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ORIGINAL ARTICLE

Sentinel Lymph Node Biopsy in Esophageal Cancer: Should It Be Standard of Care?

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Abstract
Introduction Sentinel node mapping is established in some superficial cancers but remains controversial in harder-to-access solid tumors. There are an increasing number of recent studies suggesting that isolated tumor cells have prognostic significance in predicting poor survival, in breast cancer, esophageal cancer, and others. It is for this reason that we have persevered with the sentinel lymph node concept in our esophagectomy cancer patients, and we report our results since 2008.
Methods Thirty-one of 32 consecutive patients underwent resection for invasive esophageal cancer along with sentinel lymph node retrieval (resection rate, 97%). Peritumoral injection of ^{99m}Tc antimony colloid was performed by upper endoscopy prior to the operation. A two-surgeon synchronous approach via a right thoracotomy and laparotomy was performed with a conservative lymphadenectomy. Sentinel lymph nodes were identified with a gamma probe both in and ex vivo, and sent off separately for three serial sections and immunohistochemistry with AE1/AE3.
Results The median patient age was 63.4 years (range, 45–75 years). Most patients (81%) had an adenocarcinoma, and 61% had received neoadjuvant therapy. At least one sentinel lymph node (median, 3) was identified in 29 of 31 patients (success rate, 94%). Sentinel nodes were present in more than one nodal station in 16 patients (55%). One false negative case led to a sensitivity of 90%. In 28 of 29 patients, the sentinel lymph node accurately predicted findings in non-sentinel nodes (accuracy, 96%).
Conclusions Sentinel lymph node biopsy is both feasible and accurate in esophageal resections with conservative lymphadenectomy. It allows targeted serial sectioning and immunohistochemical studies of those nodes and should become standard of care in patients undergoing esophagectomy for esophageal cancer.

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Introduction

The sentinel lymph node (SLN) concept describes the preferential lymphatic drainage of a primary tumor to a regional lymph node(s).[1] Since its inception by Morton in 1992, sentinel lymph node biopsy has become the gold standard for patients with melanoma and breast cancer. However, its use in other solid tumors has been more controversial with continued debate regarding its role, if any, in staging and treatment algorithms.[2–4]

Perhaps recent studies have strengthened the case for the routine use of sentinel lymph node biopsy in the treatment of esophageal cancer patients. First, we (and others) have

recently shown that occult tumor deposits in lymph nodes have prognostic significance for decreased survival.[5,6] These results have been replicated in larger studies in other solid tumor types such as breast cancer.[7] The smallest of the occult tumor deposits, isolated tumor cells, are on average 10 to 30 μm in size (0.01–0.03 mm), making their detection virtually impossible without the use of serial sections and immunohistochemistry. Sentinel lymph node biopsy is the only practical method in today's economic climate to identify the most important lymph nodes for more detailed histopathological analysis.

The second reason to establish this technique in esophageal cancer is to promote the introduction of improved sentinel lymph node tracers that may lead to better diagnostic and staging investigations. We do not agree that other imaging techniques "may be as accurate (as SLN biopsy) in detecting esophageal cancer metastases", as written by Zhang and colleagues in 2010.[8] Positron emission tomography/computed tomography (PET/CT) cannot distinguish positive lymph nodes in close proximity to the primary tumor due to the shine-through effect (a strong overlapping signal from the tumor),[9] nor can it detect positive lymph nodes less than 7 to 8 mm in size. It most certainly does not have the sensitivity required to detect lymph nodes containing only micrometastatic disease.[10] Similarly, endoscopic ultrasound is not able to identify occult tumor deposits within a lymph node from a fine needle aspirate.

We recently published our initial experience with sentinel lymph node biopsy with conservative lymphadenectomy in esophageal cancer and we showed that it was feasible to identify the SLN in 88% of cases, and it was accurate 92% of the time.[11] We have persevered with this approach because we do not believe the current pathological analysis for non-sentinel lymph nodes is sufficient. In this prospective study, our aims included evaluating the accuracy of the sentinel node in predicting the status of non-sentinel lymph nodes with a larger sample size, and determining the frequency of skip metastases in esophageal cancer.

Materials and Methods

Patient Selection and Preparation for Surgery

Thirty-two consecutive patients undergoing a surgical resection for invasive squamous cell carcinoma or adenocarcinoma of the esophagus were selected for the study. These patients were recruited between June 2008 and March 2011, and include 17 patients from our prior publication.[11] All operations were performed or closely supervised by one of five surgeons who are involved with our unit. The study was approved by the Research Ethics Committee at the Royal Adelaide Hospital, Adelaide, South Australia.

Preoperative clinical staging included upper gastrointestinal endoscopy, computed tomography scans (chest, abdomen, and pelvis), PET/CT scans, endoscopic ultrasonography (if minimal stricturing), and diagnostic laparoscopy (for gastroesophageal junction tumors). Selected patients (T2 or greater) were treated with neoadjuvant therapy according to protocol.[12] This consisted of two cycles of cisplatin (80 mg/m^2 on day 1) and 5-FU (800 mg/m^2 continuous infusion for 5 days) during weeks 1 and 5 of radiotherapy, plus 25 fractions of radiotherapy (over 5 weeks) to a total of 45 Gy. Patients underwent surgical resection 5 to 6 weeks after completion of neoadjuvant therapy.

Lymphoscintigraphy and Surgery

As previously described, peritumoral injection of four 1-ml aliquots of 10 MBq ^{99m}Tc antimony colloid (Lymphflo), maximum dose 40 MBq, were undertaken once the patient was under general anesthetia immediately before surgery. At endoscopy, injections were performed into the submucosal layer at both the proximal and distal margins (if possible) of the tumor.[13] In accordance with our Ethics Review Board, a licensed nuclear medicine physician (D.B.) transported and injected the radioactive tracer.

Esophagectomy was usually performed by a two-surgeon synchronous Ivor-Lewis technique via a right antero-lateral thoracotomy and an upper midline laparotomy, as described previously.[14] A gamma probe (gammasonics MK2) was used to identify any sentinel lymph node(s) in both the upper abdomen and thorax after mobilization of the esophagus and stomach. Readings were taken with the probe tip directed away from the tumor to minimize background interference. A sentinel node was defined in vivo as any node with an activity twice that of surrounding tissue.[1,13] Readings were also taken after esophageal and gastric resection to identify any residual sentinel node(s) because it is our practice to perform a conservative lymph node dissection (removal of all nodes adjacent to the tumor) rather than a two-field radical lymphadenectomy.[15] Continuity of the gastrointestinal tract was restored by either a handsewn or stapled end-to-side esophago-gastrostomy, depending on surgeon preference.

Specimen Handling and Pathology

Each specimen was dissected on the back table in the operating room by S.K.T. Lymph node stations were removed sequentially from the specimen. Using the

EANM-EORTC guidelines for sentinel node diagnosis in melanoma, a sentinel node was defined ex vivo as the hottest node plus any other hot nodes containing more than 10% of the activity in the hottest node in the lymphatic basin.[1] In our feasibility study, we had found that all sentinel nodes contained 20% or more of the activity of the hottest node.[11] Each lymph node station and sentinel node was sent separately for pathological analysis.

Non-sentinel lymph nodes were bisected once, fixed in formalin, embedded in paraffin, and stained with hematoxylin and eosin (H&E) according to standard procedures. Sentinel lymph nodes were bisected along their longitudinal axis, or cut into 2- or 3-mm slices if thicker than 5 mm. On the first section, one slide was stained with H&E, and the other with the monoclonal epithelial antibody AE1/AE3 (DAKO, Carpinteria, CA) for immunohistochemistry (IHC).[16] Sections of primary tumors were used as positive controls with each run, and a negative control (primary antibody omitted) was also included.

Sentinel lymph nodes that remained tumor free by both H&E and IHC on the first section had a minimum of two further serial step sections performed.[17–19] A lymph node metastasis was defined as a metastasis >2 mm in size (pN1). A micrometastasis was defined as a metastasis >0.2 mm and ≤2 mm [pN1mi(sn)], while isolated tumor cells were defined as single tumor cell(s) or cluster(s) of tumor cells ≤0.2 mm in size [pN0(i+)(sn)].[20–22] Strict criteria were used to designate a positive cell(s) as an isolated tumor cell(s), including increased cell size, enlarged nuclear size, and increased nuclear/cytoplasmic ratio.[21]

Statistical Analysis

Data were collected prospectively. Calculations were performed using SAS Version 9.2 (SAS Institute Inc., Cary, NC, USA). The Chi-square test was used to compare groups, if applicable. The sensitivity, specificity, and accuracy of sentinel lymph node biopsy were calculated by the standard definitions.[23] Statistical significance was set at the 5% level.

Results

Patient and Tumor Characteristics

One patient who had undergone neoadjuvant therapy was deemed unresectable at the time of operation because his tumor was invading the right atrium (resection rate, 97%). The median patient age of the remaining patients was 63.4 years (range, 45–75 years), and 28 of 31 patients were male. The average body mass index in our patient population was 28 kg/m^2, with eight patients above 30 kg/m^2 and two above 40 kg/m^2. Tumor characteristics are listed in Table 1. Twenty-five of 31 patients (81%) had an adenocarcinoma, and the majority of these (64%) were lower esophageal tumors (Siewert type I). Nineteen patients (61%) underwent neoadjuvant therapy. Of these, six (32%) had a complete pathological response with no residual viable tumor cells on final conventional pathology (i.e., without taking into account the results of immunohistochemistry).

Table 1 Patient and tumor characteristics (n=31)

Variable	No. patients (%)
Histology	
Adenocarcinoma	25 (81)
Squamous cell carcinoma	6 (19)
Neoadjuvant therapy	
No	12 (39)
Yes	19 (61)
Tumor location	
Middle 1/3 esophagus	3 (10)
Lower 1/3 esophagus	22 (71)
GOJ[a]	6 (19)
Grade of differentiation	
Well/moderate (G1+G2)	15 (48)
Poor/undifferentiated (G3+G4)	14 (45)
Not assessable	2 (7)
pT-stage	
T0[b]	6 (19)
T1a	6 (19)
T1b	6 (19)
T2	4 (13)
T3	9 (30)
pN-stage	
N0	24 (77)
N1	4 (13)
N2	3 (10)
Vascular invasion	
No	25 (81)
Yes	6 (19)
Perineural invasion	
No	24 (77)
Yes	3 (10)
Not reported	4 (13)
Barrett's esophagus	
No	9 (29)
Yes	22 (71)

[a] GOJ = gastroesophageal junction

[b] T0=no residual viable tumor cells

Sentinel Node Identification

The sentinel lymph node detection rate using lymphoscintigraphy was 94% (29 of 31 patients). One of the two patients (both Siewert type I adenocarcinomas) in whom we could not identify a sentinel lymph node had had extensive prior upper gastrointestinal surgery. The second patient was morbidly obese with a body mass index of 42. In the remaining 29 patients, there were 92 sentinel lymph nodes, with a median of three lymph nodes per patient (range, 1–8 lymph nodes). A total of 438 lymph nodes were resected (as identified by the pathologist) with a median of 14 per patient (range, 4–31 lymph nodes).

The majority of sentinel lymph nodes were located in one of the following lymph node stations (in conjunction with a conservative lymphadenectomy): lower para-esophageal, left paracardial, and left gastric artery (Fig. 1). In patients with a Siewert type I tumor, the sentinel lymph nodes were mostly located in the para-esophageal tissue (75%) although in 31% of patients, sentinel nodes were found on both sides of the diaphragm. In Siewert type II tumors, the sentinel nodes were located more often in the peri-gastric tissue (83%). Sixteen patients (55%) had sentinel nodes present in more than one lymph node station. Nine of 29 patients (31%) had sentinel lymph nodes identified in the tumor basin once the esophageal cancer and adjacent lymph nodes had been removed (in the para-esophageal, celiac artery, and carinal lymph node locations). These were all negative for metastasis except for one celiac artery sentinel node.

Accuracy of Sentinel Lymph Node(s)

Overall, sentinel lymph nodes were significantly more likely to contain tumor than non-sentinel nodes: 13 of 92 (14%) positive sentinel nodes versus 11 of 346 (3%) positive non-sentinel nodes ($P<0.001$). A total of 13 sentinel lymph nodes were positive in nine patients (9/29, 31%). Eight of these nodes contained overt metastases, three had micrometastatic disease, and two had isolated tumor cells.

The accuracy of the sentinel lymph node procedure in predicting the status of non-sentinel nodes is shown in Table 2. Six patients (21%) had overt metastases in the sentinel lymph node(s), and four of these had corresponding positive non-sentinel nodes on routine H&E staining. Three patients had positive sentinel nodes on IHC staining, two of whom had micrometastatic deposits, and one with isolated tumor cells only. The non-sentinel nodes for all three of these patients were negative on routine lymph node analysis. We had one false negative result in our series. This particular patient had an advanced long 10-cm esophageal tumor with overt metastases in four non-sentinel nodes, but no metastatic deposits in two identified sentinel nodes. The sensitivity of sentinel lymph node biopsy in our series was therefore 90% (9/10). The overall accuracy of sentinel lymph node biopsy was 96% (28/29) using immunohistochemistry and a minimum of three serial sections for all sentinel lymph nodes.

Discussion

Sentinel lymph node biopsy was performed successfully in 29 of 31 (94%) consecutive esophageal cancer patients. A median of 3 sentinel nodes per patient were removed, and the diagnostic accuracy based on SLN status was 96%. SLN mapping was successful even with a *conservative* lymphadenectomy, an average body mass index of 28, and the addition of neoadjuvant therapy in 61% of patients.

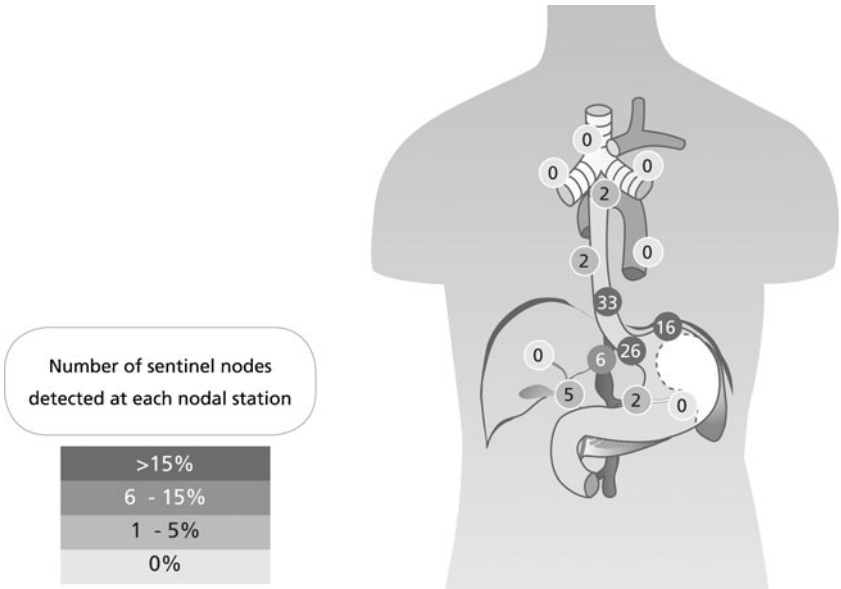

Fig. 1 Graphical depiction of 92 sentinel lymph nodes in 29 esophageal cancer patients. Sentinel nodes were most commonly located in the lower para-esophageal, left paracardial, and left gastric artery lymph node stations

Table 2 Accuracy of the sentinel node in predicting the status of non-sentinel nodes (n=29)

	Overall nodal pathology	
	H&E[a] positive	Negative
Sentinel lymph node		
H&E positive	4	2
IHC[b] positive		3
Negative	1	19

[a] H&E = hematoxylin and eosin stain (routine pathology)

[b] IHC=immunohistochemistry (with epithelial antibody AE1/AE3)

Four studies (with a sample size of at least 20 patients) using a radio-guided approach to find sentinel lymph nodes in esophageal cancer have reported success rates of 85% to 100%, and accuracy rates of 88% to 96%.[13,24–26] These results are superior to the two existing studies in the literature which used the blue dye method in esophageal cancer patients.[27,28] Grotenhuis et al. identified a sentinel lymph node in 98% of patients, but they had an unacceptably high false negative rate of 15% and an overall accuracy rate of only 85%.[27] Similarly, Bhat et al. detected a SLN in 81% of patients with an accuracy rate of only 75%.[28] Both studies had a high number of pT3 tumors (65% and 72%, respectively) but radiocolloid tracer is uniformly regarded as superior to the dye method for SLN biopsy in most solid tumor types.[4,13,29]

There is no doubt that obesity contributed to increased difficulty in our patients with surgical resection and identification of sentinel lymph nodes. It is also noteworthy that, despite some reports to the contrary, the addition of neoadjuvant therapy prior to surgical resection did not affect our results. In fact, all nine patients with overt or occult tumor in their sentinel nodes had undergone neo-adjuvant therapy. Several authors have found a significant correlation between a higher metastatic area within the node, and lower radioisotope counts.[30,31] However, these studies have used the 100 nm ^{99m}Tc-tin colloid particles. We believe that smaller particles, such as 10±3 nm ^{99m}Tc-antimony trisulfide colloid, are able to penetrate metastatic lymph nodes, contributing to our high accuracy rate in the setting of advanced esophageal cancer.

With the use of three serial sections and immunohisto-chemistry on negative sentinel lymph nodes, 14% (3/22) of patients were upstaged: two from pN0 to pN1mi(sn), and one from pN0 to pN0(i+)(sn). Lamb et al. also found that 12% (3/25) of pN0 patients were upstaged following IHC analysis in their landmark study.[13] We recently published results showing that node-negative patients with either isolated tumor cells or micrometastases detected by IHC have a significantly decreased 5-year survival compared to those who remain node negative following additional analysis of their lymph nodes (33% and 40% versus 60%, respectively).[5] These patients may benefit from adjuvant therapy. A further patient in our series was up-graded from pN1 (two positive lymph nodes) to pN2 (three or more positive lymph nodes) with the identification of a micro-metastasis within a sentinel lymph node. This patient went on to receive adjuvant chemoradiotherapy and is currently well with no evidence of tumor recurrence 21 months later.

Much of the lack of enthusiasm surrounding the routine use of sentinel lymph node biopsy in esophageal cancer is because, at present, it cannot alter or limit the extent of lymphadenectomy in the same way as is seen in breast cancer and melanoma. Most hospitals, like ours, do not have a dedicated pathologist who is willing to perform *intraoperative* rapid immunohistochemical analysis on the sentinel nodes. And in esophageal cancer, preoperative access to sentinel nodes may be as invasive, and as morbid, as the operation itself. But, if one agrees that isolated tumor cells have prognostic significance in esophageal cancer and, as shown above, are detected in 12–14% of node-negative patients using serial sections and immunohistochemistry, then the sentinel lymph node concept becomes the only practical method of improving pathological staging. So, although sentinel node biopsy has not yet been shown to minimize the extent of lymphadenectomy, it may influence postoperative therapy for a significant number of patients.

Another criticism in the literature regarding sentinel lymph node biopsy in esophageal cancer is the reported high incidence of skip metastases, although most of these findings have been in patients with squamous cell carcinomas. It is well-known that lower esophageal cancers and junctional tumors (albeit, mostly adenocarcinomas) disseminate in a longitudinal fashion (rather than segmental) to lower mediastinal and abdominal lymph nodes.[32–34] And, sentinel lymph nodes in esophageal cancer are often multiple and found in more than one nodal station (range, 21% to 55%).[13,27] However, it is important not to confuse multiple sentinel nodes with true "skip metastases". Tumor cells in esophageal cancer follow a predictable linear drainage pattern to "first tier" nodal stations, and over 90% of them seem to be within 3 cm of the primary tumor.[35] Similar to Lamb's study,[13] every one of our 29 patients had a sentinel node in one of the "first tier" lymph node groups: lower para-esophageal, right or left paracardial, or left gastric artery. One patient in our study was found to have a positive celiac lymph node in conjunction with a negative left gastric artery sentinel node. But, as celiac lymph nodes are now considered regional nodes according to the 7th edition of the American Joint Committee on Cancer/International Union Against Cancer (AJCC/UICC) staging manual,[22] not even this can be called a skip metastasis.

Probably the biggest limitation with sentinel lymph node biopsy in esophageal cancer is the variable type of sentinel lymph node tracer legislated for clinical use in each country.[30] The vastly different particle sizes hinder wide application of the concept and creation of a uniform protocol. For example, Japan's ^{99m}Tc-tin colloid (100 nm in size) allows for lymphoscintigraphy 24 h prior to surgical resection,[26] while other smaller radiocolloids (like Australia's ^{99m}Tc-antimony trisulfide colloid) have much shorter transit times in the sentinel nodes.[1,30] Facilitating preoperative lymphoscintigraphy in between endoscopic peritumoral injection and same-day surgery is often not practical. Future efforts should be made to design better sentinel lymph node tracers with dual imaging capabilities and, ultimately, the ability to differentiate a positive node (containing only micrometastatic tumor deposits) from a negative one prior to the initiation of any treatment.

Conclusion

Sentinel lymph node biopsy is both feasible and accurate in esophageal resections with conservative lymphadenectomy. There is no doubt that SLN biopsy improves pathological staging and may then influence postoperative treatment decisions. Further work is needed to optimize sentinel node tracer type particularly with recent advances in imaging technology, but it is our opinion that SLN biopsy should become standard of care in patients with esophageal cancer. Whether it will ever be useful as a tool for tailoring a lymphadenectomy is a question for the future.

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