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Long-term oncological safety of sentinel lymph node biopsy in early-stage cervical cancer: A post-hoc analysis of SENTICOL I and SENTICOL II cohorts

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HIGHLIGHTS

- Patients having bilateral negative sentinel lymph nodes or bilateral negative pelvic lymphadenectomy had similar survival.
- Sentinel lymph node biopsy alone did not increase nodal-specific recurrence compared to pelvic lymphadenectomy.
- The most important prognostic factor in node-negative patients is the pathologic risk assessment using the Sedlis criteria.

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ABSTRACT

Objectives. To compare oncologic outcomes of patients with early-stage cervical cancer and negative nodes who underwent sentinel lymph node biopsy alone (SLNB) versus pelvic lymphadenectomy (PL).

Methods. An ancillary analysis of two prospective multicentric trials on SLN biopsy for cervical cancer (SENTICOL I and II) was conducted. Only patients with early-stage cervical cancer (IA to IIA FIGO stage), bilateral detection of SLN, negative SLN after ultrastaging and negative non-SLN after final pathologic examination were included. Risk-factors of recurrence and disease-specific mortality were determined by Cox proportional hazard models.

Results. Between January 2005 and July 2012, 259 node-negative patients were analyzed: 87 in the SLNB group and 172 in the PL group. The median follow-up was 47 months [4–127]. During the follow-up, 21 patients (8.1%) experienced recurrences, including 4 nodal recurrences (1.9%), and 9 patients (3.5%) died of cervical cancer. Disease-free survival (DFS) and disease-specific survival (DSS) were similar between SLNB and PL groups, 85.1% vs. 80.4%, $p = 0.24$ and 90.8% vs. 97.2%, $p = 0.22$ respectively. By Cox multivariate analysis, SLNB compared to PL was not associated with DFS (HR = 1.78, 95%CI = [0.71–4.46], $p = 0.22$) neither with DSS (HR = 3.02, 95% CI = [0.69–13.18], $p = 0.14$). Only pathologic risk level according to the Sedlis criteria was an independent predictor of DFS and DSS.

Conclusions. Omitting full pelvic lymphadenectomy for patients with bilateral negative SLN does not seem to be associated with an increased risk of recurrence in this series. Survival non-inferiority needs to be confirmed by prospective trials.

1. Introduction

Lymph node status is a major prognosis factor in cervical cancer [1] and lymph node staging may determine the appropriate treatment for patients with early-stage cervical cancer [2]. Trends in cervical cancer surgery are focused on reducing the morbidity of surgery while maintaining its oncologic safety. A considerable amount of literature has reported the concept, the feasibility and the reliability of SLN biopsy as an alternative to pelvic lymphadenectomy in early-stage cervical cancer [3–5]. According to main international guidelines, SLN biopsy without additional lymphadenectomy is considered as acceptable for 2018 FIGO IA1 with lymphovascular space invasion (LVSI) and IA2 stages [2,6]. For IB1 stage, SLN biopsy may be considered for lymph node staging according to the 2019 NCCN guidelines [6] but is not recommended without systematic pelvic lymphadenectomy according to the ESGO/ESRO/ESP guidelines [2].

The SENTICOL I study was a prospective multicenter study which evaluated the diagnostic value of the SLN biopsy in patients with early-stage cervical cancer. We reported no false-negative cases in patients who had bilateral SLN detection [7]. The SENTICOL II trial was a prospective randomized multicenter study which compared morbidity and quality of life after SLN biopsy alone and after SLN biopsy with pelvic lymphadenectomy. SLN biopsy was associated with reduced lymphedema, reduced surgical morbidity, and better quality of life compared to complete pelvic lymphadenectomy [8,9]. Moreover, SLN mapping provides more precise node staging by identifying draining nodes in atypical anatomic areas [10] and by performing ultrastaging which detects micrometastases and isolated tumor cells [11].

However, despite all these data, SLN biopsy alone is not considered as gold-standard treatment yet. The main reason is the paucity of data about the survival and the oncologic safety of patients who underwent SLN biopsy alone. It is necessary to address the benefit of systematic completion lymphadenectomy after SLN biopsy.

The goals of this study were to assess disease-free survival (DFS) and disease-specific survival (DSS) in patients with early-stage cervical cancer and negative nodes and to compare survival after sentinel lymph node biopsy alone (SLNB) versus pelvic lymphadenectomy (PL) through both the SENTICOL I and II cohorts.

2. Methods

2.1. Population study

A post-hoc analysis of the database of two prospective multicentric trials on SLN biopsy for early-stage cervical cancer (SENTICOL I and II) was conducted. In SENTICOL I, 139 patients from seven French gynecological oncology centers were included between January 2005 and May 2007 [7]. All patients underwent SLN biopsy and systematic pelvic lymphadenectomy as well as lymphadenectomy of areas containing one or more SLNs. In SENTICOL II, 206 patients from 23 French gynecological oncology centers were included between January 2009 and July 2012 [9]. These patients had bilateral negative SLN upon frozen section examination and were randomized between SLN biopsy alone or SLN biopsy with additional pelvic lymphadenectomy.

For the current study, patients with early-stage cervical cancer (tumor size <40 mm, no parametrial involvement, no suspicious nodes) and bilateral negative SLN at the final pathologic examination were included. Patients with positive SLN (including micrometastase and isolated tumor cells) and patients with unilateral or bilateral SLNs failure detection were excluded. Paris Descartes *(Comité de Protection des Personnes "HEGP-Broussais", Ethical code: DRRC AOR 03063)* and Lyon's Hospital Ethical Committee *(Comité de Protection des Personnes "SUD-EST IV", Ethical code: 2008-A01369-46)* provided the approval to conduct this study. In both studies, an informed consent stating the use of data for secondary analyses was signed by patients.

2.2. Data analysis

Demographic and clinical characteristics, surgical data and pathological data were assessed (tumor histology, lymphovascular space invasion (LVSI), parametrial status, vaginal margin status, depth of stromal invasion, surgical margin status and tumor size). According to the pathologic prognostic factors described by Sedlis et al., patients were categorized as having high-risk, intermediate-risk and low-risk disease [12]. Adjuvant treatment was indicated according to Sedlis criteria and left at the discretion of participating institutions.

SLN detection was realized with a combined labeling technique (Patent blue and radioactive tracer). Intraoperatively, the pelvic and paraaortic lymph nodes were searched before and after the opening of the peritoneum, development of the pararectal and paravesical spaces, and exposure of the parametria. Frozen section analysis was performed either routinely or only on suspected metastasis nodes depending on the center.

Ultrastaging protocol was applied to all SLNs defined as negative by hematoxylin and eosin staining at final pathologic examination with anti-cytokeratin antibodies (AE1-AE3 antibodies).

2.3. Follow-up evaluation

Patients were followed-up with every 3 months for 2 years, every 6 months for 3 years, and yearly afterwards. At each follow-up visit, physical and pelvic examinations were performed. Computed tomography (CT) scans, pelvic magnetic resonance imaging (MRI), and/or positron emission tomography scans (PET-CT) were performed if recurrences were suspected. Disease-free survival (DFS) was defined as the interval in months between the date of surgery and the date of the first recurrence or the date of the last follow-up for patients who were still alive without any recurrence. Disease-specific survival (DSS) was defined as the interval in months between the date of surgery and the date of death from the disease or the date of the last visit.

2.4. Statistical analysis

Qualitative variables were expressed as *n* (%) and the chi-squared test was used to compare them. Quantitative variables were expressed as mean ± standard deviation (SD) and were compared by applying the Student's *t*-test or a Wilcoxon test in case of non-parametric distribution. Parametric distribution was tested using the Kolmogorov-Smirnov test. DFS and DSS curves were built using the Kaplan-Meier method, and the log-rank test was used for survival comparisons. A Cox proportional hazards regression model was applied to obtain hazard ratios (HRs) and a 95% confidence interval (CI). All statistical tests were two-sided and *p*-values lower than 0.05 were retained as significant. Significant variables were entered into a multivariate Cox proportional hazards regression model to determine variables independently associated with DFS and DSS. All statistical analyses were carried out using XLStat Biomed software (AddInsoft V19.4) and R studio (Version 1.2.5042).

3. Results

Among the 345 patients included in both studies, 47 patients had positive nodes, 2 patients had no SLN detected, 26 patients had unilateral SLN detection, and 11 patients were lost during the follow-up period. Finally, 259 patients met the inclusion criteria (87 in the SLNB group and 172 in the PL group) and were analyzed.

3.1. Patient and surgical characteristics

The median age was 41 years old [22–85 years] and the median body mass index (BMI) was 22.6 kg/m^2 [14.6–42.2 kg/m^2]. Most of patients had squamous cell carcinoma (174 patients, 67.4%) and IB1 pathologic FIGO (pFIGO) stage disease (192 patients, 74.1%). Fifty-five patients (21.3%) received preoperative brachytherapy. Patients were mainly operated on using a minimally invasive approach (242 patients, 93.4%). Most of patients underwent radical surgery: 181 patients (76.1%) had radical hysterectomy whereas 48 patients (20.2%) had radical trachelectomy. Overall, 975 SLNs were detected intraoperatively. The median number of SLNs per patients harvested was 3 [2–6]. At the final pathologic examination, 6 patients (2.6%) had parametrial involvement and 7 patients (3.0%) had vaginal spread. Eleven patients (4.6%) had positive surgical margins, including one who had first radical trachelectomy and required a secondary hysterectomy. According to the Sedlis criteria, patients were mainly classified as low-risk (212 patients – 81.9%). Thirty patients (12.0%) received adjuvant brachytherapy whereas 7 patients had EBRT (2.8%) and 8 underwent CCR (3.2%). The clinical and surgico-pathologic characteristics of the patients are presented in Table 1. Between SENTICOL I and SENTICOL II cohorts, there were no significant differences in terms of 2018 pFIGO stage ($p = 0.11$), pathologic risk-assessment ($p = 0.11$) and adjuvant treatment ($p = 0.10$).

The groups were well balanced in terms of age, BMI, histology, pFIGO disease stage, pathologic risk level, and adjuvant treatment. Patients with SLNB tended to have more preoperative brachytherapy (27.6% vs. 18.0%, $p = 0.08$), smaller tumor size (5.4 vs. 8.2 mm, $p = 0.06$), and less LVSI (20.2% vs. 30.3%, $p = 0.09$), although these differences did not reach statistical significance. Patients with PL had significantly deeper stromal invasion (4.8 vs. 2.2 mm, $p = 0.007$) (Table 1).

3.2. Disease-free survival analysis

The median follow-up period was 53 months [5–85] for the SLNB group and 46 months [4–127] for the PL group ($p = 0.09$). During the follow-up, 21 patients (8.1%) experienced recurrences with a median time to recurrence of 24 months [10–72]. The 7-year DFS of the entire population was 83.0% (95%CI = [71.9–94.1]).

In the SLNB group, there were 10 recurrences (11.5%) and the median time to recurrence was 22 months [10–55]. Among these cases, three patients had nodal recurrences (two in the external iliac area and one in the inguinal area). Three patients had centro-pelvic recurrences and 4 patients had distant metastasis (one to the liver and three to the lungs).

In the PL group, there were 11 recurrences (6.4%) and the median time to recurrence was 26 months [13–72] which was similar to that of the SLNB group ($p = 0.78$). One paraaortic recurrence occurred at 26 months of follow-up in a patient who declined initial radical hysterectomy and received only radiotherapy after lymph node staging by pelvic lymphadenectomy. Five patients had centro-pelvic recurrences and five patients had plurifocal distant metastases. The 7-year DFS was 85.1% (95%CI = [76.0–94.1]) and 80.4% (95%CI = [62.1–98.6]) for the SLNB group and PL group respectively ($p = 0.24$) (Fig. 1A). By applying Cox proportional hazards models, SLN biopsy alone compared to pelvic lymphadenectomy was not associated with DFS (HR = 1.67, 95%CI = [0.71–3.94], $p = 0.24$).

Univariate Cox analysis revealed that the depth of stromal invasion, vaginal spread, surgical margins status, pFIGO stage, pathologic risk level and adjuvant treatment were associated with DFS (Table 2). Multivariate Cox analysis confirmed that there was no association between SLNB and DFS (HR = 1.78, 95%CI = [0.71–4.46], $p = 0.22$) whereas intermediate and high pathologic risk levels were independently associated with an increased risk of recurrence with a hazard-ratio of 4.18 and 5.37 respectively (Table 2). Depth of stromal invasion, vaginal spread and margin status were not included in the multivariable model since these variables were also included in the Sedlis criteria and collinear with pathologic risk level.

3.3. Disease-specific survival analysis

During the follow-up period, 9 patients (3.5%) died of cervical cancer with a median time of 36 months [18–64]. All these patients underwent radical hysterectomy and had previous recurrences: 1 nodal, 2 vaginal, 1 pelvic recurrence, and 5 distant metastatic. In addition, a 10th patient died of a breast cancer at 40 months of follow-up in the PL group without any sign of cervical cancer recurrence. Given that this death was not linked to lymph node staging neither cervical cancer, this case was not included in the 7-year DSS. The 7-year DSS of the entire population was 94.5% (95%CI = [90.2–98.8]).

There were 5 deaths (5.7%) in the SLNB group and 4 (2.3%) in the PL group ($p = 0.16$). The median time to disease-specific death was

Table 1
Patient characteristics.

Predictive variable	Total population		BSLN		BPL		*p*
	N = 259		*N* = 87		*N* = 172		
	n Mean ± SD	[%] [range]	*n* Mean ± SD	[%] [range]	*n* Mean ± SD	[%] [range]	
Age [years]							
Mean	43.5 ± 11.9	[22–85]	43.9 ± 11.8	[22–71]	43.3 ± 11.9	[23–85]	*0.69*
< 50	196	75.7	65	74.7	131	76.2	
50–70	55	21.2	19	21.8	36	20.9	*0.95*
> 70	8	3.1	3	3.4	5	2.9	
BMI [kg/m^2]							
Mean	23.8 ± 5.1	[14.6–42.2]	23.5 ± 4.5	[16.8–41.4]	24.0 ± 5.3	[14.6–42.2]	*0.48*
< 18.5	15	5.8	5	5.7	10	5.8	
18.5–25	165	64.0	58	66.7	108	62.8	*0.24*
< 25–30	49	19.0	19	21.8	30	17.4	
> 30	29	11.2	5	5.7	24	14.0	
Histology							
Squamous cell carcinoma	174	67.2	55	63.2	119	69.2	
Adenocarcinoma	77	29.7	29	33.3	48	27.9	*0.63*
Other type	8	3.1	3	3.4	5	2.9	
Grade of differenciation							
G1	80	44.4	32	56.1	48	39.3	
G2	67	37.2	17	29.8	50	41.0	*0.11*
G3	32	17.8	8	14.0	24	19.7	
Not specified	80		30		50		
Conization							
Yes	160	61.8	59	67.8	101	58.7	*0.15*
No	99	38.2	28	32.2	71	41.3	
Preoperative brachytherapy							
Yes	55	21.2	24	27.6	31	18.0	*0.08*
No	204	78.8	63	72.4	141	82.0	
Surgical procedure							
Type of surgery							
Radical hysterectomy	181	76.1	66	78.6	115	74.7	
Radical trachelectomy	48	20.2	14	16.7	34	22.1	*0.10*
Simple hysterectomy	6	2.5	1	1.2	5	3.2	
Simple trachelectomy	3	1.3	3	3.6	0	0.0	
No surgery	1	0.1	0	0.0	1	0.1	
Not specified	20		3		17		
Type of surgical approach							
Minimal invasive surgery	242	93.4	83	95.4	159	92.4	*0.36*
Laparotomy	17	6.6	4	4.6	13	7.6	
Final pathologic examination							
Tumor size							
Mean	7.2 ± 10.4	[0–60]	5.4 ± 8.3	[0−30]	8.2 ± 11.3	[0–60]	*0.06*
< 20 mm	202	84.5	74	90.2	128	81.5	*0.08*
≥ 20 mm	37	15.5	8	9.8	29	18.5	
Not specified	20		5		15		
Deep stromal invasion							
Mean	3.9 ± 6.8	[0–40]	2.2 ± 4.5	[0−20]	4.8 ± 7.5	[0–40]	***0.007***
< 10 mm	169	83.3	63	88.7	106	80.3	*0.13*
≥ 10 mm	34	16.7	8	11.3	26	19.7	
Not specified	56		16		40		
LVSI							
Yes	64	26.8	17	20.2	47	30.3	*0.09*
No	175	73.2	67	79.8	108	69.7	
Not specified	20		3		17		
Vaginal invasion							
Yes	7	3.0	1	1.2	6	4.0	*0.24*
No	223	97.0	80	98.8	143	96.0	
Not specified	29		7		22		
Parametrial invasion							
Yes	6	2.6	1	1.2	5	3.3	*0.33*
No	228	97.4	82	98.8	146	96.7	
Not specified	25		4		21		
Positive margin							
Yes	11	4.6	4	4.8	7	4.5	*0.92*
No	229	95.4	80	95.2	149	95.5	
Not specified	19		3		16		
2018 pFIGO stage							
IA1 with emboli - IA2	26	10.0	9	10.3	17	9.9	*0.53*

Table 1 (*continued*)

Predictive variable	Total population		BSLN		BPL		*p*
	N = 259		*N* = 87		*N* = 172		
	n Mean ± SD	[%] [range]	*n* Mean ± SD	[%] [range]	*n* Mean ± SD	[%] [range]	
IB1	192	74.1	68	78.2	124	72.1	
IB2	28	10.8	6	6.9	22	12.8	
IIA-B	13	5.0	4	4.6	9	5.2	
Pathologic risk level (Sedlis criteria)							
Low	212	81.9	72	82.8	140	81.4	
Intermediate	25	9.7	7	8.0	18	10.5	*0.80*
High	22	8.5	8	9.2	14	8.1	
Adjuvant treatment							
None	205	82.0	69	81.2	136	82.4	
Brachytherapy	30	12.0	14	16.5	16	9.7	*0.17*
EBRT	7	2.8	1	1.2	6	3.6	
CCR	8	3.2	1	1.2	7	4.2	
Not specified	9		2		7		
Outcomes							
Recurrences							
None	238	91.9	77	88.5	161	93.6	
Nodal	4	1.5	3	3.4	1	0.6	
Vaginal	5	1.9	1	1.1	4	2.3	*0.23*
Pelvic	3	1.2	2	2.3	1	0.6	
Distant metastases	9	3.5	4	4.6	5	2.9	
Status							
Alive	250	96.5	82	94.3	168	97.7	*0.16*
Dead	9	3.5	5	5.7	4	2.3	

36 months (23–64) in the SLNB group and 37 months (18–40) in the PL group ($p = 0.54$). The 7-year DSS was 90.8% (95%CI = [82.0–98.7]) and 97.2% (95%CI = [94.5–99.9]) for the SLNB and PL groups respectively ($p = 0.22$) (Fig. 1B). By applying the Cox proportional hazards models, SLN biopsy alone compared to pelvic lymphadenectomy was not associated with DSS (HR = 2.24, 95%CI = [0.60–8.39], $p = 0.23$) (Table 3). In addition, univariate Cox analysis demonstrated that vaginal spread, surgical margin status, pFIGO stage, pathologic risk level and adjuvant treatment were significantly associated with DSS. Multivariate Cox analysis confirmed the absence of association between SLN biopsy alone and DSS (HR = 3.02, 95%CI = [0.69–13.18], $p = 0.14$) and retained high pathologic risk level as an independent risk-factor of DSS (HR = 15.75, 95%CI = [2.15–115.45], $p = 0.007$) (Table 3).

4. Discussion

For lymph node staging in early stage-cervical cancer, the real-world question, is whether it is necessary oncologically to undertake a complete node dissection, or whether a sentinel node biopsy can suffice, as measured by DFS and OS. In the present study, our results emphasized that there were no significant differences in DFS (85.1% vs. 80.4%, $p = 0.24$) and DSS (90.8% vs. 97.2%, $p = 0.22$) between the SLNB group and PL group, respectively.

Compared to a classic lymphadenectomy, the oncological safety of SLN biopsy has been reported in endometrial cancer [13] and in vulvar cancer [14]. However, few studies assessing the oncologic outcomes of SLN biopsy in cervical cancer are available. Most of them are retrospective and combined the SLN biopsy with pelvic lymphadenectomy [15] or included node-positive patients [16–18]. In our cohort, the recurrence rate was 8.1% and was similar to those reported in node-negative patients ranging from 6.3% to 14% [19–21]. There was no difference in recurrence rate between SLNB and PL groups (11.5% vs 6.4%, $p = 0.23$). Although three of four nodal recurrences occurred in the SLNB group, SLN biopsy alone did not significantly increase nodal-specific recurrence compared to pelvic lymphadenectomy.

Gortzak Uzan et al. reported a recurrence rate of 6.2% in 87 patients who underwent SLN biopsy alone and 5.6% in 218 matched patients who underwent pelvic lymphadenectomy, with no differences in DFS between both groups ($p = 0.72$) [18]. However, in their study, patients of SLN group had significantly more positive lymph nodes (17% vs. 7%, $p = 0.006$) and shorter median follow-up (13 months vs. 59 months). Yahata et al. did not find any significant survival differences between patients who underwent pelvic lymphadenectomy and those who were managed with SLN biopsy alone. In the group of 139 patients who underwent SLN biopsy alone (including 14 patients with positive SLN and 8 false-negative cases), none had recurrences after a median follow-up of 40 months [16]. In a retrospective cohort of node-negative patients, Lennox and Covens compared 110 patients with SLNB and 1078 PL and found no significant differences in DFS between these two groups [22]. In the PL group, they reported recurrence and mortality rates of 6.9% and 3.3%, respectively which were similar to ours. However, they reported a lower recurrence rate of 3.6% in the SLNB group and no deaths. Compared to our cohort, these main differences may be explained by a different population with more IA stage patients (59%) and a shorter median follow-up time of 32 months. In their cohort, depth of stromal invasion, presence of LVSI, and histology were independent predictors of DFS, whereas SLN biopsy alone compared to pelvic lymphadenectomy was not associated with DFS with a similar hazard ratio to ours (HR = 1.80, 95%CI = [0.62–5.4], $p = 0.277$).

This work assessed long-term oncological outcomes of SLN biopsy through a posthoc analysis of two large prospective cohorts but presented some limitations. First, patients were mainly operated by minimal invasive approach (93.4%) and only a small subset underwent open surgery due to intraoperative technical difficulties or poor tolerance of pneumoperitoneum. Although we did not find that the type of surgical approach was a risk-factor for DFS or DSS, we speculate that it might affect our results since in the minimally invasive surgery arm of the LACC trial (which also included node positive patients), the recurrence rate of 8.5% and the mortality rate of 6.0% were similar to ours [23]. However, the type of surgical approach was not associated with nodal recurrence in the LACC trial. In addition, 84.1% of our cohort had

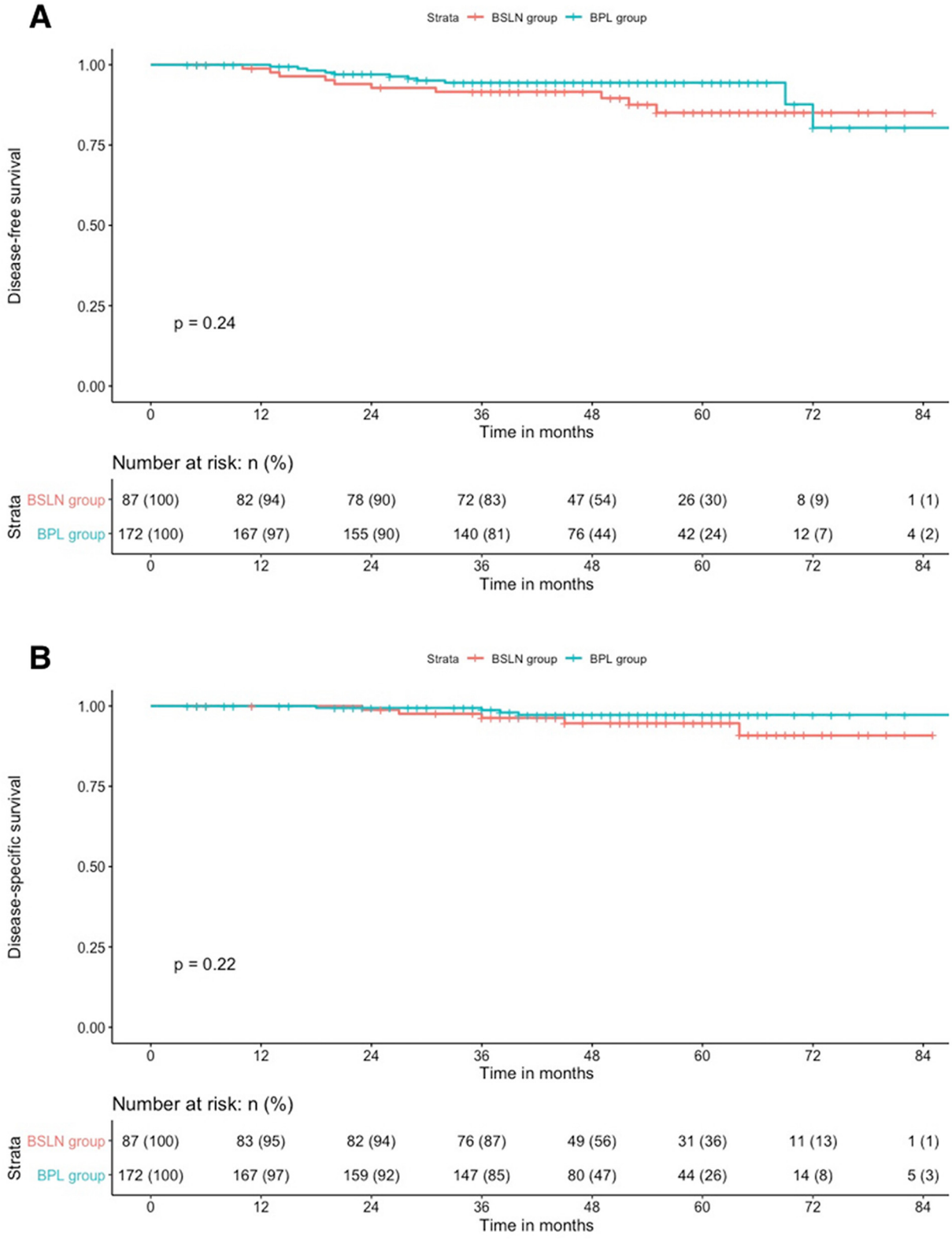

Fig. 1. Kaplan-Meier disease-free survival (A) and disease-specific survival (B) curves of SLNB and PL groups.

pIB1 2018 FIGO stage or lower and Kim et al. have shown that minimally invasive surgery was not associated with poorer DFS in patients with cervical mass size ≤2 cm. Secondly, there was a discordance between the number of patients classified as intermediate-risk and high-risk and the number of patients who received EBRT and CCR. A non-negligible proportion of patients might have been undertreated which would lead to some observed recurrences. However, patients came from multiple institutions with different practices, and we believe that these results might reflect real-life practices. Another limitation was the use of combined labeling technique (blue dye and radiotracer)

Table 2
Cox proportional hazards models of disease-free survival.

	Univariate			*Multivariate*		
Risk-factors	Hazard ratio	95% CI	*p*	Hazard ratio	95% CI	*p*
Age	1.02	0.98–1.05	*0.33*			
BMI [kg/m^2]	0.99	0.90–1.08	*0.75*			
Histology						
Squamous cell carcinoma	1	–	–			
Adenocarcinoma	0.85	0.33–2.22	*0.74*			
Other type	–	–	–			
Grade of differentiation						
G1	1	–	–			
G2	0.80	0.26–2.45	*0.69*			
G3	1.45	0.43–4.84	*0.55*			
Conization						
No	1	–	–			
Yes	0.68	0.29–1.61	*0.38*			
Preoperative brachytherapy						
No	1	–	–			
Yes	0.65	0.19–2.22	*0.49*			
Type of surgery						
Radical hysterectomy	1	–	–			
Radical trachelectomy	0.59	0.17–2.01	*0.4*			
Simple hysterectomy	–	–	–			
Simple trachelectomy	–	–	–			
Type of surgical approach						
Minimal invasive surgery	1	–	–			
Laparotomy	1.60	0.37–6.90	*0.53*			
Type of lymph node staging						
BPL	1	–	–			
SLN biopsy alone	1.67	0.71–3.94	*0.24*	1.78	0.71–4.46	*0.22*
Tumor size						
< 20 mm	1	–	–			
> 20 mm	2.62	1.00–6.92	*0.05*			
Depth of stromal invasion						
< 10 mm	1	–	–			
> 10 mm	2.79	1.03–7.54	***0.04***			
LVSI						
No	1	–	–			
Yes	1.48	0.59–3.70	*0.41*			
Vaginal invasion						
No	1	–	–			
Yes	5.61	1.60–19.68	***0.007***			
Parametrial invasion						
No	1	–	–			
Yes	2.35	0.31–17.69	*0.41*			
Margin status						
Negative	1	–	–			
Positive	4.36	1.26–15.05	***0.02***			
2018 pFIGO stage						
IA1 with emboli – IA2	–	–	–	–	–	–
IB1	1	–	–	–	–	–
IB2	1.56	0.45–5.46	*0.48*	0.62	0.14–2.71	*0.53*
IIA-B	4.43	1.45–13.54	***0.009***	0.69	0.16–2.90	*0.61*
Pathologic risk level						
Low	1	–	–	–	–	–
Intermediate	4.83	1.47–15.85	***0.009***	4.18	1.01–17.27	***0.05***
High	9.19	3.53–23.94	***< 0.0001***	5.37	1.44–20.09	***0.01***
Adjuvant treatment						
None	1	–	–	–	–	–
Brachytherapy	3.82	1.38–10.60	***0.01***	2.03	0.65–6.29	*0.22*
EBRT	4.88	1.07–22.36	***0.04***	2.42	0.41–14.37	*0.33*
CCR	9.89	2.68–36.50	***0.001***	3.05	0.51–18.25	*0.22*

during inclusion period of SENTICOL I and II and not ICG which will probably be the gold-standard for SLN mapping [24].

In this study, patients having negative SLN or negative SLN and PL had similar survival. Our results raise the question of omitting the full lymphadenectomy for the low-risk patients with bilateral negative SLN without jeopardizing oncologic outcomes. However, survival outcomes between the two types of lymph node staging were not the main objective of the SENTICOL I and II studies. In addition, all the patients had at less SLN biopsy, and no patients had only PL due to the design of both studies. Even if patient follow-up was prospectively recorded in a quality-checked database, this post-hoc analysis should be interpretated with caution in regard with the number of patients included and statistical considerations. Although the length of follow-up between both groups was not significantly different, the median of follow-up of PL group tended to be shorter and some late recurrences might have been missed. As a result, the recurrence rate in PL group might have been underestimated. By contrast, the sample size of this series is limited and induces a power of 66.5%. Considering the PL group DFS of 80.4%, the inclusion of a total of 517 patients would have been required to put in evidence a non-inferiority of SLN biopsy alone with a statistical power of 90% and a unilateral alpha error of 5%. Consequently, prospective clinical trials with large cohort are mandatory to prove

Table 3
Cox proportional hazards models of disease-specific survival.

	Univariate			*Multivariate*		
Risk-factors	Hazard ratio	95% CI	*p*	Hazard ratio	95% CI	*p*
Age	1.01	0.96–1.06	*0.70*			
BMI [kg/m^2]	1.02	0.90–1.15	*0.78*			
Histology						
Squamous cell carcinoma	1	–	–			
Adenocarcinoma	1.09	0.27–4.35	*0.90*			
Other type	–	–	–			
Grade of differentiation						
G1	1	–	–			
G2	0.96	0.16–5.80	*0.96*			
G3	2.07	0.34–12.45	*0.43*			
Conization						
No	1	–	–			
Yes	1.23	0.31–4.91	*0.77*			
Preoperative brachytherapy						
No	1	–	–			
Yes	2.06	0.51–8.25	*0.31*			
Type of surgery						
Radical hysterectomy	1	–	–			
Radical trachelectomy	–	–	–			
Simple hysterectomy	–	–	–			
Simple trachelectomy	–	–	–			
Type of surgical approach						
Minimal invasive surgery	1	–	–			
Laparotomy	3.90	0.8–19.02	*0.09*			
Type of lymph node staging						
BPL	1	–	–			
SLN biopsy alone	2.24	0.60–8.39	*0.23*	3.02	0.69–13.18	*0.14*
Tumor size						
< 20 mm	1	–	–			
> 20 mm	2.65	0.66–10.63	*0.17*			
Depth of stromal invasion						
< 10 mm	1	–	–			
> 10 mm	2.84	0.68–11.91	*0.15*			
LVSI						
No	1	–	–			
Yes	1.32	0.33–5.30	*0.69*			
Vaginal invasion						
No	1	–	–			
Yes	9.21	1.88–45.09	***0.006***			
Parametrial invasion						
No	1	–	–			
Yes	5.84	0.73–46.81	*0.10*			
Margin status						
Negative	1	–	–			
Positive	5.17	1.07–24.99	***0.04***			
2018 pFIGO stage						
IA1 with emboli – IA2	–	–	–	–	–	–
IB1	1	–	–	–	–	–
IB2	1.14	0.14–9.46	*0.90*	0.34	0.03–3.56	*0.37*
IIA-B	5.07	1.02–25.24	***0.047***	0.77	0.07–8.25	*0.83*
Pathologic risk level						
Low	1	–	–	–	–	–
Intermediate	8.42	1.69–42.06	***0.009***	4.71	0.44–50.40	*0.20*
High	9.15	1.85–45.35	***0.007***	15.75	2.15–115.45	***0.007***
Adjuvant treatment						
None	1	–	–	–	–	–
Brachytherapy	2.32	0.45–12.07	*0.32*	0.74	0.11–5.10	*0.76*
EBRT	–	–	–	–	–	–
CCR	10.34	2.00–53.55	***0.005***	4.54	0.26–77.99	*0.30*

survival non-inferiority SLN biopsy alone compared to pelvic lymphadenectomy for lymph node staging in early-stage cervical cancer.

To date, three ongoing prospective studies aim to validate the oncological safety of the paradigm shift moving from systematic pelvic lymphadenectomy to targeted SLN biopsy: the SENTIX trial [25], the PHENIX trial [26] and the SENTICOL III trial [27]. In SENTIX trial, a sample size of 300 patients is needed to prove a non-inferiority of SLN biopsy alone and would enhance a power of 90% to detect a non-inferiority proportion of 12% compared to a reference value of 7% of 2-year recurrence rate [25]. The PHENIX trial is a multi-center randomized controlled trial which aim to compare the oncological outcomes of SLN biopsy with pelvic lymphadenectomy in patients without (PHENIX-I) and with SLN metastasis (PHENIX-II). In PHENIX-I, a sample size of 830 patients should be randomized to prove a non-inferiority of SLN biopsy alone with a power of 90% and a non-inferiority margin of 5% compared to a reference value of 94% of 3-year DFS [26]. In SENTICOL III trial, 900 patients should be randomized to demonstrate a non-inferiority of SLN biopsy vs. SLN biopsy + PLN with a non-inferiority margin of 5%, with a unilateral alpha error of 5%, a power of 80%, and with 5 years of follow-up [27].

5. Conclusion

Omitting full pelvic lymphadenectomy for patients with bilateral negative SLN does not seem to be associated with an increased risk of recurrence in this series. In the population of node-negative patients, the most important prognostic factor is the risk assessment using the Sedlis criteria. Survival non-inferiority needs to be confirmed by prospective trials.

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Declaration of Competing Interest

The authors have nothing to disclose.

References

[1] C.-M. Ho, T.-Y. Chien, S.-H. Huang, C.-J. Wu, B.-Y. Shih, S.-C. Chang, Multivariate analysis of the prognostic factors and outcomes in early cervical cancer patients undergoing radical hysterectomy, Gynecol. Oncol. 93 (2) (2004 May) 458–464.
[2] D. Cibula, R. Pötter, F. Planchamp, E. Avall-Lundqvist, D. Fischerova, C. Haie Meder, et al., The European Society of Gynaecological Oncology/European Society for Radiotherapy and Oncology/European Society of Pathology Guidelines for the Management of Patients with Cervical Cancer, Int. J. Gynecol. Cancer 28 (4) (2018 May) 641.
[3] C. Tax, M.M. Rovers, C. de Graaf, P.L.M. Zusterzeel, R.L.M. Bekkers, The sentinel node procedure in early stage cervical cancer, taking the next step; a diagnostic review, Gynecol. Oncol. 139 (3) (2015 Dec) 559–567.
[4] S. Kadkhodayan, M. Hasanzadeh, G. Treglia, A. Azad, Z. Yousefi, L. Zarifmahmoudi, et al., Sentinel node biopsy for lymph nodal staging of uterine cervix cancer: a systematic review and meta-analysis of the pertinent literature, Eur. J. Surg. Oncol. J. Eur. Soc. Surg. Oncol. Br. Assoc. Surg. Oncol. 41 (1) (2015 Jan) 1–20.
[5] I. Ruscito, M.L. Gasparri, E.I. Braicu, F. Bellati, L. Raio, J. Sehouli, et al., Sentinel node mapping in cervical and endometrial cancer: indocyanine green versus other conventional dyes-a meta-analysis, Ann. Surg. Oncol. 23 (11) (2016 Oct) 3749–3756.
[6] W.-J. Koh, N.R. Abu-Rustum, S. Bean, K. Bradley, S.M. Campos, K.R. Cho, et al., Cervical cancer, Version 3.2019, NCCN clinical practice guidelines in oncology, J. Natl. Compr. Cancer Netw. JNCCN 17 (1) (2019 Jan) 64–84.
[7] F. Lécuru, P. Mathevet, D. Querleu, E. Leblanc, P. Morice, E. Daraï, et al., Bilateral negative sentinel nodes accurately predict absence of lymph node metastasis in early cervical cancer: results of the SENTICOL study, J. Clin. Oncol. 29 (13) (2011 May 1) 1686–1691.
[8] M. Gianoni, P. Mathevet, C. Uzan, A.S. Bats, L. Magaud, F. Boutitie, et al., Does the sentinel lymph node sampling alone improve quality of life in early cervical cancer management? Front Surg. 7 (2020) 31.
[9] P. Mathevet, F. Lécuru, C. Uzan, F. Boutitie, L. Magaud, F. Guyon, et al., Sentinel lymph node biopsy and morbidity outcomes in early cervical cancer: results of a multicentre randomised trial (SENTICOL-2), Eur. J. Cancer Oxf. Engl. 1990 148 (2021 May) 307–315.
[10] V. Balaya, P. Mathevet, L. Magaud, H. Bonsang-Kitzis, M. Delomenie, R. Montero Macias, et al., Predictive factors of unexpected lymphatic drainage pathways in early-stage cervical cancer, Gynecol. Oncol. 154 (1) (2019) 102–109.
[11] B. Guani, V. Balaya, L. Magaud, F. Lecuru, P. Mathevet, The clinical impact of low-volume lymph nodal metastases in early-stage cervical cancer: the Senticol 1 and Senticol 2 trials, Cancers 12 (5) (2020 Apr 25).
[12] A. Sedlis, B.N. Bundy, M.Z. Rotman, S.S. Lentz, L.I. Muderspach, R.J. Zaino, A randomized trial of pelvic radiation therapy versus no further therapy in selected patients with stage IB carcinoma of the cervix after radical hysterectomy and pelvic lymphadenectomy: a Gynecologic Oncology Group Study, Gynecol. Oncol. 73 (2) (1999 May) 177–183.
[13] G. Bogani, F. Murgia, A. Ditto, F. Raspagliesi, Sentinel node mapping vs. lymphadenectomy in endometrial cancer: a systematic review and meta-analysis, Gynecol. Oncol. 153 (3) (2019) 676–683.
[14] L.P. Froeding, C. Høgdall, E. Kristensen, V. Zobbe, I. Niemann, G. Ørtoft, et al., Recurrence and survival rates in node negative patients after sentinel node biopsy for early-stage vulva cancer - a nationwide study, Gynecol. Oncol. 156 (1) (2020) 124–130.
[15] D. Cibula, N.R. Abu-Rustum, L. Dusek, M. Zikán, A. Zaal, L. Sevcik, et al., Prognostic significance of low volume sentinel lymph node disease in early-stage cervical cancer, Gynecol. Oncol. 124 (3) (2012 Mar) 496–501.
[16] H. Yahata, H. Kobayashi, K. Sonoda, K. Kodama, H. Yagi, M. Yasunaga, et al., Prognostic outcome and complications of sentinel lymph node navigation surgery for early-stage cervical cancer, Int. J. Clin. Oncol. 23 (6) (2018 Dec) 1167–1172.
[17] H. Niikura, S. Okamoto, T. Otsuki, K. Yoshinaga, H. Utsunomiya, S. Nagase, et al., Prospective study of sentinel lymph node biopsy without further pelvic lymphadenectomy in patients with sentinel lymph node-negative cervical cancer, Int. J. Gynecol. Cancer Off. J. Int. Gynecol. Cancer Soc. 22 (7) (2012 Sep) 1244–1250.
[18] L. Gortzak-Uzan, W. Jimenez, S. Nofech-Mozes, N. Ismiil, M.A. Khalifa, V. Dubé, et al., Sentinel lymph node biopsy vs. pelvic lymphadenectomy in early stage cervical cancer: is it time to change the gold standard? Gynecol. Oncol. 116 (1) (2010 Jan) 28–32.
[19] A. Ayhan, R.A. Al, C. Baykal, E. Demirtas, A. Ayhan, K. Yüce, Prognostic factors in FIGO stage IB cervical cancer without lymph node metastasis and the role of adjuvant radiotherapy after radical hysterectomy, Int. J. Gynecol. Cancer Off. J. Int. Gynecol. Cancer Soc. 14 (2) (2004 Apr) 286–292.
[20] E. Sartori, G. Tisi, F. Chiudinelli, B. La Face, R. Franzini, S. Pecorelli, Early stage cervical cancer: adjuvant treatment in negative lymph node cases, Gynecol. Oncol. 107 (1 Suppl 1) (2007 Oct) S170–S174.
[21] D. Cibula, N.R. Abu-Rustum, D. Fischerova, S. Pather, K. Lavigne, J. Slama, et al., Surgical treatment of "intermediate risk" lymph node negative cervical cancer patients without adjuvant radiotherapy-a retrospective cohort study and review of the literature, Gynecol. Oncol. 151 (3) (2018) 438–443.
[22] G.K. Lennox, A. Covens, Can sentinel lymph node biopsy replace pelvic lymphadenectomy for early cervical cancer? Gynecol. Oncol. 144 (1) (2017 Jan) 16–20.
[23] P.T. Ramirez, M. Frumovitz, R. Pareja, A. Lopez, M. Vieira, R. Ribeiro, et al., Minimally invasive versus abdominal radical hysterectomy for cervical cancer, N. Engl. J. Med. 379 (20) (2018 Nov 15) 1895–1904.
[24] M. Frumovitz, M. Plante, P.S. Lee, S. Sandadi, J.F. Lilja, P.F. Escobar, et al., The FILM Trial: a randomized phase III multicenter study assessing near infrared fluorescence in the identification of sentinel lymph nodes (SLN), Gynecol. Oncol. 149 (2018 Jun 1) 7.
[25] D. Cibula, J. Dusek, J. Jarkovsky, P. Dundr, D. Querleu, A. van der Zee, et al., A prospective multicenter trial on sentinel lymph node biopsy in patients with early-stage cervical cancer (SENTIX), Int. J. Gynecol. Cancer Off. J. Int. Gynecol. Cancer Soc. 29 (1) (2019) 212–215.
[26] H. Tu, H. Huang, B. Xian, J. Li, P. Wang, W. Zhao, et al., Sentinel lymph node biopsy versus pelvic lymphadenectomy in early-stage cervical cancer: a multi-center randomized trial (PHENIX/CSEM 010), Int. J. Gynecol. Cancer Off. J. Int. Gynecol. Cancer Soc. 30 (11) (2020 Nov) 1829–1833.
[27] F.R. Lecuru, M. McCormack, P. Hillemanns, A. Anota, M. Leitao, P. Mathevet, et al., SENTICOL III: an international validation study of sentinel node biopsy in early cervical cancer. A GINECO, ENGOT, GCIG and multicenter study, Int. J. Gynecol. Cancer 29 (4) (2019 May) 829–834.