Updates Surg (2017) 69:319–325
DOI 10.1007/s13304-017-0429-9

REVIEW ARTICLE

Siewert III adenocarcinoma: treatment update

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Received: 23 August 2016 / Accepted: 8 March 2017 / Published online: 16 March 2017

Abstract Siewert III cancer, although representing around 40% of EGJ cancers and being the EGJ cancer with worst prognosis, does not have a homogenous treatment, has few dedicated studies, and is often not considered in study protocols. Although staged as an esophageal cancer by the TNM 7th ed., it is considered a gastric cancer by new TNM 8th ed. Our aim was to consolidate the current literature on the indications and treatment options for Siewert III adenocarcinoma. A review of the literature was performed to better delineate treatment indications (according to stage, surgical margins, type of lymphatic spread and lymphadenectomy) and treatment strategy. The treatment approach is strictly dependent on cancer site and nodal diffusion. T1m cancers have insignificant risk of nodal metastases and can be safely treated with endoscopic resections. The risk of nodal metastases increases markedly starting from T1sm cancers and requires surgery with lymphadenectomy. The site of this type of cancer and the nodal diffusion require a total gastrectomy and distal esophagectomy, with 5 cm of clear proximal and distal margins and a D2 abdominal and inferior mediastinal lymphadenectomy. Multimodal treatments are indicated in all locally advanced and node positive cancers. Siewert III cancers are gastric cancers with some peculiarities and require dedicated studies and deserve more consideration in the current literature, especially because their treatment is particularly challenging.

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Keywords Esophagogastric junction adenocarcinoma · Siewert III adenocarcinoma · Treatment · Surgery

Introduction

Esophagogastric junction (EGJ) adenocarcinoma has been classified differently over time. Siewert classification is the most used classification. Siewert type III are those of the proximal stomach invading the EGJ, with tumor epicenter from 2 to 5 cm below the EGJ [1].

Surgery with lymphadenectomy is still considered the standard approach to EGJ cancer, with some differences due to Siewert type. Surgery aims at reaching a curative R0 resection and good survival. If this is normally possible for superficial cancers, especially for T1m, where also endoscopic resections are now widespread, the high risk of non-curative resections and the low survival achieved with surgery alone in locally advanced and N+ cases encouraged the development of multimodal treatments. Many meta-analyses of randomized trials [2, 3] and a recent Cochrane review [4] clearly reported a survival advantage and an increased rate of curative resections, after multimodal approaches compared to surgery alone.

These results have clinical implications, and consensus conferences [5] and international guidelines [6–8] now recommend multimodal approaches for all fit patients with locally advanced cancers and/or nodal involvement.

Also the type of multimodal treatment is related to Siewert type. Radiotherapy alone is not supported as a possible treatment choice, for no trial demonstrated any advantage in rate of curative resections and survival [2, 3]. Also adjuvant CT is to proscribe, because it did not demonstrate any survival advantage [9]. While for Siewert type I cancers, the standard approach consists in induction

CRT [2, 5, 6, 10–12], and Siewert type II is treated with either CRT or peri-operative CT [13, 14], Siewert III cancer, although representing around 40% of EGJ cancers and being the EGJ cancer with worst prognosis [15–17], does not have a homogenous treatment, has few dedicated studies, and is often not considered in study protocols.

From a pathological point of view, the origin of Siewert type III is quite well recognized and it is considered a gastric cancer invading the esophagus by consensus conferences and guidelines [5, 6]. Now also new TNM 8th edition defines Siewert III as a gastric cancer [18]. As aforementioned, Siewert III is frequently explicitly excluded from specific trials on gastric or esophageal cancers. Multimodal approaches focus on chemotherapy that might be peri-operative, both pre- and post-surgery, or neoadjuvant, if used only before surgery.

Our objective is to consolidate the current literature on Siewert III adenocarcinoma, to better delineate treatment indications (according to stage, surgical margins, type of lymphatic spread and lymphadenectomy) and treatment strategy.

Indications according to stage

Superficial cancer

The approach to upper G.I. cancers depends on stage. Superficial cancers are those confined to mucosa and submucosa, while those invading beyond submucosa are defined advanced.

Endoscopic techniques are gaining interest for esophageal and gastric cancer in all cases in which the risk of nodal involvement is absent or reasonably low. In EGJ cancer, as in esophageal squamous cell carcinoma and in gastric carcinoma, the risk of nodal metastases is high in T1sm cancers and surgery with lymphadenectomy is mandatory. Endoscopic resection is indicated instead in mucosal tumors $\leq$2 cm with well differentiate intestinal histology, without ulceration. Otherwise surgical resection is indicated also in mucosal cancer.

When subdividing into Siewert types, data on Siewert III are real "gold dust". Most studies are either about cancer on Barrett's esophagus, i.e. Siewert I, or on gastric cancer. Siewert III cancers resemble strictly gastric cancers of the upper third, but they are difficult to discover, since they are normally diagnosed only in advanced stage.

Advanced cancer

Surgery with lymphadenectomy is the standard approach to Siewert type III. Although T1sm cancers are not defined as advanced, the high risk of nodal metastases for these patients makes them comparable to advanced cases in terms of treatment approach.

Alongside R status, the other important prognostic factor in EGJ cancer is nodal involvement [19, 20].

Multimodal treatments operate on both T and N level, both increasing the rate of R0 resections and probably reducing nodal involvement. The risk of nodal involvement is so high in T3 and T4a cancers and the probability to obtain a R0 resection so low, that induction or peri-operative CT is indicated in all patients $\geq$T3 irrespective of clinical nodal status.

According with American NCCN guidelines, also all patients with clinical nodal involvement should be offered a multimodal treatment [6].

Debate is still open for cT2N0, with some Authors doubting that induction treatments are needed in this class of patients. NCCN guidelines indicate that post-operative cycles should be performed in all N+ patients and in $\geq$T3 cases. The non-negligible risk of nodal involvement in case of clinical T2N0 cases pushes many clinicians to offer multimodal treatments also to cT2N0. Indeed the risk of nodal involvement of T2 patients is considerable, reaching 55% as reported by Stiles et al. [21].

For T4b patients, multivisceral resections might be considered after induction CT, if only spleen and pancreas tail are involved and an R0 resection seems possible [20].

In all cases of R + resection, post-operative chemoradiation can be considered.

Among multimodal treatments, peri-operative is more frequently used, especially after MAGIC protocol has become a standard of care for gastric cancer in Western countries. Nonetheless, post-operative cycles are completed in less than 50% of the cases with any chemotherapy regimen. If the risk on non-completion of the proposed CT treatment is substantial for distal gastric cancer, it is even more so for Siewert III patients, who undergo more complicated procedures. Probably induction or neoadjuvant CT, without post-operative cycles, would better fit Siewert III patients, but literature on the topic is scanty. In summary, induction or peri-operative CT followed by surgery is the preferred approach in all locally advanced Siewert type III cancers and in all cN+ cases.

Indications according to margins

Longitudinal margins

Outcome after non-curative resections is poor for all types of cancer, and achieving an R0 surgery is the mainstay of treatment also in EGJ adenocarcinoma [22]. The effect of positive margins on locoregional recurrences and survival is hence highly disadvantageous.

Curative R0 surgery is defined as resection of the primary tumor without any residual disease.

Both longitudinal (proximal and distal) and circumferential margins can be involved.

Taking into account proximal margins, resection margins greater than 3.8 cm ex vivo in the esophagus (corresponding to 5 cm of in situ esophagus) was associated with improved survival for patients with all Siewert types [23]. Again, considering only types II and III, no positive proximal margins were reported with a 6 cm wide resection [24]. On the opposite, Mine et al. found that a proximal margin measured on resected specimen stretched on a corkboard of more than 20 mm (approximately 28 mm in vivo) was independently related to better survival in Siewert types II and III [25].

A distal margin of 4–6 cm is considered safe for all Siewert types [24, 26, 27].

In summary, 5 cm both proximal and distal margins seem appropriate for all Siewert types. In Siewert III cancers a wider proximal margin is probably unnecessary and thus if a 5 cm proximal margin can be obtained with an abdominal approach, it would not be necessary a thoracic approach. Total gastrectomy is necessary to obtain both a 5 cm distal margin and complete lymphadenectomy.

CRM

The concept of circumferential resection margin (CRM) was derived from rectal cancer.

Circumferential margins are studied for fixed tubular structures and so its use is limited to the portion of esophagus of the specimen and in particular for Siewert types I and II. This margin is instead not considered in gastric and Siewert III cancers.

Indications according to lymphatic spread and lymphadenectomy

Total number, number positive and ratio

The importance of the number of positive nodes or of Lymph Node Ratio (LNR) has been studied extensively. LNR is defined as the ratio between involved and total resected nodes.

Between 3 and 8 positive nodes and 20% LNR are the most common cut-off values. Where more than 8 nodes are involved, no survival benefit was reported after surgery [28–30].

Number of involved nodes and LRN seems to retain their role also after neoadjuvant treatments. Mariette and coworkers found on esophageal cancer that, after subdividing patients in adequately staged and inadequately staged ($\geq$15 nodes and <15 nodes removed, respectively) the number of involved nodes correlated better with survival in the former, while LNR was more important in the latter [29].

While the role of number of involved nodes in determining prognosis is pretty straightforward, LNR is confounding. LNR is a quotient mixing cancer biology (nodal metastasis potential) with surgical technique (extent of lymphadenectomy): a similar LNR of 25% can result from 1 positive node of 4 resected, 4 of 16, or 10 of 40 [31].

Total number of resected nodes is a good marker of lymphadenectomy adequacy. Moreover, more nodes harvested provide more precise staging, reducing stage migration and giving more accurate survival information. However, extended lymphadenectomy would be justified only if it correlated to improved survival.

Many trials investigated the topic, reporting a 5-year overall survival advantage and/or a reduced hazard of death in case of increased number of resected nodes [32–34]. Rizk et al. proposed to remove at least 10, 20, and 30 nodes for T1, T2, and T3, respectively [32]. According to Altorki et al., 16 nodes are needed to obtain a survival benefit for N + patients, while more than 40 nodes are requested for N0 patients [33]. An international multicenter study, confirmed that the number of resected nodes is a strong and independent predictor of survival [34].

The need of correct lymphadenectomy remains also after neoadjuvant treatments [35, 36]. Although nodes are harder to detect after neoadjuvant treatments, their number seems not influenced by the treatment [37].

Two studies on Siewert types II and III demonstrated that both total number of resected nodes and number of involved nodes are strong prognostic factors [38, 39]. The cut-off value for number of retrieved nodes was 15 and 16, respectively. Barbour et al. reported that in locally advanced patients, N0 cases with inadequate staging (<15 nodes removed) had a prognosis similar to N1 cases with more than 15 nodes removed.

The reason why increasing the number of resected nodes reflects on survival in not fully understood. However, a possible explanation is the elimination of micrometastases, defined as metastases detectable only with immunostaining, in nodes considered negative with imaging and by routine histological examination. The presence of micrometastases in supposed node-negative patients could explain the improved survival after extended lymphadenectomy in pathological N0 patients.

In summary, number of involved nodes is a main prognostic determinant. In inadequately staged patients, hence in patients with few nodes removed, LNR might be used, even if with caution, to differentiate between N+ patients.

Table 1 Sites of nodal diffusion in Siewert III

	Pedrazzani et al. [40]	Meier et al. [41]	Mönig et al. [42]	Kakeji et al. [43]	Nakamura et al. [44]	Yuasa et al. [45]
Abdomen and chest	7%	18%	13%	2%	10%	2%
Only abdomen	91%	82%	87%	88%	90%	98%
Only chest	2%	–	–	–	–	–

Table 2 Nodal diffusion in Siewert III related to depth of tumor invasion (pT)

	Pedrazzani et al. [40]	Meier et al. [41]	Goto et al. [52]
T1is (HGD) (m1)	–	17%	50%
T1m (m2)			
T1m (m3)			
T1sm (sm1)			
T1sm (sm2)			
T1sm (sm3)			
T2	61%	78%	76%
T3	88%	86%	
T4	100%	90%	

Extended lymphadenectomy increases the number of total nodes removed and this correlates with improved survival, even after neoadjuvant treatments. The correct cut-off number of nodes to remove remains controversial, but it seems to increase with increasing T stage. Probably at least 15 nodes should be resected, according to most studies and TNM.

Nodal spread

Surgical approach and type of lymphadenectomy are strictly related to nodal diffusion. The risk of nodal metastases increases with depth of tumor invasion, but nodal spread is dependent on cancer site. 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. As shown in Table 1 [40–45], nodal abdominal stations are always involved in N+ patients, and around 10% of them have simultaneous positive mediastinal nodes (station 110 according to IGCA classification) [46]. The risk of mediastinal nodal involvement increases with the length of esophageal invasion: Hosokawa et al. reported an increased risk of inferior mediastinal nodal metastases by 21 times in case of esophageal invasion ≥2 cm [47].

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 patients [40, 48, 49]. Using the index of estimated benefit from lymph node dissection (IEBLD), proposed by Sasako in 1995, to compute the usefulness and priority of dissection of nodal stations [50], Hasegawa et al. and Nunobe et al. reported a survival benefit from dissection of para-aortic nodes similar to that obtained from second-tier nodes like celiac trunk station (station 9) [4, 48].

The incidence of nodal metastases at splenic hilum (station 10) ranges 10–20% of cases, but no survival advantage is reported adding splenectomy to carry out a D2 lymphadenectomy [48, 49, 51]. Hence reviews and consensus conferences are concordant to propose splenectomy only to obtain an R0 resection [5, 20].

While the nodal spread is associated to cancer site, the risk of nodal metastasis is related to depth of tumor invasion (pT). Nodal involvement varies markedly going from superficial to advanced cancers. Few studies describe nodal frequency by T status in Siewert type III patients (Table 2) [40, 41, 52]. Nodal involvement increases with depth of invasion, being more than 60% in T2 patients and mostly present in T3–4 cases.

In summary, because of risk of nodal involvement and nodal diffusion, all patients ≥T1sm should undergo a D2 abdominal and inferior mediastinal lymphadenectomy. Probably patients diagnosed with T1m cancer might theoretically avoid lymphadenectomy, but definitive data are

lacking. A D3 lymphadenectomy has been proposed for advanced cases but it is still debated.

Treatment strategy

Surgery aims to completely remove the cancer with clear margins and potentially involved nodes. Surgical approach principles remain valid also after multimodal treatments. Type of surgery is not modified by the clinical response to chemotherapy.

The typical surgical approach consists of total gastrectomy with, if necessary, resection of nearby organs to achieve an R0 resection [19].

In a Japanese randomized trial [53] and its results after a 10-year follow-up [54], a left thoraco-abdominal (LTA) approach for Siewert III with esophageal infiltration limited to 3 cm did not show any survival benefit compared to total gastrectomy and distal esophagectomy from a solo abdominal approach.

For T1sm and more advanced cancers, the correct approach requires 5 cm of clear proximal margin. An abdominal approach is possible only if the invasion of the esophagus is limited to 2 cm. In case of esophageal invasion of more than 2 cm, adequate margins cannot be obtained through a solo abdominal approach. Moreover, the risk of inferior mediastinal N + increases significantly, making a trans-thoracic approach necessary [49, 50].

Clear 5 cm distal margins are also required: hence a total gastrectomy is normally needed. Furthermore, a total gastrectomy is necessary to obtain a complete abdominal lymphadenectomy. Splenectomy is recommended to reach an R0 resection, but not to carry out lymphadenectomy.

Reconstruction of the digestive tract can be achieved with a Roux-en-y esophago-jejunal anastomosis, performed via a solo abdominal approach if esophageal invasion is inferior to 2 cm or else with a trans-thoracic approach.

Conclusions

In conclusion, Siewert III cancers are gastric cancers with some peculiarities and require dedicated studies and deserve more consideration in the current literature, especially because their treatment is particularly challenging.

The treatment of Siewert III cancer requires a total gastrectomy and distal esophagectomy, with 5 cm of clear proximal and distal margins and a D2 abdominal and inferior mediastinal lymphadenectomy. D3 lymphadenectomy might be considered in advanced cases.

Multimodal treatments are indicated in all locally advanced and node positive Siewert III patients and surgical principles remain unaltered after multimodal treatments.

Compliance with ethical standards

Conflict of interest The Authors declare that they have no conflict of interest. No financial support.

Research involving human participants and/or animals This article does not contain any studies with human participants or animals performed by any of the authors.

Informed consent None.

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