Technetium-99m SPECT-CT versus planar lymphoscintigraphy for preoperative sentinel lymph node detection in cervical cancer: a systematic review and meta-analysis

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ABSTRACT

We aim to compare single photon emission computed tomography with computed tomography (SPECT-CT) and lymphoscintigraphy (LSG) on the overall and bilateral sentinel lymph node (SLN) detection in cervical cancer patients.

Methods: A systematic search was performed on August 1st 2014 in PubMed, Embase, Scopus and the Cochrane library. The syntax was based on synonyms of the terms ‘cervical cancer’, ‘SPECT-CT’ and ‘LSG’. Retrieved articles were title/abstract screened and eligible when a SLN procedure was performed using both imaging modalities and if detection results were reported. Two independent reviewers assessed all included studies on methodological quality using QUADAS-2. Studies were pooled on their odds ratios (OR) with a random effects model.

Results: The search yielded 962 unique articles of which 8 were ultimately included. Studies were recent retrospective or prospective cohort studies of limited size (n = 7–51) but sufficient methodological quality. The median overall detection (≥1 SLN in a patient) was 98.6% for SPECT-CT (range: 92.2–100.0%) and 85.3% for LSG (range: 70.0–100.0%). This corresponded to a pooled overall SLN detection OR of 2.5 (95%CI: 1.2–5.3) in favor of SPECT-CT. The reported median bilateral detection (≥1 SLN in each hemipelvis) was 69.0% for SPECT-CT (range: 62.7–79.3%) and 66.7% for LSG (range: 56.9–75.8%) yielding a pooled OR of 1.2 (95%CI: 0.7–2.1). No significant difference in the number of visualized SLN’s was observed at a pooled ratio of 1.2 (95%CI: 0.9–1.6).

Conclusion: In cervical cancer patients, preoperative SLN imaging with SPECT-CT results in a superior overall SLN detection when compared to planar LSG.

Keywords: SPECT-CT, lymphoscintigraphy, sentinel lymph node, cervical cancer, meta-analysis
INTRODUCTION

In recent years, the sentinel lymph node (SLN) procedure has been increasingly adopted in the staging of cervical cancer patients eligible for surgery. It allows for individualized treatment decisions by accurately ascertaining the lymph nodal status before radical surgery is commenced (1). This comprises the exclusion of fertility sparing surgery or replacing a radical hysterectomy with chemoradiotherapy in patients with tumor-positive lymph nodes.

Besides blue dye, the colloid bound radionuclide technetium-99m ($^{99m}$Tc) is commonly added as a second tracer and has shown to improve the intraoperative SLN detection (2). A second advantage of this tracer is that preoperative lymphatic mapping by either single photon emission computed tomography with regular computed tomography (SPECT-CT) or planar lymphoscintigraphy (LSG) becomes possible, which predicts the surgical detectability and number of SLN’s in an individual patient. This aids the surgeon in a more direct SLN resection, with less disruption of the lymphatic architecture when compared to a full retroperitoneal exploration (3-5).

Although SPECT-CT is associated with both increased upfront cost and ionizing radiation, its cross-sectional anatomical reference allows for accurate three-dimensional SLN localization which is considered an important advantage over planar LSG (5-9). Both SPECT-CT and LSG should ideally have a high detection ability for the SLN which largely determines the clinical value of the entire procedure.

We compared, based on a systematic search of the literature, the detection of SLN’s on preoperative mapping by SPECT-CT and LSG in cervical cancer patients. Through a meta-analysis of the retrieved studies, we aimed to quantify both the overall and bilateral SLN detection differences between these two imaging modalities.
MATERIALS AND METHODS

Systematic Search
We conducted a systematic review and meta-analysis of the medical literature in adherence to the PRISMA guideline (10). Before the search was initiated, a protocol was devised which specified the research question, search strategy, in- and exclusion criteria, quality assessment, data-collection and statistical analysis.

A title and abstract based literature search was simultaneously performed on August 1st 2014 for four online databases PubMed/MEDLINE, Embase, Scopus and the Cochrane library. To attain a comprehensive search, the syntax was based on multiple synonyms, abbreviations and common adjectives of the search terms representing our study domain (i.e. population) and determinants (i.e. intervention and comparison). These search terms were cervical cancer, SPECT-CT and LSG. The outcome measure was deliberately omitted from the search given that this could be a secondary finding in some articles and not included in the title or abstract. As an example, figure 1 outlines the exact search syntax used in PubMed/MEDLINE. Syntaxes for the other databases used identical terms. No Medical Subject Headings, filters or publication date limits were used.

All identified references were exported to the online reference management software RefWorks (RefWorks-COS, ProQuest LLC) for removal of duplicate articles.

Eligibility Assessment
All unique articles were screened by a single reviewer (JPH) on their title and abstract for their respective eligibility. The inclusion of individual studies required that a SLN procedure was performed in cervical cancer patients with preoperative SLN mapping by both SPECT-CT and LSG within the same study. Also, the study had to report unilateral and/or bilateral detection results of both these imaging modalities. To allow a valid comparison, we aimed to include only studies which directly compared both techniques. Studies were excluded from the review when they did not contain original data or were not written in English, Dutch, German or French. Conference abstracts and case reports or series with \( \leq 3 \) valid cases were also excluded. When multiple eligible articles reported on the same patients, only the article demonstrating the most comprehensive results with respect to our research question, was selected.

Full-text assessment was performed when the eligibility of an article, based on title and abstract screening, remained uncertain. Articles deemed eligible based on initial screening were also read in full-text, during which their eligibility was rechecked. The references of all included studies were carefully cross-checked with our initial search result for possible additional literature.

Quality Assessment And Data-collection
A structured quality assessment of all included studies was performed using the ‘Quality Assessment of Diagnostic Accuracy Studies’ instrument version 2 (QUADAS-2) (11). The QUADAS-2 is designed for grading individual diagnostic studies on their respective risk of bias and applicability in the context of systematic reviews and meta-analyses. In adherence to the QUADAS-2 recommendations, signaling questions were optimized for our research aim, though without changing its overall content or structure. The critical appraisal was independently
performed by two reviewers (JPH and RPZ). Discrepancies between both reviewers were resolved via consensus discussion or, when persisting, by an independent third referee (WBV).

The data from the original studies were collected by a single reviewer (JPH) using a standardized form which was created in advance. This form contained variables on the research question, study design, study population, imaging modalities, intraoperative SLN procedure and outcome level effects.

**Statistical Analysis**

All analyses were performed using the statistical software R, version 3.0.3 (R Foundation for Statistical Computing). Herein, the package 'meta', version 3.7-1, was installed and used for all meta-analyses and corresponding plots. This R package is programmed and kindly provided by G. Schwarzer (Freiburg university, Germany).

The main outcome measures were the differences between SPECT-CT and planar LSG for the overall (≥1 SLN in a patient) and bilateral (≥1 SLN in each hemipelvis) SLN detection. For both outcomes, an inverse variance weighted random effects meta-analysis was performed to pool the original studies based on their odds ratios (OR) (12). Studies with zero values in any of the boxes in the two by two tables underlying OR calculation were continuity corrected (n +0.5). To facilitate easy interpretation of the OR’s and their clinical relevance, pooled OR’s and median LSG detection ratios were used to transform the pooled OR into a percentage.

As a secondary analysis, the difference in number of SLN’s detected between both imaging modalities was analyzed. This constitutes count-type data for which an inverse variance weighted random effects meta-analysis was performed based on incidence (i.e. detection) rate ratios (12). Forest plots were created to summarize all studies, the pooled estimate and corresponding 95% confidence intervals (95%CI) in a single overview.

The heterogeneity of the results from the original studies is tested by calculating Cochrane’s Q-value, which follows a Chi² distribution. Its derived percentage $I^2$ is calculated and used to represent the variability of results relative to chance. The between study variance is presented by the tau²-statistic ($\tau^2$). Statistical significance was defined as $P < 0.05$. 
RESULTS

Literature Search And Assessment
The four databases yielded 432 (PubMed), 604 (Embase), 735 (Scopus) and 23 articles (Cochrane library) (Fig. 2). After the removal of duplicates, 962 unique articles were screened on their eligibility. Full-text assessment was needed in 22 articles, of which 4 did not meet the inclusion criteria because either SPECT-CT or LSG was not used (13-15) or the SLN detection results were not reported for both modalities (6). A further 9 studies were excluded because of their language (n = 1; (16)), being a conference abstract (n = 7; (17-23)) or were case report/series (n = 1; (24)). One article (25) was discarded due to an overlap in patients with an included study (8). The references cited in the remaining 8 articles were cross-checked and did not yield any additional eligible studies (3-5,8,9,26-28).

These 8 articles were QUADAS-2 assessed (Fig. 3). The risk of bias was mainly scored as low or remained unclear due to absent reporting on patient inclusion criteria, consecutiveness of inclusions or details of the SPECT-CT and LSG evaluation procedure. All seven paired studies did not specify if and how blinding between both imaging modalities was assured. No real concerns on the applicability of studies for this meta-analysis existed.

SLN Detection
The characteristics of the studies included in the meta-analysis are outlined in Table 1. Three studies (3-5) exclusively investigated patients with cervical cancer, others did so in combination with endometrial cancer (n = 3; (9,26,27)), vulvar cancer (n = 1; (28)) or both (n = 1; (8)). In total, SPECT-CT and LSG were performed in 207 and 208 cervical cancer patients respectively. Except for one single FIGO Stage IIIA case from Klapdor et al., all these subjects had early stage disease (FIGO stage I/II) (5). Lymph node involvement for cervical cancer was reported in all studies, except Kraft et al. (8), and ranged between 0.0–28.6% (overall mean: 19.8%) (3-5,9,26-28). The outlier of 0% lymph node metastasis occurred in a single study with 10 patients (26).

All included studies, with the exception of Diaz et al. (3), reported a higher overall SLN detection for SPECT-CT when compared to LSG. The median overall detection was 98.6% for SPECT-CT (range: 92.2–100.0%) and 85.3% for LSG (range: 70.0–100.0%). At the pooled level, a statistically significant OR of 2.5 (95%CI: 1.2–5.3) was detected, favoring SPECT-CT (Fig. 4). The consistency of the detection results was confirmed by the negligible heterogeneity across the included studies. Based on the median 85.3% overall SLN detection for LSG and the pooled OR, a calculated 93.6% (95%CI: 87.3–96.9%) overall detection on SPECT-CT should be achieved. This equals a detection increase of 8.3% (95%CI: 2.0–11.6%).

Three of the 8 studies reported data on the bilateral SLN detection ratios, covering a total of 122 (SPECT-CT) and 123 (LSG) patients. The median bilateral detection was 69.0% for SPECT-CT (range: 62.7–79.3%) and 66.7% for LSG (range: 56.9–75.8%) (4,5,9). A pooled OR of 1.2 (95%CI: 0.7–2.1) was detected for bilateral SLN detection, indicating absence of a significant difference (Fig. 5). This equals to a 4.1% bilateral detection difference (95%CI: -8.1–14.0%).

Five studies could be pooled on the number of SLN’s detected by both modalities (3,4,9,26,28). On SPECT-CT 345 SLN’s were visualized in 110 patients, relative to 299 SLN’s in 111 patients on LSG. The pooled ratio in SLN count was 1.2 (95%CI: 0.9–1.6) which reflects no significant increase in the number of SLN’s detected on SPECT-CT (Fig. 6).
DISCUSSION

All 8 original studies showed excellent and consistent overall SLN detection ratios for SPECT-CT, ranging between 92.0 and 100.0%. Its pooled SLN detection was superior to LSG with an OR of 2.5 (95%CI: 1.2–5.3) corresponding to a relevant 8.3% (95%CI: 2.0–11.6%) increase. Clinically, this means that of the median 14.7% non-visualization cases on LSG, more than half can be prevented through the use of SPECT-CT (6.4% non-visualization). Its significantly improved overall SLN detection supplements other potential advantages. The cross-sectional nature and anatomical reference of SPECT-CT has been reported, though rarely formally analyzed, to lead to better anatomical SLN localization (4,6-8). This has always been regarded as a weakness of LSG (29). In addition, a single report has indicated a possible reduction of 25.4 minutes for the intraoperative SLN retrieval length by robot assisted laparoscopy, when preoperative SPECT-CT is used (4).

The cervix is a midline organ with bilateral lymphatic drainage, making it clinically relevant to identify minimally one SLN in each hemipelvis (1,6,30-32). Unfortunately, only 3 studies specifically reported bilateral SLN detection results which led to a meta-analysis of insufficient statistical power to (dis)prove a difference. The wide confidence interval relative to the limited OR of 1.2 (95%CI: 0.7–2.1), indicates that further research is needed before any conclusive statement can be made. In general, researchers should be urged to always report bilateral SLN results in cervical cancer, even though these are often substantially lower and less attractive than the overall detection ability.

Some investigators use 99m-Tc-nanocolloid and blue dye via a cervical injection for the sentinel procedure in endometrial cancer patients. While the validity and reliability are not without debate for this indication, the methodology is similar to the cervical cancer approach and identifies the SLN’s of the cervix uteri. Four such studies (n = 21–40) from our initial search reported the overall SLN detection results of both SPECT-CT and LSG, which ranged between 84.6–100.0% and 40.0–85.9% respectively (8,9,26,27). In addition, Garcia et al. demonstrated an overall detection at the first imaging session of 77.8% (n = 14/18) on SPECT-CT compared to 73.7% (n = 14/19) for planar LSG in stage IA-IIIA endometrial cancer patients (33). While these results, especially for LSG, are lower when compared to the cervical cancer estimates used in our meta-analysis, the superiority of SPECT-CT is maintained.

By definition, the SLN is the first efferent nodal station to receive lymphatic drainage from the tumor and therefore represents the overall lymph nodal status. Consequently, some authors question the necessity of routine pelvic lymphadenectomy when tumor-negative SLN’s are identified in cervical cancer (30,32,34,35). While the as of yet unpublished randomized SENTICOL-2 trial primarily studies the complications after a SLN procedure, as opposed to full lymphadenectomy, oncological safety is a secondary endpoint of this study (36). When found to be equal, abstaining from the systematic lymphadenectomy would safeguard lymph node negative patients from an associated 2% intraoperative risk of vascular, nerve, bowel or ureteric injury (37). Also, long term morbidity caused by lymphedema and (infected) lymphocysts can be minimized and will likely improve quality of life (30,38).

The ability to safely abstain from a systematic lymphadenectomy also depends on the reliability of the SLN procedure. Besides the high SLN detection shown in this meta-analysis, this is mainly determined by the intraoperative risk of a false-negative diagnostic outcome (i.e. misclassifying a patient with lymph node metastases). A large multicenter study (n = 645) by
Cibula et al. published a false-negative SLN ratio of 1.3% when bilateral detection with histopathological ultrastaging is performed (1).

Several arguments offer a rationale for the improved SLN detection by SPECT-CT. In addition to its higher spatial resolution, various authors have reported that the anatomical reference and cross-sectional nature of SPECT-CT allows for less frequently overlooked SLN’s near the injection depot (e.g. parametrial SLN’s) or at unusual anatomical locations (e.g. paravesical, epigastric or pre-sacral SLN’s) (5,6,28). Furthermore, SPECT undergoes superior attenuation correction through the availability of concurrent CT data (39). This CT based correction reduces the inherent overestimation of (peripheral) background activity (i.e. noise), leading to more valid $^{99m}$Tc tracer uptake quantification in the SPECT dataset (40).

Some limitations at the level of the original studies merit further explanation. First, in studies with a paired design, adequate blinding during the review of both imaging modalities is of the utmost importance for an unbiased comparison. However, none of the 7 paired studies had a blinded design. This could possibly favor SPECT-CT because it is commonly performed after LSG. Secondly, all available studies had an observational design (4 prospective, 4 retrospective) with a relatively small sample size. The limited number of original studies did not permit a formal sensitivity analysis wherein only low risk of bias studies are pooled and compared to the effect derived from all studies. Instead, we aimed to clearly assess the methodological quality and pool all studies.

A limitation of this study is our choice of the outcome measure. While the detection on preoperative imaging is relevant and insightful, a more clinically important outcome would be to examine differences in the intraoperative SLN resection. However, this is currently not possible since all but one original study in our meta-analysis followed a paired design and consequently had identical intraoperative SLN resection results for both imaging modalities. The single parallel study included did not report a statistically significant difference between SPECT-CT and LSG for the overall (93.1 vs 93.9%) or bilateral intraoperative SLN resection (89.7 vs 84.8%) (4).

A limitation of our meta-analysis on the number of SLN detected, which follows a Poisson distribution, is the absence of a uniformly accepted summary statistic for count-type data. We followed a common approach in which pooling was based on the rate ratio (i.e. detection rate LSG divided by detection rate SPECT-CT), instead of treating it as a continuous variable (12). However, in detection rate calculation the SLN count should be divided by person-time, a nonexistent entity in our imaging setting, which was therefore replaced by the respective number of scans made.

CONCLUSION

Preoperative SPECT-CT provides a higher overall SLN detection in cervical cancer patients when compared to LSG. Larger studies are still needed before any significant conclusions on bilateral detection, or the number of SLN’s visualized, can be reached. Nonetheless, the overall detection ability is high and the difference with LSG substantial. The more than half reduction in non-visualization cases is a relevant clinical improvement achieved through the use of SPECT-CT. This study supplements other advantages of SPECT-CT, including possibly shortened surgical SLN retrieval times and more precise preoperative information on the anatomical location of the SLN’s. Combined, few reasons remain for continuing the use of planar LSG for SLN detection in cervical cancer when SPECT-CT is available.
DISCLOSURE
All authors declare to have no conflicts of interest.

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REFERENCES


Sentinel node detection cervical cancer

FIGURE 1: The PubMed/MEDLINE search syntax.
FIGURE 2: A flow diagram of the performed search and study assessment with the associated number of articles at each stage.
FIGURE 3: Summary of the methodological quality scored according to the Quality Assessment of Diagnostic Accuracy Studies (QUADAS) version 2.
FIGURE 4: Forest plot of the overall SLN detection (≥1 SLN detected in a patient) on SPECT-CT compared to LSG. Heterogeneity statistics: Cochrane’s Q = 2.3 (7 degrees of freedom; $P = 0.945$), $I^2 = 0.0\%$ and $\tau^2 = 0.0$.

Pandit et al. reports conflicting detection ratios of 70.0% versus 80.0% for their overall SLN detection on lymphoscintigraphy. The most conservative estimate was selected (26).
### FIGURE 5: Forest plot of the bilateral SLN detection (≥1 SLN detected in each hemipelvis) on SPECT-CT compared to LSG. Heterogeneity statistics: Cochrane’s Q = 0.1 (2 degrees of freedom; \( P = 0.976 \)), \( I^2 = 0.0\% \) and \( \tau^2 = 0.0 \).

Belhocine et al. reports bilateral SLN detection in 71.4% (\( n = 5/7 \)) without specifying the imaging modality by which this was achieved and was therefore excluded from this sub-analysis (28).
FIGURE 6: Forest plot of the number of SLN’s detected on SPECT-CT compared to planar lymphoscintigraphy. Heterogeneity statistics: Cochrane’s Q = 7.7 (4 degrees of freedom; \( P = 0.105 \)), \( I^2 = 47.8\% \) and \( \tau^2 = 0.0 \).
### TABLE 1: Characteristics of studies included in the meta-analysis

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Data-collection</th>
<th>Sample size</th>
<th>FIGO stages</th>
<th>Tracer and dosing</th>
<th>Tracer injection technique</th>
<th>SPECT-CT</th>
<th>LSG</th>
<th>Moment of imaging</th>
<th>Intraoperative SLN procedure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pandit 2010</td>
<td>Prospective cohort</td>
<td>Paired</td>
<td>10</td>
<td>Not specified</td>
<td>37-144 MBq Tc-99m-sulfur colloid</td>
<td>Two quadrant</td>
<td>SPECT and low dose CT, &lt;60 min post-injection</td>
<td>Preoperative day or day of surgery</td>
<td>Laparotomy or laparoscopy (with blue dye)</td>
<td></td>
</tr>
<tr>
<td>Diaz 2011</td>
<td>Prospective cohort</td>
<td>Paired</td>
<td>22</td>
<td>IB1 – IIA</td>
<td>144 MBq Tc-99m-albumin nanocolloid</td>
<td>Four quadrant</td>
<td>SPECT and CT of unknown dosing, 120-240 min post-injection</td>
<td>Preoperative day</td>
<td>Laparotomy or laparoscopy (with blue dye)</td>
<td></td>
</tr>
<tr>
<td>Kraft 2012</td>
<td>Retrospective cohort</td>
<td>Paired</td>
<td>36</td>
<td>IA1 – II</td>
<td>40 MBq Tc-99m-nanocolloid</td>
<td>Four quadrant</td>
<td>SPECT and low dose CT, directly after LSG</td>
<td>Anterior and posterior static, 25-60 min post-injection</td>
<td>Day of surgery</td>
<td>Not specified (with blue dye)</td>
</tr>
<tr>
<td>Buda 2012</td>
<td>Retrospective cohort</td>
<td>Paired</td>
<td>10</td>
<td>IA2 – IB1</td>
<td>30-44 MBq Tc-99m-albumin nanocolloid</td>
<td>Four quadrant</td>
<td>SPECT and low dose CT, 180 min post-injection</td>
<td>Dynamic and anterior static, directly and 180 min post-injection</td>
<td>Preoperative day or day of surgery</td>
<td>Laparotomy or laparoscopy (with blue dye)</td>
</tr>
<tr>
<td>Hoogendam 2013</td>
<td>Retrospective cohort</td>
<td>Parallel</td>
<td>33 vs 29</td>
<td>IA1 – IIA</td>
<td>220-290 MBq Tc-99m-nanocolloid</td>
<td>Four quadrant</td>
<td>SPECT and low dose CT, 90 min post-injection</td>
<td>Dynamic and 4 directional static, 10-90 min post-injection</td>
<td>Preoperative day</td>
<td>Robot assisted laparoscopy (with blue dye)</td>
</tr>
<tr>
<td>Belhocine 2013</td>
<td>Prospective cohort</td>
<td>Paired</td>
<td>7</td>
<td>IA – IB1</td>
<td>37 MBq Tc-99m-cysteine rhenium colloid</td>
<td>Two to four quadrant</td>
<td>SPECT and low dose CT, directly after LSG</td>
<td>Dynamic and 4 directional static, timing not specified</td>
<td>Day of surgery</td>
<td>Laparotomy or laparoscopy (with blue dye)</td>
</tr>
<tr>
<td>Bournard 2013</td>
<td>Retrospective cohort</td>
<td>Paired</td>
<td>42</td>
<td>IA1 – IIA</td>
<td>60-120 MBq Tc-99m-sulfur rhenium colloid</td>
<td>Four quadrant</td>
<td>SPECT and low dose CT, 60-120 min post-injection</td>
<td>Anterior static, 60-120 min post-injection</td>
<td>Preoperative day or day of surgery</td>
<td>Laparoscopy (with blue dye)</td>
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<tr>
<td>Klapdor 2014</td>
<td>Prospective cohort</td>
<td>Paired</td>
<td>51</td>
<td>IA1 – IIIA</td>
<td>10 MBq Tc-99m-nanocolloid</td>
<td>Four quadrant</td>
<td>No details specified, 30 min post-injection</td>
<td>No details specified, 30 min post-injection</td>
<td>Day of surgery</td>
<td>Laparotomy or laparoscopy (with blue dye)</td>
</tr>
</tbody>
</table>

**TABLE 1:** FIGO: International Federation of Gynecology and Obstetrics, SPECT-CT: single-photon emission computed tomography and regular computed tomography, LSG: lymphoscintigraphy, SLN: sentinel lymph node, MBq: megabecquerel, Tc-99m: $^{99m}$Technetium, min: minutes, vs: versus.