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Sentinel node mapping, sentinel node mapping plus back-up lymphadenectomy, and lymphadenectomy in Early-sTage cERvical caNcer scheduled for fertilItY-sparing approach: The ETERNITY project

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A R T I C L E I N F O

Keywords:
Cervical cancer
Fertility-sparing
Conization
Sentinel node
Lymphadenectomy

A B S T R A C T

Objective: To investigate the safety of sentinel node mapping for patients with early-stage cervical cancer undergoing cervical conization plus nodal evaluation.
Methods: The ETERNITY project is a retrospective, multi-institutional study collecting data of patients with early-stage cervical cancer undergoing fertility-sparing treatment. Here, we compared outcomes related to three methods of nodal assessment: sentinel node mapping (SNM), SNM plus backup lymphadenectomy (SNM + LND); pelvic lymphadenectomy (LND).
Results: Charts of 123 patients (with stage IA1-IB1 cervical cancer) were evaluated. Median patients' age was 34 (range, 22–44) years. SNM, SNM + LND, and LND were performed in 32 (26 %), 31 (25.2 %), and 60 (48.8 %) patients, respectively. Overall, eight (6.5 %) patients were diagnosed with positive nodes. Two (3.3 %), three (9.7 %), and three (9.4 %) patients were detected in patients who had LND, SNM + LND, and SNM respectively. Considering the 63 patients undergoing SNM (31 SNM + LND and 32 SNM alone), macrometastases, micrometastases, and isolated tumor cells were detected in four (3.2 %), three (2.4 %), and one (0.8 %) patients, respectively. All patients with positive nodes discontinued the fertility sparing treatment. Other two patients (one (1.7 %) in the LND group and one (3.1 %) in the SNM group) required hysterectomy even after negative nodal evaluation. After a median follow-up of 53.6 (range, 1.3, 158.0) months, nine (7.3 %) and two (1.6 %) patients developed cervical and pelvic nodes recurrences, respectively. Disease-free ($p = 0.332$, log-rank test) and overall survival ($p = 0.769$, log-rank test) were similar among groups.
Conclusions: In this retrospective experience, SNM upholds long-term oncologic effectiveness of LND, reducing morbidity.

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1. Introduction

Although the introduction of effective primary and secondary prevention methods has reduced the burden of HPV-related diseases, cervical cancer remains a significant global health concern, impacting the lives of millions of women worldwide [1, 2]. Among the various stages of cervical cancer, early detection, and conservative intervention play a pivotal role in achieving favorable outcomes and minimizing the burden on affected individuals [3]. Early-stage cervical cancer, offers a unique window of opportunity for targeted therapeutic interventions that can significantly improve survival rates and preserve the quality of life for affected women [4, 5].

The advent of screening programs, such as Pap smears and human papillomavirus (HPV) testing, has enabled the identification of cervical abnormalities at their incipient stages, leading to early diagnosis and treatment intervention [2, 3]. Consequently, an increasing number of cases are being diagnosed during the early stages, prompting the need for a nuanced understanding of optimal treatment strategies tailored to this specific cohort of patients [4].

Interestingly, it is estimated that about 40 % of patients diagnosed with cervical cancer are of childbearing age. Hence, fertility-sparing techniques have emerged as an alternative treatment for young women with early-stage cervical cancer who strongly desire to preserve their childbearing potential [6]. The European Society of Gynecologic Oncology (ESGO) suggests that a fertility-sparing approach can be offered to patients with early FIGO 2018 stage (IA1-IB1) cervical cancer (greatest diameter <2 cm) and favorable histology (i.e., squamous cell carcinoma, adenocarcinoma, adenosquamous carcinoma) [5]. These recommendations are based on the results of several studies that reported encouraging outcomes of fertility-sparing treatment for cervical cancer, using cervical surgery (e.g., conization, trachelectomy) and node dissection (e.g., sentinel node mapping or pelvic lymphadenectomy) [4, 5, 7, 8]. However, these studies are characterized by small sample sizes, great heterogenicity, and limited follow-up data. Hence, to overcome this gap we designed the present study. This paper aims to report the outcomes of a large series of early-stage cervical cancer cases undergoing fertility-sparing treatment. As a secondary endpoint, we sought to identify predictors of recurrence, thus identifying patients requiring more scrupulous surveillance.

2. Methods

This is a retrospective, multicenter study focusing on Early-sTage cERvical caNcer undergoing for fertilItY-sparing approach (ETERNITY). Charts of patients with a histological diagnosis of cervical cancer undergoing fertility-sparing treatment were retrieved from referral centers in Italy. Institutional Review Board (IRB) approval was obtained (IRB#6812). This study is registered with ClinicalTrials.gov, NCT06351228. Patients treated between January 1, 2000 and December 31, 2022 were included. For the purpose of this study, we included patients with (i) histological diagnosis of cervical cancer; (ii) age equal or greater than 18 years; (iii) early-stage disease at risk of nodal involvement (2009 FIGO stage IA1 with lymphovascular space invasion, stage IA2, and stage IB1); and (iv) at least 90-day follow-up. Data included in the present research were collected in twelve centers. Exclusion criteria were: (i) consent withdraw; (ii) patients with preoperative suspicious of nodal disease; and (iii) execution of neoadjuvant chemotherapy.

The primary outcome measure was to report oncologic outcomes of patients undergoing sentinel node mapping (SNM), sentinel node mapping plus back-up lymphadenectomy (SNM + LND), and lymphadenectomy (LND)alone. As secondary endpoints measure, we sought to (i) report reproductive outcomes; (ii) compare surgery-related outcomes after various type of node assessment; and (iii) describe outcomes of a large series of patients undergoing conservative approach. Patients were staged according to the 2018 International Federation of Obstetrics and Gynecologists (FIGO) staging system [9]. Histological classification and the degree of cell differentiation were performed according to the World Health Organization (WHO) and FIGO classification systems [9]. Preoperative workup included the execution of transvaginal ultrasound, pelvic magnetic resonance imaging and computed tomography scan (abdomen and thorax). The execution of PET/CT is generally limited to case with enlarged nodes or other incidental findings [7]. Over the study period, no significant differences in referral patterns occurred, in included centers. Multidisciplinary teams discussed the options for those patients. All patients were counselled about the experiential nature of fertility-sparing treatment. Patients included in the study had counselling about their fertility potential. Details of surgical technique and pathological evaluation were previously described [7, 10]. Briefly, all patients underwent surgical treatment including conization or trachelectomy plus nodal evaluation. Cervical surgery allows tumor removal and the evaluation of risk factors. Nodal evaluation allows to identify patients requiring definitive chemo-radiation. According to the American Joint Committee on Cancer (AJCC) classification, macrometastasis, micrometastasis, and isolated tumor cells are defined by the presence of cluster of neoplastic cells >2 mm, between 0.2 and 2 mm, and less than 0.2 mm [10].

Pathological characteristics of the cervical specimens are used to tailor the need of adjunctive surgical or medical procedures. The option to continue fertility-sparing option was denied to patients detected with positive nodes; chemo-radiation was delivered to those patients. Neoadjuvant therapy was not an option for patients included in this study.

The Clavien-Dindo severity system was used to classify severe complications and the Martin criteria to improve quality of complications' reporting [11]. We reported data about 90-day severe morbidity (grade 3 or more) [11].

Data regarding obstetrical details were collected by medical records. Similar, details about follow-up were updated on regular basis by trained nurses and residents.

According to institutional protocols, patients were evaluated in outpatients' setting on regular basis. Briefly, patients had a follow-up scheduled including Pap-smear, colposcopy and colposcopic-guided biopsy if clinically indicated, every 6 months for the first 5 years, and annually thereafter. CT scan pelvic RMN and PET/CT were performed when clinically indicated. A dedicated team of gynecologists performed all gynecological and colposcopic examinations. Dates and sites of recurrence were also registered. Recurrence was assessed using imaging techniques and histological assessment was carried out (when feasible), to confirm the presence of the recurrent disease. Basic descriptive statistics were used. Normality testing (D'Agostino and Pearson test) and Kruskal-Wallis test were used to compare the three groups, according to the parametric and nonparametric distribution, respectively. The Chi-square test was used to analyze proportions. Ninety-five percent confidence intervals (95%CI) were calculated for each comparison. When indicated, odds ratio (OR) and 95 % confidence intervals (95%CI) were calculated. The Kaplan-Meier model was used to evaluate survival outcomes (disease-free and overall survivals). The risk of developing recurrence and the risk of death between the two groups over time were compared using the log-rank test. P values < 0.05 were considered statistically significant. Statistical analysis was developed with GraphPad Prism version 6.0 (GraphPad Software, San Diego CA) and IBM-Microsoft SPSS version 20.0 (SPSS Statistics. International Business Machines Corporation IBM 2013 Armonk, USA) for Mac.

3. Results

Charts of 395 patients with cervical cancer undergoing fertility-sparing treatment were retrieved. Among those, 123 patients met the inclusion criteria. Those patients had cervical surgery plus nodal dissection for the diagnosis of IA1-IB1 cervical cancer. Fig. 1 shows details about the study design.

Median patients' age was 34 (range, 22–44) years. Squamous cell carcinoma, adenocarcinoma, and adenosquamous carcinoma accounted in 76 (61.8 %), 30 (24.4 %), and 17 (13.8 %) cases, respectively. Table 1 reports baseline characteristics of the study population. Cervical conization and trachelectomy were performed in 118 (96 %) and five (4 %) patients, respectively. SNM, SNM + LND, and LND were performed in 32 (26 %), 31 (25.2 %), and 60 (48.8 %) patients, respectively.

Baseline characteristics were similar between patients undergoing SNM, SNM + LND, and LND. Nodal evaluation was performed via minimally invasive surgery in all patients. One patient (in the LND group) required conversion to open surgery due to adhesion. Table 2 shows characteristics of those three groups. Overall, eight (6.5 %) patients were diagnosed with positive nodes. Three (9.4 %), three (9.7 %), two (3.3 %), and patients were detected in patients who had SNM, SNM + LND, and LND respectively.

Details regarding positive nodes are reported in Supplemental material 1. Considering together the 63 patients undergoing SNM (31 SNM + LND and 32 SNM alone), mapping failure occurred only in one patient in the SNM + LND group. This patient (with stage IB1 squamous cell carcinoma) had unilateral right SNM, followed by bilateral pelvic LND. Accuracy, sensitivity, and predictive negative value are reported in Supplemental material 2. Macrometastases, micrometastases, and isolated tumor cells were detected in four (3.2 %), three (2.4 %), and one (0.8 %) patients, respectively. All patients with positive nodes discontinued the fertility sparing treatment. In addition, two patients (one (1.7 %) in the LND group and one (3.1 %) in the SNM group) required hysterectomy even after negative nodal evaluation.

Three 90-day surgery-related severe (grade 3 or more) complications occurred. Two in the LND group, including: hematometra in a patient developing cervical stenosis and a symptomatic lymphocele requiring laparoscopic drainage. In the SNM + LND group one patient developed an infected lymphocele causing sepsis, requiring open abdominal surgery. No 90-day severe complication occurred in patients having SNM alone.

Looking at reproductive outcomes, 48 (42.5 %) out of 113 patients (who complete the planned fertility-sparing treatment) declared to attempt to have a pregnancy. Among those, 33 women succeeded, corresponding to a live birth rate of 68.7 %. Supplemental material 3 reports details about reproductive outcomes.

After a median follow-up of 53.6 (range, 1.3, 214.0) months, nine (7.3 %) patients developed cervical recurrences, two had cervical surgery alone (trachelectomy) and the remaining seven patients had hysterectomy (with or without node dissection). Two (1.6 %) pelvic nodes recurrences occurred. One in a patient with a stage IB1 cervical cancer in the SNM group, and the other in a patient who had chemoradiation due to positive nodes in the LND group. This latter patient died of disease. No distant (i.e., peritoneal or hematogenous) recurrences were registered. Disease-free ($p = 0.332$, log-rank test) and overall survival ($p = 0.769$, log-rank test) were similar among groups (Fig. 2). Type of nodal dissection have not an impact on disease-free ($p = 0.223$, log-rank test) and overall survival ($p = 0.860$, log-rank test), even in stage IB1.

4. Discussion

The present study compared three different approaches for nodal evaluation in early-stage cervical cancer, reporting interesting outcomes. First, we observed that the execution of SNM alone did not impact negatively oncologic outcomes in patients undergoing fertility-sparing treatment. Second, patients undergoing SNM (alone or followed by LND) had more likely to be detected with positive nodes, than patients undergoing LND alone. Third, mapping failure rate in low and SNM correlates with a high accuracy and high negative predictive value. Additionally, data about reproductive outcomes suggested the safety and effectiveness of adopting a fertility-sparing treatment in women willing to preserve their childbearing potential.

Cervical cancer is one of the most common cancer occurring in women aged less than 40 years. It is estimated that about 40 % of cervical cancer cases occur in childbearing age [6]. Hence, the identification of the optimal management of those young women is of paramount importance. Accumulating data suggested the adoption of even less invasive fertility-sparing approaches in young women wishing to preserve their childbearing potential [7, 8]. Even in the setting of conservative surgery, cervical conization or simple trachelectomy uphold oncologic effectiveness of radical trachelectomy [8]. Similarly, SNM was introduced with the aim to reduce surgical- and lymphatic specific-morbidity related to LND. SNM allows the removal of the first nodes draining from the uterus, assessing nodal status, without the need of complete nodal dissection. Growing evidence supported the adoption of SNM in early-stage cervical cancer, but limited evidence is available in the setting of fertility-sparing treatment []. The prospective multicenter SENTIX (ENGOT-CX2/CEEGOG-CX1) trial tested the value of SNM in 395 patients with stage IA1 (with LVSI) – IB1 cervical cancer. The study showed that SNM is safe and effective, being characterized by a bilateral detection rate of 91 % [12]. The study included also patients having fertility-sparing treatment but data of this subgroup of patients are not reported, yet [12]. Other investigations confirmed the value of SNM in patients undergoing hysterectomy [13]. Recently, a meta-analysis (collecting data of more than 2200 patients from studies comparing SNM and LND, in the setting of early-stage cervical cancer) showed that 3-year recurrence-free survival is not influenced by SNM nor LND [13]. As aforementioned, data on SNM in the context of ferity-sparing approach are limited to small series [7, 14].

The main strength of the present paper is the peculiar clinical setting. To the best of our knowledge, this is the first study comparing three different approaches of node dissection in early-stage cervical cancer undergoing conservative approach. While, the main weaknesses of this study included the inherited biases of the retrospective study design. Although the retrospective nature of this study might influence the process of patients inclusion (selection bias), we stressed participating center in including in this data collection, all patients who attempted of receive a fertility-sparing approach. Moreover, it is important to underline that the lack of a process of independent (internal) validation for each center might influence the reporting of adverse outcomes (publication bias). Additionally, five points of the present study deserve to be addressed. First, although our study represents the largest clinical experience testing SNM, SNM + LND, and LND in patients undergoing fertility-sparing surgery, the relative small sample size might influence the interpretation of our results. Hence, it would be very difficult to demonstrate a statistically significant results in this setting. Second, our results highlight the need for a strong collaboration with fertility specialists. Fertility-sparing management could be complex, burdensome and might expose women to some additional risks. It is of paramount importance to restrict this intervention to women who may really have children in their future and to properly counsel them on their fertility potential and possible options of treatment. In our series, less than half of the included subjects actively attempt to become pregnant and two thirds succeeded. This later proportion is satisfactory and indirectly suggests that surgery was not harmful, and that the selection of patients was appropriate. On the other hand, the former observation, i.e. the low rate of women looking for pregnancy, suggests that there is room for improvement in the selection process. Overall, a strict collaboration is needed to avoid useless fertility sparing intervention in women. Third, our study included an experience from referral centers with great background in managing cervical cancer patients and performing SNM; thus, our results cannot be projectable in a setting lacking of oncologic expertise. Fourth, we included only patients with tumor <2 cm. Hence, our data are not supporting the execution of SNM in patients with larger tumors. Fifth, SNM detected four patients with low volume disease (three patients with micrometastases and one patient with isolated tumor cells). We can speculate that some low volume disease could be missed in the LND group. However, oncologic outcomes were similar. The low prevalence of nodal disease, the possibility of detecting (about 50 %) micrometastases via conventional pathological evaluation, and

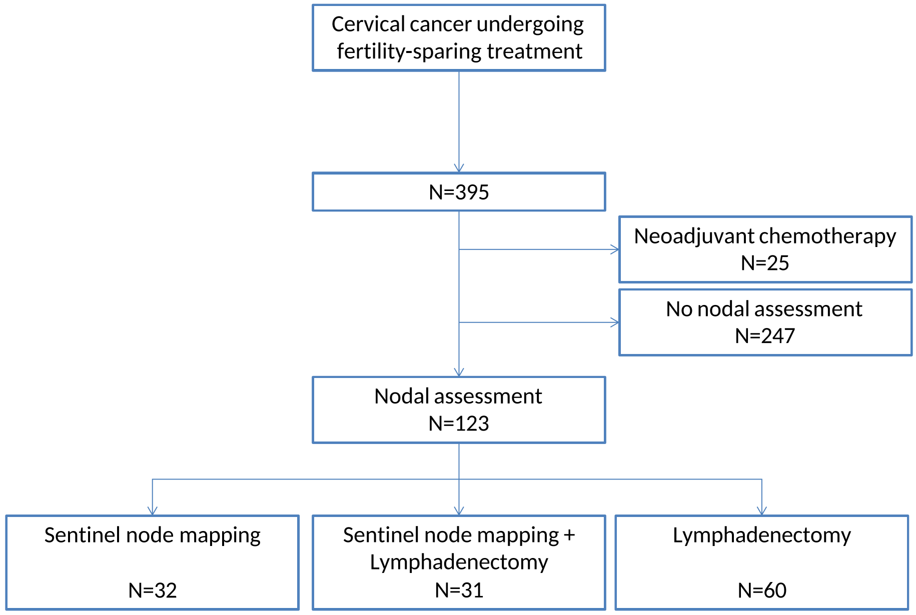

Fig. 1. Study design.

Table 1
Baseline characteristics of the study population.

	N = 123
Age, years	34 (22–44)
BMI, Kg/m^2	21.4 (16–33)
Histology	
Squamous	76 (61.7)
Adenocarcinoma	30 (24.3)
Adenosquamous	17 (14)
FIGO grade	
G1&2	84 (68.2)
G3	39 (31.8)
Deep of stromal invasion	4.14 (0.5–8)
LVSI	
No	46 (37.3)
Yes	77 (62.7)
Preoperative imaging	
Ultrasound	23 (18.6)
CT scan	13 (10.5)
MRI	88 (71.5)
PET-CT	50 (40.6)
Unknown	2 (1.6)
Sentinel node mapping	
No	60 (48.7)
Yes	63 (51.3)
Bilateral systematic pelvic lymphadenectomy	
No	32 (26.0)
Yes	91 (74.0)
Positive nodes	
No	115 (93.4)
Yes	8 (6.6)
Other therapies*	
Total hysterectomy	2 (1.6)
Other conization	43 (34.9)
Chemo-radiation	1 (0.8)
Follow-up, mo	53.6 (1.3, 158)

Data are expressed in median (range) or number (%); Abbreviation, BMI, body mass index; FIGO, International Federation of Obstetrics and Gynecology; LVSI, lymphovascular space invasion; *, before recurrence; mo, months. CT-scan: Computerized Tomography scan; MRI: Magnetic Resonance Imaging; PET-CT: Positron Emission Tomography with Computed Tomography.

Table 2
Baseline characteristics of patients.

	SNM (n = 32)	SNM + LND (n = 31)	LND (n = 60)	P value
Age, years	34 (22–42)	33 (22–41)	36 (24–44)	0.663
BMI, Kg/m^2	22.0 (16, 29)	20.6 (18, 27)	20 (16, 31)	0.242
Previous delivery				0.244
No	19 (59.3)	14 (45.1)	38 (63.3)	
Yes	13 (40.7)	17 (54.9)	22 (36.7)	
Histology				0.921
Squamous	19 (59.4)	20 (64.5)	38 (63.3)	
Adenocarcinoma	9 (28.1)	8 (25.8)	13 (21.7)	
Other	4 (12.5)	3 (9.7)	9 (15.0)	
FIGO grade				0.175
G1&2	23 (71.8)	17 (54.9)	44 (73.3)	
G3	9 (28.2)	14 (45.1)	16 (26.7)	
Available data for deep of stromal invasion				0.07
No	18 (56.2)	18 (58.0)	46 (76.7)	
Yes	14 (43.8)	13 (42.0)	14 (23.3)	
Deep of stromal invasion, mm	2.9 (0.5–7)	4.2 (2–6)	4.0 (0.5–8)	0.017
LVSI				0.015
No	13 (40.6)	5 (16.1)	28 (46.6)	
Yes	19 (59.4)	26 (83.9)	32 (53.4)	
Preoperative imaging				
Ultrasound	5 (15.6)	4 (12.9)	14 (23.4)	0.437
CT scan	4 (12.5)	3 (9.7)	8 (13.3)	0.878
MRI	4 (12.5)	27 (87.0)	42 (70.0)	<0.001
PET-CT	9 (28.1)	17 (54.9)	24 (40.0)	0.096
Unknown	10 (31.2)	0 (0)	4 (6.6)	0.001
Positive nodes				0.379
No	29 (90.6)	28 (90.3)	58 (96.7)	
Yes	3 (9.4)	3 (9.7)	2 (3.3)	
Subsequent therapies*				
Other conization	12 (37.5)	13 (41.9)	18 (30.0)	0.495
Hysterectomy	1 (3.1)	0 (0)	1 (1.6)	0.598
Radiotherapy (with or without chemotherapy)	3 (9.3)	3 (9.6)	2 (3.3)	0.379
Follow-up, mo	56 (1.3, 69)	40.6 (7.5, 80.4)	63.1 (2.2, 158)	0.014

Data are expressed in median (range) or number (%); Abbreviation, BMI, body mass index; FIGO, International Federation of Obstetrics and Gynecology; LVSI, lymphovascular space invasion; *, before recurrence; mo, months.

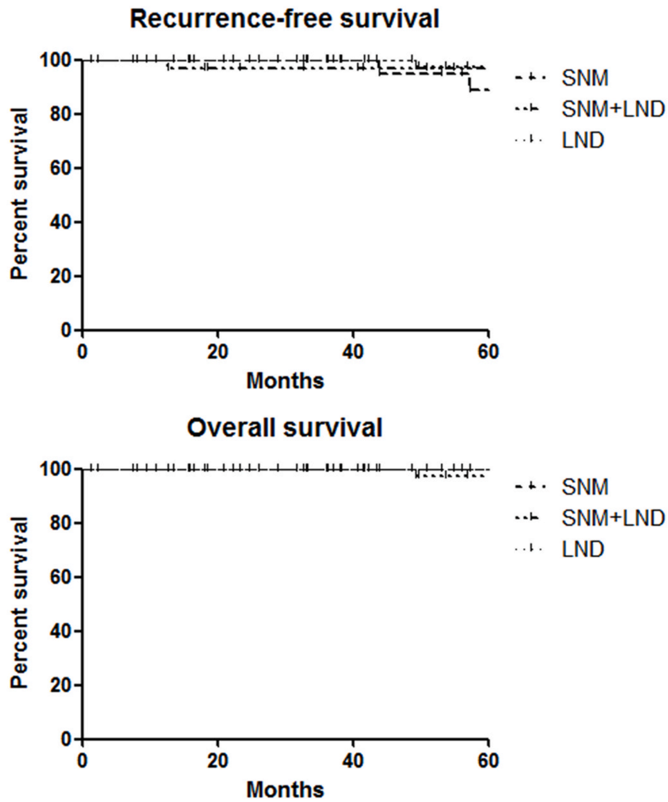

Fig. 2. Survival outcomes.

(potentially) the role of lymphatic tissue removal during LND might explain this feature.

5. Conclusions

The present paper represents the first study comparing three approaches for nodal dissection in early-stage cervical cancer undergoing fertility sparing treatment. We observed that SNM is not inferior to SNM + LND and LND. Conization and minimally invasive SNM represents a safe and effective method to manage early-stage cervical cancer. It minimizes invasiveness, upholding oncological safety of more extensive procedures. Further prospective experiences should be carried out to confirm our results.

Trial registration

ClinicalTrials.gov, NCT06351228.

Conflict of interest

None.

Funding

None.

Conflicts of interest

The Authors declare no conflicts of interest. No funding sources supported this investigation.

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Author contribution

Conceptualization: GB, GS, FR., Methodology: All authors.; Project administration: GB, FR. GS; Supervision: MM, FG, GS, FR.; Writing – original draft: All authors; Writing – review & editing: all authors.

Appendix ASupplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejso.2024.108467.

Table A1
Details about nodal disease

	Macrometastasis	Micrometastasis	Isolated tumor cells
SNM (n = 32)	1 (3.1 %)	1 (3.1 %)	1 (3.1 %)
SNM + LND (n = 31)	1 (3.2 %)	2 (6.4 %)	0
LND (n = 60)	2 (3.3 %)	0	0

Data are expressed in number (%).

Table A2
Accuracy of sentinel node mapping

	SNM + LND
Sensitivity	66.7 %
Specificity	100 %
Positive predictive value	100 %
Negative predictive value	96.5 %
Accuracy	96.7 %

Table A3
Obstetrical outcomes

	SNM (N = 32)	SNM + LND (N = 31)	LND (N = 60)
Fertility-sparing treatment	4 (12.5)	3 (9.7)	3 (5.0)
Discontinued Completed	28 (87.5)	28 (90.3)	57 (95.0)
Attempt to have pregnancy	9 (28.1)	17 (54.9)	22 (36.7)
In vitro fertilization	1 (3.1)	2 (6.4)	4 (6.6)
Pregnancy achieved	7 (21.8)	13 (42.0)	16 (26.7)
Live birth rate	7 (21.8)	12 (38.7)	14 (23.3)

Data are expressed in number (%), SNM, sentinel node mapping; LND, lymphadenectomy.

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