Mashhad University of Medical Sciences (MUMS)

Reviews in Clinical Medicine

Clinical Research Development Center Ghaem Hospital

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

Susan Shafiei (MD)[1],Reza Bagheri (MD)[2], Kayvan Sadri (MD)[1], Amir Hossein Jafarian (MD)[3], Davood Attaran (MD)[4], Shahrzad Mohammadzadeh Lari (MD)[4], Reza Basiri (MD)[4], Amir Mohammad Hashem Asnaashari (MD)[4], Ramin Sadeghi (MD)[1*]

[1]*Nuclear Medicine Research Center, Mashhad University of Medical Sciences, Mashhad, Iran*
[2]*Minimally Invasive and Endoscopic Surgery Research Center, Mashhad University of Medical Sciences, Mashhad, Iran*
[3]*Pathology Department, Ghaem Hospital, Mashhad University of Medical Sciences, Mashhad, Iran*
[4]*Lung Disease Research Center, Ghaem Hospital, Mashhad University of Medical Sciences, Mashhad, Iran*

ARTICLE INFO

Article type
Systematic review article

Article history
Received: 22 Dec 2014
Revised: 18 Jan 2015
Accepted: 22 Jan 2015

Keywords
Esophageal cancer
Non-small cell lung cancer
Sentinel
Systematic review

ABSTRACT

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:
Shafiei S,Bagheri R, Sadri K, Jafarian AH, Attaran D, Mohammadzadeh Lari SH, Basir R, Asnaashari AMH, Sadeghi R. Sentinel node mapping for intra-thoracic malignancies: systematic review of the best available evidence . Rev Clin Med. 2015;2(2):52-57.

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

***Corresponding author:** Ramin Sadeghi.*
Nuclear Medicine Research Center, Mashhad University of Medical Sciences, Mashhad Iran
***E-mail:** sadeghir@mums.ac.ir; raminsadeghi1355@yahoo.com*
***Tel:** 05138012794*

This is an Open Access article distributed under the terms of the Creative Commons Attribution License (http://creativecommons.org/licenses/by/3.0), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

led to several less invasive methods including CT scanning, ultrasonography, magnetic resonance imaging (MRI) and 18-F Flourodeoxy 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 rout 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

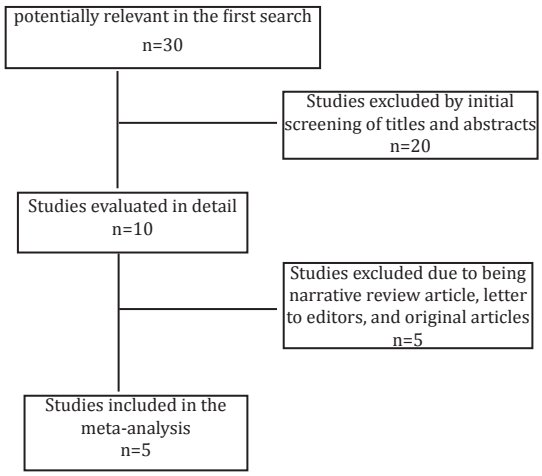
Following items were extracted from each included systematic review: first author, publication year, affiliation, main results of the systematic review (detection rate and false negative rate of the technique), auxiliary results (including the number of sentinel nodes, location of SN, skip metastasis, 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.

Figure 1. PRISMA flowchart of the study



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

Author Year	Evaluated malignancy	Number of included studies	Main findings: detection and false negative rates	Sub-group analyses (DR/sensitivity)		Auxiliary findings
Dabbagh Kakhki 2014	EC	18	Pooled DR=89.2 % [82.6–93.5], Pooled sensitivity = 84 % [78–88 %].	Mapping material Blue dye Radiotracer Combined Injection site Sub-mucosal Sub-serosal Type of surgery Open Endoscopic Histology AC SCC Tumor location Upper Mid Distal Tumor size T1,2 T3,4 Post-chemotherapy	 87.2[63.4–96.4]/93 [84–98] 90.8[86.4–93.9]/79 [71–86] 80.4[40–96.2]/80.4 [40–96.2] 89.1[81.4–93.8]/83 [77–88] 85.9[63.7–95.5]/88 [70–98] 90.5[87.1–93]/84 [77–89] 80.6[43.6–95.7]/86 [68–96] 93.1 [86.9–96.4]/91 [80–97] 90.5 [86.6–93.3]/81 [73–87] 88.1 [62.6–97.1]/N/A 90.5 [79.8–95.5]/N/A 84.5 [69.2–92.9]/N/A 94.4 [90.5–96.8]/91 [76–98] 77.5 [57.4–89.8]/57 [37–75] 54 [29.1–77]/25 [1–81]	-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 by 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
Sgourakis 2011	EC	10	DR ranged from 80% to 100% and sensitivity ranged from 75% to 100%	N/A	N/A	-CT lymphography was used in a study with excellent results. -IHC and rapid PCR resulted in better staging in a study.
Nagaraja 2014	EC	23	Pooled DR: 93%[89.4-95], Pooled sensitivity: 84%[74-91]	Histology AC SCC Mapping material Tc-99m-nanocolloid Tc-99m-Rhenium Sulphide Tc-99m-Tin colloid Tc-99m-Antimony colloid Tc-99m-HSA Methylene Blue Patent Blue V	 98[92-99]/84[74-91] 89[79-94]/91[75-97] 94[90-97]/81[64-91] 86[80-90]/93[81-97] 90[81-95]/75[66-83] 94[78-99]/98[84-100] 98[71-100]/N/A 96[80-99]/91[71-98] 69[48-84]/92[73-98]	-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
Filip 2014	EC	12	Pooled DR: 91.6[88.4-94], Pooled sensitivity: 77.5[71.1-82.8]	Mapping material Radiotracer Blue dye	 97[81-99]/86[81-89] 97[89-99]/81[70-90]	-CT lymphography showed excellent DR and sensitivity -Location 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

Taghizadeh Kermani 2013	NSCLC	41	Pooled DR:80.6[76.8-84], Pooled sensitivity: 87% [83–90%].	Mapping material Radiotracer alone Blue dye alone Combined CT lymphography Fluorescence imaging Magnetic material Patient variables Excluding N1 patients Technique related variables No intra-tumoral injection Intra-operative injection Pre-operative injection Intraoperative peri-tumoral Video assisted surgery	 84.4 [78.4–89]/89 [83–92] 64.4 [49.2–77.2]/83 [74–90] 90.4 [61.6–98.2]/89 [77–96] 91.7[77.3–97.3]/100 [48–100] 80.4 [59.9–91.8]/83 [52–98] 81.6 [75.3–86.5]/83 [62–94] 86 [79.8–90.6]/96 [91–98] 87.4 [81.7–91.5]/92 [72–98] 88.5 [75.4–95.17]/N/A 82.1 [75.4–87.3]/97 [90–99] 95.3 [89.9–97.9]/ 79 [68–87] 81.8 [71.1–89.1]/N/A	- One study used carbon nano-particles with pooled DR of 73.3[46.7–89.6] and sensitivity of 86% [42–100]. -Indocyanine green injection showed extremely poor DR -Sentinel node location: included studies reported 5-96% N2 location of SN -IHC and rapid PCR increased the sensitivity of SN mapping -Skipped metastases were reported in 18 of the included studies -Learning curve effect was reported in two studies.

DR: Detection Rate; AC: Adenocarcinoma; SCC: Squamous Cell Carcinoma; IHC: Immunohistochemistry; SN: Sentinel Node; EC: Esophageal Carcinoma; NSCLC: Non-Small Cell Lung Cancer

in better detection rate and sensitivity, which outweighs the complications of blue dye.

However, for intra-thoracic tumors, the anthracosis 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 does 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

Author year	Search strategy	Inclusion criteria	Quality assessment of the included studies	Heterogeneity evaluation	Publication bias evaluation
Dabbagh Kakhki 2014	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.	For sensitivity pooling at least D2 lymphadenectomy should be performed. At least 5 patients should be included.	Evaluated by CEBM checklist	Evaluated by Cochrane Q and I^2 index I^2 for DR pooling was 65.9% and for sensitivity pooling was 64.1%	Evaluated by funnel plot and trim and fill method Funnel plots were asymmetric and trim and fill method showed possible important publication bias
Sgourakis 2011	Medline, Embase, Ovid, and the Cochrane Controlled Trials Registry were used. Only English studies were included.	Not provided definitely	Not evaluated	Not evaluated	Not evaluated
Nagaraja 2014	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"	All studies on SN mapping in esophageal cancer were included.	Not evaluated	Evaluated by Cochrane Q and I^2 index. I^2 for DR pooling was 7% and for sensitivity pooling was 39%.	Evaluated by funnel plot and Egger's regression method. No important publication bias was reported.
Filip 2014	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.	All studies on SN mapping in esophageal cancer were included.	Based on Cochrane Handbook for Systemic Review of interventions	Not evaluated	Not evaluated
Taghizadeh Kermani 2013	Medline, SCOPUS and ISI web of knowledge were searched with the following search terms: (lung AND sentinel) with no date or language limit.	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.	Evaluated by CEBM checklist	Evaluated by Cochrane Q and I^2 index. I^2 for DR pooling was 77.6% and for sensitivity pooling was 37.3%.	Evaluated by funnel plot, trim and fill method. Funnel plots were asymmetric and trim and fill method showed possible important publication bias .

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 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.

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

1. Li QL, Chen FJ. Review of relationship between vascular endothelial growth factor C & D and lymph node metastasis of malignant tumor. Ai Zheng. 2002;21:696-700.
2. Cousins A, Thompson SK, Wedding AB, et al. Clinical relevance of novel imaging technologies for sentinel lymph node identification and staging. Biotechnol Adv. 2014;32:269-279.
3. Kroon BK, Horenblas S, Nieweg OE. Re: Gipponi M, Solari N, Di Somma FC, et al.: New fields of application of the sentinel lymph node biopsy in the pathologic staging of solid neoplasms: review of literature and surgical perspectives. J Surg Oncol 2004: 85:171-179. J Surg Oncol. 2004;87:107.
4. Gipponi M, Solari N, Di Somma FC, et al. New fields of application of the sentinel lymph node biopsy in the pathologic staging of solid neoplasms: review of literature and surgical perspectives. J Surg Oncol. 2004;85:171-179.
5. Sadeghi R, Hasanzadeh M. Sentinel lymph node biopsy algorithm: can it be a universal method for midline tumors? Gynecol Oncol. 2014;132:273-274.
6. Sadeghi R. Sentinel node mapping diagnostic studies warrant a unique reporting criteria: Comment on Xiong et al. systematic review. Eur J Surg Oncol. 2014;40:1025-1026.
7. Sadeghi R, Zakavi SR, Forghani MN, et al. The efficacy of Tc-99m sestamibi for sentinel node mapping in breast carcinomas: comparison with Tc-99m antimony sulphide colloid. Nucl Med Rev Cent East Eur. 2010;13:1-4.
8. http://www.cebm.net/wp-content/uploads/2014/04/SR_Appraisal_sheet_2005_English.doc.
9. Dabbagh Kakhki VR, Bagheri R, Tehranian S, et al. Accuracy of sentinel node biopsy in esophageal carcinoma: a systematic review and meta-analysis of the pertinent literature. Surg Today. 2014;44:607-619.
10. Taghizadeh Kermani A, Bagheri R, Tehranian S, et al. Accuracy of sentinel node biopsy in the staging of non-small cell lung carcinomas: systematic review and meta-analysis of the literature. Lung Cancer. 2013;80:5-14.
11. Sgourakis G, Gockel I, Lyros O, et al. Detection of lymph node metastases in esophageal cancer. Expert Rev Anticancer Ther. 2011;11:601-612.
12. Filip B, Scarpa M, Cavallin F, et al. Minimally invasive surgery for esophageal cancer: a review on sentinel node concept. Surg Endosc. 2014;28:1238-1249.
13. Nagaraja V, Eslick GD, Cox MR. Sentinel lymph node in oesophageal cancer-a systematic review and meta-analysis. J Gastrointest Oncol. 2014;5:127-141.
14. Sadeghi R, Alesheikh G, Zakavi SR, et al. Added value of blue dye injection in sentinel node biopsy of breast cancer patients: do all patients need blue dye? Int J Surg. 2014;12:325-328.
15. Jangjoo A, Forghani MN, Mehrabibahar M, et al. Anaphylaxis reaction of a breast cancer patient to methylene blue during breast surgery with sentinel node mapping. Acta Oncol. 2010;49:877-878.
16. Leijte JA, van der Ploeg IM, Valdes Olmos RA, et al. Visualization of tumor blockage and rerouting of lymphatic drainage in penile cancer patients by use of SPECT/CT. J Nucl Med. 2009;50:364-367.
17. Bagheri R, Naghavi F, Kakhki VRD, et al. Sentinel node mapping in esophageal squamous cell carcinoma using intra-operative combined blue dye and radiotracer techniques. Esophagus. 2013;10:211-216.
18. Liptay MJ, D'Amico T A, Nwogu C, et al. Intraoperative sentinel node mapping with technitium-99 in lung cancer: results of CALGB 140203 multicenter phase II trial. J Thorac Oncol. 2009;4:198-202.
19. Liptay MJ. In vivo sentinel lymph node mapping in lung cancer. Ann Surg Oncol. 2005;12:102-103.
20. Abdollahi A, Jangjoo A, Dabbagh Kakhki VR, et al. Factors affecting sentinel lymph node detection failure in breast cancer patients using intradermal injection of the tracer. Rev Esp Med Nucl. 2010;29:73-77.