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Clinical Trial

Sentinel lymph node biopsy and morbidity outcomes in early cervical cancer: Results of a multicentre randomised trial (SENTICOL-2)☆

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Abstract ***Introduction:*** Pelvic lymph node dissection has been the standard of care for patients with early cervical cancer. Sentinel node (SN) mapping is safe and feasible and may increase the detection of metastatic disease, but benefits of omitting pelvic lymph node dissection in terms of decreased morbidity have not been demonstrated.

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Sentinel node biopsy;
Lymphadenectomy;
Morbidity;
Quality of life

Materials and methods: In an open-label study, patients with early cervical carcinoma (FIGO 2009 stage IA2 to IIA1) were randomly assigned to SN resection alone (SN arm) or SN and pelvic lymph node dissection (SN + PLND arm). SN resection was followed by radical surgery of the tumour (radical hysterectomy or radical trachelectomy). The primary end-point was morbidity related to the lymph node dissection; 3-year recurrence-free survival was a secondary end-point.

Results: A total of 206 patients were eligible and randomly assigned to the SN arm (105 patients) or SN + PLND arm (101 patients). Most patients had stage IB1 lesion (87.4%). No false-negative case was observed in SN + PLND arm. Lymphatic morbidity was significantly lower in the SN arm (31.4%) than in the SN + PLND arm (51.5%; $p = 0.0046$), as was the rate of postoperative neurological symptoms (7.8% vs. 20.6%, $p = 0.01$, respectively). However, there was no significant difference in the proportion of patients with significant lymphoedema between the two groups. During the 6-month postoperative period, the difference in morbidity decreased over time. The 3-year recurrence-free survival was not significantly different (92.0% in SN arm and 94.4% in SN + PLND arm).

Conclusion: SN resection alone is associated with early decreased lymphatic morbidity when compared with SN + PLND in early cervical cancer.

1. Introduction

The most important prognostic factor in early cervical cancer is lymph node status [1,2]. Primary surgical treatment, including radical hysterectomy and pelvic lymph node dissection (PLND), is considered the standard of care [3]. Currently, sentinel node (SN) identification is considered an effective method for the evaluation of lymphatic dissemination [4–6]. In early cervical carcinoma, SN identification has important advantages including a low rate of false-negative rates. The other advantages are as follows: identification of possible ectopic metastatic SN due to aberrant lymphatic drainage, identification of a limited number of nodes sent for frozen section assessment during surgery and the ability to provide more precise information, such as detection of micrometastases. These advantages lead to more tailored recommendations for adjuvant treatment [5,6]. Intraoperative complications of PLND include haemorrhage as well as ureteral and nerve lesions [7,8], and postoperative complications such as lymphocyst or lymphoedema may develop [8]. In addition, it has been shown that the impact of lymphadenectomy on lower limb oedema, pain, or heaviness is underestimated [8–10]. These consequences may be related to the number of nodes sampled during lymph node dissection [10,11].

Quality of life is another crucial element for patients with early cervical cancer who are typically young women [10]. In many tumours (breast cancer, vulvar cancer, melanoma), SN biopsy alone has been reported to decrease morbidity in comparison with regional complete lymph node dissection [12–14], but this has not been demonstrated in a prospective study in cervical cancer. We report herein a multicentre prospective randomised controlled trial comparing SN resection alone to SN resection and PLND in early cervical cancer patients evaluating early and late complications.

2. Materials and methods

2.1. Eligibility criteria

SENTICOL-2 (INCA trials and Clinical trials #NCT01639820) was approved by an ethics committee (Comité de Protection des Personnes Sud-Est IV, decision A08-223), and all patients provided written informed consent before inclusion. Patients were recruited at 28 French centres (16 university hospitals, 11 cancer centres and 1 private hospital), with experience in laparoscopic surgery and SN biopsy in cervical cancer. Patients had biopsy-proven early primary cervical cancer meeting International Federation of Gynecology and Obstetrics (FIGO 2009) criteria for stage IA1 with lymphovascular space invasion, IA2, IB1, or IIA1. Inclusion and exclusion criteria are listed in the Supplementary files.

2.2. Study design and objectives

SENTICOL-2 was a multicentre prospective randomised controlled trial comparing SN biopsy alone (SN arm) to SN biopsy and PLND (SN + PLND arm) in early cervical cancer (1st March 2009 to 30th June 2012). Randomisation was performed during surgery when eligible patients fulfilled the following criteria: performance of a double detection of the SN (isotopic + colorimetric), lymphoscintigraphy obtained,

bilateral identification of the SNs, and negative intraoperative assessment of the SNs, when performed. A dynamic balanced open-label randomisation stratified by centre with a 1:1 allocation using block size of 4 was performed during surgery.

Adverse events were evaluated using the National Cancer Institute Common Toxicity Criteria (NCI-CTCAE) version 3.0. Minor complications were defined as grade I–II adverse events and major complications were grade III–V adverse events. The primary end-point was the frequency of patients having one or more early lymphatic complications (≤6 months) following the lymphatic section of the NCI-CTCAE classification (Table 1 of the Supplementary files). Secondary end-points included quality of life (SF-36), SN detection rates and oncologic assessment (recurrence, death) up to 3 years in both arms and false-negative rate of the SN technique in the control arm (SN + PLND arm).

2.3. SN technique, surgery and lymph node processing

One or more surgeon(s) per recruiting centre were trained in the SN technique for cervical cancer before participation in the study. These surgeons had performed previously more than 20 SN biopsies through laparoscopy for cervical cancer. These surgeons performed SN biopsy, PLND and other surgical procedures in all patients. All patients underwent SN identification with a combined method, according to the protocol described in the previous SENTICOL study [15] and detailed in the Supplementary files. After bilateral identification of the SN and eventually negative intraoperative assessment of the SN by frozen section evaluation, patients were randomised to one of the two arms and, if required, the PLND was performed. In case of no SN detection or unilateral detection, the patient was withdrawn from the study and a bilateral PLND was systematically performed (Fig. 1 of the Supplementary files). In case of metastatic SN on frozen sections, the patients were not randomised. The patient underwent bilateral PLND + eventual para-aortic laparoscopic lymph node dissection and then adjuvant chemoradiotherapy.

2.4. Oncological management

The treatment of the primary tumour was performed in each centre following an oncological management protocol (Fig. 2 of the Supplementary files).

Owing to metastatic nodes at final pathology, secondary lymphatic surgery was performed in nine patients of the SN arm and five patients in the SN + PLND arm. In the SN arm, one patient underwent PLND, two para-aortic lymph node dissection (PALND) and six both. In the SN + PLND arm, five patients underwent PALND. These patients were included in the final analysis even if they have increased morbidity because of the re-staging.

2.5. Patient follow-up

Patients were followed-up according to current guidelines at 1, 3 and 6 months after surgery. Early postoperative (up to 30 days after surgery) and late (between 30 days and 6 months after surgery) complications were recorded and classified as minor or major according to the NCI-CTCAE classification. In accordance with the protocol, the follow-up concerning the adverse events ceased at 6 months after the surgery.

The data necessary for the evaluation of lower limb lymphoedema were acquired atinclusion and at the 1, 3 and 6 months visit. They were composed of objective measurements done by the gynaecologist and two questionnaires, one completed by the patient and another completed by the investigator. Also at inclusion, the gynaecologist evaluated if the patient was at risk of lower limb oedema (presence of renal, cardiac or severe venous insufficiency, and measurement of Stemmer sign). Assessment of lymphoedema included a measurement of the circumference at different levels of the right and left lower limbs (root of the thigh, thigh, knee, shrank, ankle). Patients also completed a visual analogue scale (VAS) for four symptoms (heaviness, pain, tiredness and cutaneous tension) at inclusion, 1, 3 and 6 months follow-up. The visual scale goes from 0 to 10 points, with a linear progression with 0 = no symptom and 10 = maximal symptom. The minimally important difference was 1 point.

Patients filled out the SF 36 quality of life questionnaire at inclusion and each follow-up visit (1, 3 and 6 months). Oncological events (recurrence and all deaths) were noted over 3 years of follow-up.

2.6. Statistical analysis

The sample size calculation was based on the use of a Chi-square test to detect a reduction in at least one early lymphatic complication from 17% in the SN + PLND group to 5.6% in the SN arm (26–28), with a type I error of 5% and a power of 80%. After correction for reasons of non-randomisation (SN not detected, node positive at frozen sections, major deviation to protocol, unilateral detection of SN), a total of 124 patients per arm were required.

Categorical variables were described and compared between the two groups using the Chi-square test (or Fisher's exact test when appropriate). The distribution of continuous variables was summarised using mean, standard error, median, first and third quartiles, and compared between the two groups with the Wilcoxon rank-sum test.

To evaluate the functional signs, we determined, for each postoperative visit (1, 3 and 6 months), the VAS score for the following four symptoms: heaviness, pain, tiredness and cutaneous tension. We then

compared the values between the SN group and the SN + PLND group using the Chi-square test.

Primary and secondary end-points were assessed according to the intention to treat principle, which included all randomised patients. The primary end-point (proportion of patients with at least one complication) was compared between the two groups using the Chi-square test. Recurrence-free survival up to 3 years was estimated using the Kaplan–Meier method, and compared using the Log-rank test. P values less than 0.05 were considered to be significant. SAS software (Windows Version 9.2, SAS Institute Inc.) was used for the statistical analysis.

2.7. Role of the funding source

The study was supported by the French National Cancer Institute (STIC 2008 and 2012). The study sponsor had no role in the design, or conduct of the study, interpretation of data, or the writing of the manuscript.

3. Results

Among the 267 patients assessed for eligibility, 61 patients were not randomised because of unilateral SN (n = 21), absence of SN detection (n = 11), positive SN on frozen sections (n = 15), incomplete SN procedure (n = 12), or because lymphoscintigraphy was not performed (n = 2). Of the remaining 206 patients, 105 were randomised to the SN arm and 101 to the SN + PLND arm (Fig. 1). There was no significant difference in terms of patient or tumour characteristics between the two arms (Table 1). Tumours were mainly squamous cell carcinoma (n = 141, 68.4%) and stage IB1 (n = 181, 87.9%).

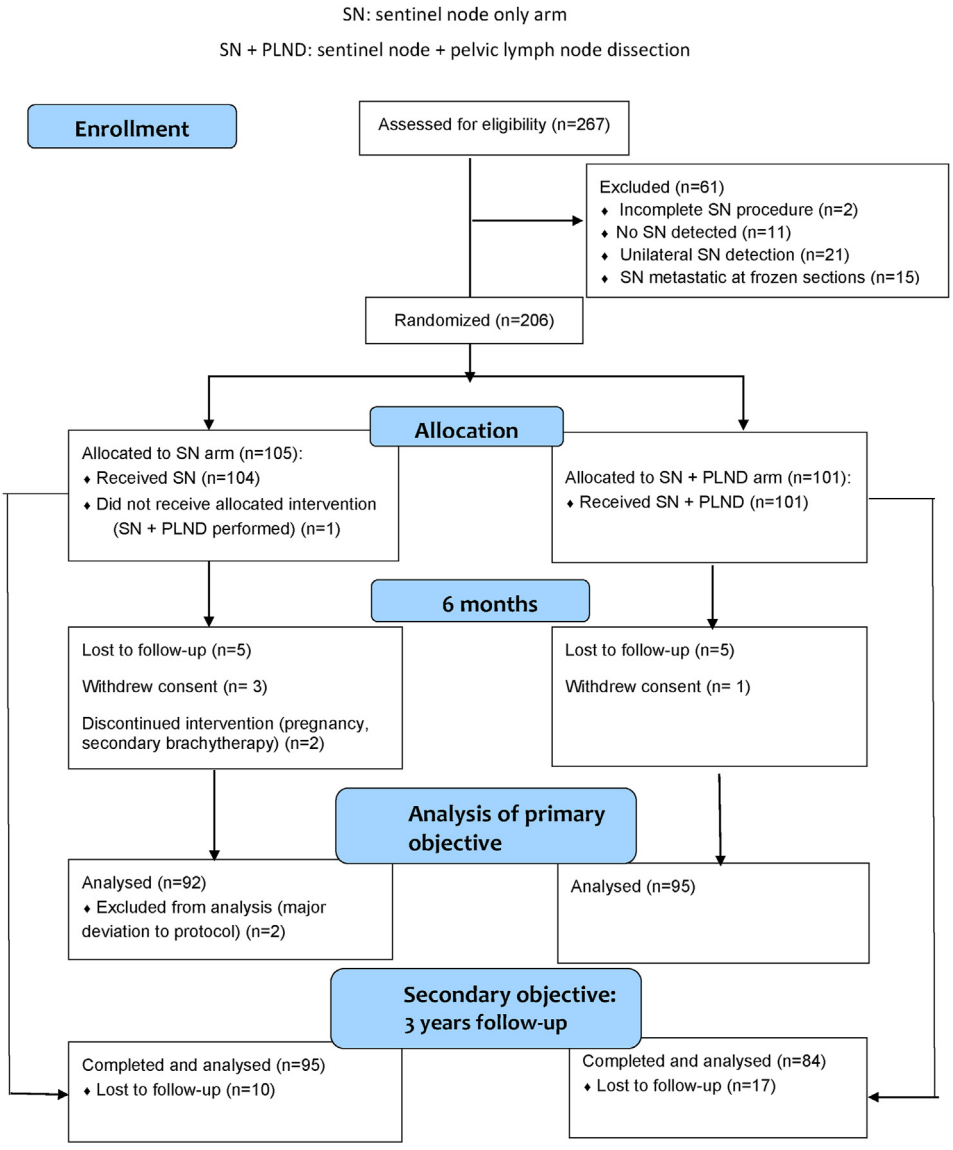

Fig. 1. Consort flow chart. SN, sentinel node only arm; SN + PLND, sentinel node + pelvic lymph node dissection.

3.1. SN detection and surgery

No adverse event, in particular no allergic reaction due to Patent Blue® (Bleu Patente V sodique, Guerbet, Roissy, France) or Nanocys® (Nanocis, Cis Bio International, Gif sur Yvette, France) injections, was observed during the detection period. Intraoperative frozen section examination was performed in 173 cases (n = 83, 79.0%, in the SN arm vs. n = 90, 89.1%, in the SN + PLND arm; p = 0.06). Tumour surgery is described in Table 2 of the Supplementary files. There were 15 intra- or immediate postoperative complications: six (5.7%) were observed in the SN arm, and nine (8.9%) in the SN + PLND arm (p = 0.43): characteristics of these complications are presented in the Supplementary files.

3.2. SN histological analysis

A total of 770 SNs were analysed. The histopathological protocol of the SN and non-SN is presented in the Supplementary files. The median number of SNs identified was 3 per patient and 1 per side, and was identical in the two arms. In the SN + PLND arm, the median number of non-SNs analysed per patient was 13 (3–40). At final pathologic evaluation, there were 21 (10.2%) patients who had metastatic disease to the SN, and 26 SN had metastasis, including eight macrometastases, nine micrometastases and nine isolated tumoural cells. Table 2 summarises the cases of metastatic SN without significant difference between the two groups. In the SN + PLND arm, there was no false-negative result using the SN technique. Also, there was no statistically difference in the proportion of patients with metastatic lymph nodes when comparing patients with frozen sections performed and patients with frozen sections not performed (due to absence of suspicious SN): 18 cases of 173 patients (10.3%) versus three cases of 33 patients (9.1%) (p = 0.72).

3.3. Postoperative treatments

In the 21 patients with metastatic nodes, nine patients (8.6%) underwent a secondary lymph node dissection in the SN arm (pelvic dissection: 1 case, para-aortic dissection only: 2 cases and pelvic + para-aortic: 6 cases) and five patients (5%) underwent a secondary lymph node dissection in the SN + PLND arm (all para-aortic dissection) (p = 0.021).

Adjuvant radiochemotherapy was delivered in 29 patients because of metastatic nodes, parametrial invasion, or final tumoral diameter larger than 4 cm. The rate of adjuvant radiochemotherapy was similar in both arms: 13 patients (12.5%) in the SN arm and 16 patients (15.8%) in the SN + PLND arm (p = 0.55).

All morbidities (including lymphatic morbidity) related to these adjuvant treatments were included in the final analysis of the primary and secondary end-points.

3.4. Patient follow-up

Ninety percent of patients in the SN arm and 94% of patients in the SN + PLND arm reached their three follow-up visits. The presence of preoperative risk factor of lymphoedema at baseline was similar in the two arms: 12 patients (12.1%) in the SN arm and 10 patients (11.2%) in the SN + PLND arm (p = 1.0). The proportion of patients with any grade lymphatic morbidity at 6-month follow-up was significantly lower in the SN arm (n = 33, 31.4%) than in the SN + PLND arm (n = 52, 51.5%; p = 0.0046, Table 3). We also evaluated clinically the postoperative neurological complications

Table 1
Characteristics of patients and tumours according to study arm.

	SN arm N = 105	SN + PLND arm N = 101	P-value
Mean age (SD), year	44.2 (12.0)	44.6 (11.2)	0.80
Mean BMI (SD), kg/m^2	23.6 (4.6)	23.9 (5.4)	0.92
Histotype: N (%)			
Squamous	68 (64.8)	73 (72.3)	0.68
Adenocarcinoma	33 (31.4)	24 (23.8)	
Adenosquamous	4 (3.8)	4 (4)	
LVSI (+): N (%)	19 (27.9)	16 (25.4)	0.84
FIGO 2009 stage: N (%)			
IA1 LVSI+	7 (6.7)	2 (2.0)	0.29
IA2	5 (4.8)	6 (6.0)	
IB1	90 (85.7)	91 (91.0)	
IIA	3 (2.9)	1 (1.0)	
Mean tumour diameter in mm (SD)	18.4 (9.3)	16.9 (8.7)	0.28
Presence of risk factor for lymphoedema N (%)	12 (12.1)	10 (11.2)	1.0

SN, sentinel node; SN + PLND, sentinel node + pelvic lymph node dissection; SD, standard deviation; BMI, body mass index; LVSI, lymph-vascular space invasion.

Table 2
Cases of metastatic SN according to study arm.

	SN arm N = 105	SN + PLND arm N = 101	P-value
All SN	410	360	
Metastatic N (%)	15 (3.7)	11 (3.1)	0.88
Macrometastases N (%)	5 (1.2)	3 (0.8)	0.87
Micrometastases N (%)	3 (0.7)	6 (1.7)	0.48
Isolated tumour cells N (%)	7 (1.7)	2 (0.6)	0.11
Patients	105	101	
Macrometastases N (%)	3 (2.9)	3 (3.0)	1.0
Micrometastases N (%)	3 (2.9)	4 (4.0)	0.72
Isolated tumour cells N (%)	6 (5.7)	2 (2.0)	0.28

SN, sentinel node; SN + PLND, sentinel node + pelvic lymph node dissection.

Table 3
Six-month postoperative lymphatic morbidity according to study arm.

Complications	SN arm N = 105	SN + PLND arm N = 101	P-value
All complications	33 (31.4%)	56 (55.4%)	0.004
Major complications	1 (1.2%)	6 (5.9%)	0.061
Minor complications	32 (30.4%)	50 (49.5%)	0.007

SN, sentinel node; SN + PLND, sentinel node + pelvic lymph node dissection.
Major complications are grade III, IV or V lymphatic complications of the NCI CTCAE classification.
Minor complications are grade I or II lymphatic complications of the NCI CTCAE classification.

following the NCI-CTCAE classification. These troubles were sensory and motor disturbances of obturator nerves or genitofemoral nerves. The proportion of patients with any grade postoperative neurological symptoms was significantly lower in the SN arm (n = 8, 7.8%) than in the SN + PLND arm (n = 20, 20.6%, p = 0.01) at 1-month follow-up, with a smaller difference at 3 months (8.7% vs. 19.1%, p = 0.06) and 6 months (11.0% vs. 17.9%, p = 0.21). There was no significant difference in the proportion of patients with significant lymphoedema (grades II–V) in the two arms (month 1: 0% [n = 0] vs. 2.1% [n = 2], ns, month 3: 2 (2.2%) vs. 3 (3.2%), ns, month 6: 2 [2.2%] vs. 0 [0%], ns). Tiredness was significantly greater for patients in the SN + PLND arm at 1 month but was not significant at 3 and 6 months (Table 4). The difference between the two arms concerning the other symptoms (heaviness, pain and cutaneous tension) was not significant. Concerning lymphoedema, the main results are presented in Table 3 of the Supplementary files. There was no significant difference in the proportion of patients with significant lymphoedema between the two groups.

Other 6-month postoperative morbidities are shown in Table 4 of the Supplementary files.

There was no difference at the different follow-up visits in postoperative complication rate, therapeutic management after SN procedure, readmission and times of hospitalisation, supplementary ambulatory visits, medical treatment, supplementary unplanned imaging or biology prescribed in outpatient clinic (Table 5 of the Supplementary files).

Patient follow-up was censored at 3 years and at that time, 27 patients were lost to follow-up (10 in the SN arm and 17 in the SN + PNLD arm). Eight recurrences or deaths were observed in the SN arm versus five in the SN + PNLD arm, yielding an estimated 3-year recurrence-survival of 92% and 94% in each arm, respectively (Log-rank: p = 0.48; Fig. 2). Only two nodal recurrences were observed: one in the pelvic area in the SN arm and one in para-aortic location in the SN + PLND arm. Distant metastases were observed in four patients in the SN arm and two patients in the SN + PNLD arm. In addition, vaginal or parametrial recurrences were observed in three patients in the SN arm and two patients in the SN + PLND arm. No port-site metastasis was reported during oncological follow-up.

4. Discussion

Our study showed that SN biopsy alone was associated with a significant reduction in lymphatic-related morbidity when compared to SN biopsy + PLND in early cervical cancer. Sensory and motor disturbances were also significantly reduced at postoperative month 1 in the SN arm. In a preliminary feasibility study (SENTICOL), we found a detection rate of 97% with no false negative in case of bilateral detection, which is crucial for SN technique in early cervical cancer [15]. Although the SN technique has been widely studied in early cervical cancer [16], this is the first study to the best of our knowledge to prospectively compare the

Table 4
Symptoms related to lymphoedema at the 1, 3 and 6 months visits. Visual scale evaluation (from 0 to 10).

Time	Symptoms	SN arm		SN + PLND arm		P-value
		N	Mean VAS	N	Mean VAS	
V1 (1 month)	Heaviness, mean (SD)	73	0.90 (1.62)	72	1.58 (2.49)	0.28
V1	Pain, mean (SD)	74	0.58 (1.2)	71	1.37 (2.42)	0.16
V1	Tiredness, mean (SD)	72	0.92 (1.9)	71	1.87 (2.61)	0.03
V1	Cutaneous tension, mean (SD)	73	0.31 (1.04)	68	0.69 (1.86)	0.70
V2 (3 months)	Heaviness, mean (SD)	64	1.31 (2.14)	67	1.77 (2.42)	0.16
V2	Pain, mean (SD)	64	0.86 (1.79)	67	1.28 (2.26)	0.29
V2	Tiredness, mean (SD)	64	1.22 (2.18)	67	1.94 (2.78)	0.11
V2	Cutaneous tension, mean (SD)	62	0.60 (1.60)	67	0.75 (1.59)	0.31
V3 (6 months)	Heaviness, mean (SD)	66	1.25 (1.90)	71	1.66 (2.44)	0.53
V3	Pain, mean (SD)	67	0.84 (1.82)	71	1.11 (1.93)	0.48
V3	Tiredness, mean (SD)	67	1.67 (2.43)	70	1.29 (2.11)	0.31
V3	Cutaneous tension, mean (SD)	67	0.65 (1.71)	70	0.57 (1.46)	0.91

SN, sentinel node; SN + PLND, sentinel node + pelvic lymph node dissection; SD, standard deviation; VAS, visual analogue scale; V1, 1-month visit; V3, 3-month visit; V6, 6-month visit.

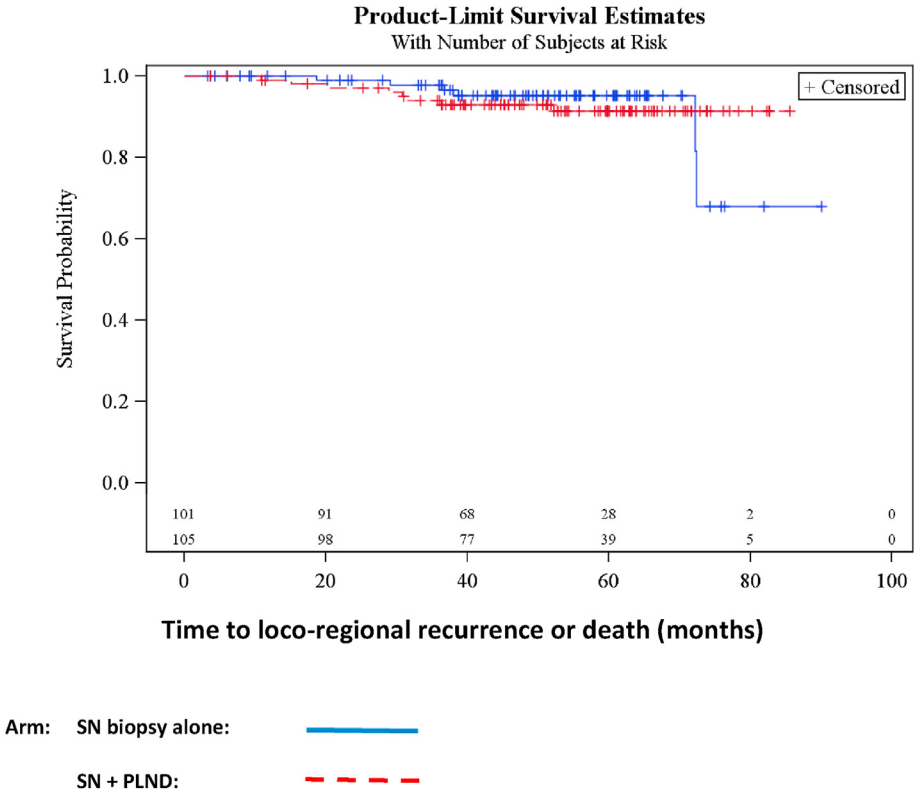

Fig. 2. Recurrence-free survival.

morbidity, namely lymphatic, of SN biopsy alone versus full lymphadenectomy. Moreover, this is one of the expected benefits of the SN technique, which is regularly argued to justify its indication. Indeed, the number of sampled nodes is a well-known risk factor for lower limb lymphoedema [10,11,17,18] as well as the removal of the lateral external iliac chain or the circumflex iliac lymph nodes. Thus, SN biopsy, which relies on targeted and limited sampling of nodes, mainly located in interiliac region [19,20], should reduce the risk of lower limb lymphoedema.

Lower limb lymphoedema is a main component in quality of life in patients with gynaecologic cancers [21]. In our study, we reported an increased risk of symptoms related to lymphoedema and nerve complications in the SN + PLND arm. In their retrospective study including 152 gynaecological cancers, Biglia *et al.* [17] showed that short-term incidence of lower limb lymphoedema and nerve complications after lymphadenectomy was 36% and predictive of long-term persistence. Among the risk factors analysed, the number of lymph nodes removed and adjuvant radiotherapy were significantly associated with increased incidence of minor complications. In our study, there was no difference in adjuvant treatment between the two arms, and thus the number of lymph nodes removed may explain the observed difference. Another possible risk factor is secondary reoperation for complementary lymph node dissection [8]. Only one patient having secondary surgery had another metastatic node. She was in the SN group and underwent a secondary para-aortic lymph node dissection with one positive node at final pathology. As all these patients with positive nodes at final pathology were treated with postoperative chemoradiotherapy, and considering the worsened lymphatic morbidity of reoperation, we can suggest that omitting re-staging is a possible option in case of positive SN.

We report a low rate of lymphoceles that was comparable in both arms (maximum 3.2% at month 3). In their prospective study examining the incidence of lymphoceles following lymphadenectomy in 800 patients with gynaecological cancer, Zikan *et al.* [21] found that higher number of lymph nodes obtained, and radical hysterectomy were independent risk factors for the development of symptomatic lymphoceles. However, one should note that most lymphoceles were asymptomatic. We must acknowledge that we did not perform systematic imaging in our patients, potentially explaining the low rate of lymphoceles in our patients. Patients in SN arm had neither hospitalisation/consultation nor additional imaging after surgery compared with the SN + PLND arm. In our study, there was no significant difference in the proportion of patients with significant

lymphoedema between the two groups. At the 3-month visit (Table 3 of the Supplementary files), there is a trend to less lymphoedema at the thigh level in the SN arm, but the difference is not significant, probably in relation with an insufficient number of patients evaluated, as 27% of measurements are missing.

The analyses of postoperative neurological symptoms show a difference at the 1-month visit in favour of the SN arm. However, later evaluation of this symptom displays no significant difference. This result can be related to several factors: spontaneous recovery of nerve function after neural astonishment due to PLND, increased number of secondary lymph node dissection in the SN arm leading to increased number of neural troubles.

As far as oncological follow-up, the recurrence-free survival was similar in both arms of our study. Our data suggests that omitting PLND was not associated with an increased risk of recurrence in this cohort of patients with early cervical cancer. However, one must note that oncologic outcome was not the primary objective of our study, also 27 patients (13.1%) were lost to follow-up and 29 patients (14.1%) had postoperative chemoradiotherapy.

The strengths of our study include the fact that it is the first prospective multicentre randomised trial comparing SN biopsy versus SN biopsy and PLND, and assessing the morbidity of the two procedures. All participating centres had a prolonged experience with SN technique, as reflected by the high SN detection rate and the absence of false-negative cases. Furthermore, 92.3% of patients attended their three follow-up consultations and the response rate for all QoL questionnaire was 69.3%. Similarly, we recognise that our study is not without limitations. The multicentre nature of the study may have led to variations in pre- and postoperative management of the patients mainly due to variations in local treatment protocols. The follow-up for postoperative morbidity was limited to 6 months, and therefore we might have missed late manifestations of lymphatic complications. The median number of non-SNs was 13 per patient. More extensive nodal dissection may induce more lymphatic morbidities [21–23]. In our study, 95.9% of surgeries were performed through laparoscopy or laparoscopically assisted vaginal approach. The recent publication of the LACC (Laparoscopic Approach to Cervical Cancer) study [24] demonstrated that on an oncological point of view, laparotomy should be the surgical approach of choice for the management for early cervical cancer. Our results may not be extrapolated to patient treated through laparotomy. Finally, the measurement of limb circumferences was missing in 27% of cases and this may have underestimated the incidence of lower limb lymphoedema.

5. Conclusion

SN biopsy alone is associated with a lower rate of early lymph-related complications compared with full PLND. This study confirms that SN alone is associated with decreased early morbidity and improved quality of life. Further randomised controlled studies, with longer follow-up, are encouraged to confirm these data. In addition, the impact of SN biopsy alone on oncologic outcomes must be confirmed in prospective randomised trials. Such is the aim of the SENTICOL III trial [25] that is currently underway.

Authors' Contributions

Patrice Mathevet: Conceptualization; Funding acquisition; Investigation; Methodology; Writing – original draft. Fabrice Lécuru: Conceptualization; Investigation; Methodology; Writing – review & editing. Catherine Uzan: Investigation; Writing – review & editing. Florent Boutitie: Methodology; Data curation; Formal analysis; Writing – review & editing. Laurent Magaud: Methodology; Data curation; Project administration; Frederic Guyon: Investigation; Writing – review & editing. Denis Querleu: Investigation; Writing – review & editing. Virginie Fourchotte: Investigation; Writing – review & editing. Marc Baron: Investigation; Writing – review & editing. Anne-Sophie Bat: Investigation; Writing – review & editing.

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Conflict of interest statement

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejca.2021.02.009.

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