recommended for T1b tumors, and for T2 tumors and greater, surgery with chemotherapy or chemoradiotherapy is recommended.

Surgical resection remains the mainstay of potentially curative therapy for gastric adenocarcinoma. Surgical cure requires excision of the tumor with clear gross and microscopic margins. An R0, or margin negative resection, requires wide local excision of the primary tumor with en bloc resection of involved adjacent organs, lymphatics, and blood vessels.

The type of gastric resection for gastric adenocarcinoma will vary depending on the location of the tumor. For tumors originating from the distal esophagus, an esophagectomy is the procedure of choice. For tumors of the cardia, a total gastrectomy is preferred to an esophagogastrectomy as long as an R0 resection can be

Table 1 American Joint Committee on Cancer TNM Clinical Classification of Gastric Carcinoma, 7th Edition

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, or submucosa
Tla	Tumor invades lamina propria or muscularis mucosae
T1b	Tumor invades submucosa
T2	Tumor invades muscularis propria
T3	Tumor penetrates subserosal connective tissue without invasion of visceral peritoneum or adjacent structures. T3 tumors also include those extending into the gastrocolic or gastrohepatic ligaments, or into the greater or lesser omentum, without perforation of the visceral peritoneum covering these structures
T4	Tumor invades serosa (visceral peritoneum) or adjacent structures
T4a	Tumor invades serosa (visceral peritoneum)
T4b	Tumor invades adjacent structures such as spleen, transverse colon, liver, diaphragm, pancreas, abdominal wall, adrenal gland, kidney, small intestine, and retroperitoneum

Table 2 American Joint Committee on Cancer Staging of Gastric Carcinoma, 7th Edition

Stage 0	Tis	N0	M0
Stage IA	Tl	N0	M0
Stage IB	T2	N0	M0
	Tl	N1	M0
Stage IIA	T3	N0	M0
	T2	N1	M0
	Tl	N2	M0
Stage IIB	T4a	N0	M0
	T3	N1	M0
	T2	N2	M0
	Tl	N3	M0
Stage IIIA	T4a	N1	M0
	T3	N2	M0
	T2	N3	M0
Stage IIIB	T4b	N0 or N1	M0
	T4a	N2	M0
	T3	N3	M0
Stage IIIC	T4b	N2 or N3	M0
	T4a	N3	M0
Stage IV	Any T	Any N	M1

performed. Lesions in the proximal stomach and fundus can be resected with a total gastrectomy and a Roux-en-Y esophagojejunostomy. For lesions in the antrum of the stomach, a subtotal gastrectomy with a Billroth II reconstruction can be performed.

1.6 Lymph Node Dissection

Extent of lymph node dissection has been an area of controversy in gastric adenocarcinoma for many years. Some surgeons believe that cancer metastasizes through a stepwise progression, and an extensive lymphadenectomy is necessary to improve survival and/or cure the patient. Other physicians argue that extensive lymphadenectomies only add perioperative morbidity and mortality and do not improve survival. Asian countries have been performing extended lymphadenectomies routinely for many years with promising survival data, although Western countries have not been able to reproduce those results. The debate is all the more relevant in the United States where the majority of patients present with advanced disease [14].

Much of the controversy surrounding lymphadenectomies started in the 1980s when Japanese studies reported superior survival rates matched stage for stage, compared to the United States. This was theorized to be secondary to the more extensive lymphadenectomy performed in Japan compared to the United States [15]. This was the impetus for future randomized control trials in gastric cancer.

A United Kingdom study randomized 400 patients to either a D1 or a D2 lymph node dissection (see Fig. 3 for lymph node stations) [16]. Those patients with tumors in the upper or middle third of the stomach underwent a distal pancreaticosplenectomy to obtain retropancreatic and splenic hilar nodes. While the 5-year survival rates were not statistically significant between the two groups, on multivariate analyses it was noted that those patients in the D2 group that did not undergo the distal pancreaticosplenectomy had an increased survival compared with the D1 group. A trial in the Netherlands randomized 380 gastric cancer patients to a D1 lymphadenectomy and 331 patients to a D2 lymphadenectomy [17]. Similar to

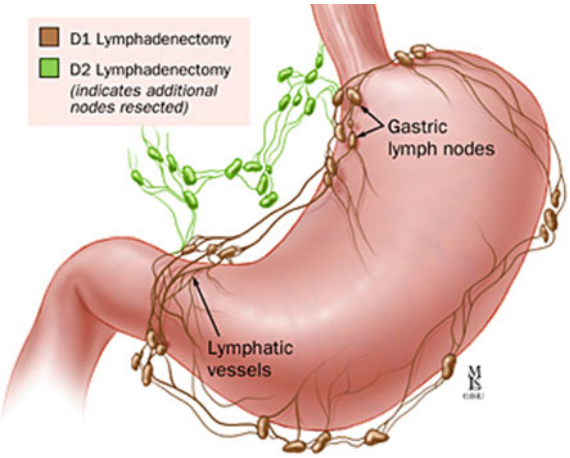

Fig. 3 Gastric Lymph Node Stations. A D1 lymphadenectomy includes lymph nodes along the greater and lesser curve of the stomach. A D2 lymphadenectomy includes D1 lymph nodes in addition to lymph nodes along the common hepatic, splenic, left gastric, and left hepatoduodenal arteries

the United Kingdom study, there was not a significant difference in survival between the two groups, even when followed out to 11 years [18]. There was a significant increase in postoperative complications in the D2 group compared with the D1 group (43 % vs. 25 %, respectively) as well as mortality (10 % vs. 4 %, respectively). The data from these two studies suggest that a pancreaticosplenectomy performed to harvest lymph nodes seems to only add morbidity and mortality while not improving survival.

One concern raised about the prior two studies was the variation in surgical technique and lack of standardization of surgeon experience. A Taiwanese study accounted for this by performing the study at a single institution with three surgeons, each of whom had completed at least 25 D3 lymph node dissections prior to the study. Patients with gastric cancer were randomized to a D1 lymph node dissection (defined as resection of perigastric lymph nodes along the lesser and greater curves of the stomach) or a D3 lymph node dissection (defined as resection of additional lymph nodes surrounding the splenic, common hepatic, left gastric arteries, nodes in the hepatoduodenal ligament, and retropancreatic lymph nodes). There was an overall 5-year survival benefit with the D3 group of 60 % compared with the D1 group of 54 % [19]. A Japanese study evaluated a more aggressive lymph node dissection and randomized patients to a D2 dissection or a para-aortic lymph node dissection (PAND). There was no significant difference in 5-year survival between the two groups with a trend toward an increase in complications in the PAND group [20].

Multiple studies have shown that the number of positive lymph nodes is a significant predictor of survival [21, 22]. Current AJCC guidelines stipulate that at least 15 lymph nodes are needed for pathologic examination to obtain adequate staging [23].

1.7 Endoscopic Mucosal Resection

Early gastric cancer (EGC) is defined as cancer that is confined to the mucosa or submucosa. Traditionally surgical resection was the only curative option available for patients with EGC although studies demonstrated that only 3 % of patients would have nodal metastases [24]. The advent of endoscopic mucosal resection (EMR) about 25 years ago has changed the treatment options for EGC. Several studies have demonstrated high survival and cure rates. A Japanese study included 131 patients with EGC (defined in this study as a tumor less than 2 cm and no ulcerative change) who underwent EMR [25]. The overall 5-year and 10-year survival rates were 84 and 64 %, respectively. A German study included 39 patients with EGC (defined here as tumor less than 3 cm, no invasion of lymph or vessels) and showed a 97 % remission with one treatment, and recurrent lesions in 29 % which were all successfully treated with a second treatment [26].

According to the NCCN guidelines, EMR can be considered for tumors less than 2 cm in diameter, without lymphovascular invasion, with clear deep and lateral margins, and without invasion beyond the submucosa [27]. It is important to note that for EMR to be successful, routine follow-up and surveillance are critical.

1.8 Neoadjuvant Therapy

Several large randomized trials have shifted the standard of care for gastric cancer from surgery alone to surgical resection in addition to perioperative chemotherapy or chemoradiation therapy. The advantages cited for neoadjuvant therapy include the possibility of "downstaging" a tumor in those patients who present with borderline or locally advanced tumors. Neoadjuvant therapy also has the potential to spare patients with aggressive tumor biology the morbidity of a large operation if their disease advances during a trial of neoadjuvant therapy. The NCCN guidelines recommend neoadjuvant therapy for T2 tumors and larger.

The guidelines for neoadjuvant therapy are based on several large trails. The largest trial is the United Kingdom Medical Research Council Adjuvant Gastric Infusion Chemotherapy MAGIC trial which randomized 250 patients to perioperative chemotherapy and surgery, and 253 patients to surgery alone [28]. The patients included in the trial consisted of those with resectable adenocarcinoma of the stomach (74 %), gastroesophageal junction (GEJ) (11 %), and lower esophagus (15 %). The chemotherapy included three cycles of cisplatin, epirubicin, and 5-FU given pre- and postoperatively. Both treatment groups had similar complication and 30-day mortality rates. The perioperative chemotherapy group demonstrated a significantly improved 5-year survival rate compared to the surgery alone group (36 % vs. 23 %, respectively). Limitations of the study include the mix of cancer locations as well as the fact that only 42 % of the chemotherapy group were well enough to receive the postoperative chemotherapy treatment.

A similar multicenter French trial (FNCLCC/FFCD) included patients with resectable distal esophagus, GEJ, and gastric adenocarcinoma [29]. Patients were randomized to perioperative chemotherapy (n = 113) or surgery alone (n = 111). The chemotherapy regimen used was cisplatin and 5-FU. Two to three cycles were given preoperatively, and 3–4 cycles were given postoperatively. The 5-year survival of the perioperative chemotherapy group was significantly higher than the surgery alone group (38 % vs. 24 %, respectively). In addition, the perioperative chemotherapy group was significantly more likely to achieve an R0 resection compared to the surgery alone group (84 % vs. 73 %, respectively). When comparing this trial to the MAGIC trial, it is important to note the difference in cancer locations. The MAGIC trial had a higher percentage of patients with gastric cancer compared to this trial (74 % vs. 25 %, respectively). Similar to the MAGIC trial, of those patients in this study that received at least one cycle of preoperative chemotherapy, only one half received any postoperative chemotherapy.

1.9 Adjuvant Therapy

Given the fact that over 80 % of patients that die from gastric cancer have local recurrence at some point, the utility of radiation therapy has been studied [30]. The Adjuvant Chemoradiotherapy in Stomach Tumors (ARTIST) trial compared adjuvant chemoradiation with adjuvant chemotherapy alone [31]. The trial included 458

patients with completely resected gastric cancer (including a D2 lymph node dissection) randomly assigned to six courses of capecitabine and cisplatin or two courses of capecitabine and cisplatin followed by 45 Gy of radiotherapy with concurrent capecitabine, followed by two courses of capecitabine and cisplatin. While the addition of radiotherapy did not reduce local recurrence rates, it was found to improve disease-free survival in those patients with positive lymph nodes. Those with nodal disease that received chemoradiotherapy had a 3-year disease-free survival of 76 % compared to 72 % for those that received chemotherapy alone.

The largest trial thus far is the INT 0116 trial which has the added advantage of using contemporary radiotherapy techniques. This trial randomized 556 patients with potentially curative esophagogastric junction or gastric cancer to observation alone versus adjuvant chemoradiotherapy [32]. The chemoradiotherapy included one cycle of 5-FU and leucovorin for 5 days with subsequent radiation therapy with 5-FU and leucovorin, followed by two more cycles of chemotherapy one month after the radiotherapy. The majority of the patients had T3 or T4 tumors and 85 % of the patients had nodal metastases. The 3-year overall survival rate was significantly improved in the combined modality group compared to the observation group (50 % vs. 41 %, respectively). Median survival was also significantly improved in the chemoradiotherapy group compared to the observation group (36 months vs. 27 months, respectively). The main criticism of this study is that only 10 % of the patients underwent a D2 lymphadenectomy. The majority, 54 %, underwent a D0 resection and 38 % had a D1 resection. This most likely resulted in falsely elevated surgical failure rates as well as falsely elevated adjuvant benefit.

The Japanese S-1 trial demonstrated the benefit of adjuvant chemotherapy for patients with stage II or III gastric cancer who had undergone potentially curative surgery, including a D2 lymphadenectomy [33]. S-1 is an oral fluoropyrimidine that is made of three agents: ftorafur (tegafur), oteracil, and gimeracil. In this Japanese ACTS-GC trial, 1059 patients were randomized to surgery alone or S-1 therapy daily for 4 weeks repeated every 6 weeks for one year. The overall 5-year survival was significantly improved in the S-1 group compared to the surgery alone group (72 % vs. 61 %, respectively). One year of postoperative S-1 treatment is now the standard of care for East Asian patients with gastric cancer. Unfortunately, the efficacy of S-1 has not been demonstrated in non-Japanese patient populations.

As a result of the above randomized trials, it is clear that surgery alone is insufficient treatment for local advanced gastric cancer. Consensus groups such as the NCCN recommend perioperative chemotherapy or postoperative chemoradiotherapy for locally advanced gastric adenocarcinoma, and preoperative chemoradiotherapy for localized GEJ adenocarcinoma.

2 Gastrointestinal Stromal Tumor

Gastrointestinal stromal tumors (GIST) are the most common sarcoma of the GI tract, although overall relatively rare [34]. The annual incidence in the United States is about 4000–6000 new cases per year. The most common site in the GI tract for

GISTs is the stomach (60–70 %), followed by the small intestine (25 %), the rectum (5 %), and the esophagus (2 %) [35]. GISTs were initially classified as a leiomyosarcoma due to their appearance on light microscopy although with the advent of immunohistochemistry (IHC), they were found to have both smooth muscle and neural cell elements. The cell of origin of GISTs is thought to be an intestinal pacemaker cell, or a precursor of the interstitial cells of Cajal [36]. Diagnosis of a GIST tumor is confirmed with IHC staining for the CD117 antigen which is part of the KIT transmembrane tyrosine kinase receptor. More than 95 % of GISTs in adults overexpress KIT and about two-thirds also express CD34 [37]. The histology of GISTs usually fall into three categories: spindle cell type, epithelioid type, or mixed type.

2.1 Clinical Evaluation

The median age at diagnosis is 63 years [37]. The tumors can grow to be very large and patients may present with mass-related symptoms such as early satiety, bloating, and abdominal pain. One study demonstrated three major presentations: GI bleeding (44 %), abdominal mass (47 %), and abdominal pain (21 %) [38]. Despite the above symptoms, often these tumors are discovered incidentally on imaging or endoscopy.

Once a GIST is suspected, a CT of the chest, abdomen, and pelvis should be performed with contrast. Occasionally magnetic resonance imaging (MRI) is useful depending on the anatomic location of the tumor. Imaging is used to determine the extent of the tumor as well as evaluate the presence of distant metastases. Occasionally, endoscopy can aid in surgical planning although it is rarely diagnostic because the tumors are submucosal and usually do not involve the mucosa [27]. Surgical consultation is recommended to determine if the tumor is resectable with an acceptable morbidity. Generally biopsy of the tumor should be avoided to prevent tumor rupture or intraabdominal dissemination. Biopsy can be considered if tissue is needed to confirm a diagnosis prior to neoadjuvant therapy for those unresectable or metastatic lesions.

2.2 Staging

The biologic behavior of GISTs and prognosis is best predicted by the size and mitotic rate of the tumor. GISTs are notoriously difficult to predict in terms of the biologic behavior of individual cases. Low-risk gastric GISTs are those tumors less than 2 cm with less than 5 mitoses per 50 high-powered fields (HPF) (metastases rate or tumor-related mortality is 0 %). High-risk tumors are those greater than 10 cm in diameter and have greater than 10 mitoses per HPF (metastases rate or tumor-related mortality is 86 %) [27].

2.3 Surgical Management

The surgical management of GISTs involves tumor resection with grossly negative margins, without violating the capsule. Formal gastric resections are rarely necessary unless the tumor is near the pylorus or GEJ. Extended lymph node dissections are also not necessary because GISTs generally do not spread through the lymphatics.

2.4 Nonsurgical Management

If a GIST is locally advanced and not technically feasible to resect, or if there are distant metastases, neoadjuvant therapy with imatinib mesylate can be initiated. Imatinib is a small molecule tyrosine kinase inhibitor, and was initially used for the treatment of chronic myelocytic leukemia, although it has been approved for the treatment of KIT-positive GISTs since 2002. Most GISTs express the KIT tyrosine kinase receptor which can be inhibited by imatinib. Patients with borderline resectable disease should be treated with imatinib and reimaged periodically to determine if surgical resection is technically possible. Even those patients with distant metastases can benefit from surgical resection of the primary tumor if they exhibit some response to imatinib.

The benefit of imatinib compared to surgery alone was demonstrated in the American College of Surgeons Oncology Group (ACOSOG) Z9001 phase III, double-blinded, multicenter trial [39]. It randomized 713 patients with completely resected gastrointestinal GISTs (at least 3 cm in diameter and KIT positive) to one year of adjuvant imatinib vs placebo. The trial was stopped early due to evidence that imatinib was superior to placebo. The recurrence-free survival at one year was 98 % for the imatinib group versus 83 % in the placebo group. Subsequent analysis showed that imatinib was more effective in those patients with high-risk GISTs.

The Scandinavian Sarcoma Group (SSG) XVIII trial evaluated a longer duration of imatinib treatment in 400 patients with high-risk GIST [40]. The trial compared 36 months to 12 months in those patients with at least one of the following: tumor diameter greater than 10 cm, mitotic count greater than 10 per 50 HPF, tumor diameter great than 5 cm with a mitotic rate greater than 5 per HPF, or tumor rupture. About half of the patients had gastric GISTs. The prolonged treatment group demonstrated significantly improved 5-year recurrence-free survival (66 % vs. 48 %) as well as overall survival (92 % vs. 82 %). Due to these results, the standard treatment for high-risk GIST includes 36 months of imatinib. Within 6–12 months of discontinuing the imatinib, recurrence rates were similar between the two treatment groups which raises the possibility that treatment longer than 36 months may be beneficial.

3 Small Bowel Tumors

Malignant tumors of the small bowel account for less than 5 % of all GI tract malignancies, and are very rare. The incidence of small bowel cancer in the United States is about 6000 annually [41]. Traditionally adenocarcinoma of the small

bowel was reported to be the most common tumor, although carcinoid tumors, lymphomas, sarcomas, and GISTs are increasing in frequency [42]. The majority of small bowel adenocarcinomas occur in the duodenum (46–55 %) and about 13 % occur in the ileum [42–46].

3.1 Clinical Evaluation

Patients with small bowel tumors can present with a variety of symptoms including nausea, vomiting, GI bleeding, weight loss, and abdominal pain. Tumors can also cause small bowel obstructions or intussusception. Occasionally duodenal tumors are discovered during endoscopy. Tumors elsewhere in the small bowel can be found with CT imaging or small bowel follow-through. Wireless capsule endoscopy can also be used [47].

3.2 Surgical Management

Surgical resection is the treatment of choice for small bowel adenocarcinoma [48]. Periampullary lesions often require a pancreaticoduodenectomy. Distal duodenal lesions can often be removed with a sleeve resection and a duodenojejunosotmy. As long as resection margins are negative, more aggressive resections are not necessary. A study from Mayo Clinic evaluated 68 patients with duodenal adenocarcinoma, and the overall 5-year survival rates of those that underwent a pancreaticoduodenectomy versus a sleeve resection were similar [49]. Lesions distal in the small bowel should be removed with a segmental resection including a wide margin of mesenteric lymph nodes. Involved organs should be resected en bloc as technically feasible [50].

Small bowel adenocarcinoma is often diagnosed late, and only about 65–76 % of patients are potentially resectable at the time of diagnosis and about half of these have nodal disease [45, 51]. A series that used the SEER database looked at 1991 patients with small bowel adenocarcinoma and demonstrated the 5-year survival by stage: stage I, 85 %, stage II, 69 %, stage III, 50 % [52]. Predictors of improved overall survival include complete R0 resection, location in the jejunum, low AJCC tumor stage, and low-grade tumors [45, 51, 53, 54]. There is a paucity of data regarding the use of adjuvant therapy for small bowel adenocarcinoma. Often treatment modalities used in colon cancer are used for small bowel adenocarcinoma.

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Pathologic Features of Esophageal and Gastric Malignancies

Eduard Matkovic, Michael Schwalbe and Kristina A. Matkowskyj

Abstract

Esophageal and gastric carcinomas affect millions of individuals worldwide, placing a considerable burden on society. Unfortunately, preventative medicine falls short as screening methods for the upper gastrointestinal tract lack the ability to detect early onset disease. The overwhelming majority of cases present after symptoms appear when individuals have advanced disease with a poor prognosis. Further complicating matters, the anatomic location of these neoplasms engenders rapid tumor progression, which repeatedly thwarts successful surgical treatment. This chapter will focus on the pathological features of malignant neoplasms of the esophagus and stomach.

Keywords

Esophageal squamous cell carcinoma · Esophageal adenocarcinoma · Adenosquamous carcinoma · Adenoid cystic carcinoma · Gastric adenocarcinoma · Helicobacter pylori

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1 Esophagus

Esophageal cancer affects more than 450,000 people worldwide and currently ranks sixth among cancer-related mortality [45]. The prognosis is poor as many patients present with locally incurable or metastatic disease. The incidences rates vary dramatically worldwide, which can be attributed to demographic and socioeconomic factors. Although the vast majority of esophageal neoplasms arise from the epithelial layer and include squamous cell carcinoma (SCC) and adenocarcinoma (AC), a subset of neuroendocrine and soft tissue tumors can also occur in the esophagus (Table 1). Several tasks are presented to the surgical pathologist when dealing with esophageal carcinoma: rendering a diagnosis, classifying the histological type, and assessing prognostic factors. Therefore, we will focus on these topics as we discuss various esophageal neoplasms.

1.1 Squamous Cell Carcinoma

Worldwide, squamous cell carcinoma (SCC) is the most common variant of esophageal carcinoma. The highest incidence rates are seen in underdeveloped settings, particularly in parts of Iran, China, and Africa. In contrast, western countries have seen a considerable decrease in squamous lesions, with an accompanying increase in adenocarcinoma [13]. This demographic discrepancy is not completely understood, and possibly attributed to varying etiological factors as no single causative agent has been identified. Males are affected more commonly than females, and incidence peaks in the sixth decade [6]. The pathogenesis remains incompletely defined, but thought to be a

Table 1 Classification of esophageal tumors

Epithelial tumors	Premalignant Squamous Glandular	Malignant Squamous cell carcinoma Adenocarcinoma Adenoid cystic carcinoma Adenosquamous carcinoma Basaloid squamous cell carcinoma Mucoepidermoid carcinoma Verrucous (squamous) carcinoma Spindle cell (squamous) carcinoma Undifferentiated carcinoma
Mesenchymal tumors	Benign Granular cell tumor Hemangioma Leiomyoma Lipoma	Malignant Kaposi sarcoma Gastrointestinal stromal tumor Leiomyosarcoma Melanoma Rhabdomyosarcoma Synovial sarcoma
Neuroendocrine tumors	Neuroendocrine tumors (NET)	Neuroendocrine carcinoma Mixed adenoneuroendocrine carcinoma
Lymphoma		

multistep process stemming from precancerous changes in the squamous epithelium. It was once believed that esophagitis was a precursor for SCC as prospective studies in high-risk areas have documented a dysplasia-to-carcinoma progression [47, 59]. Risk factors include tobacco, alcohol, poverty, dietary N-nitroso compounds, lack of dietary fruits and vegetables, and poor nutritional status. A history of smoking and alcohol use account for the majority of cases in Europe and North America, however the importance of these factors is substantially different in developing nations. The current literature remains inconclusive on whether human papilloma virus (HPV) is a prominent carcinogen in esophageal SCC [36].

1.1.1 Clinical Features

The most common symptoms of advanced lesions are dysphagia and weight loss. Pain occurs in the epigastrium or retrosternal area. Superficial lesions have vague and nonspecific symptoms, sometimes associated with a tingling sensation or persistent cough. The majority of SCCs are located in the lower two-thirds of the esophagus, followed by the upper segment. The lesion presents as either a depression or elevation of the mucosa.

1.1.2 Gross Pathology

Superficial lesions more frequently appear as plaques or small ulcers, while advanced lesions are often deep ulcerations or fungating masses. However, features do overlap and depth of invasion is not always clearly discernible on endoscopy. Misinterpreting an infiltrative luminal narrowing for a benign stricture is a common pitfall. Alternatively, benign esophagitis presents as an extensive, diffusely ulcerated, flat lesion similar to superficial-type SCC. Imaging techniques like three-dimensional CT, endoscopic ultrasound, or 18-fluoro-2deoxyglucose-positron emission tomography (PET) can effectively demonstrate certain staging parameters. While preoperative imaging and endoscopy are nearly diagnostic, a biopsy is required for confirmation and accurate histological classification, no matter how high the index of clinical suspicion.

1.1.3 Microscopic Pathology

Dysplasia evolves through a spectrum, where changes begin at the base of the epithelium (low-grade) and progress to the surface (high-grade). The cytological features include large, dark staining nuclei with coarse chromatin (hyperchromasia), variation in nuclear size and shape (pleomorphism), loss of epithelial order, and mitotic activity above the basal layer. Atypical cells trailing off into the lamina propria or deep aberrant keratinization are potentially worrisome signs of invasion. Squamous cell carcinoma is composed of polygonal cells with abundant eosinophilic (pink) cytoplasm, intercellular bridges (tight junctions between neighboring cells), and variable amounts of keratinization. The nucleus is large, dark, and contains a prominent nucleolus. Tumor grading evaluates cellular differentiation, the degree of atypia, and mitotic activity. Generally, tumor grading is a means to predict the tumors biological behavior. A low-grade SCC has a lesser degree of atypia as the cells are well-differentiated (Grade 1), thus resembling native squamous epithelium (Fig. 1a). High-grade SCC (Grade 3) has severe atypia and is

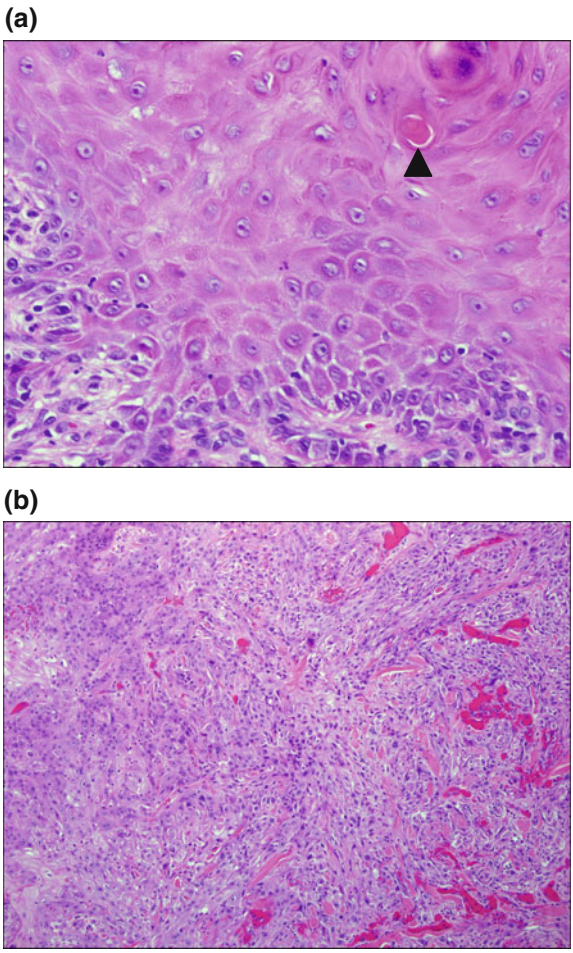

Fig. 1 Squamous cell carcinoma (SCC). **a** In well-differentiated SCC (Grade 1), the tumor cells have abundant pink cytoplasm and keratin formation is evident (*arrowhead*). **b** In poorly-differentiated SCC, the tumor cells are more difficult to appreciate as being squamous in origin and invade as single cells or small clusters of cells

inherently aggressive (Fig. 1b). The frequency of lymphatic and blood vessel invasion increases with increasing depth of invasion [52]. Immunohistochemistry is used judiciously, as most diagnoses can be made solely on histological grounds, however, squamous cell carcinomas are typically positive for cytokeratin 5/6, p63, and p40 by immunohistochemistry. There are currently three histological variants of SCC recognized:

Verrucous Carcinoma: Verrucous carcinoma grossly has a distinctive wart-like appearance (Fig. 2). It is considered a low-grade tumor with pushing borders (bulbous growth of neoplastic cells which push normal tissue aside). The behavior is defined by slow growth with local spread and infrequent metastases. If not properly excised, recurrence tends to be local. Endoscopic correlation is essential as superficial biopsies can underdiagnose the low-grade histology [37].

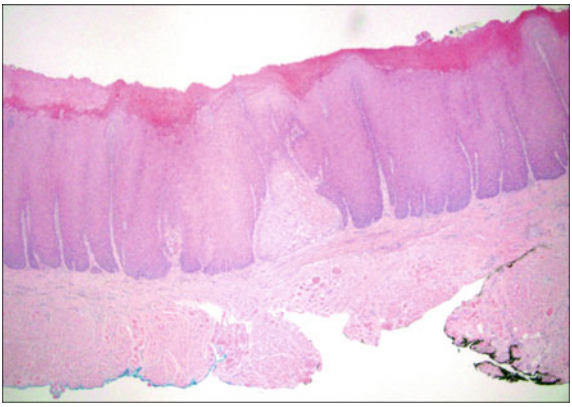

Fig. 2 Verrucous carcinoma. This low-power photomicrograph reveals well-differentiated hyperplastic squamous epithelium with orderly maturation, hyperkeratinization, and broad "finger-like" projections with a typical downward, pushing border characteristic of this entity

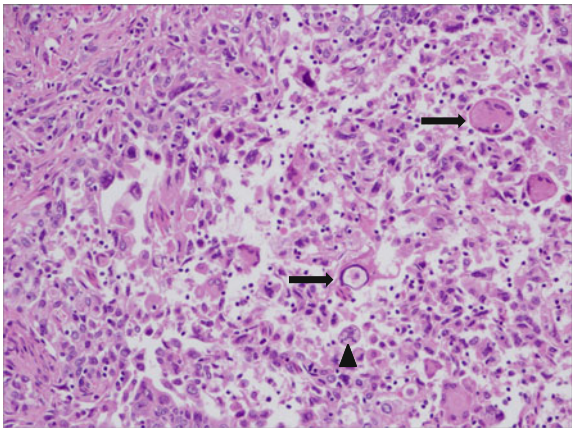

Fig. 3 Spindle cell (squamous) carcinoma. The tumor cells have lost their epithelioid morphology and appear more spindled with bizarre, pleomorphic nuclei (*arrows*) and atypical mitoses (*arrowhead*)

Spindle Cell (Squamous) Carcinoma: The key diagnostic feature is biphasic morphology; well- to moderately differentiated squamous cells admixed with sarcoma-like spindle cells (Fig. 3). The spindle cell component is usually high grade with increased pleomorphism. Overall the prognosis is favorable because the tumor tends to grow outward in a polypoid fashion [48]. Immunohistochemical staining for pancytokeratin can be used to highlight the epithelial differentiation of the neoplastic cells.

Basaloid Squamous Cell Carcinoma: Basaloid squamous cell carcinoma is distinctive for its proximal location. Characterized by large, rounded nests of small blue cells with peripheral palisading and central necrosis (Fig. 4). These tumors tend to be deeply invasive with widespread metastasis at the time of diagnosis. Patients demonstrate poor cancer-related and disease-free survival rates [51].

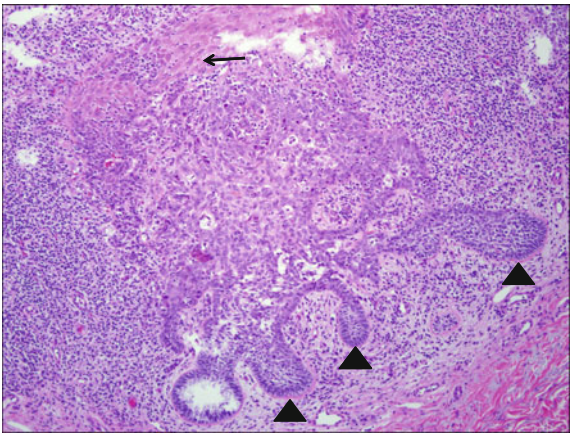

Fig. 4 Basaloid squamous cell carcinoma. Both squamous and basaloid components are present within this tumor. Basaloid cells are *blue* cells with peripheral palisading row of elongated nuclei parallel to one another) (*arrowhead*). The squamous cell component reveals a densely *pink* cytoplasm (*arrow*)

1.1.4 Prognostication

The TNM system used by the American Joint Commission on Cancer (AJCC) is the most widely accepted staging system [14, 56, 61]. The extent of tumor spread is determined by specific staging parameters (TNM classification) and the type of

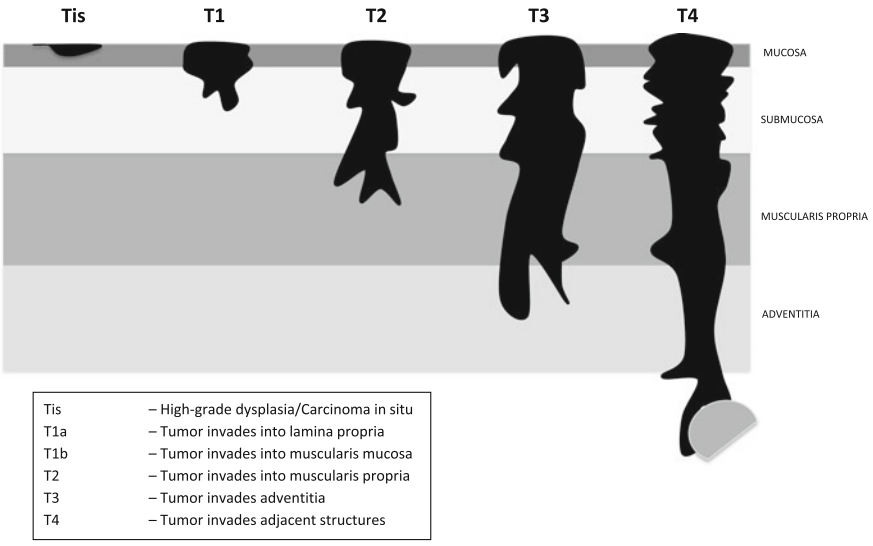

Fig. 5 Tumor staging based on depth of invasion. The single most important parameter, in terms of prognostics, is depth of invasion. Lymphatics originate within the lamina propria and invasion into the lamina propria or beyond results in a T1 stage or higher. Invasion of tumor cells beyond the adventitia with involvement of other structures is a T4 stage

treatment a patient receives is dependent on the extent of disease. The best predictor of outcome and treatment response is the depth of invasion (T-stage), and therefore demands an accurate microscopic measurement. Like all segments of the gastrointestinal tract, the esophagus can be divided into four distinct histological layers: mucosa, submucosa, muscularis propria, and serosa (Fig. 5). The mucosa consists of a protective stratified squamous epithelium and is contained by a basement membrane. Any dysplastic process contained within the mucosa is defined as high-grade dysplasia or carcinoma in situ (Tis). Any neoplastic process invading beyond the basement membrane of the mucosa into deeper layers will be upstaged from Tis into T1 through T4. The reason for this is because the lymphatic system originates in the lamina propria, where neoplastic cells have the potential to metastasize [52, 58]. At the time of diagnosis, most patients present with advanced lesions invading into the muscularis propria, heralding a grim prognosis. The 5-year survival rate amidst tumors restricted to the esophageal wall is roughly 50 %, while penetration into or beyond the adventitia is associated with a worse outcome. Roughly 60 % of patients demonstrate lymph node involvement as the frequency of lymph node involvement is related to depth of invasion (40 % in submucosal extension compared to 5 % for intramucosal lesions) [1]. In addition to traditional features such as invasion and lymph node involvement, tumor grading is implemented to help clinically stratify patients and further predict outcome. Although controversy exists as to whether tumor grading significantly influences survival, over the last decade the American Joint Committee on Cancer (AJCC) has incorporated histology as a parameter for clinical staging of esophageal carcinoma [14, 39].

1.1.5 Molecular Pathology

The loss of several tumor suppressor genes is associated with SCC, of which mutation in the TP53 gene is an early event sometimes detectable in high-grade dysplasia [39]. Other molecular factors include: alterations in p16/INK4a [64], amplification of cyclin D1 [26], and inactivation of CDKN2A [53]. TP53 is mutated in 35–80 % of SCCs [38], and its nuclear accumulation has shown to be a negative prognostic indicator [54].

1.2 Esophageal Adenocarcinoma

Adenocarcinoma (AC) differs from squamous cell carcinoma based on histology, but also on various epidemiological characteristics. For the past three decades, the occurrence of adenocarcinoma has increased dramatically [7, 46]. This trend has been particularly dominant in Western countries, like the United States and United Kingdom, where rates have exceeded that of squamous cell carcinoma. Epidemiological factors of adenocarcinoma overlap with Barrett esophagus (BE), as the incidence of BE has increased in tandem with the increasing rates of AC [62].

At the gastroesophageal junction, complications of chronic gastroesophageal reflux disease (GERD) result in the development of intestinal metaplasia. That is, after repeat bouts of injury, the healing process transforms squamous epithelium