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Clinical management of early-stage cervical cancer: The role of sentinel lymph node biopsy in tumors ≤2 cm

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ABSTRACT

Objective: To evaluate the experience with sentinel lymph node (SLN) biopsy in patients with early-stage cervical cancer at our hospital, and to analyze factors influencing the rate of false negatives.
Study design: This study was carried out at the Vall d'Hebron Hospital (Barcelona, Spain) between September 2000 and October 2016. All patients underwent SLN biopsy and systematic and bilateral pelvic lymphadenectomy, followed by radical hysterectomy. SLNs were analyzed by the pathologist by staining with hematoxylin-eosin and immunohistochemistry.
Results: Patients (N = 128) had been diagnosed with early-stage cervical cancer (FIGO-2009 stages 1A2, IB1, and IIA1). The combined SLN detection rate (99-technecium and a blue dye) was 98.4%, bilateral in 76% of the patients. Positive SLNs were found in 19 patients (14.8%). Sensitivity of detection was 79.2% (CI95, 57.9–92.9), false negative rate 20.8% (CI95, 7.1–42.2), and negative predictive value 95.4% (CI95, 89.6–98.5). False negative cases were observed in 5 patients with tumors >2 cm and presenting lymphovascular space invasion. Micrometastases were detected during SLN ultrastaging in 3 patients (2.3%). The median follow-up was 8.24 years and the 5-year overall survival (OS) was 88.4% (CI95, 80.9–93.1).
Conclusion: SLN mapping and biopsy in early-stage cervical cancer is feasible and has high sensitivity to detect patients with initial metastases. The risk of false negatives could be lower in certain groups of patients, such as those with tumors ≤2 cm and no lymphovascular space invasion, but future studies will be required to test this hypothesis.

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Introduction

Sentinel lymph node (SLN) biopsy is a widely-used technique in patients with early-stage cervical cancer to avoid the morbidity associated with pelvic lymphadenectomy [1,2]. Most women diagnosed with cervical cancer (>80%) do not present lymph node involvement and therefore general pelvic lymph node removal in these patients would have no benefit. The morbidity related to pelvic lymphadenectomy includes life-long lymphedema in the lower abdomen and lower extremities, resulting in limb swelling, feelings of heaviness, tightness, and pain.

Since tumor cells originating at the cervix follow a predictable path of dissemination in the lymph nodes, detailed pathological analysis of the first node in which the tumor drains allows a high degree of certainty regarding metastases [3]. SLN status is one of the most important prognostic factors for the need for adjuvant treatment in cervical cancer [4]. SLN biopsy allows for the identification of micrometastases (MIC) and isolated tumor cells (ITCs) in lymph nodes through ultrastaging. When a metastasis is detected, radical hysterectomy can be abandoned and instead the patient can be given only curative primary chemoradiotherapy, thus avoiding the morbidity associated with two treatments [5]. Additionally, another advantage of SLN biopsy is that it allows identification of aberrant lymphatic drainage sites outside the

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standard dissection boundaries [6]. Since up to 21% of the presence of pelvic metastases is accompanied by aortic metastases, the patient can also undergo pelvic and aortic staging lymphadenectomy if necessary [7].

The current NCCN guidelines include SLN mapping in endometrial, cervical, and vulvar cancer to assess lymph node involvement. According to the NCCN, SLN mapping is adequate to detect lymph node involvement, especially in patients with tumors ≤2 cm, and contributes to the reduction in morbidity associated with the treatment procedures [8]. Similarly, the ESGO/ESTRO/SP guidelines recommend SLN biopsy as the primary approach before surgery of early-stage cervical cancer [5]. However, reduction of false negative rates is still a priority. Cervical cancer recurrence can take long to be diagnosed and the morbidity and mortality is very high in young patients. Additionally, there is uncertainty as of the relative risk of micrometastases in other pelvic lymph nodes in SLN-negative patients [9].

The objective of this study was to describe our results of SLN detection and biopsy since 2000–2016, as well as to analyze the factors that influenced the false negative rate, in order to assess the groups of patients in which the SLN biopsy technique can be implemented safely.

Methods

Patient selection

This study was carried out at the Gynecology Service of the Vall d'Hebron Hospital (Barcelona, Spain) from September 2000 to October 2016. The study (IRB: PR[AMI]53/2005) was approved by the institutional review board and all patients gave their written informed consent. This study was carried out following the ethical principles established in the current revised version of the Declaration of Helsinki (Ethical Principles for Medical Research in Humans, Seoul 2008). The inclusion criteria were: patients with histologically-confirmed early-stage cervical cancer (International Federation of Gynecology and Obstetrics [FIGO 2009] stages 1A2, IB1, and IIA1) [10], tumor size of ≤4 cm measured clinically and by MRI, and absence of enlarged lymph nodes in preoperative imaging tests (MRI or PET-CT).

SLN mapping procedures

SLN detection followed previously-described methodologies [11–13]. We used a combination of two detection techniques: 99-technecium (Tc99, Albu-res®, Pharmaceutical Nycomed Amersham, Braunschweig, Germany) and isosulfan blue (Lymphazurin 1%, US Surgical Co., Norwalk, CT, USA). However, after reports of anaphylaxis caused by isosulfan blue [14], we changed to methylene blue in the same dilution.

To guide the localization of the SLN we used preoperative lymphoscintigraphy, the auditory signal secondary to the level of Tc99 radiation, and visualization of the blue-stained lymph node. Since 2007 we used SPECT-CT, as previously described [15]. To identify the Tc99-positive SLN, a polar probe was used intraoperatively during manual laparotomy surgery (Europrobe®) or, in laparoscopic surgery, a probe adapted to the laparoscopic surgical field (Navigator®, Tyco-Mallinckrodt) at the level of the retroperitoneal pelvic or para-aortic lymph nodes.

We did not analyze the SLN intra-operatively systematically because there is no validated technique and the decision was left to the surgeon in cases of suspected metastasis.

Surgery

Systematic and bilateral pelvic lymphadenectomy was completed in all cases by 4 surgeons. The lymph node extraction was always carried out in a bag (Endo-Catch Gold 10 mm, AutoSuture, Norwalk, Connecticut, USA). Paraaortic lymphadenectomy was performed in cases in which the lymphoscintigraphy guided the location of the SLN at this level and if there was suspicion of metastasis in pelvic nodes. Radical B1 hysterectomy followed in cases of tumors ≤2 cm and type C1 in cases of tumors >2 cm [16].

Pathologic exam

All SLNs were inspected and analyzed thoroughly by experienced gynecopathologists, who processed them by perpendicular sectioning (0.2 cm) and staining with hematoxylin-eosin. If the initial section was negative, all sections were prepared for immunohistochemical analysis with broad spectrum anti-cytokeratin AE1 and AE3. A frozen section was only done if required by the gynecologist-oncologist. Low-volume metastatic disease in lymphatic nodes was defined as micrometastases (MIC), in which the tumor size ranges from 0.2 to 2 mm; and isolated tumor cells (ITCs), in which microscopic clusters and single cells are <0.2 mm. If macrometastases or micrometastases were detected in any of the SLNs by pathologic ultrastaging after surgery, adjuvant therapy was recommended.

Definitions of study outcomes

The detection rate was defined as the proportion of patients with at least one SLN detected. The sensitivity was defined as the SLN-positive patients divided by all metastatic patients (true positive tests/all positive patients). The negative predictive value (NPV) was defined as the SLN-negative, non-metastatic, patients divided by all SLN-negative patients (true negative tests/true negative + false negative tests). The false negative rate was defined as SLN-negative, metastatic, patients divided by all metastatic patients (false negative tests/false negative + true positive tests) [17].

Statistical analysis

We used Student's *t*-test for the comparison of continuous or quantitative descriptive variables and the chi-square test to compare categorical or qualitative descriptive variables. Estimates of disease's time to progression and overall survival were made using the Kaplan and Meier model, calculated from the day of surgery until the date of death or recurrence or the last date of follow-up. The univariate comparison of the survival curves for two clinical factors was performed using the log-rank test. A value of $p < 0.05$ was considered as the level of statistical significance in all analyses. The analysis was carried out with SPSS 21 (IBM Corporation, 2012).

Results

Table 1 shows the characteristics of the patients (N = 128) included in this study.

SLN mapping with Tc99 allowed pre-surgical SLN mapping, which was combined with intraoperative detection of the most reactive and most intensely blue-stained lymph nodes. The combined techniques allowed SLN detection in 98.4% of patients (Table 2). The lack of drainage caused failure in Tc99 detection in 6 patients (5.5%) and of blue dye detection in 11 patients (8.59%). In 76% of the patients the detection of the SLN was bilateral.

After SLN mapping all patients underwent laparotomic, laparoscopic, or robotic radical hysterectomy, except for 5 patients who underwent staging pelvic lymphadenectomy and aortic lymphadenectomy because the SLN was macroscopically suspicious and histologically positive for metastasis, and 1 patient who

Table 1
Patient demographic and clinical characteristics (N = 128).

Age, years (mean ± SD)	48.4 ± 12.2
BMI, median (range)	25 (18-28)
Previous abdominal surgery, N (%)	31 (33)
Clinical stage[a], N (%)	
IA2	5 (4)
IB1 ≤ 2 cm	64 (50)
IB1 > 2 cm	50 (39)
IIA1	9 (7)
Lymphovascular space invasion, N (%)	49 (38)
Histological type, N (%)	
Squamous cell carcinoma	79 (61.7)
Adenocarcinoma	49 (38.3)

Abbreviations: BMI=body mass index; SD=standard deviation.
[a] According to FIGO classification of 2009 [10].

Table 2
Surgery and lymph node detection and resection data (N = 128).

Surgical approach for radical hysterectomy, N (%)		
Laparotomy		40 (31.8)
Laparoscopy		62 (50.9)
Robotic		20 (16.4)
SLN detection rate, N (%)		
Tc99		117 (94.3)
Blue dye		100 (90.0)
Combination		126 (98.4)
SLN per patient, median (range)		
Tc99		2.0 (2.0-3.0)
Isosulfan blue		2.0 (1.0-3.0)
Bilateral detection		76%
Resected lymph nodes per patient, median (range)		20 (17.0-26.5)
SLN location, N (%)		
Interiliac	Right	65 (23.7)
	Left	54 (19.7)
External iliac	Right	23 (8.4)
	Left	24 (8.8)
Obturator fossa	Right	38 (13.9)
	Left	26 (9.5)
Common iliac	Right	20 (7.3)
	Left	8 (3.0)
Internal iliac	Right	4 (1.5)
	Left	3 (1.1)
Parametric	Right	5 (1.8)
	Left	2 (0.7)
Lumbo-sacral fossa		2 (0.7)

Abbreviations: SLN=sentinel lymph node; Tc99=technecium-99.

underwent a trachelectomy. The median (interquartile range, IQR) number of resected lymph nodes per patient was 20 (17.0–26.5). The time (mean ± SD) of surgery was 265 ± 54 min and the average loss of blood per patient 333 ± 257 mL. Fifty-seven patients (44%) received adjuvant treatment.

As shown in Table 3, SLN were negative in 109 patients (85.16%) but metastatic lymph nodes at other locations of the lymphadenectomy were found in 5 patients (false negatives). Positive SLN were detected in 19 patients (14.84%). Therefore, the sensitivity of SLN biopsy was 79.2%, and the FNR 20.8%. All cases of false negative SLN were observed in patients with tumors >2 cm and presenting lymphovascular space invasion.

Low-volume disease was detected by immunohistochemistry as micrometastases (MIC) in the SLNs from 3 patients (2.3%).

With a median follow-up of 8.24 years, the 5-year overall survival (OS) was 88.4% (CI95, 80.9–93.1) and the disease-free survival 86.7% (CI95, 78.9–91.7). The OS of the groups with positive (N = 24) or negative (N = 104) SLN is shown in Fig. 1. The 5-year OS for patients with positive or negative SLN were 65.3% (CI95, 40.6–81.7) and 93.5% (CI95, 86.0–97.0), respectively. The higher number of positive metastatic lymph nodes or the presence of MIC increased the risk of death. Thus, compared with negative SLN, the hazard ratio in case of 1–5 positive lymph nodes, >5 lymph nodes, or confirmed MIC were 5.6 (CI95, 1.7–18.4), 17.4 (CI95, 3.4–88.5) and 29.4 (CI95, 3.1–283.5), respectively (p = 0.0003).

Table 3
SLN detection rates (N = 128).

SLN, N (%)	
- *Tumor ≤2 cm*	
True positive	4 (3.1)
False negative	0
- *Tumor >2 cm*	
True positive	15 (11.7)
False negative	5 (3.9)
Lymph nodes, N (%)	
Positive	24 (18.7)
Negative	104 (81.2)
Specificity, % (CI95)	100.0 (96.5-100.0)
Sensitivity, % (CI95)	79.2 (57.9-92.9)
FNR, % (CI95)	20.8 (7.1-42.2)
NPV, % (CI95)	95.4 (89.6-98.5)

Abbreviations: CI95=confidence interval 95%; FNR=false negative rate; NPV = negative predictive value; SLN = sentinel lymph node.

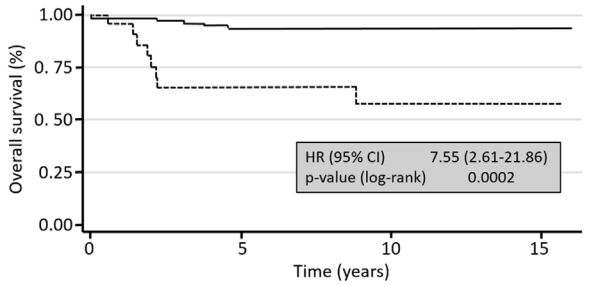

Fig. 1. Overall survival of the patients with positive (N = 24, dashed line) or negative (N = 104, continuous line) SLNs. HR = hazard ratio.

Comment

In this study we described our experience in the application of SLN mapping in patients with early-stage cervical cancer. We show that SLN biopsy alone identified 79.2% of patients with positive lymph nodes, with a specificity of 100% and a NPV of 95.4%. Our results show that the technique is feasible and viable as an alternative to systematic pelvic lymphadenectomy for most patients. However, our study also suggests that improved efforts should be placed in reducing the FNR. Possible approaches could include better patient selection, improvement of SLN mapping techniques, or bilateral ultrastaging in cases of unilateral drainage.

Numerous studies have shown that combined Tc99 and dye detection improves SLN mapping. In our study SLN detection reached 98.5% of patients when using the combined techniques. We currently use SPECT-CT to increase the detection rate and improve localization of SLN. In our experience, SPECT-CT imaging increases the number of SLN detected and improves the anatomic localization, allowing easier intra-operative detection with a gamma probe [15]. Also in recent years indocyanine green has also been used effectively in SLN mapping [18,19]. In the future, indocyanine green could be shown to be equivalent to the combination of Tc99 and blue dyes in terms of overall and bilateral detection rates in both cervical and endometrial cancers [20].

An algorithm designed to optimize accurate detection of lymph node metastases in the context of SLN mapping suggested that all suspicious nodes should be removed regardless of mapping, and that if no nodes were mapped on a hemi-pelvis, then a side-specific lymphadenectomy should be performed [21]. It is possible that in our study metastases escaped detection in those patients in which unilateral SLN biopsy was performed (24% of the cases). We estimate that if we had initially performed contralateral lymphadenectomy in these cases we could have reduced the FNR to 12.5%. A recent extensive review of the literature showed that, for early-stage cervical cancer patients (N = 1257) presenting tumor sizes <40 mm, bilateral negative SLNs after ultrastaging, and no other suspicious lymph nodes, the metastases risk is only 0.08% [22]. Bilateral ultrastaging of SLNs is a more reliable indicator of pelvic lymph node metastases than full pelvic lymphadenectomy, and also it is more cost-effective strategy with respect to 5-year progression-free survival and morbidity-free survival [23,24].

Ultrastaging of all SLNs in our study detected MIC in 2.3% of the patients; no ITCs were found. Although as a prognostic factor the presence of MIC could be equal to macrometastases [25], some studies suggest that they are a strong prognostic factor for disease recurrence, if compared to tumor size or lymphovascular space invasion [26]. A study of 17 patients showed that, after ultrastaging of all pelvic lymph nodes, there were no cases of positive non-SLN and negative SLN, therefore suggesting that SLN ultrastaging had 100% sensitivity for the presence of MIC [27]. Recently standardized protocols of ultrastaging have been proposed, which would allow more accurate comparisons between surgical approaches [9].

In our study we did not process any lymph nodes intraoperatively. Intraoperative SLN analysis is aimed towards the quick detection of patients with metastases, who in this case do not undergo radical hysterectomy and are derived directly to radiation or chemotherapy [5]. As our study was designed for the evaluation and validation of SLN biopsy, all our patients underwent systematic bilateral pelvic lymphadenectomy and radical hysterectomy, regardless of subsequent adjuvant treatment or not. However, a review of numerous studies have shown that generally intraoperative SLN assessment has poor sensitivity [4,9,28–30]. Future prospective studies will be necessary to determine the value of intraoperative lymph node assessment. In this regard, we are currently validating 'one-step nucleic acid amplification' (OSNA) as a quantitative molecular methodology for real-time detection of cytokeratin 19 (CK19) mRNA in our histological samples. OSNA has been successfully applied intraoperatively in lymph node metastasis detection in a variety of gynecological cancers, including early-stage cervical cancer [31,32].

SLN biopsy allows for the identification of women in which lymph nodes are affected, avoiding lymphadenectomy in all the rest. However, it is critical that the sensitivity of lymph node detection is high, as recurrent disease has a high mortality. In our study the 5 false negatives SLN occurred in patients with tumors >2 cm, who also presented lymphovascular space invasion. Although the low number of patients prevented reaching statistical significance, the observation suggests that these prognostic factors could be helpful in assessing the reliability of SLN biopsy in these types of patients. However, a recent study suggested that if tracer amounts are adjusted for larger tumor sizes, the bilateral detection rate and FNR of SLN biopsy is equal for tumors ≥4 cm [33]. Currently there are two ongoing studies analyzing the safety of SLN biopsy compared with systematic pelvic lymphadenectomy in early-stage cervical cancer: the SENTIX (ClinicalTrials.gov NCT02494063), and SENTICOL III (NCT03386734), expected to end in 2021 and 2026, respectively. It should be expected that these large-sale and long-term studies will shed light on the patients who could best benefit of SLN biopsy.

There are several limitations in our study. First, this was a single-center study, which could therefore be subject to bias derived from the technology and expertise available at our center. Second, we had too few patients to power conclusive results in some aspects of the study, and future randomized studies will be required to formally validate the technique. In this regard, Spain has one of the lowest incidence rates of cervical cancer in Europe, mostly due to effective screening and prevention programs [34]. And third, as the study took place over 16 years, inevitably there were changes of the methodologies used. For instance, we started using isosulfan blue as the blue dye for SLN detection, but this changed after realization that there was a risk of anaphylaxis. In contrast, one of the strengths of this work is that it reflects our long-term experience in these surgical techniques, and the long follow-up of a large number of patients.

In conclusion, our study of 128 patients with early-stage cervical cancer shows that the SLN biopsy approach could be a feasible alternative to full pelvic lymphadenectomy, especially in patients with tumors ≤2 cm and no lymphovascular space invasion. These patients with a better prognosis could possibly benefit from lesser radical surgery, a possibility that is currently being tested by ongoing clinical trials (ClinicalTrials.gov NCT01048853, NCT01658930, and NCT01649089).

Authorship & contributorship

All authors equally contributed to data acquisition and validation. BDF formally analyzed the data and wrote the draft. All authors revised and edited the draft and approved the final version of the manuscript.

Declaration of Competing Interest

None.

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