The sentinel node concept in adenocarcinomas of the distal esophagus and gastroesophageal junction

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Objective: The sentinel node concept is of great value in the treatment of various malignancies. In this study we investigated whether the application of the sentinel node procedure is feasible in esophageal adenocarcinoma and whether it can tailor surgical treatment of the individual patient.

Methods: In 40 patients with an adenocarcinoma of the distal esophagus or gastroesophageal junction, blue dye was injected around the tumor intraoperatively. Sentinel nodes (blue-stained) and nonsentinel nodes were identified and dissected during transhiatal esophagectomy. In sentinel nodes negative for tumor cells on routine hematoxylin-eosin examination, multilevel sectioning and immunohistochemical staining were performed to search for micrometastases.

Results: The sentinel node procedure was technically successful in 39 of 40 patients (98%). The median number of sentinel nodes identified was 4. Sentinel nodes were present in more than 1 nodal station in 8 patients (21%). In 6 patients in whom the sentinel node was negative for metastasis, nonsentinel nodes were positive for tumor cells (false-negative rate 6/39 = 15%). Micrometastases and isolated tumor cells were detected in 7 of 19 patients (37%) with sentinel nodes, but this finding did not affect the false-negative rate.

Conclusion: Detection of sentinel nodes is technically feasible during esophagectomy for cancer. However, given the relatively high false-negative rate of 15% and the high frequency of sentinel nodes in more than 1 nodal station, the clinical relevance of the sentinel node concept (through application of the blue dye technique) in the current treatment of patients with an adenocarcinoma of the distal esophagus or gastroesophageal junction seems limited.

Most esophageal adenocarcinomas arise from the lower esophagus and the gastroesophageal junction (GEJ).^{1,2} Prognosis after diagnosis is still poor, and overall 5-year survivals rarely exceed 20%. One of the strongest predictors of long-term survival after radical (R0) esophagectomy is the presence of lymph node metastasis.³⁻⁵ However, extended lymphadenectomy for the removal of all locoregional nodes can be at the cost of increased perioperative morbidity.^{6,7} Therefore, this approach should ideally be restricted to those patients who are most likely to benefit.

A tailored surgical treatment for the individual patient may be applicable with the help of the sentinel node concept. It states that the first lymph nodes (or a single lymph node) that receive the most direct lymph drainage from the primary tumor have the greatest potential to harbor metastatic disease when present.^{8,9} On this basis, examination of the sentinel

node can be used to predict overall lymph node status. Thus, applying the sentinel node concept to esophageal cancer may have 2 important clinical implications. First, it may allow for the selection of patients who are not likely to benefit from an extended lymphadenectomy. If the sentinel node is not involved, then patients could be spared more extensive surgery by tailoring the extent of lymphadenectomy. Second, it may affect the process of pathologic examination of the resected lymph nodes. Immunohistochemical detection of micrometastases and isolated tumor cells has been reported¹⁰⁻¹² and was found to be clinically relevant in one study.¹²

The sentinel node concept has not been studied extensively in esophageal cancer. We hypothesize that identification of the sentinel node(s) in esophageal adenocarcinoma can be achieved with a low false-negative rate and a high accuracy. In this study, we determined the feasibility of application of the sentinel node procedure in adenocarcinomas of the distal esophagus and GEJ (with the false-negative rate as the primary outcome parameter) and evaluated its value in the clinical setting.

PATIENTS AND METHODS

Patients

During a 14-month period (May 2000 to June 2001), 101 patients underwent an esophageal resection and reconstruction for cancer of the distal

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Abbreviations and Acronyms

H&E = hematoxylin-eosin
GEJ = gastroesophageal junction

esophagus or GEJ at the Erasmus Medical Center. These patients were evaluated for inclusion in the study on the basis of the following criteria: histologically proven adenocarcinoma of the distal esophagus or GEJ preoperatively (Siewert type I or II, respectively) and no application of neo-adjuvant chemotherapy or radiotherapy. Induction chemotherapy or radiotherapy was given in patients with a cT4-tumor without distant metastases or in patients with involvement of celiac trunk lymph nodes (M1a), who were not considered eligible for primary surgical therapy. Chemotherapy or radiotherapy was performed before surgery in 30 patients; histologic examination confirmed a squamous cell carcinoma in 20 patients; surgery for high-grade dysplasia was performed in 2 patients; and a double tumor of the esophagus led to exclusion in 1 patient. Eight patients did not participate in the study for logistic reasons. Consequently, 40 patients were included in this study, and the sentinel node procedure was performed as described below. Informed consent was obtained from the patients before operation. The Medical Ethics Committee of the Erasmus Medical Center approved the study.

Sentinel Node Mapping

Mapping of the sentinel nodes was carried out in vivo after opening the hiatus of the diaphragm and mobilizing the GEJ under direct vision. Minimal dissection was performed to maintain intact lymph channels. At 3 different sites in the vicinity of the tumor, 1 to 2 mL Patent Blue V (Guerbet-Laboratories, Issy les Moulineaux, France) was injected into the submucosal layer. Within the next 5 minutes, the sentinel node(s) were identified by following the blue-stained lymphatic vessels. These nodes were tagged with a suture. Once the resection specimen was taken out, the sentinel nodes were harvested ex vivo and sent as a separate specimen to the Department of Pathology. The remaining non-blue-stained lymph nodes present in the resection specimen (nonsentinel nodes) were identified by the pathologist and categorized according to the location as paraesophageal, perigastric, or celiac trunk nodes.

Surgery

All patients underwent a transhiatal esophagectomy. The primary tumor and its adjacent lymph nodes were dissected under direct vision through the widened hiatus of the diaphragm up to the level of the inferior pulmonary vein. Subsequently, a gastric tube was created. The left gastric artery was transected at its origin, with en bloc resection of celiac trunk lymph nodes. After mobilization and transection of the cervical esophagus, the intrathoracic esophagus was mobilized bluntly from the neck to the abdomen with a vein stripper. Esophagogastrectomy was performed in the neck, without a formal cervical lymphadenectomy.

Pathology

Pathologic evaluation of all lymph nodes consisted of conventional hematoxylin-eosin (H&E) staining. If no tumor cells were identified in the sentinel node(s), multilevel serial sectioning was performed. These lymph nodes were cut at 10 levels of approximately 100 μm (dependent on lymph nodes' size). Subsequently, sections were cut with a thickness of 4 μm and examined for tumor cells with H&E staining and immunohistochemistry to reveal micrometastases (metastatic lesions > 0.2 mm in dimension but < 2.0 mm) and isolated tumor cells (metastatic lesions < 0.2 mm in dimension).^{13,14} The mouse-monoclonal antibody CAM 5.2 (NCL5D3, Novo Castra, Wetzlar, Germany), which is specific for intracellular cytokeratin-8 and 18, was used for this experiment.¹⁵

TABLE 1. Patients' characteristics

Gender	
Male	30 (75%)
Female	10 (25%)
Age ^a	62 y (range 41–80 y)
pT-stadium	
pT1	9 (23%)
pT2	5 (13%)
pT3	26 (65%)
Barrett's metaplasia	
Yes	24 (60%)
No	16 (40%)
Tumor location	
Siewert I	20 (50%)
Siewert II	17 (43%)
Siewert I/II	3 (8%)

^aAge is given as median.

Statistics

To allow for inpatient dependencies between outcomes of the investigated lymph nodes, the method of generalized estimating equations was used (SAS PROC GENMOD, SAS Institute Inc, Cary, NC).

RESULTS

The sentinel node procedure was attempted in 40 patients who underwent a transhiatal esophagectomy. Patients' characteristics are described in Table 1. In 3 patients a large tumor covered both the distal esophagus and the GEJ (type I/II), and no proper distinction between a type I or II tumor could be made.

The sentinel node procedure was successful in identifying 1 or more sentinel nodes in 39 of 40 patients (98%). Technical failure occurred in 1 patient: The blue specimen that was presumed to be the sentinel node did not contain any lymphatic tissue when examined by the pathologist. Thus, the data of this patient were excluded from further analysis.

A total of 424 lymph nodes were resected, comprising both sentinel nodes (N = 143) and nonsentinel nodes (N = 281). The median number of sentinel nodes identified per patient was 4 (range 1–9), whereas the number of nonsentinel nodes accounted for a median of 7 nodes per patient (range 1–22). The location of the identified sentinel nodes in relation to tumor site is shown in Table 2. The percentage of paraesophageal sentinel nodes was significantly higher in patients with a Siewert type I tumor than in patients with a Siewert type II tumor: 64% (45/70) versus 11% (7/64) ($P < .001$). On the other hand, for sentinel nodes situated in the perigastric area, these percentages were 29% (20/70) for Siewert type I tumors and 77% (49/64) for Siewert type II tumors ($P = .002$). In 1 patient with a type I tumor, no sentinel node could be identified during the abdominal phase of the operation; however, 2 blue nodes (5%) were detected coincidentally in the cervical region, implicating an upward lymphatic drainage. Eight patients (21%) had sentinel nodes present in more than 1 nodal

TABLE 2. Relation between location of the sentinel node and tumor site

Tumor site	Sentinel node location				Total
	Cervical	Paraesophageal	Perigastric	Celiac trunk	
Siewert I (N = 20)	2	45	20	3	70
Siewert II (N = 16)	0	7	49	8	64
Siewert I/II (N = 3)	0	2	7	0	9
Total (N = 39)	2	54	76	11	143

station. In the 39 patients in whom the sentinel node concept was applied successfully, the sentinel node was located adjacent to the tumor in 30 patients (77%).

Of the total number of 424 lymph nodes examined by means of standard H&E staining, the sentinel nodes were more likely to contain tumor cells than the nonsentinel nodes; 40 of 143 (28%) sentinel nodes were positive versus 52 of 281 (19%) nonsentinel nodes ($P = 0.046$, Table 3).

In 20 of 39 patients (51%), the sentinel node contained tumor metastasis diagnosed on routine H&E examination. In 8 patients (21%), only the sentinel node accounted for the N1-status of the patient; in 12 patients (31%), there were also nonsentinel nodes in which a metastasis was found. In the remaining 19 patients (49%), the sentinel node was scored negative for tumor cells (Table 4). However, in 6 of these 19 patients, metastases were found in the nonsentinel nodes, which involved 1 patient with a pT1 tumor, 1 patient with a pT2 tumor, and 4 patients with a pT3 tumor. These data correspond with a false-negative rate of 15% (6/39 patients), a negative predictive value of 68% (13/19), an accuracy of 85% (33/39), a sensitivity of 77% (20/26), and a specificity of 100% (13/13) of the sentinel node procedure in our study (Table 5).

In patients in whom no metastasis was detected in the sentinel node by H&E staining (N = 19), multilevel serial sectioning and immunohistochemical staining with CAM 5.2 were performed (in the sentinel nodes only). In 1 patient this revealed a macrometastasis that was not present in the conventional H&E section; a micrometastasis was identified in 1 patient and isolated tumor cells were identified in 5 patients, resulting in upstaging of the histologic diagnosis in 7 patients (Table 4). These results did not affect the false-negative rate of 15% (Table 5) because patients' lymph node status was not revised in any of the 6 patients in whom only nonsentinel nodes were scored positive (false-negatives in this study).

DISCUSSION

In this study we investigated the application of the sentinel node procedure in the surgical treatment of patients with esophageal adenocarcinoma. The sentinel node procedure was technically successful in 39 of 40 patients (98%). The median number of sentinel nodes identified per patient was

TABLE 3. Total number of lymph nodes derived from esophagectomy specimens of 39 patients: Relation between sentinel and nonsentinel nodes and tumor involvement as judged by hematoxylin-eosin examination

	Sentinel node	Nonsentinel node	Total
Positive (N+)	40	52	92
Negative (N-)	103	229	332
Total	143	281	424

4 (range 1–9), and these sentinel nodes were present in more than 1 nodal station in 8 patients (21%). In 6 patients in whom the sentinel node was negative for metastasis, nonsentinel nodes were positive for tumor cells (false-negative rate $6/39 = 15\%$). Micrometastases and isolated tumor cells were detected in 7 of 19 patients (37%) with negative sentinel nodes, but this finding did not affect the false-negative rate.

The term “sentinel node” was introduced in 1960 by Gould and colleagues¹⁶ in their study to detect lymphatic metastases in parotid carcinoma. The procedure was further refined in patients with melanoma⁸ and breast cancer.⁹ Especially in breast cancer, the procedure has become a widely accepted element in the routine surgical management.¹⁷ In gastrointestinal tumors, the use of this procedure is still under investigation. During the last 10 years, a considerable number of clinical trials evaluating the feasibility and accuracy of the sentinel node procedure primarily in gastric and colorectal carcinoma have been published. With regard to gastric cancer, a complex lymphatic drainage is considered to result in high frequencies of skip metastases (15%–20%).^{18,19} These trials show high false-negative rates (ranging from 0%–39%).^{20,21} Thus, a tailored surgical approach with regard to lymphadenectomy based on this procedure in patients with gastric cancer is not justified. In colorectal cancer, all regional lymph nodes are routinely removed with the resected bowel segment. Thus, minimizing surgical resection is not a major goal of the sentinel

TABLE 4. Nodal status (tumor positive [+] and negative [-] of 39 patients after esophagectomy for cancer: Relation between sentinel and nonsentinel nodes

Before multilevel sectioning and immunohistochemistry			
	Nonsentinel node +	Nonsentinel node –	Total
Sentinel node +	12	8	20
Sentinel node –	6	13	19
Total	18	21	39
After multilevel sectioning and immunohistochemistry			
	Nonsentinel Node +	Nonsentinel node –	Total
Sentinel node +	12	15	27
Sentinel node –	6	6	12
Total	18	21	39

TABLE 5. Definitions of diagnostic test parameters and corresponding values in 39 patients (before and after multilevel sectioning and immunohistochemistry)

	Definition	Value before IHC	Value after IHC
False-negative rate	No. of false-negative SNs/No. of patients with an identified SN	6/39 = 15%	6/39 = 15%
Negative predictive value	No. of patients with true-negative node (SN+NSN)/No. of patients with true-negative node + patients with false-negative SN	13/19 = 68%	6/12 = 50%
Accuracy	No. of patients with positive SN + No. of patients with true-negative SN/No. of patients with an identified SN	33/39 = 85%	33/39 = 85%
Sensitivity	No. of patients with true-positive SN/No. of patients with true-positive SN + patients with false-negative SN	20/26 = 77%	27/33 = 82%
Specificity	No. of patients with true-negative SN/No. of patients with true-negative SN + patients with false-positive SN	13/13 = 100%	6/6 = 100%

SN, Sentinel node; NSN, nonsentinel node.

node procedure in patients with colorectal cancer. Instead, improved prognostication is the main target.²²

The lymphatic drainage of the esophagus is complex with abundant lymph-capillary networks, especially in the submucosa.^{23,24} This results in a longitudinal lymphatic drainage, which is presumed to be the reason for the phenomenon of skipping lymph node metastases in esophageal cancer.²⁵ Skip metastases are present when there is no tumor cell spread from the primary tumor into the adjacent peritumoral lymph nodes in the presence of positive distant nodes. For esophageal adenocarcinomas, skip metastases have been reported in 0% to 35% of patients.^{7,25,26} Because all patients in our study underwent transhiatal esophagectomy, a thorough analysis of the lymphatic spread in the upper part of the chest was not possible. In patients with a Siewert type I tumor, the sentinel node was mainly located along the esophagus, whereas in most patients with a Siewert type II tumor the gastric nodal station contained the sentinel node. These results correlate with the patterns of lymphatic spread for these tumor entities as described in the literature.²⁷ Furthermore, 2 sentinel nodes were found coincidentally in the cervical region (5%), representing the complex and unpredictable lymphatic spread of esophageal cancer cells.

We found a false-negative rate of 15%, which is higher in comparison with other malignancies. For example, false-negative rates between 0% and 5% for breast cancer have been reported and are considered to be acceptable worldwide.^{17,28} Furthermore, sentinel nodes were identified in more than 1 nodal station in 8 patients (21%), whereas ideally the sentinel node presents as a solitary lymph node to enhance the usefulness of the sentinel node concept in clinical practice. In our study, a median of 4 sentinel nodes per patient were detected, indicating that half of the patients had 4 or more (up to 9) blue-stained nodes. These sentinel nodes were harvested during a transhiatal approach with a limited lymphadenectomy. One could hypothesize that if a transthoracic esophagectomy with a 2-field lymphadenectomy had been performed, the false-negative rate may have been lower (blue-stained lymph nodes may have been present in the upper mediastinum) as well as higher (if mediastinal

nonsentinel nodes positive for tumor could have been detected). One study investigating the use of the sentinel node procedure in esophageal adenocarcinomas showed that when extended lymphadenectomy was performed, the lower paraesophageal and left gastric artery nodal stations were the most common sites of sentinel node identification.²⁹ In contrast, the upper mediastinal nodal basins accounted for only 3% (4/131) of the sentinel node stations. Therefore, we do not believe that the applied transhiatal approach with a limited lymphadenectomy is a major drawback in the current study.

Two other studies have been published thus far that investigated the sentinel node procedure in esophageal adenocarcinomas.^{29,30} In the first study, Lamb and colleagues²⁹ identified at least 1 sentinel node by means of peritumoral injection (before the operation) of radioactive nanocolloid in all 57 patients with a type I or II tumor (no blue dye was used). A false-negative rate of 5% was reported. Hence, one could argue that in our study the use of blue dye only is a technical shortcoming. However, this approach has been described before.^{20,21} Nonetheless, blue dye and radiocolloid are considered to act as complementary techniques in breast cancer.²⁸

The second study demonstrated that sentinel node detection was feasible in 17 of 20 patients using a combination of blue dye and radiocolloid injection (N = 10) and radiocolloid injection only (N = 10).³⁰ No data were shown to clarify whether the use of blue dye and radiocolloid are complementary. Lymph node status was correctly predicted in all type I tumors and in 75% of type II and III tumors. Furthermore, advanced tumors had a higher false-negative rate, and therefore it was concluded that the sentinel node procedure was only applicable in patients with early (pT1-2) cancer. However, in our study both early and advanced tumors belonged to the group of false-negatives (1 T1 tumor, 1 T2 tumor, and 4 T3 tumors).

Overall, the use of blue dye only without radiocolloid injection as a complementary technique may be a potential drawback in this study. Nevertheless, in our opinion, the 2 above-mentioned studies together with our present findings

do not justify the application of the sentinel node concept in clinical decision making in patients with an adenocarcinoma of the distal esophagus or GEJ at the Erasmus Medical Center.

CONCLUSIONS

The sentinel node procedure is technically feasible during transhiatal esophagectomy for esophageal cancer. However, given the high false-negative rate and the high frequency of sentinel nodes in more than 1 nodal station, the clinical relevance of the sentinel node concept by application of the blue dye technique only in the current treatment of patients with an adenocarcinoma of the distal esophagus or GEJ seems limited. More studies are needed that should focus on using the blue-dye technique in combination with radio-colloid injection and extended lymphadenectomy.

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