

Current Status of Sentinel Lymph Node Biopsy in Adenocarcinoma of the Distal Esophagus, Gastric Cardia, and Proximal Stomach

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Abstract The resection of the adenocarcinoma of the esophagogastric junction should be considered to the extent of the lymphatic drainage. This, on the other hand, depends on the possible lymphatic metastasizing. As an adenocarcinoma of the esophagogastric junction is located along the borderline between two visceral cavities (mediastinal/abdominal), it can, in principle, metastasize in both cavities. There is not, however, an imaging (CT, MRI, PET) that can adequately assure the detection of a beginning lymph node metastasis in particular. The sentinel lymph node biopsy could provide the beginning of a solution in this case. The initial results, with all of the necessary accompanying technical work, have been encouraging. The paper presented here provides an introduction to the challenge of the SLNB and the background of a specialized surgical therapy of the AEG. If a lymph nodal metastasis can be definitely confirmed or ruled out, many patients could be spared an unnecessary lymphadenectomy. This is especially important at the AEG because minimizing the evasiveness of the surgery with

adequate radical oncological resection (e.g., without thoracotomy) would mean a substantial reduction of postoperative mortality.

9.1 Introduction

Adenocarcinoma of the esophagogastric junction (AEG) is an emerging distinct entity and shows increasing incidence (Blot et al. 1991; Powell and McConkey 1992). Surgical approach and extent of resection of AEG remain areas of controversy and pose specific challenges because of its critical anatomic location between the thoracic and abdominal cavity.

9.2 Pattern of Lymph Node Metastases

Lymph node metastases occur either in the mediastinum or in the abdominal drainage pathway of the stomach. Dresener et al. (2001) showed that 77% of type I (Siewert) junctional tumors have lymph node metastases in both mediastinal and abdominal cavity. Confirmed by Feith et al., a group from Netherlands found that 22% of patients with adenocarcinoma of

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the cardia (Siewert III) have lymph node metastases in the proximal station of the chest (Lagarde et al. 2005; Feith et al. 2003). Further assessment of the cranial extent of junctional tumors' preoperative staging endoscopy is crucial, but it is essential to decide between transabdominal/transhiatal or transthoracic approach. Although the incidence of lymphatic metastases of AEG is relatively high, it remains limited to regional lymph nodes. Feith also showed that the initial lymphatic spread of type I follows the regional nodes in the lower posterior mediastinum, the left and right pericardial region, and along the lesser gastric curvature following the left gastric artery (Feith et al. 2003). Lymphographic studies from Aikou detected that main lymphatic pathways originating in type II and III AEG-tumors preferentially make their way to the celiac axis, the splenic hilum, and the para-aortic lymph nodes (Aikou et al. 1987). Skipping the regional lymph node stations remains uncommon, but partly occurs (Li et al. 2008; Moenig et al. 2005). Distant lymph nodes (second step) appeared to be only involved in patients with advanced tumors after tumor dissemination in regional lymph nodes (first step). This stepwise lymphatic spread is in contrast to squamous cell carcinoma of the esophagus, in which skipping of regional lymph node stations appears as common (Saito et al. 2007; Matsubara et al. 2000).

9.3

Extension of Resection

According to Siewert, extension of resection (type I: esophagectomy with resection of proximal stomach, type II: total gastrectomy with thoracic esophagectomy, type III: total gastrectomy with distal transhiatal esophageal resection) is often associated with high morbidity (Siewert and Stein 1998). In a randomized prospective study, Hulscher et al. showed that transthoracic

esophagectomy with extended en bloc lymphadenectomy was associated with significant higher morbidity than transmediastinal esophagectomy, but the median overall-, disease free-, and quality-adjusted survival did not show significant differences between the two groups (Hulscher et al. 2002). Pulmonary complications, rising ventilation time, and prolonged hospital stay are the main problems. Especially, there is a high risk for the elderly people and patients having high ASA-classification (Sauvanet et al. 2005). Siewert et al. published their experienced results of a local resection with regional lymphadenectomy and jejunal interposition (Merendino procedure) in patients with Type I and II early AEG and precancerous lesions. It was shown to be an attractive alternative to radical esophagectomy with less complications, tending to have better survival (Stein et al. 2000a; Merendino and Dillard 1955). If nodal spread was ruled out, the resection often is performed less invasive or even minimal-invasive for all these patients, presumably with a lower morbidity. Nevertheless, the use of perioperative imaging (CT, MRI, PET) currently is not determining the existence and location of lymph node metastases prior to resection (mediastinal/abdominal). sentinel lymph node biopsy (SLNB) is a useful diagnostic tool in completing preoperative strategies.

9.4

The Techniques of Sentinel Node Biopsy

The concept of the SLNB is based on the finding that lymphatic drainage does not occur at random, but rather to a designated, e.g., the sentinel lymph node. Therefore, the spread of metastases via the lymphatic pathways is supposed to be evident in the sentinel node first.

Both techniques, the dye technique (DT) and the radiocolloid technique (RCT), were described in detail elsewhere (Gretschel et al. 2003, 2004, 2007). The essential steps are the followings:

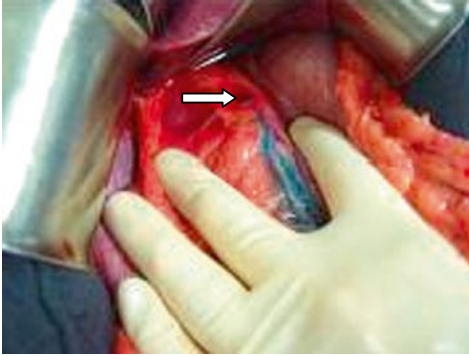


Fig. 9.1 Dye method: 3 min after endoscopic peritumoral injection of blue dye in AEG type III, a blue lymph channel and the SLN in perigastric lymph node station number 1 are identified

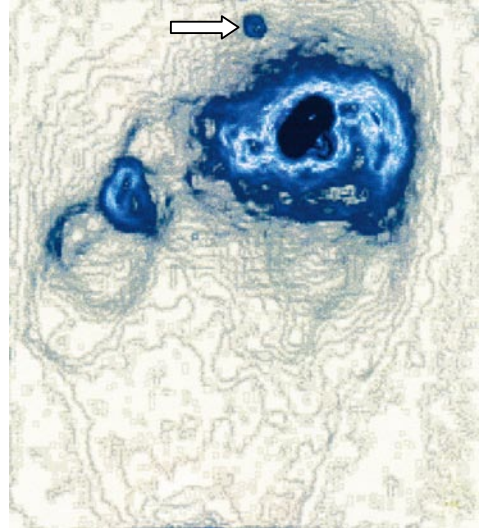


Fig. 9.2 Radiocolloid technique 15 h after endoscopic peritumoral injection of Technetium 99 in AEG type I, one radionuclide enriched SLN (arrow) is detected in the neighborhood of tumor

The *(DT)* (Fig. 9.1) is a strictly intraoperative technique that uses several substances for gastric-cancer patients: Indocyanine-green, Isosulfan blue (Lymphazurin[®]), and Patent Blue Dye V. The method includes the following steps:

- Subserosal or submucosal (endoscopic) peritumoral injection of the dye.
- Clip-marking or excision of the first stained lymph nodes.
- Postoperative selective histopathological examination of the marked lymph nodes in accordance with a specific protocol.

The *RCT* (Fig. 9.2) usually is a two-step technique with preoperative tracer injection and intraoperative SLN identification:

- Preoperative injection of a radiocolloid (4–17 h prior to surgery), in Europe mostly Tc^{99m}-Nanocoll[®] with a dosage of 180 MBq.
- Optional preoperative lymphoscintigraphy.
- Intraoperative detection of the nuclide enriched lymph node(s).
- Clip-marking or excision of the nuclide enriched lymph nodes.
- Scanning of the situs for residual activity after specimen resection.

- Optional excision of iuxtaregional nuclide enriched lymph nodes.
- Optional scanning of the specimen for further nuclide enriched nodes.
- Selective histopathological examination of the marked lymph nodes in accordance with a specific protocol.

The disadvantage of the RCT becomes clear in the scattering effect of the radionuclide-injection site, if the first draining lymph nodes are close to the tumor. Thus, SLN identification sometimes becomes difficult or impossible. High body mass index (BMI) was associated with a low detection rate in DM. In AEG the lymph drainage is even more difficult to determine because of the varying anatomical location in the abdomen or in the thorax.

Recently, there has been a consideration of the combination of both the blue dye technique and the radiocolloid-method (*dual technique*) in AEG as complementary techniques.

9.5 Upstaging

The use of SLNB in AEG requires preparation of SLN according to a certain protocol. If there is a request to perform serial sections and immunohistochemistry for the SLN as location with the highest probability of metastatic involvement, a procedure that requires too much technical and financial effort should be performed routinely for all resected nodes. Moreover, various markers such as CEA, c-MET, CK20, MAGE-A3, and GalNAc-T are used for immunohistochemistry. Biopsy of the sentinel lymph node also requires surgical skill and experience. Therefore, it is to be expected that a significant percentage of additional micro metastases (0.2–2 mm) or isolated tumor cells (<0.2 mm) will be detected by serial sections with immunohistochemistry or PCR (Fig. 9.3). As stated above, the clinical implication of minimal residual disease (MRD) is not yet defined, but micrometastases have shown high proliferate activity (Yanagita et al. 2008; Yonemura et al. 2007) and prognostic significance (Doekhie et al. 2005; Heeren et al. 2005; Horstmann et al. 2004). In tumor genesis, macrometastases are the result of highly proliferate micrometastases. Therefore, the existence of MRD is of (yet undetermined) prognostic significance.

9.6 Using the SLN as Frozen Section During Surgery

A reliable histological evaluation of the sentinel node during surgery will enable the surgeon to adapt the extent of resection of lymphatic stations. Currently, sensitivity and specificity of potential methods that are fast enough to be applied like Imprint-cytology or frozen section vary between 30 and 96% (Ajisaka and Miwa 2003; Levine et al. 2003; Matsumoto et al. 2003). PCR methods are evaluated to increase sensitivity and specificity (Matsuda et al. 2004). Further development of fast histological detection techniques will be as important as the improvement of sentinel node detection and biopsy.

9.7 Current Status of Sentinel Lymph Node Biopsy in Gastric Cancer

The current evidence concerning the reliability of SLNB to detect lymph node metastases in gastric cancer indicates that detection rate is generally high (90–100%), whereas sensitivity

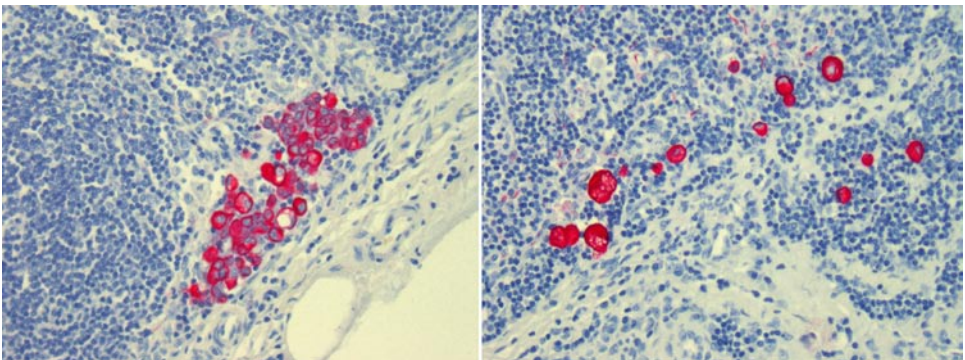


Fig. 9.3 Micrometastasis (*left*, ×200) and isolated tumor cells (*right*, ×400) in SLN, which were detected by intense histological examination by the use of immunohistochemistry with cytokeratin-antibody (MNF-116)

ranges between 80 and 95%. Experience is still limited to a small number of centers. Thus, the still limited experience of most of the centers is considered (Ishizaki et al. 2006; Isozaki et al. 2004; Kitagawa et al. 2002; Miwa 2001; Park et al. 2006; Uenosono et al. 2005). Evaluation of lymph node metastases in early cancers also showed that positive nonsentinel nodes mostly were located in the same region as the sentinel node. A regional lymph node resection can improve the sensitivity of SLNB (Miwa et al. 2003). Based on these findings, a resection of the peritumoral sentinel node basin with intraoperative histopathologic evaluation is under evaluation. If no lymph node metastases are found, the chance for additional lymph node metastases is low (Lee et al. 2008a, b). In perspective, the next step is the clinical application of the laparoscopic SLNB with intraoperative SLN-detection. Nevertheless, initial first studies on laparoscopic SLNB did not achieve sensitivity comparable to the open approach (Kitagawa et al. 2001; Kitagawa and Kitajima 2005; Saikawa et al. 2006; Tonouchi et al. 2003, 2005). However, technical improvements show promising results. As a consequence, many Asian centers started with limited laparoscopic-assisted resection of early gastric cancer after SLNB (Ishikawa et al. 2007; Orsenigo et al. 2008; Tonouchi et al. 2007; Wang et al. 2008; Ishigami et al. 2007).

9.8 Sentinel Lymph Node Concept in AEG

Applying the sentinel lymph node technique in AEG might have increased clinical significance similar or higher than in gastric cancer because of the outstanding anatomical tumor location between two cavities and varying lymphatic drainage. However, the clinical impact of SLNB on AEG is currently open to interpretation. Most of the trials, according to degree of resection in AEG, included many patients with advanced AEG. But early AEG due to Barrett metaplasia is diagnosed more frequently and the surgical approach is not well defined, but should be treated with a less invasive approach (Ell et al. 2000) (Fig. 9.4). A study from UK showed that 80% of T1 AEG and 60% of T2 AEG did not show metastatic lymph node involvement (Dresner et al. 2001). Another characteristic finding was a close proximity of sentinel nodes to the primary AEG (Feith et al. 2003; Li et al. 2008; Moenig et al. 2005; Stein et al. 2000b). Therefore, SLNB of AEG from abdominal cavity is a feasible technique. Accordingly, the initial step is to determine all the patients without lymph node metastases. Certainly, if nodal spread is ruled out, the resection could be performed less invasive or even minimal-invasive,

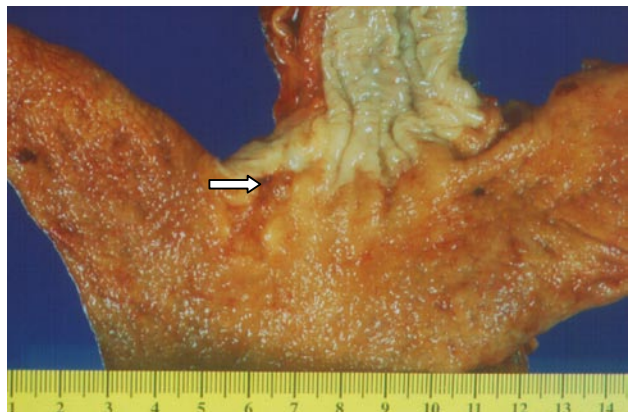


Fig. 9.4 Early cancer of the esophagogastric junction directly on the dental line (Type Siewert II)

presumably with a lower morbidity. Thus, a limited resection without transthoracic esophagus resection (Type I) or without complete gastrectomy (Type II and III) is possible.

Unfortunately, results of sentinel node biopsy in AEG are limited. In 2004, Burian et al. from Munich reported their first results of SLNB in Barrett's and cardia cancer (Burian et al. 2004a, b). The preliminary experience indicated that the AEG for SLNB is feasible, despite the anatomic complexity of this area. However, the overall sensitivity of 85% was reported in the study and yield good results, especially in early tumors (90%). Burian et al. preferred a combination of both radio colloid and dye technique because in AEG the lymphatic drainage was easier to follow after radioactive labeling. Mostly the SLN was in close relation to the primary tumor. Regarding SLNB in Barrett's cancer, the area of malignant transformation is difficult to be detected by endoscopy in any case and further technical advances are required. We also have to consider the possibility of multicentric locations, which makes lymphatic mapping more difficult. However, only the establishment of SLNB in AEG leads to development of individual therapeutic concepts.

In summary, we must aim to confirm recent studies of Burian et al. for clinical implementation. Nodal-negative tumors can be approached in a more limited resection with less morbidity. Furthermore, this might limit postoperative complications of AEG resections, such as reflux or dumping syndrome.

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