Siewert III Adenocarcinoma: Indications and Treatment

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23.1 Introduction

Siewert III are cancers of the proximal stomach invading the esophagogastric junction (EGJ), with tumor epicenter from 2 to 5 cm below the EGJ, according to the Siewert classification [1]. According to TNM 8th ed., they are considered gastric cancers [2]. Nonetheless, infiltration of distal esophagus makes them a separate entity. Siewert III cancer, although representing around 40% of EGJ cancers and being the EGJ cancer with the worst prognosis [3, 4], does not have a homogenous treatment [5–12]. The rationale for a separate discussion of this entity is the boundary position of this disease, which makes its biological and spreading behavior peculiar; consequently, treatment strategies must be distinctive, also in consideration of the surgical challenge.

23.2 Surgical Strategy

23.2.1 Indications According to Margins

Outcome after non-curative resections is poor and achieving an R0 surgery is the mainstay of treatment also in Siewert III adenocarcinoma.

Both proximal and distal margins can be involved. Taking into account proximal margins, resection margins greater than 3.8 cm *ex vivo* in the esophagus

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(corresponding to 5 cm of *in situ* esophagus) were associated with improved survival for all Siewert types [13]. Again, considering only types II and III, no positive proximal margins were reported with a 6 cm wide resection [14]. Conversely, Mine et al. found that a proximal margin of more than 20 mm measured on the resected specimen stretched out on a corkboard (approximately 28 mm in vivo) was related to better survival in Siewert II and III [15]. A distal margin of 4–6 cm is considered safe for all Siewert types [14].

In summary, abdominal total gastrectomy with distal esophagectomy is the treatment of choice for Siewert III adenocarcinoma. A transthoracic approach should be reserved for cases where proximal margins of 5 cm cannot be achieved.

23.2.2 Indications According to Lymphatic Spread and Lymphadenectomy

The role of lymphadenectomy in gastric cancer has been extensively discussed in previous chapters. Siewert III is staged as a gastric cancer in TNM 8th ed. and for correct staging at least 16 nodes must be removed. An adequate number of collected lymph nodes is important not only for staging and to avoid stage migration, but also for prognosis. Total number of resected nodes is a good indicator of lymphadenectomy adequacy also in the esophageal cancer: many trials reported a 5-year overall survival advantage in the case of increased number of resected nodes [16, 17], even considering only pN0 gastric cancer [2]. This advantage was noted especially in advanced cancers.

The need for correct lymphadenectomy remains also after induction treatments. Although nodes are harder to detect after induction treatments, their number seems uninfluenced by the treatment [18].

The number of nodes is not the only selection criterion for lymph node dissection: the other key element is lymphatic spread: Siewert type III cancers arise on the proximal stomach and invade the distal esophagus, and nodal diffusion is mainly towards the abdomen in both Western and Eastern series. Nodal abdominal stations are always involved in N+ patients, and around 10% of them have simultaneous positive mediastinal nodes (station 110 according to the IGCA classification) [19–22]. The risk of mediastinal nodal involvement increases with the length of esophageal invasion, also after induction treatments, with a cut-off of esophageal invasion ≥2 cm [23, 24].

Paracardial (stations 1 and 2), lesser curvature (station 3) and left gastric artery nodes (station 7) are the most frequent abdominal stations involved, followed by celiac trunk, common hepatic artery, splenic artery and infrapyloric nodes (stations 9, 8a, 11 and 6). Para-aortic nodes around the left renal vein (station 16A2lat) are positive in around 22–30% of locally advanced cases [19, 25, 26]. Some authors reported a survival benefit from dissection of para-aortic nodes similar to that of second-tier nodes like station 9 [25]. Moreover, prophylactic para-aortic lymphadenectomy after induction treatment could also be beneficial in patients with poorly cohesive and signet-ring cell tumors [27].

As in proximal gastric cancer, no survival advantage is reported when adding splenectomy to D2 lymphadenectomy [25, 26], and splenectomy should only be added to obtain an R0 resection [9].

In summary, because of the risk of nodal involvement and nodal diffusion, all patients ≥T1sm should undergo a D2 abdominal and inferior mediastinal lymphadenectomy. A D3 lymphadenectomy should be considered in advanced poorly cohesive cancers after induction chemotherapy.

23.3 Multimodal Treatment

Surgery with lymphadenectomy is the standard approach to Siewert III ≥ cT1sm. R status and nodal involvement are the main prognostic factors [8, 9]. Surgery alone is possible for cT1smN0 patients. However, the high risk of non-curative resections and low survival with surgery alone in locally advanced and N+ cases encouraged the development of multimodal treatments, which reported a survival advantage and increased rate of curative resections after multimodal approaches compared to surgery alone [5, 6]. Multimodal treatments may increase R0 rate and reduce nodal involvement. Induction or perioperative chemotherapy is indicated in all ≥cT3 patients irrespective of clinical nodal status (cN), due to the very high risk of nodal involvement and non-curative resections.

Also all cN+ patients should be offered multimodal treatment [6, 10]. Debate is still open for cT2N0. Risk of nodal involvement of cT2 patients is considerable, reaching 55% as reported by Stiles et al. [11], thus many clinicians and guidelines offer multimodal treatments also to cT2N0 patients [6, 10].

Among multimodal treatments, perioperative chemotherapy is more frequently used. Nonetheless, postoperative cycles are completed only in around half of the cases with any chemotherapy regimen [12]. Among gastric cancers, Siewert III undergo more complicated procedures and the risk of non-completion of postoperative chemotherapy is higher, hence probably induction chemotherapy, without postoperative cycles, would better fit Siewert III patients, but the literature on the topic is scanty [6, 10].

23.4 Hot Topics

Tumors at the level of the EGJ are a “zone disease” rather than an “organ disease” [28]: that is the reason why it is difficult to consider all the three Siewert types as a single disease, sharing the same biology, but showing a different behavior only due to their position. Likewise, Siewert III does not seem to be just a slightly higher proximal gastric cancer. As stated several times in this volume, the real revolution in the understanding of gastric cancer started with its molecular classification; nevertheless, most of EGJ cancers were classified as chromosomal instability (CIN). Only Siewert III tumors exhibited features attributable to the other three molecular types, although in different percentages with respect to the other gastric sites [29].

Recently, transcriptomic profiling revealed a different gene expression when comparing Siewert I and Siewert III or Siewert II and Siewert III tumors [30]. For this reason, in the near future we do not only need to borrow the rules of esophageal and gastric cancer as regards resection margins and lymphadenectomy: we will need to evaluate tumors not by site but by molecular pattern. A practical and current example is represented by Siewert III genomically stable/poorly cohesive cancer: considering its highly aggressive submucosal and lymphatic spread, esogastrectomy should be considered to achieve a truly R0 resection. A further evolution of the concept could be to perform esogastrectomy also in Siewert II and proximal gastric genomically stable/poorly cohesive cancers.

The last hot topic is related to a technical aspect: Siewert III cancer surgery requires, as mentioned above, a proximal resection margin of at least 5 cm in the distal esophagus. This implies that the anastomosis would fall very high into the posterior mediastinum, and performing this reconstruction via a minimally invasive approach is demanding and few data are provided the in literature.

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