Review

Sentinel Lymph Node Staging in Early-Stage Cervical Cancer: A Comprehensive Review

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Sentinel lymph node staging in early-stage cervical cancer: a comprehensive review

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Abstract: Cervical cancer (CC) continues to be a significant global public health concern, even with preventive measures in place. In women with early-stage CC, the status of lymph nodes is of paramount importance, not only for final prognosis but also for determining the best therapeutic strategy. According to main international guidelines, pelvic full lymphadenectomy (PLND) is recommended for lymph node staging. However, in these early stages of CC, Sentinel lymph node biopsy (SLNB) has emerged as a precise technique for evaluating lymph node involvement, improving its morbidity profile. We performed a literature review through PubMed articles about progress on the application of SLNB in women with early-stage CC focusing on the comparison with PET/CT and PLND in terms of oncological outcomes and diagnostic accuracy. While the superiority of SLNB is clear compared to radiologic modalities, it demonstrates no clear oncologic inferiority over PLND, given the higher detection rate of positive lymph nodes and predominance of no lymph node recurrences. However, due to a lack of prospective evidence, particularly concerning long-term oncological safety, SLNB is not the current gold standard. With careful patient selection and adherence to straightforward protocols, a low false negative rate can be ensured. The aim of the ongoing prospective trials is to address these issues.

Keywords: Lymph Nodes; Lymphadenectomy; Diagnostic Imaging; Survival Analysis

INTRODUCTION

Cervical cancer (CC) remains a significant health concern, as it still ranks as the second most common cancer among women and the third leading cause of cancer-related deaths in females [1]. The burden of this cancer is particularly high in developing countries due to limited screening programs. Strategies to mitigate its impact include patient education, changes in sexual behavior, and the introduction of HPV vaccination, especially considering that over 54% of patients diagnosed are under 50 years of age [2]. Oncologic outcomes of cervical cancer are widely depended on stage at diagnosis as overall survival rates are over 85-90 % for early-stage disease, in contrary with the poor results observed for high-stage disease [3].

In the context of early-stage CC, the assessment of lymph node status holds utmost significance, as it plays a pivotal role in selecting the most appropriate treatment approach and significantly influences prognostic outcomes. The presence of lymph node metastasis significantly affects prognosis, with a drop in five-year Disease-Free Survival (DFS) from

88% to 57% [4]. According to European and American guidelines, Sentinel lymph node biopsy (SLNB) without additional pelvic lymphadenectomy (PLND) is acceptable for FIGO IA1 with lymphovascular space invasion (LVSI) and IA2 stages. However, for IB1 stage, SLNB alone is not recommended without systematic PLND for lymph node staging except in the context of prospective clinical trials (as per ESGO/ESTRO/ESP guidelines), although the 2019 NCCN guidelines suggest considering SLNB biopsy for these cases [5,6]. PLND is mainly performed for staging reasons as it may tailor the decision to administer adjuvant radiotherapy, thereby achieving effective loco-regional disease control.

The size of metastatic lymph nodes is typically quite small, with dimensions smaller than 2 mm observed in 22% to 60% of patients with positive nodes (7-9). Since most metastatic nodes measure less than 10 mm (10), both pelvic MRI and PET-CT tend to exhibit limited sensitivity and struggle to detect patients with positive lymph nodes (11). However, the percentage of positive lymph node involvement in primary CC is estimated to be 15-20%, leading to 80% of patients undergoing PLND without benefit and resulting in associated complications, including an extended operative duration, increased blood loss, postoperative infections, the development of lymphocysts, and the occurrence of lower limb lymphedema. [9,12,13]. Even though PLND is performed, it's worth noting that 10% to 15% of patients initially categorized as N0 (lymph node-negative) may still encounter cancer recurrences in the lymphatic region. This occurrence can be attributed to the presence of unconventional or atypical lymphatic drainage pathways [14.].

In recent years, there has been a shift towards tailoring treatment, with increasing interest in less radical surgery for low-risk pathologic features. Sentinel node biopsy (SLNB) has been proposed to detect nodal invasion due to its acceptable effectiveness and improved morbidity profile [13]. Mapping studies have demonstrated that roughly 10% of sentinel nodes are situated in regions not universally encompassed within a conventional pelvic lymphadenectomy [15]. In the FIRES trial, it was observed that 17% of patients with node-positive disease exhibited disease that extended beyond the typical or traditional locations, with the most common sites of involvement being the presacral space, internal iliac region, and parametrial regions [16].

The main objective of this review is to summarize current evidence on whether surgical staging with sentinel node or lymphadenectomy or imaging examinations is the optimal way to assess nodal status for early-stage cervical cancer patients, both in terms of diagnostic accuracy and final survival outcomes.

MATERIALS AND METHODS

This is a comprehensive review of literature aiming to summarize current evidence regarding the diagnostic accuracy and survival outcomes of SLNB versus radiographic evaluation of nodal status and systematic lymphadenectomy in early-stage CC.

Searching strategy

MEDLINE, UpToDate and PubMed electronic databases were searched up to July 2023 for relevant published articles discussing the application of surgical and imaging nodal staging in early-stage CC. Searching strategy was formed by combining the following MeSH terms and keywords “cervical cancer”, “Sentinel Lymph Node”, “Sentinel Lymph Node Biopsy”, “lymphadenectomy”, “surgical staging” and “imaging staging”.

Eligibility criteria

Articles comparing SLNB staging with PLND and/or imaging staging that reported on survival outcomes of patients were mainly set in the scope of this present comprehensive review. Furthermore, studies indicating diagnostic accuracy in terms of false-positive, false negative rates (FPR, FNR), sensitivity and specificity regarding all staging modalities based on final pathology outcome were also eligible for inclusion. Additionally, studies addressing the impact of low-volume disease (micrometastases and isolated tumor cells)

in the sentinel node to the survival outcomes or recurrence risk were also considered eligible. Regarding types of studies, prospective and retrospective randomized control trials (RCTs), cohort studies, case-control and case series studies, as well as systematic review articles and meta-analyses were considered eligible to report, while case reports and published guidelines were also evaluated and reviewed for their content in order to extract relative data and information. References of included studies would additionally be cross-referenced to find additional publications eligible for inclusion in our review.

Exclusion criteria

There was no exclusion criterion regarding the type of surgery (laparotomy, laparoscopy, robotic surgery) as well as regarding the imaging modality used (MRI, CT or PET-CT,). Studies would be excluded in case lacked information on case numbers, FIGO stage, lymph node metastasis and injection techniques (blue dye, radiocolloid tracers, both or indocyanine green). Animal studies, abstract- or protocol-only publications, and video reports would also be excluded. Studies of patients with non-cervical malignancies, or studies where radiologic-assisted biopsies were used to assess nodal status were also excluded. Finally, non-English articles, published abstracts without full-text manuscripts were all excluded from this review.

Study selection process and results organization

All studies identified from the search strategy were imported in a reference management software (Zotero) for elimination of duplicate data and further assessment. All identified studies were screened by two of the authors based on their full-text manuscript while articles irrelevant to the objective of the present study were excluded. The eligibility of retrieved articles was independently determined by 2 reviewers (S.P., A.A.). Finally, at the end of evaluation process, the included articles were divided into 3 main categories: a) articles comparing staging SLNB with imaging staging b) articles comparing staging SLNB with systematic PLND and c) articles reporting on oncological outcomes in patients with low-volume disease staged with SLNB. Moreover, the included articles in each category were additionally subdivided based on type of study in the following four categories: a) prospective cohorts b) RCTs c) retrospective cohort studies and case series and d) systematic reviews and meta-analyses articles.

RESULTS

Study selection

Electronic searches and complementary hand-searching retrieved 433 articles. After review of titles and abstracts, 390 articles were excluded and 43 studies were assessed for eligibility based on their full-text manuscript and. There were finally 10 articles meeting the inclusion criteria. Specifically, 2 retrospective observational studies [17,18], 1 prospective [19] and 1 systematic review and meta-analysis [20] reported the higher diagnostic accuracy of SLNB vs imaging staging. Regarding the survival outcomes of SLNB vs PLNB, no clear inferiority of the former was demonstrated by a systematic review and meta-analysis, while 1 systematic review [13] was retrieved that showed the high diagnostic accuracy in terms of negative predictive value (NPV) and sensitivity. Additionally, regarding the impact of low-volume disease, 2 retrospective cohort studies showed conflicting results, with micrometastases (MIC) being associated with increased and decreased survival rates [22,23]. Another retrospective case-control indicated MIC as an independent risk factor for recurrence [24]. Lastly, 1 prospective cohort study demonstrated no impact on survival outcomes [3].

DISCUSSION

Current evidence suggests that surgical staging is the gold standard method for nodal evaluation in early-stage CC, while systematic pelvic lymphadenectomy has been the standard of care in the nodal status assessment.

Sentinel node vs imaging staging

In the context of imaging management, magnetic resonance imaging (MRI) has consistently been regarded as the optimal choice for the primary tumor assessment [25,26]. Conversely, when it comes to evaluating lymph node involvement, positron emission tomography (PET) has emerged as the preferred option [20]. From the 10 studies included in this review, 4 demonstrated the superiority of diagnostic accuracy of SLNB vs PET/CT in early-stage patients.

Specifically, according to 2 retrospective observational studies and 1 prospective multicenter study, NPV, sensitivity and specificity ranged between 97-100%, 75-96,3% and 94-100% respectively for the SLNB group. On the other hand, for the imaging group NPV, sensitivity and specificity ranged between 74-88%, 8-68% and 84-98% respectively [17-19]. In concordance with these data, but also displaying an even more accountable level of evidence, a systematic review and meta-analysis of 72 primary studies involving 5042 patients, Selman et al. [20] demonstrated that SNLB had a pooled positive likelihood ratio of 40.8 and a pooled negative likelihood ratio of 0.18 for the determination of lymph node status. For PET/CT the corresponding ratios were significantly lower (15.3 and 0.27). Furthermore, PET/CT offers superior sensitivity and specificity rates (73% and 98%, respectively) in comparison with MRI, which yields sensitivity and specificity rates of 56% and 93%, while CT shows rates of 58% and 92%.

In conclusion, SNLB emerged as tool with greater accuracy in determining lymph node status among women with primary CC in comparison with all other advanced imaging modalities, from which, PET is regarded as the optimal choice. Table 1 presents overview of published studies reporting on the diagnostic accuracy of SLNB and FDG-PET/CT.

Table 1. Overview of published studies reporting on the diagnostic accuracy of SLNB and FDG-PET/CT nodal status evaluation in early-stage cervical cancer.

Title	Type of study	Number of patients (n)	Negative predictive value imaging vs surgical (95% CI)	Positive predictive value imaging vs surgical (95% CI)	Sensitivity imaging vs surgical (95% CI)	Specificity imaging vs surgical (95% CI)	Pooled positive likelihood ratio imaging vs surgical (95% CI)	Pooled negative likelihood ratio imaging vs surgical (95% CI)
Papadia et al.[17]	Retrospective observational study	n=60	88% (0.76–0.94) **vs** 97% (0.88–0.99)	61% (0.47–0.73) **vs** 100% (0.91–0.1)	68% (0.55–0.79) **vs** 93% (0.82–0.98)	84% (0.71–0.91) **vs** 100% (0.91–0.1)	NR	NR
Tanaka et al.[18]	Retrospective observational study	n=48	88.2% **vs** 100%	NR	8.3% **vs** 75.0%	97.6% **vs** 94.0%	NR	NR
Sponholtz et al. [19]	Prospective multicenter study	n=245	73.9% (63.4–82.7) **vs** 98.7% (93.0–100)	**-imaging only** 26.7% (7.8–55.1)	14.8% (4.2–33.7%) **vs** 96.3% (81.0–99.9%)	**-imaging only** 85.5% (75.6–92.5%)	NR	NR

Selman et al. [20]	Systematic review and metanalysis	n=5042	NR	NR	74.7% (63.3–84.0) **vs** 91.4% (87.1–94.6)	97.6% (95.4–98.9) **vs** 100% (99.6–100)	15.3 (7.9–29.6) **vs** 40.8 (24.6–67.6)	0.27 (0.11–0.66) **Vs** 0.18 (0.14–0.24)

Sentinel node vs systematic lymphadenectomy

The use of SLN detection has gained popularity on the concept that once lymph node involvement is confirmed, extensive lymph node dissection (PLND) does not offer a significant prognostic advantage, with the focus shifting towards adjuvant treatment. Thus, the central question is whether a complete lymph node dissection may have an additional therapeutic and survival impact.

A systematic review and meta-analysis was conducted to address this question including 4 studies, of which one was prospective randomized multicentric study, while the remaining three were retrospective cohorts [21]. The meta-analysis encompassed 1,952 patients of FIGO Stage IA1 to IIA, with 383 undergoing exclusively SLNB and 1,569 undergoing PLND. Over a 4.5-year period, DFS rates varied between 85.1% and 93.8% for the SLN group and between 80.4% and 93.1% for the PLND group. There was no significant difference between these two groups (OR 1.04, 95% CI 0.66–1.66, p = 0.85). In contrast, recurrence rate ranged from 3.6% to 11.5% for the SLN group, while the range was narrower, namely between 6.4% to 7.3% for the PLND group. Unfortunately, only three out of the four comparative studies provided data on OS, involving 302 patients in the SLN group and 1,351 in the PLND group. Interestingly, the analysis did not reveal any significant difference in OS benefits between the SLN and PLND groups.

Regarding the detection superiority in nodal staging, SLN mapping has displayed considerable accuracy. In retrospective series, the incidence of false-negative findings has been documented at less than 1% and high sensitivity and NPV percentages of 96.4% (95% CI 79.8%–99.8%) and of 99.3% (95% CI 95.6%–100%) respectively [27,28]. Furthermore, a recent systematic-review focusing on early-stage CC revealed an SLN metastasis prevalence of 21%. The sensitivity of SLN mapping in this context was notably high at 94%, accompanied by a NPV ranging from 91% to 100%. Impressively, the FNR was found to be as low as 1.5% [13]. These findings underline the efficacy and reliability of SLN mapping as an integral component in the management of early-stage CC.

Diagnostic accuracy of SLNB-impact of low-volume disease

The National Comprehensive Cancer Network (NCCN) guidelines recommend ultrastaging of sentinel lymph nodes (SLNs) [6]. Ultrastaging involves meticulously examining SLNs with serial sectioning and immunohistochemistry for cytokeratin, particularly on hematoxylin and eosin (H&E) negative slides. This approach detects low-volume metastases that conventional lymphadenectomy might miss. Metastatic lymph nodes are categorized by size: macrometastases (MAC) (>2 mm), micrometastases (MICs) (0.2-2 mm), and isolated tumor cells (ITC, <0.2 mm) as defined by American joint committee on cancer (AJCC) [29].

Routine lymphadenectomy typically does not undergo ultrastaging. When SLN ultrastaging is employed, it increases the likelihood of diagnosing stage IIIC disease due to the presence of MICs and isolated tumor cells [30]. Consequently, patients undergoing SLNB are more likely to be identified with metastasis and receive adjuvant therapy compared to those undergoing complete lymphadenectomy. A debate surrounds the significance of these low-volume metastases in SLN biopsy. They may either improve traditional staging by identifying previously overlooked disease or introduce "false positive" results if these small metastatic foci are clinically inconsequential.

While the clinical relevance of MAC and the indication of adjuvant treatment is clear, the impact of MICs and ITCs remains uncertain. Multiple retrospective studies have

explored the impact of low-volume metastases, specifically MIC and ITCs, in cervical cancer, demonstrating mixed results. The largest among them was conducted by Cibula et al. [22] involving 645 patient and revealed an association between the presence of MAC or MIC and reduced OS. Additionally, Marchiolé et al. [24] identified MIC as an independent risk factor for recurrence. However, Zaal et al. [23.] reported that when MIC was present, OS improved with the dissection of more than 16 lymph nodes. Notably, ITCs did not exhibit prognostic relevance in their study.

Comparing these studies is challenging due to variations in methodology, particularly in ultrastaging techniques and patient selection. In an attempt to address these discrepancies, Guani et al. [3] conducted a prospective study assessing recurrence and survival in early-stage CC patients with MIC or ITCs. Surprisingly, they found no impact of MIC or ITCs on progression-free survival (PFS). However, the authors acknowledged that although the study was prospective, its relatively small sample size (139 patients) limited its ability to provide definitive answers. Small-scale studies suggest that it still remains a question whether low-volume disease may have limited clinical impact since long-term data is lacking. In conclusion, further research is necessary to establish the true clinical significance of low-volume metastases in cervical cancer progression.

Finally, there are currently three active prospective clinical trials being performed in order to evaluate the oncological consequences of SLNB in early-stage CC. These trials include the SENTIX trial (NCT02494063) [31] a prospective multicenter observational study focused on assessing the 2-year recurrence rate following solitary SLNB. The PHENIX trial (NCT02642471) [32] is a multi-center randomized controlled trial designed to compare oncological outcomes, with a specific focus on patients with SLN metastasis (evaluating 2-year DFS) and those without it (evaluating 3-year DFS). Lastly, the SENTICOL III trial [33] is a prospective multicenter randomized study with the primary aim of comparing 3-year DFS rates between two approaches: SLNB as a standalone procedure and SLNB in conjunction with PLND. These trials collectively contribute to advancing our understanding of SLN biopsy's role in managing early-stage CC.

Limitations

The present article represents only a critical review trying in a systematic way to evaluate current evidence in this issue. However, retrieval of studies and interpretation of results rather lead to specific conclusions standing firmly in favor of safety and effectiveness of SLNB in early-stage CC cases. To our knowledge, this is potentially the first review article trying and potentially achieving to map all heterogeneous results mentioned in an issue for which profound methodological difficulties have not yet permitted the performance of a large RCT.

Main conclusions

The present critical review demonstrated that majority of published evidence firmly stands in favor of safety and effectiveness of SLNB over imaging staging, since SNL mapping presented higher sensitivity and specificity rate compared with PET/CT. Furthermore, SLNB has emerged as a surgical strategy with comparable accuracy and reduced complications compared with full lymphadenectomy. However, there is no compelling evidence to abandon PLND in early-stage CC, and major international guidelines still recommend it. Further research based on large multicenter prospective RCT could potentially lead to definitive conclusions.

Supplementary Materials: Table S1: Overview of published studies reporting on the diagnostic accuracy of SLNB and FDG-PET/CT nodal status evaluation in early-stage cervical cancer.

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