Lung Cancer 80 (2013) 5–14

Contents lists available at SciVerse ScienceDirect

Lung Cancer

journal homepage: www.elsevier.com/locate/lungcan

Review

Accuracy of sentinel node biopsy in the staging of non-small cell lung carcinomas: Systematic review and meta-analysis of the literature

Ali Taghizadeh Kermani[a], Reza Bagheri[b], Shahrzad Tehranian[c], Pardis Shojaee[d], Ramin Sadeghi[c,*], David N. Krag[d]

[a] Cancer Research Center, Mashhad University of Medical Sciences, Mashhad, Iran
[b] Endoscopic & Minimal Invasive Surgery Research Center, Mashhad University of Medical Sciences, Mashhad, Iran
[c] Nuclear Medicine Research Center, Mashhad University of Medical Sciences, Mashhad, Iran
[d] Division of Surgical Oncology, Department of Surgery, College of Medicine, University of Vermont, Given Building, Rm E309, 89 Beaumont Ave, Burlington, VT 05405, USA

ARTICLE INFO

Article history:
Received 30 August 2012
Received in revised form
28 November 2012
Accepted 4 January 2013

Keywords:
NSCLC
Non-small cell lung cancer
Sentinel node biopsy
Systematic review
Meta-analysis
Detection rate
False negative rate

ABSTRACT

Background: Not all patients with non-small cell lung carcinoma (NSCLC) have mediastinal lymph node involvement and development of less invasive methods for evaluating mediastinal lymph nodes is important. Sentinel node biopsy has been used for NSCLC since 1999 to decrease the need for mediastinal lymph node dissection. In this review, we searched the literature in this regard and reported the results in a meta-analysis format.
Methods: Medline, SCOPUS, and ISI web of knowledge were searched using: "(lung AND sentinel)" with no date or language limit. Any study with more than 5 patients and enough information to calculate detection rate and sensitivity was included.
Results: Overall 47 and 43 studies (including subgroups) had the criteria for detection rate and sensitivity pooling respectively. Pooled detection rate was 80.6% [76.8–84%] and pooled sensitivity was 87% [83–90%]. Using radiotracers or both radiotracers and dyes had higher detection rate and sensitivity compared to dye alone. Among studies using radiotracers, highest detection rate was in intra-operative peri-tumoral injection group and highest sensitivity was in peri-tumoral pre-operative injection group. Emerging methods of sentinel node surgery including magnetic materials, fluorescent dyes, CT contrast agents, and carbon nano-particles had promising results.
Conclusions: Sentinel node mapping using radiotracers is a feasible technique for mediastinal lymph node staging of N0 NSCLC patients. Alternative methods of sentinel node mapping are promising and warrant further studies.

1. Introduction

Despite recent advances in systemic therapy and radiotherapy, surgery remains and integral component of curative treatment of non-small cell lung cancer (NSCLC) [1]. Mediastinal lymph node dissection is an important part of NSCLC surgery which is associated with improved staging and survival [2]. However, mediastinal lymph node dissection may not be therapeutic for the majority of patients with NSCLC, since less than 30% of clinically stage I patients have mediastinal lymph node involvement [3]. Due to this fact and significant morbidity of mediastinal lymph node dissection [4], development of less invasive methods for evaluating mediastinal lymph nodes is important.

Sentinel node (SN) biopsy is an important technique for regional lymph node staging of many solid tumors [5]. This method allows determination of pathological node status by removing a limited number of lymph nodes and this in decreased morbidity. This procedure was applied to patients with NSCLC beginning in 1999 [6] and since then there has been an expanding body of literature.

In the current study, we systematically searched the literature on SN biopsy in NSCLC and report the results in a systematic review and meta-analysis format.

2. Materials and methods

This study was approved by Institutional Review Board of Mashhad University of Medical Sciences under the approval number of 910245.

* Corresponding author at: Nuclear Medicine Research Center, Imam Reza Hospital, Faculty of Medicine, Mashhad University of Medical Sciences, Ebn Sina Street, Mashhad, Iran. Tel.: +98 511 8599359; fax: +98 511 8593038.
E-mail addresses: sadeghir@mums.ac.ir, raminsadeghi1355@yahoo.com (R. Sadeghi).

0169-5002/$ – see front matter © 2013 Elsevier Ireland Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.lungcan.2013.01.001

Medline, SCOPUS, and ISI web of knowledge were searched with the following search terms: (lung AND sentinel) with no date or language limit. The last search was done on 11 January 2012. Meeting abstracts were also included if meeting below-mentioned criteria. The reference lists of the retrieved studies as well as citing articles were searched for any other possible relevant study. Corresponding authors of the relevant studies were contacted via e-mail if indicated.

2.1. Inclusion criteria

1. A sample size of at least 5 patients.
2. The total number of patients with positive lymph nodes and number with false negative results were reported.
3. The total number of patients and the rate of SN detection were reported.

Retrieved studies were independently reviewed by two authors and any controversy regarding inclusion of the studies was resolved by a 3rd author and a consensus was obtained. Duplicate publications were excluded.

The quality of the retrieved studies was evaluated by the Oxford Center for Evidence Based Medicine Checklist of the diagnostic studies [7].

Two authors performed data abstraction independently and the following items were extracted for each study: authors, publication year, characteristics of the patients, method of SN mapping (blue dye, radiotracer, other methods), location of SNs, using of immunohistochemistry (IHC), skipped metastases, detection rate and sensitivity.

2.2. Statistical analysis

For sensitivity and detection rate pooling, random effects model (Der-Simonian and Laird method [8]) was used. Random effects model is a pooling method by which the heterogeneity of the included studies is accounted for and was particularly suitable for the current meta-analysis due to considerable variations in the methods and patients of the included studies.

Cochrane Q-test was used for statistical evaluation of heterogeneity (p value less than 0.05 was considered statistically significant). For quantifying the extent of heterogeneity, I^2 index was used which shows the amount of the heterogeneity among the included studies that is not caused by sampling errors.

Funnel plots were used for publication bias evaluation, which are the plots of effect size (sensitivity or detection rate in our meta-analysis) against standard error of each study. Any asymmetry in this plot can be due to publication bias. Egger's regression method was used to statistically evaluate the asymmetry of funnel plots [9]. Duval and Tweedie's trim and fill method was also used for quantifying possible publication bias [10]. In this technique, an iterative method is used to omit the smallest studies from the funnel plot until a symmetrical plot results. The new measured effect size by this method shows the impact of possible publication bias.

Meta-Disc (version 1.4) [11] and CMA (version 2) were used for statistical analyses.

3. Results

Fig. 1 shows the summary of literature search outcomes. Overall, 41published reports were included in the systematic review [3,6,12–50]. Four reports had 2 patient groups and one report had 3 patient groups for a total of 47 patient groups [22,29,30,38,46]. Five studies were in Chinese [15–18], 3 were in Czech [13,43,44], 2 were in Italian [22,25], and the remainder were in English. Three reports were meeting abstracts [31,33,45].

Table 1 shows the quality assessment of the included studies and Table S1 (Supplementary data) summarizes the retrieved data.

3.1. Surgical detection rate

The pooled detection rate was 80.6% [95% CI: 76.8–84%] and is shown in Fig. 2. Cochrane Q-value was 205 ($p < 0.0001$) and I^2 index was 77.6%.

Fig. 3 shows the funnel plot of the detection rate pooling. Egger's regression intercept was 1.3 ($p = 0.01$). After trimming 9 studies using trim and fill method, a symmetrical funnel plot was achieved with adjusted pooled detection rate 4.3% less that the observed one.

Subgroup analysis regarding the mapping method showed the following pooled detection rates: 64.4% [49.2–77.2%] for dye alone (including blue dyes and indocyanine green), 84.4% [78.4–89%] for radiotracer alone, 90.4% [61.6–98.2%] for studies using both methods. Un-conventional methods have also been used for SN mapping of NCSLC and pooled detection rates of these studies include: 91.7%

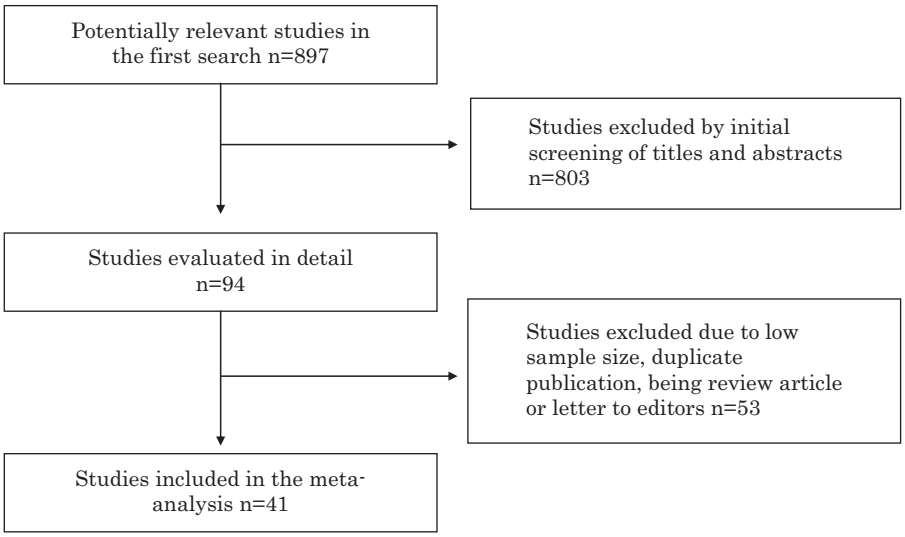

Fig. 1. PRISMA flow diagram of the study search.