Sentinel node mapping for intra-thoracic malignancies: systematic review of the best available evidence

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ARTICLE INFO

Introduction: Sentinel node mapping is a new technique of lymph nodal staging in solid tumors, which can decrease the morbidity of regional lymph node dissection considerably. Intra-thoracic tumors including non-small cell lung cancer (NSCLC) and esophageal carcinoma (EC) are among the solid tumors in which sentinel node (SN) mapping has been applied. In the current systematic review, we gathered the best available evidence (systematic reviews) in this regard and presented the results in a systematic review format.

Material and methods: We searched MEDLINE and SCOPUS since the inception till 13 December 2014 using the following keywords: (lung OR esophagus OR esophageal) AND sentinel AND (“systematic review” OR meta-analysis OR metaanalysis). No language limit was imposed on the search strategy. Systematic reviews and meta-analyses on SN mapping in EC or NSCLC were included in the current study. Narrative review articles were excluded from the study.

Results: Overall five systematic review were included. One of the included studies was on SN mapping in NSCLC and four were on EC. Overall detection rate and sensitivity for EC and NSCLC were high and both were related to mapping technique, pathological involvement of the mediastinal nodes, size and location of the tumors.

Conclusion: SN mapping is feasible and highly accurate in EC and NSCLC. Attention to the technique (using radiotracers, peri-tumoral injection) and restriction of the patients to less advanced cases (cN0 and T1, 2) would ensure the best results with high detection rate and sensitivity.

Please cite this paper as:

Introduction

Lymph node staging is an important aspect of solid tumor management, which is of prognostic and therapeutic importance. Regional lymph node dissection plays an important role in lymph node staging of many solid tumors, however the complications of this surgical procedure have
led to several less invasive methods including CT scanning, ultrasonography, magnetic resonance imaging (MRI) and 18-F Fluorodeoxy Glucose Positron Emission Tomography 18-F-FDG PET imaging. However, these imaging methods do not have an ideal sensitivity and/or specificity for regional lymph node staging of solid tumors (1,2).

Sentinel node mapping is a new technique of lymph nodal staging in solid tumors, which can decrease the morbidity of regional lymph node dissection considerably (3,4). This technique is actually the standard method of regional lymph nodal staging in breast cancer and melanoma patients and is going to play an important role in other neoplasms as well (5-7).

Sentinel node is the first node in the lymphatic drainage route of a solid tumor and can be used as a surrogate of the remainder of the regional lymph nodes. If the sentinel node is not pathologically involved, the remainder of the nodes in the lymph nodal basin are not involved either. Therefore, regional lymph node dissection would not be necessary in this case.

Intra-thoracic tumors including non-small cell lung cancer (NSCLC) and esophageal carcinoma (EC) are among the solid tumors in which sentinel node (SN) mapping has been applied. In the current systematic review, we gathered the best available evidence (systematic reviews) in this regard and presented the results in a systematic review format.

Material and methods

We searched MEDLINE and SCOPUS since the inception till 13 December 2014 using the following keywords: (lung OR esophagus OR esophageal) AND sentinel AND ( “systematic review” OR meta-analysis OR metaanalysis). No language limit was imposed on the search strategy.

Inclusion criteria and quality assessment

Systematic reviews and meta-analyses on SN mapping in EC or NSCLC were included in the current study. Narrative review articles were excluded from the study.

The quality of the included studies were evaluated by the quality assessment toolkit for systematic reviews published by Oxford Center for Evidence Based Medicine. This toolkit has five items including: PICO question of the systematic review, search strategy, inclusion and exclusion criteria, quality assessment of the included studies, assessment of the heterogeneity and publication bias (8).

Data extraction

Following items were extracted from each included systematic review: first author, publication year, affiliation, main results of the systematic review (detection rate and false negative rate of the technique), auxiliary results (including the number of sentinel nodes, location of SN, skip metastasis, etc) and sub-group analyses according to method, patient and cancer-related variables.

Detection rate was defined as the number of patients with at least one identified sentinel node to all included patients. False negative rate was defined as the number of patients with involved regional lymph node basin despite pathologically negative sentinel nodes.

Results

Figure 1 shows the PRISMA flowchart of the study. Overall five systematic review were included (9-13). One of the included studies was on SN mapping in NSCLC and four were on EC. Table 1 shows the characteristics of the included studies as well as their main and auxiliary results.

Discussion

Our systematic review showed that SN mapping is feasible and fairly accurate in intra-thoracic tumors including EC and NSCLC. SN mapping can decrease the morbidity of lymph node dissection in patients without pathological SN involvement. In addition, aberrant skip lymph drainage could also be identified with certain effect on the management of the patients.

Several factor could affect the feasibility and accuracy of SN mapping in intra-thoracic tumors, which we explained in detail below.

Mapping material

The conventional mapping material for SN mapping are radiotracers and blue dye. Usually, combination of radiotracers and blue dye results
Table 1. Characteristics of the include studies

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Type</th>
<th>Number of included studies</th>
<th>Main findings: detection and false negative rates</th>
<th>Sub-group analyses (DR/sensitivity)</th>
<th>Auxiliary findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dabbagh Kakhki</td>
<td>2014</td>
<td>EC</td>
<td>18</td>
<td>Pooled DR: 89.2% [82.6–93.5], Pooled sensitivity = 84 % [78–88%].</td>
<td>87.2[63.4–96.4]/93 [84–98]</td>
<td>- Blue dye method was challenging due to anthracosis</td>
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<td></td>
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<td></td>
<td>Blue dye</td>
<td>- CT lymphography and indocyanine green were also used for mapping with excellent results</td>
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<td></td>
<td>Radiotracer</td>
<td>- Detection rate and sensitivity were lower in N1 patients</td>
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<td></td>
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<td></td>
<td>Combined</td>
<td>- Sentinel node location was very diverse and could be in cervical, thoracic, and abdominal locations</td>
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<td></td>
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<td>Injection site</td>
<td>- Only two studies reported learning curve effect which seemed to be of importance in esophageal carcinoma</td>
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<td></td>
<td>Sub-mucosal</td>
<td>- IHC increased the sensitivity of SN mapping and resulted in upstaging</td>
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<td>Sub-serosal</td>
<td>- IHC and rapid PCR resulted in better staging in a study.</td>
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<td>Type of surgery</td>
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<td>SCC</td>
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<td>Tumor location</td>
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<td>Upper</td>
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<td>Tumor size</td>
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<td></td>
<td>Post-chemotherapy</td>
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<tr>
<td>Sgourakis</td>
<td>2011</td>
<td>EC</td>
<td>10</td>
<td>DR ranged from 80% to 100% and sensitivity ranged from 75% to 100%</td>
<td>N/A</td>
<td>- CT lymphography was used in a study with excellent results.</td>
</tr>
<tr>
<td>Nagaraja</td>
<td>2014</td>
<td>EC</td>
<td>23</td>
<td>Pooled DR: 93%[89.4-95], Pooled sensitivity: 84%[74-91]</td>
<td>98[92-99]/84[74-91]</td>
<td>- Near infrared imaging was done in a study with excellent results</td>
</tr>
<tr>
<td>Filip</td>
<td>2014</td>
<td>EC</td>
<td>12</td>
<td>Pooled DR: 91.6[88.4-94], Pooled sensitivity: 77.5[71.1-82.8]</td>
<td>97[81-99]/86[81-89]</td>
<td>- CT lymphography showed excellent DR and sensitivity</td>
</tr>
</tbody>
</table>

Methylene Blue
Patent Blue V

- Blue dye method was challenging due to anthracosis
- CT lymphography and indocyanine green were also used for mapping with excellent results
- Detection rate and sensitivity were lower in N1 patients
- Sentinel node location was very diverse and could be in cervical, thoracic, and abdominal locations
- Only two studies reported learning curve effect which seemed to be of importance in esophageal carcinoma
- IHC increased the sensitivity of SN mapping and resulted in upstaging
- IHC and rapid PCR resulted in better staging in a study.

- Near infrared imaging was done in a study with excellent results
- IHC resulted in better staging in several studies.
- Skipped metastasis reported in SCC patients which can limit the SN mapping use
- SN mapping was not accurate in patients with neo-adjuvant chemotherapy
- Detection of SNs was highly related to the location of tumor in the esophagus: for middle esophagus in the peri-tumoral area and for gastroesophageal junction tumors in the abdominal locations
in better detection rate and sensitivity, which outweighs the complications of blue dye.

However, for intra-thoracic tumors, the anesthesia of the mediastinal lymph nodes makes the SN mapping by blue dye very hard if not impossible. Therefore, it seems that the complication risks of blue dye use (for example anaphylactic reactions) do outweigh the benefits of blue dye addition to SN mapping of intra-thoracic tumors (14,15).

Several novel techniques such as CT lymphography, magnetic materials and fluorescent imaging were also used for SN mapping in EC and NSCLC with excellent results. However, the sample size of the studies used these techniques was low and larger studies are definitely needed to draw any better conclusion in this regard.

Mediastinal lymph node involvement (cN1 patients)

SN mapping is the best fit for cN0 patients. In patients highly suspicious or proven regional lymph node involvement, SN mapping, would result in a high false negative rate. This is due to the phenomenon of complete replacement of the regional lymph nodes with tumoral cells (16).

Our systematic review also showed the same findings, as SN mapping in cN1 patients was less successful and less accurate than cN0 patients. In intra-thoracic tumors, cN0 patients are those with suspicious mediastinal lymph nodes on three dimensional imaging such as CT-scanning.

Histological variation of the tumors

For EC, it seems that adenocarcinoma has higher detection rate and sensitivity as compared to squamous cell carcinoma. The reason is attributed to the more predictable lymphatic drainage of adenocarcinoma in contrast to squamous cell carcinoma.

For NSCLC, the histological variants of the tumor do not seem to be related to the feasibility and/or accuracy of SN mapping.

### Location of mapping material injection and surgical technique

For EC, two injection methods have been used. Most studies used sub-mucosal injection with excellent results. However, the need for additional endoscopy seems to be a limitation to this technique. Intra-operative injection in the direction against the mucosa is another method used by some groups with satisfactory results as well (17).

For NSCLC, two several injection techniques were used. Intra-tumoral injection was used by several groups with sub-optimal results, which can be due to poor lymphatic development inside the tumor (18,19). It seems that peri-tumoral injection is much more satisfactory, especially when done intra-operatively. Pre-operative percutaneous or trans-bronchial injections had less satisfactory results.

Video-assisted surgery has been used for SN mapping of both EC and NSCLC with fairly high success. However, detection rate of this technique was lower that the open technique and further studies with more experience is needed to validate this method for SN mapping.

### Tumor size and location

For EC, effect of tumor size and location has been evaluated in detail. Detection rate for the tumors in the mid-part of the esophagus was higher than the upper and lower parts. This can be due to out of reach SN in the upper and lower locations (in the cervical and abdominal areas). Larger studies are still needed to evaluate this result in detail.

The size of the tumor and history of previous neo-adjuvant chemotherapy were also reported to affect the accuracy of SN mapping in EC. The larger tumors and history of neo-adjuvant chemotherapy were both associated with more detection failure and false negative cases. This is most likely due to
blockage of the lymphatics in the large tumors and post-chemotherapy changes in patients with neo-adjuvant chemotherapy. Restriction of patients to T1, 2 patients would result in the highest success rate and sensitivity (17).

**SN location and its implication**

The lymphatic drainage of NSCLC and especially EC is not that predictable. High rate of skip metastases is in accordance to this fact. Location of SN for EC was specifically highly diverse and could be in cervical, mediastinal and abdominal areas, but the location of the tumor was to some extent related to the SN location.

SN mapping also shows skip pattern of lymphatic drainage in both NSCLC and EC, which is an important finding, which shows that mediastinal lymph nodes can be involved even in patients with N0 first echelon nodes. SN mapping can be helpful

### Table 2. Quality assessment of the included studies

<table>
<thead>
<tr>
<th>Author</th>
<th>Search strategy</th>
<th>Inclusion criteria</th>
<th>Quality assessment of the included studies</th>
<th>Heterogeneity evaluation</th>
<th>Publication bias</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dabbagh Kakhki</td>
<td>PUBMED, SCOPUS, the ISI web of knowledge and information from the annual meetings of the Japan Esophageal Society were searched using the terms “(esophagus OR esophageal) AND sentinel” without any language or date limitation.</td>
<td>For sensitivity pooling at least D2 lymphadenectomy should be performed. At least 5 patients should be included.</td>
<td>Evaluated by CEBM checklist</td>
<td>Not evaluated</td>
<td>Evaluated by funnel plot and trim and fill method</td>
</tr>
<tr>
<td>Sgourakis</td>
<td>Medline, Embase, Ovid, and the Cochrane Controlled Trials Registry were used. Only English studies were included.</td>
<td>All studies on SN mapping in esophageal cancer were included.</td>
<td>Not evaluated</td>
<td>Not evaluated</td>
<td>Not evaluated</td>
</tr>
<tr>
<td>Nagaraja</td>
<td>MEDLINE, PubMed, EMBASE, Current Contents Connect, Cochrane library, Google scholar, Science Direct and Web of Science were searched. The search terms included “Oesophageal-cancer” AND “Sentinel Lymph Node Biopsy”</td>
<td>All studies on SN mapping in esophageal cancer were included.</td>
<td>Not evaluated</td>
<td>Evaluated by Cochrane Q and I² index.</td>
<td>Evaluated by funnel plot and Egger’s regression method.</td>
</tr>
<tr>
<td>Filip</td>
<td>MEDLINE, EMBASE, Scopus, the Cochrane Database of Systematic Review and CENTRAL were searched. Keywords: ‘esophageal cancer’, ‘esophageal adenocarcinoma’, ‘esophageal squamous cell carcinoma’, ‘gastroesophageal adenocarcinoma’ and ‘SLN’. Only clinical studies in English, French, German, Dutch, Spanish and Italian were considered.</td>
<td>Based on Cochrane Handbook for Systematic Review of interventions</td>
<td>Not evaluated</td>
<td>Not evaluated</td>
<td>No important publication bias was reported.</td>
</tr>
<tr>
<td>Taghizadeh Kermani</td>
<td>Medline, SCOPUS and ISI web of knowledge were searched with the following search terms: (lung AND sentinel) with no date or language limit.</td>
<td>1. A sample size of at least 5 patients. 2. The total number of patients with positive lymph nodes and number of false negative results were reported. 3. The total number of patients and the rate of SN detection were reported.</td>
<td>Evaluated by CEBM checklist</td>
<td>Evaluated by Cochrane Q and I² index.</td>
<td>Evaluated by funnel plot, trim and fill method.</td>
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</tbody>
</table>

Rev Clin Med 2015; Vol 2 (No 2)  
Published by: Mashhad University of Medical Sciences (http://rcm.mums.ac.ir)
in this regard by detecting the very first location of lymph node involvement.

**Learning curve effect**

The experience of the surgeon has been evaluated in detail for SN mapping in breast cancer. The more experienced surgeons would have less false negative results (14,20). Limited studies also showed the same findings in EC and NSCLC; however, larger studies are needed to be able to draw any definite conclusion in this regard.

**Quality of the included systematic reviews**

Not all included systematic reviews were of high quality in our study. For example, two of the included studies (40% of the studies) did not evaluate the publication bias or quality of their included studies. The search strategies of the included systematic reviews were not optimal in two studies.

In the future, better-performed systematic reviews are needed with optimal search strategy (no language limit) and better evaluation of publication bias and heterogeneity.

**Conclusion**

SN mapping is feasible and highly accurate in EC and NSCLC. Attention to the technique (using radio tracers, peri-tumoral injection) and restriction of the patients to less advanced cases (cN0 and T1, 2) would ensure the best results with high detection rate and sensitivity.

There is still a need for larger studies especially for EC to validate this technique with more certainty. Specifically large multicenter randomized controlled trials are need in this regard.

**Acknowledgements**

We would like to thank Clinical Research Development Center of Ghaem Hospital for their assistant in this manuscript. This study is a result of the residency thesis under the approval number of 910245. The thesis was financially supported by the vice chancellery of research of Mashhad University of Medical Sciences.

**Conflict of Interest**

The authors declare no conflict of interest.

**References**


