Siewert III Adenocarcinoma

Still Searching for the Right Treatment Combination

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KEYWORDS

• Siewert tumor • Esophageal cancer • Gastric cancer • Neoadjuvant chemoradiation • Esophagectomy • Gastrectomy

KEY POINTS

- It remains uncertain whether Siewert III tumors should be treated as esophageal or gastric cancers.
- Neoadjuvant therapy has been shown to improve survival in both esophageal and gastric trials. Randomized control trials comparing neoadjuvant chemotherapy versus chemoradiation should help define the most optimal treatment regimen.
- Surgical treatment follows general oncology principals: resect to negative margins with complete lymph node dissection, and, the extent of resection often extends more proximal onto the esophagus in addition to the total/subtotal gastrectomy.

INTRODUCTION

Borders invite contest. Not too differently from geopolitical divides, our attempts to classify gastroesophageal junction (GEJ) tumors based on arbitrary borders have met similar discourse. Siewert and Stein were the first to propose a map of this territory, drawing the confines of the esophagus and the stomach (**Fig. 1**).[1] However, from this map, it is difficult to determine which parts of the GEJ belong to the esophagus and which belong to the stomach. This debate generally involves the Siewert III tumor, which was originally described as a "subcardial gastric carcinoma which infiltrates the

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Surg Oncol Clin N Am 29 (2020) 647–653
https://doi.org/10.1016/j.soc.2020.07.002
surgonc.theclinics.com

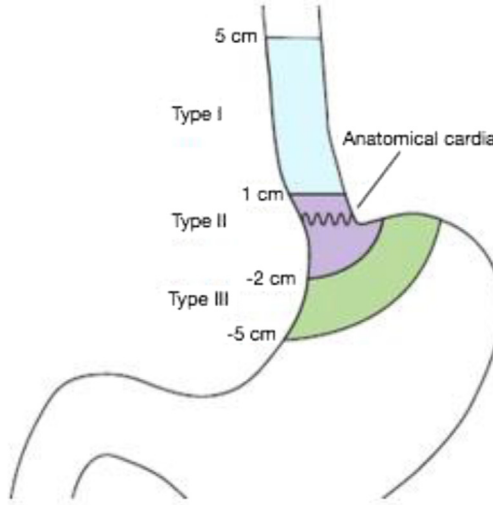

Fig. 1. Siewert classification. (*Adapted from* Yang Z, Wang J, Wu D, Zheng J, Li Y. Retrospectively analysis of the pathology and prognosis of 131 cases of adenocarcinoma of the esophagogastric junction (Siewert type II/III). *Transl Cancer Res.* 2017;6(5):949-959. https://doi.org/10.21037/tcr.2017.09.18.)

esophagogastric junction and distal esophagus from below" (see **Fig. 1**).[1] Even now, it remains unclear if this tumor is in the domain of the esophagus or the stomach, and not surprisingly, it remains controversial how to best treat Siewert III tumors- as esophageal cancers or as gastric cancers.

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Tumor location can be difficult to determine clinically and precisely how much extension into the esophagus is necessary for a gastric cardia tumor to be classified as a Siewert III tumor is nebulous. In the seventh edition of the American Joint Commission on Cancer (AJCC), tumors extending from the lower esophagus to within the first 5 cm of the gastric cardia were classified as Siewert III and staged as esophageal cancers.[2] This definition was adjusted in the eighth edition of the AJCC, which classifies tumor location by its epicenter regardless of how far proximally or distally the tumor extends.[3] Different from 7th AJCC, the eighth edition categorizes Siewert III tumors as gastric carcinomas. Admittedly, the authors of the eighth edition AJCC esophageal cancer staging state that this anatomic boundary is more of a placeholder until the pathogenesis and molecular differences between esophageal and gastric carcinomas are better understood in this region.[4]

LANDMARK CLINICAL TRIALS: NEOADJUVANT THERAPY? IF SO, WHICH ONE?

As ruling jurisdictions over territories change, governing laws become jumbled over time. This confusion has fostered Siewert III tumors inclusion into both esophageal and gastric cancer trials.

The Radiation Therapy Oncology Group trial 8911 (RTOG 8911) trial randomized patients with epidermoid (squamous cell carcinoma) and adenocarcinomas of the esophagus and GEJ to undergo either neoadjuvant cisplatin and fluorouracil and

surgery versus surgery alone (Table 1).[5] Unfortunately, the authors did not specify how many patients had GEJ tumors. They were only able to show the importance of a complete resection (R0) on overall survival but did not find neoadjuvant chemotherapy improved overall survival.[5]

Role for neoadjuvant chemotherapy in esophageal and GEJ cancers was demonstrated by the Medical Research Council Oesophageal Cancer Working Group (OEO2) trial, which definitively proved a survival benefit for neoadjuvant chemotherapy.[6] However, while the OEO2 trial demonstrated the importance of neoadjuvant chemotherapy, only 10% of patients in that study had cardia tumors (see Table 1). There was no description of proximal tumor extent or tumor epicenter.[6] The OEO2 trial dovetailed into the Medical Research Council Adjuvant Gastric Infusional Chemotherapy (MAGIC) trial, which randomized patients with clinical T2 and greater biopsy proven adenocarcinoma of the stomach/lower third of the esophagus. Patients were randomized to 6 cycles of perioperative chemotherapy and surgery versus surgery alone (see Table 1).[7] This landmark trial was originally designed for gastric cancers; however, due to the increasing incidence of lower esophageal adenocarcinomas in addition to the positive findings from the OEO2 trial, the authors extended eligibility criteria to include esophageal and GEJ carcinomas.[6,7] While the MAGIC trial showed survival benefits in the group that received perioperative epirubicin, cisplatin, and fluorouracil (ECF), only 11.5% of patients had tumors in the GEJ. In the chemotherapy arm, 90% of patients completed all 3 cycles of neoadjuvant chemotherapy; however, only 42% tolerated all 6 perioperative cycles. While these trials demonstrate survival benefits of neoadjuvant chemotherapy for both esophageal and gastric cancer, only a small minority of patients actually had Siewert III cancers. The question therefore remains: do we treat Siewert III tumors as esophageal or gastric cancers?

The ChemoRadiotherapy for Esophageal cancer followed by Surgery Study (CROSS) trial served to solve this question (see Table 1). Patients with clinically resectable, locally advanced esophagus or GEJ cancers (clinical T1–3N0–1M0, according to AJCC 6) were randomized to receive either weekly administration of 5 cycles of neoadjuvant chemoradiotherapy (intravenous carboplatin [area under the curve 2 mg/mL per min] and intravenous paclitaxel [50 mg/m of body-surface area] for 23 days) with concurrent radiotherapy (41.4 Gy, given in 23 fractions of 1.8 Gy 5 days per week) followed by surgery, or surgery alone. In contrast to previous trials, nearly a quarter of patients enrolled in the CROSS trial had GEJ tumors. Neoadjuvant chemoradiation was generally well tolerated, as 95% of patients in the chemoradiation arm completed their full course. Patients in the chemoradiation arm had improved overall survival and 29% of patients even had a complete pathologic response.[8]

Although the data strongly favored neoadjuvant therapy, a persistent question that remains is which regimen is better? One study tried to answer the question of neoadjuvant chemotherapy versus chemoradiation for patients with GEJ tumors, however, it was closed due to low recruitment.[9] Patients with locally advanced GEJ adenocarcinomas (cT3-4NXM0) were randomized to undergo either 15 weeks of neoadjuvant chemotherapy or 12 weeks of neoadjuvant chemotherapy and 3 weeks of radiation followed by surgery.[10] Although there was no difference in overall survival, patients who underwent neoadjuvant chemoradiation had more pathologic complete response (15.6% vs 2.0%) and tumor-free lymph nodes (64.4% vs 37.7%) at resection.[10] The study was unfortunately underpowered to demonstrate a difference in overall survival.

Currently, there are multiple randomized control trials comparing neoadjuvant chemotherapy to neoadjuvant chemoradiation.[11–13] The NEOadjuvant Trial in Adenocarcinoma of the oEsophagus and oesophagoGastric Junction International Study (NEO-AEGIS) trial randomizes patients with cT2-3N0-3M0 esophageal and GEJ adenocarcinomas to

Table 1
Landmark trials

Study	Study Population	Study Arms	Results	Limitations
RTOG 8911	Esophageal squamous and adenocarcinoma	Neoadjuvant cisplatin and fluorouracil + surgery (n = 216) vs surgery (n = 227)	No survival difference between groups. R0 resection most important for survival.	Did not specify how many patients had GEJ tumors.
OEO2	Esophageal squamous and adenocarcinoma	Neoadjuvant cisplatin and fluorouracil + surgery (n = 400) vs surgery (n = 402)	Neoadjuvant chemotherapy hazard ratio for death 0.84 (95% CI, 0.72–0.98; *P* = .03).	10% cardia tumors
MAGIC	Gastric and lower esophageal adenocarcinomas	Perioperative epirubicin, cisplatin and fluorouracil + surgery (n = 250) vs surgery (n = 253)	Perioperative chemotherapy hazard ratio for death, 0.75 (95% CI, 0.60–0.93; *P* = .009).	11.5% GEJ tumors. Only 42% patients tolerated all 6 perioperative cycles.
CROSS	Esophageal squamous and adenocarcinoma	Neoadjuvant carboplatin and paclitaxel with 41.4 Gy + surgery (n = 178) vs surgery (n = 188)	Neoadjuvant chemoradiation hazard ratio for death 0.657; (95% CI, 0.495–0.871; *P* = .003). 29% complete response rate.	24% GEJ tumors

Abbreviations: CI, confidence interval; GEJ, gastroesophageal junction.

receive either a modified version of the MAGIC trial chemotherapy or the CROSS regimen.[11] Similarly, the ESOPEC trial is randomizing patients with cT1N + M0 or cT2-4aNxM0 esophageal and GEJ adenocarcinoma to either receive neoadjuvant FLOT (5-fluorouracil/leucovorin/oxaliplatin/docetaxel) or the CROSS regimen.[13] Finally, the Trial Of Preoperative therapy for Gastric and Esophagogastric junction AdenocaRcinoma (TOPGEAR) is grouping Siewert III tumors with gastric cancers and randomizing patients to undergo either neoadjuvant ECF or neoadjuvant ECF with radiation (45 Gy) followed by surgery.[12] Subanalyses of results from these trials, focusing on patients with Siewert III hopefully will help us better understand how to best treat these tumors: as esophageal or gastric cancers.

SURGICAL APPROACH: HOW HIGH SHOULD WE GO?

Although GEJ tumor location influences the choice of neoadjuvant regimen, anatomic location becomes even more important in choosing the optimal surgical approach. Where the tumor originates determines the extent of resection and which region encompasses the lymphatic drainage basin. In their institutional series, Siewert and colleagues[14,15] performed extended gastrectomy on 97% of patients with type III GEJ adenocarcinomas. Their extended gastrectomy consists of total gastrectomy with D2-level lymph node dissection and lower posterior mediastinum lymph node dissection. Occasionally these tumors extend higher into up the thoracic esophagus. It may be beneficial to sample subcarinal lymph nodes to ensure that there is no locoregional tumor metastases to thoracic lymph nodes. A proximal resection margin of $\geq$6 cm may be required to achieve a microscopically negative proximal margin, therefore mandating additional dissection from the thoracic cavity.[16] This may require a thoracoabdominal approach versus a transhiatal approach, depending on the level of surgeon comfort in the chest.[16] One randomized control trial suggested that the left thoracoabdominal approach was associated with worse survival and worse perioperative morbidity.[17] However, on closer examination of the complications, the investigators note that the left thoracoabdominal approaches was associated with worse pancreatic fistula, abdominal abscess, pneumonia, anastomotic, leak, empyemas, and mediastinitis. Pancreatic fistulas and abdominal abscesses atypically occur after a left thoracoabdominal approach; however, this finding is likely due to the investigators' aggressive D2 dissections that included splenectomy, which has been shown to increase perioperative morbidity and overall mortality.[18]

SUMMARY

Our understanding of gastroesophageal junction tumors is limited to our clinical determination of where the tumor lies and how far it extends. This has hindered our ability to develop more targeted treatment regimens. While neoadjuvant regimens have been shown to be beneficial in treating Siewert III tumors, it is unclear if a course of neoadjuvant chemotherapy is sufficient or if the addition of neoadjuvant radiation helps improve survival. Depending on the proximal extent of the tumor, there are different approaches for resection. Outcomes from these resections can differ depending on the degree of lymphadenectomy performed, as well as the surgeon level of comfort in the thoracic cavity. Results from ongoing randomized control trials hopefully will shed more light on the true biologic behavior of the Siewert III tumor.

FUTURE DIRECTIONS

As cancer care moves toward targeted molecular therapies, immunotherapy is being added to the arsenal of treatment. For patients with metastatic gastric and GEJ cancers adenocarcinoma, the KEYNOTE-059 phase II trial showed that pembrolizumab 200 mg, administered intravenously every 3 weeks until disease progression, or patient withdrawal, provided 11.6% of patients with objective response and 2.3% with complete response.[19] Similarly, the KEYNOTE-180 study showed that patients with metastatic esophageal squamous cell carcinoma and adenocarcinoma could similarly derive some radiologic improvement in tumor response.[20] Although pembrolizumab is a monoclonal antibody targeting programmed death 1 ligand (PD-L1), both studies found objective tumor response to pembrolizumab even in patients with PD-L1–negative tumors. This suggests that the mechanism behind these targeted therapies may involve multiple pathways that are yet fully understood. However, the response to these therapies may help us better understand the true cell origin of Siewert III tumors in this contested anatomic region. Immunotherapy may also potentially bring previously unresectable tumors into the fold of resectability.

DISCLOSURE

The authors have nothing to disclose.

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