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Review

Sentinel node biopsy for lymph nodal staging of uterine cervix cancer: A systematic review and meta-analysis of the pertinent literature

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Abstract

Background: We reviewed the available literature on the accuracy of sentinel node mapping in the lymph nodal staging of uterine cervical cancers.
Methods: MEDLINE and Scopus were searched by using "sentinel AND (cervix OR cervical)" as key words. Studies evaluating the accuracy of sentinel node mapping in the lymph nodal staging of uterine cervical cancers were included if enough data could be extracted for calculation of detection rate and/or sensitivity.
Results: Sixty-seven studies were included in the systematic review. Pooled detection rate was 89.2% [95% CI: 86.3–91.6]. Pooled sensitivity was 90% [95% CI: 88–92]. Sentinel node detection rate and sensitivity were related to mapping method (blue dye, radiotracer, or both) and history of pre-operative neoadjuvant chemotherapy. Sensitivity was higher in patients with bilaterally detected pelvic sentinel nodes compared to those with unilateral sentinel nodes. Lymphatic mapping could identify sentinel nodes outside the routine lymphadenectomy limits.
Conclusion: Sentinel node mapping is an accurate method for the assessment of lymph nodal involvement in uterine cervical cancers. Selection of a population with small tumor size and lower stage will ensure the lowest false negative rate. Lymphatic mapping can also detect sentinel nodes outside of routine lymphadenectomy areas providing additional histological information which can improve the staging. Further studies are needed to explore the impact of sentinel node mapping in fertility sparing surgery and in patients with history of neoadjuvant chemotherapy.

Keywords: Sentinel node; Lymphatic mapping; Meta-analysis; Evidence based; Cervical cancer

Introduction

In surgically treated patients with early cervical cancer, lymph nodal status is the most important predictor of disease free and overall survival.[1–3] Pelvic lymphadenectomy has long been considered the standard procedure of lymph nodal staging in early cervical cancer. However, complete pelvic lymph node dissection is associated with several complications and morbidities such as lymphedema, lymphocele formation, prolonged surgical duration, etc.[4] On the other hand, prevalence of lymph nodal involvement in early stage cervical cancer is estimated to be approximately 15–20%. This means that the majority of

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early cervical cancer patients who undergo pelvic lymph node dissection will not gain any benefit from the procedure whilst being subjected to considerable complications and morbidities.[5]

The concept of the sentinel node as the first node(s) receiving lymphatic drainage of a tumor has attracted the attention of surgical oncologists since its introduction two decades ago. As the sentinel lymph node is the first site of tumor metastasis, pathological condition of sentinel node should reflect metastatic disease in the other lymph nodes of the basin (non-sentinel lymph nodes). Therefore, lymphatic mapping and sentinel lymph node biopsy can make full regional lymphadenectomy unnecessary in a large number of patients.[6]

In gynecological cancers, sentinel node mapping has long been used with favorable results.[7,8] Several multicenter studies have also been published on sentinel node mapping in cervical cancer including SENTICOL,[9] AGO,[10] and an international multicenter cohort study.[11]

Despite an exhaustive body of literature regarding sentinel node mapping in cervical cancer, no comprehensive systematic review has been published over recent years to cover this topic. Factors associated with sentinel node detection rate and the sensitivity of this procedure in cervical cancer have not before been addressed in detail. In the current study, we reviewed the available literature regarding sentinel node mapping in cancers of the uterine cervix, presenting the results in systematic review and meta-analysis formats.

Material and methods

Search strategy

MEDLINE and Scopus databases were searched by two authors independently by using "sentinel AND (cervix OR cervical)" as key words (last search on June 2014) without any language or time restriction on the retrieved publications. The reference lists of relevant studies were also searched in order to find possible missing articles.

Inclusion criteria

All studies evaluating sentinel node mapping in cervical cancers were included if enough data could be collected for calculation of identification (detection) rate and/or sensitivity. For sensitivity, only studies validated by pelvic with/without para-aortic lymph node dissection were included. Case reports (studies with fewer than 5 patients), editorials, review articles, and meeting abstracts were excluded.

Two authors reviewed the retrieved articles independently and any discrepancy was resolved by the third author's opinion. Duplicate publications were also discussed and only the most recent reports with more complete data were used for further analysis.

Data abstraction

Data abstraction was performed by two authors independently. Data on first authors, publication year, mapping method, patient characteristics, quality of the study (according to Oxford Center for Evidence Based Medicine diagnostic studies checklist[12]), detection rate and/or sensitivity (if available for different subgroups of patients according to tumor size, history of neoadjuvant chemotherapy, history of conization, or tumor stage) were recorded.

If possible, sensitivity was calculated in patients with unilateral and bilateral pelvic sentinel node identification.

Statistical analysis

PRISMA recommendations were followed in the current systematic review (www.prisma-statement.org). The DerSimonian and Laird method (random effects model) was applied for statistical pooling of detection rate and sensitivity.[13] The results were shown graphically as forest plots. Pooled results are reported with 95% confidence intervals (95% CI). Cochran's Q test was used for heterogeneity evaluation ($p < 0.05$ was considered statistically significant). I^2 index was used to quantify heterogeneity, analyzing how much of the variance between included studies was real and not due to sampling error.

Funnel plots, Egger's regression intercept,[14] and Duval and Tweedie's "trim and fill" method[15] were used for publication bias evaluation.

Meta-DiSc (version 1.4)[16] and Comprehensive Meta-analysis (CMA version 2) were used for statistical analyses.

Results

A PRISMA flowchart of the study is shown in Fig. 1. Overall, 67 articles were included in our systematic review.[17–83] Table 1 shows characteristics of the included studies as well as their quality assessment.

In addition to the studies included in our systematic review, 36 duplicate studies had additional pertinent information. Although these studies had duplicate information regarding detection rate or sensitivity, other unique relevant information could be extracted from them. These studies were not included in the main analyses (detection rate and sensitivity pooling) but their relevant data were used for subgroup analyses of our systematic review. Supplementary file 1 shows these duplicate studies plus the relevant data we used from each study.

Detection rate

Pooled detection rate of sentinel node mapping was 89.2% [95% CI: 86.3–91.6], Cochran Q value = 345 ($p < 0.000001$), and I^2 index = 80%. Forest plot of detection rate pooling is shown in Fig. 2. Funnel plot of detection