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ORIGINAL ARTICLE

Comparison of clinical outcomes in women with surgically treated early primary cervical cancer: Lymphadenectomy vs sentinel lymph node biopsy

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Abstract

Background: The primary objective of this study was to elucidate the impact of sentinel lymph node (SLN) mapping and biopsy techniques on the clinical outcomes of women with early primary cervical cancer.

Methods: All consecutive women with clinically determined stage I-IIA cervical cancer who underwent lymph node assessment with either SLN mapping or conventional pelvic/para-aortic lymphadenectomy were reviewed.

Results: Women in the SLN group (n = 33) had fewer total dissected pelvic nodes (8.3 ± 5.9 vs 17.4 ± 7.7, $p < 0.001$), less intraoperative blood loss (513 ± 332 vs 1228 ± 1170 mL, $p < 0.001$), a shorter length of hospital stay (7.1 ± 2.4 vs 10.2 ± 6.1 days, $p = 0.004$) than women in the conventional lymphadenectomy group (n = 74). The rates of recurrence-free survival (3-year: 87.6% vs 82.9%) and overall survival (3-year: 100% vs 91.0%) did not differ between the SLN group and the conventional lymphadenectomy group ($p = 0.846$ and $p = 0.254$, respectively).

Conclusion: SLN biopsy does not seem to be associated with an inferior survival outcome compared with conventional lymphadenectomy in women with early primary cervical cancer. In addition, it is associated with less blood loss and a shorter length of hospital stay.

Keywords: Cervical cancer; Lymphadenectomy; Sentinel lymph node

1. INTRODUCTION

Pelvic lymph node status is of paramount importance for personalized decision-making about whether to administer adjuvant therapy to patients with cervical cancer. The percentage of lymph node involvement in patients with early-stage cervical cancer is estimated to be 15% to 20%.[1–3] Consequently, a substantial number of women may undergo unnecessary pelvic lymphadenectomy and thus be exposed to extensive surgical risk. The National Comprehensive Cancer Network (NCCN) guidelines recommend the consideration of sentinel lymph node (SLN) biopsy in patients with early-stage cervical cancer, preferably in patients with tumors <2 cm in diameter.[4] Similarly, SLN biopsy has also been approved for endometrial cancer staging procedures in both low- and high-risk patients, thus suggesting the value of incorporating SLN biopsy into clinical practice.[5] Despite these guidelines, SLN biopsy has not gained popularity in the field of gynecology oncology due to a lack of prospective evidence related to long-term oncological safety.[6] The three ongoing prospective trials, namely, SENTIX, PHENIX, and SENTICOL III, will most likely provide more solid and robust clinical evidence.[7–9]

Our institution began to use the SLN mapping technique in women with clinically uterine-confined endometrial cancer and cervical cancer in July 2017. In our previous study on the impact of SLN mapping and biopsy on the clinical outcomes of women with clinically uterine-confined endometrial cancer, SLN biopsy was found to be associated with lower numbers of total dissected pelvic nodes, a lower incidence of para-aortic lymph node dissection, less intraoperative blood loss, and lower complication rates without compromising survival.[10] Thus, the primary aim of this study was to compare the recurrence-free survival (RFS) between women with early primary cervical cancer who received conventional lymphadenectomy and those who received SLN mapping and biopsy. The secondary aims of this study include between-group comparisons of overall survival (OS), total number of dissected lymph nodes, and perioperative clinical outcomes.

2. METHODS

This retrospective study analyzed all consecutive women aged 20 years and older with biopsy-proven early primary cervical

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cancer of any histology, who met the International Federation of Gynecology and Obstetrics (FIGO 1994, 2009, or 2018) staging system criteria for stages I-IIA, and received surgical treatment in a tertiary referral center from January 2008 until July 2023. The clinical staging was determined based on preoperative physical examination (inspection, palpation), conization or amputation of the cervix, and imaging survey, including X-ray examination of the lungs and skeletons, hysteroscopy, colposcopy, proctoscopy, cystoscopy, and intravenous pyelography. Computerized tomography, magnetic resonance imaging, and positron emission tomography–computed tomography have been considered acceptable imaging tools for formal staging since 2019. This study was approved by the Research Ethics Review Committee of the hospital.

All the women underwent surgical treatment via either an open abdominal approach, a laparoscopic approach, or a robotic approach. The surgical method that was used was chosen at the discretion of the surgeon and personal financial considerations. The open abdominal approach has become the standard choice since the publication of a prospective randomized trial (the phase III LACC trial, NCT00614211), which demonstrated poorer oncologic outcomes and survival after minimally invasive radical hysterectomy than after open abdominal radical hysterectomy.[3] The standard surgical treatment included radical or modified radical hysterectomy, bilateral salpingectomy, and pelvic lymph node assessment and dissection. SLN mapping and/or robotic surgery were performed on women who could afford the additional medical cost incurred by the application of an endoscopic fluorescence imaging system (PINPOINT; Novadaq, Mississauga, Canada) for SLN mapping and the da Vinci Si Surgical System (Intuitive Surgical Inc., Sunnyvale, CA), because these costs are not covered by the National Health Insurance in Taiwan. Para-aortic lymphadenectomy was performed at the discretion of the attending surgeon on basis of the presence of risk factors such as larger primary tumor size (>2 cm), suspicious nodal status, or the presence of positive para-aortic SLN mapping results. In the SLN group, the indocyanine green tracer was diluted to a dose of 2.5 mg/mL and injected into the cervix at the 3:00 and 9:00 positions. At each position, 1 mL of the indocyanine green tracer was injected into the cervical submucosa (1 cm deep) and deep cervical stroma (3 cm deep), resulting in a total volume of 4 mL. The SLN was detected by visualizing of colored lymph nodes with the endoscopic fluorescence imaging system. Because we do not have the SPY portable handheld imager (SPY-PHI) for open abdominal surgery, a folded drape was used to cover the open wound to create a closed environment identical to that of the laparoscopic or robotic approach while the lymph node basins were examined with the endoscopic fluorescence imaging system. The protocol for SLN mapping in cervical cancer is identical to the one that is used in endometrial cancer, which was adopted from the SLN algorithm developed by the Memorial Sloan Kettering Cancer Center.[11] All mapped SLNs and grossly enlarged suspicious nodes, regardless of mapping, were removed. Ipsilateral pelvic lymphadenectomy (including the external iliac, internal iliac, and obturator regions) was performed in any patients for whom mapping failed.[11]

SLN samples were processed according to the size of the nodes. If the node was small (ie, ≤1 cm in its long axis), it was bivalved and examined by pathologists with routine hematoxylin and eosin (H&E) staining. If the node was large (ie, >1 cm), it was sliced at 2 to 3-mm intervals perpendicular to the long axis. Additional cytokeratin immunohistochemistry (IHC) staining was performed at the discretion of an individual pathologist and/or if the routine H&E staining results were negative.[10] Nodal status was reported in a standardized fashion according to the American Joint Committee on Cancer.[12] Macrometastasis was defined as a disease volume >2 mm, micrometastasis was defined as a disease volume of 0.2 to 2 mm, and isolated tumor cells were defined as foci of disease measuring <0.2 mm in greatest dimension.[12]

Disease recurrence was assessed according to the appearance of abnormal radiological findings, or histological evidence from biopsy analyses, whichever occurred first. RFS was defined as the time interval from the date of surgery to the date of clinically defined recurrence, disease progression, or last follow-up. OS was defined as the time interval from the date of surgery to the date of death, or the last follow-up.

Stata version 11.0 (Stata Corp, College Station, TX) was used for the statistical analyses. The Chi-square test and Fisher exact test were used as appropriate. A p value of <0.05 was considered statistically significant. Survival curves were generated via the Kaplan-Meier method, and the significant differences in the survival curves were estimated with the log-rank test. Multivariable Cox proportional hazards model was performed by using clinically relevant variables and all variables with $p < 0.05$.

3. RESULTS

A total of 107 women with early primary cervical cancer were included in the study. The baseline and clinicopathologic characteristics of these women are shown in Table 1. The most common histological type in both groups was squamous cell carcinoma, followed by adenocarcinoma. Thirty-three (30.8%) women underwent SLN mapping and biopsy, whereas the remaining women (n = 74) underwent pelvic lymphadenectomy. Except for parity, the baseline characteristics were similar in both groups (Table 1). However, women in the SLN group had fewer total dissected pelvic nodes, less intraoperative blood loss, and a shorter length of hospital stay than did those in the traditional group (Table 1). Additionally, women in the SLN group tended to have a lower incidence of pelvic lymphocysts than did those in the traditional group (p = 0.090, Table 1). In the SLN group, bilateral mapping was achieved in 81.8% (n = 27) of the women.

Survival analysis did not reveal any difference in RFS or OS (p = 0.846 and 0.254, respectively; log-rank test; Figs. 1 and 2, Table 1). The 3-year RFS was 87.6% (95% CI, 70.2%-95.2%) in the SLN group, and 82.9% (95% CI, 71.9%-89.9%) in the lymphadenectomy group (Fig. 1). The 3-year OS was 100% in the SLN group, and 91.0% (95% CI, 81.0% to 95.8%) in the lymphadenectomy group (Fig. 2).

The locations of the detected SLNs in women who underwent SLN mapping are shown in Table 2. The most common location of detected SLNs was the external iliac area, followed by the obturator area (Table 2).

The application of SLN mapping and biopsy tended to be a predictor of a shorter length of hospital stay (coefficient = –2.16, 95% CI, –4.38 to 0.05, p = 0.055), adjusted by blood loss (coefficient = 0.0014, 95% CI, 0.0004-0.0024, p = 0.005) in multivariable linear regression analysis.

Survival analysis did not reveal any difference in RFS or OS among the subgroup of patients with squamous cervical cancer (p = 0.272 and 0.429, respectively, Fig. 3A, B). The 3-year RFS was 80.0% (95% CI, 55.1% to 92.0%) in the SLN group, and 87.1% (95% CI, 73.4% to 94.0%) in the lymphadenectomy group (Fig. 3A). The 3-year OS was 100% in the SLN group, and 91.2% (95% CI, 78.1%-96.6%) in the lymphadenectomy group (Fig. 3B).

Survival analysis did not reveal any difference in RFS or OS in the subgroup of nonsquamous cervical cancer patients (p = 0.075 and 0.403, respectively; Fig. 4A, B). The 3-year RFS was 100% in the SLN group, and 74.9% (95% CI, 52.3%-87.9%)

Table 1

Baseline and clinic-pathological characteristics of women with early primary cervical cancer who underwent surgical treatment with and without sentinel lymph node mapping (n = 107)

Variables	SLN (n = 33)	Traditional (n = 74)	p^a
Age, y	50.8 ± 15.2	51.7 ± 12.2	0.606
Parity	1.5 ± 1.2	2.5 ± 1.5	<0.001
Body mass index, kg/m^2	25.8 ± 4.7	25.2 ± 4.3	0.670
SCC, ng/mL	5.3 ± 8.7	2.9 ± 2.7	0.706
ECOG score			
0	3 (9)	18 (24)	0.162
1	29 (88)	54 (73)	
2	1 (3)	1 (1)	
3	0	1 (1)	
FIGO stage			
IA	2 (6)	12 (16)	0.372
IB	29 (88)	57 (77)	
IIA	2 (6)	5 (7)	
Age, y	50.8 ± 15.2	51.7 ± 12.2	0.606
Open	32 (97)	66 (89)	0.269
Robotic	1 (3)	8 (11)	—
Surgical method			
Radical hysterectomy	29 (88)	71 (96)	0.163
Radical trachelectomy	3 (9)	3 (4)	—
Conization	1 (3)	0 (0)	—
Surgical time, min	264 ± 69	275 ± 58	0.160
Blood loss, mL	513 ± 332	1228 ± 1170	<0.001
SLN mapping			
Left pelvis			
Detected	31 (94)	—	—
Failed	2 (6)		
Right pelvis			
Detected	28 (85)	—	—
Failed	5 (15)		
Total dissected pelvic LN number	8.3 ± 5.9	17.4 ± 7.7	<0.001
Women with LN metastases	7 (21.2)	11 (14.9)	0.420
Isolated tumor cell	1 (11)	0 (0)	
Micrometastasis	1 (11)	0 (0)	
Macrometastasis	7 (79)	11 (100)	
Use of cytokeratin staining	8 (24)	4 (5)	0.008
Cell type			
Squamous	20 (61)	48 (65)	0.885
Adenocarcinoma	11 (33)	21 (28)	
Others	2 (6)	5 (7)	
Cell grade			
1	1 (3)	5 (7)	0.603
2	14 (42)	38 (51)	
3	11 (33)	19 (26)	
Not specified	7 (21)	12 (16)	
Lymphovascular space invasion	19 (58)	49 (66)	0.167
Deep stromal invasion	19 (58)	44 (59)	0.964
Parametrium involvement	4 (12)	5 (7)	0.453
Tumor size, mm	33.0 ± 18.4	25.5 ± 14.9	0.055
≤2 cm	9 (27)	34 (46)	
2-4 cm	14 (42)	25 (34)	
≥4 cm	10 (30)	14 (19)	
Length of hospital stay, d	7.1 ± 2.4	10.2 ± 6.1	0.004
Adjuvant therapy	16 (48)	34 (46)	0.643
Adjuvant radiotherapy	6 (18)	7 (9)	—
Adjuvant chemotherapy	0 (0)	1 (1)	—
Adjuvant concurrent chemoradiation	10 (30)	26 (35)	—
Complications			
Bladder perforation	1 (3)	3 (4)	1.000
Vesicovaginal fistulae	1 (3)	2 (3)	1.000

(Continued)

Table 1
Continued

Variables	SLN (n = 33)	Traditional (n = 74)	*p*[a]
Lymphocyst	1 (3)	10 (14)	0.090
Others	2 (6)	1 (1)	0.224
Recurrence	4 (12)	17 (23)	0.846
Death	0 (0)	14 (19)	0.254

Data were presented as mean ± SD or number (percentage).
ECOG = Eastern Cooperative Oncology Group, FIGO = International Federation of Gynecology and Obstetrics, LN = lymph node, SCC = squamous cell carcinoma antigen, SLN = sentinel lymph node.
[a]Spearman rank-sum test, Chi-square test, Fisher exact test, or log-rank test.

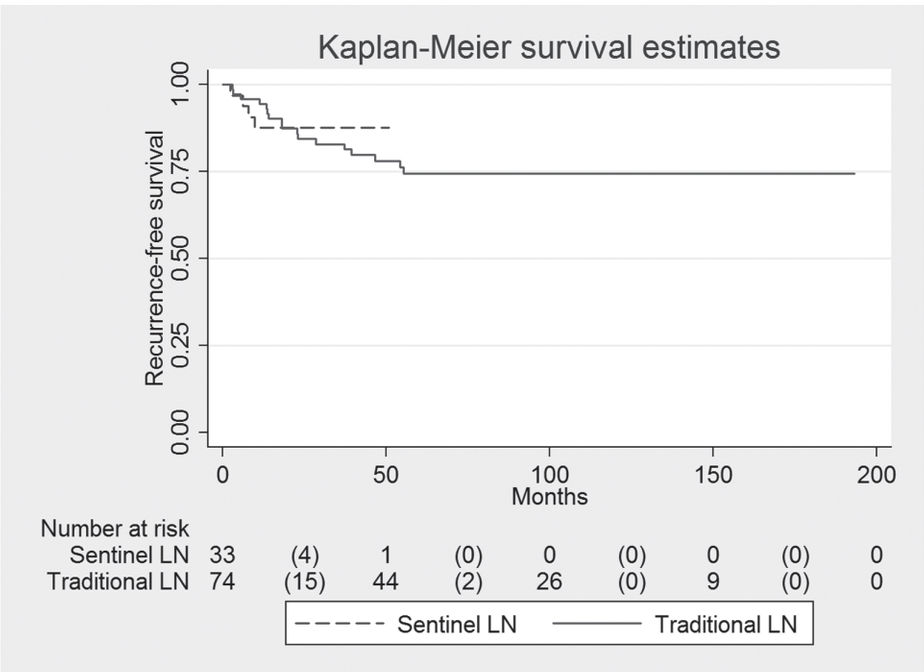

Fig. 1 Probabilities of recurrence-free survival in surgically treated early-stage cervical cancer women who received sentinel lymph node mapping and biopsy (n = 33) vs lymphadenectomy (n = 74). LN = lymph node.

in the lymphadenectomy group (Fig. 4A). The 3-year OS was 100% in the SLN group, and 90.7% (95% CI, 67.6%-97.6%) in the lymphadenectomy group (Fig. 4B).

Comparisons of the perioperative outcomes of women with early primary cervical cancer who underwent radical hysterectomy between laparotomic and robotic radical hysterectomy are tabulated in Table 3. Except for blood loss, there were no differences in surgical time, perioperative complications, or length of stay (Table 3).

4. DISCUSSION

Our study did not reveal a difference in survival between women with early-stage cervical cancer who underwent SLN mapping and biopsy or those who underwent conventional lymphadenectomy. Similarly, three meta-analyses reported no detrimental effects of SLN biopsy on oncological outcomes in women with early-stage cervical cancer, confirming the safety of this technique.[13–15] Ronsini et al[14] reported that most of the cases of recurrences among women who underwent SLN biopsy alone did not have recurrence sites that were directly correlated with lymphadenectomy failure. In our study, nodal recurrence was observed only in one woman who underwent SLN biopsy and had histologically proven pelvic SLN metastasis. There was no nodal recurrence in the pelvic lymphadenectomy group. Chiyoda et al[13] identified several studies that revealed no negative impact of SLN biopsy alone on recurrence or survival in early-stage cervical cancer patients with a tumor size ≤2 to 4 cm. Additionally, a national prospective multicenter study (SENTIREC trial) reported that SLN mapping is highly sensitive but demands full adherence to the SLN algorithm for tumors >2 cm.[16] In our study, we included women with bulky tumors >2 cm (equivalent to 2018 FIGO stage IB2, IB3, IIA2), as shown in Table 1. There was no impact of tumor size on the survival outcome of women in the SLN group.

SLN mapping identifies an additional 15% of women with positive lymph nodes, including those with low-volume nodal disease (micrometastasis and isolated tumor cells).[17] In this study, the total number of pelvic lymph nodes that were dissected was lower in the SLN group than in the pelvic lymphadenectomy group (Table 1). However, this did not translate into a lower detection rate of lymph node metastases in the SLN group, and it did not compromise the survival outcome. In fact,

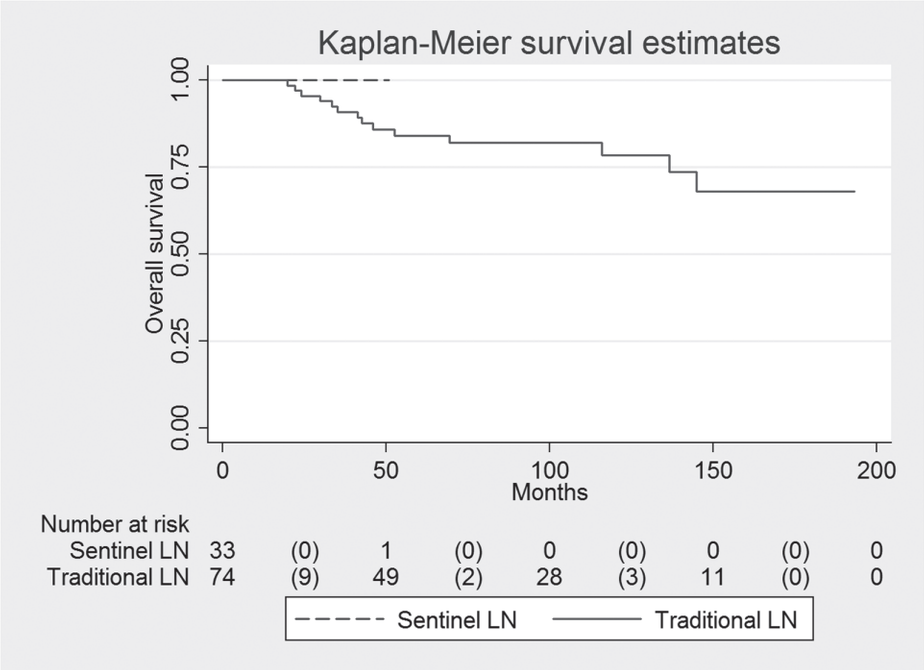

Fig. 2 Probabilities of overall survival in surgically treated early-stage cervical cancer women who received sentinel lymph node mapping and biopsy (n = 33) vs lymphadenectomy (n = 74). LN = lymph node.

Table 2

Location of detected sentinel lymph nodes in women who underwent sentinel lymph node mapping (n = 33)

Location	Left hemipelvis (n = 31)	Right hemipelvis (n = 28)
External iliac	26	24
Obturator	12	12
Common iliac	2	5
Presacral	0	0
Para-aortic	0	0
Not specified	0	0

Values are expressed as number.

the detection rates of lymph node metastases in both groups of women were comparable with those reported in the literature (21.2% in the SLN group and 14.9% in the pelvic lymphadenectomy group, $p = 0.420$). Two possible explanations for this finding include technical proficiency and the use of cytokeratin IHC staining. Given the extensive experience gained from endometrial cancer, the SLN detection rates of at least one hemipelvic and bilateral hemipelvic mapping by our surgeons were 97% and 81.8%, respectively. Second, studies have shown that cytokeratin IHC staining with an anti-cytokeratin AE1:AE3 antibody helps in the identification of occult metastases that are difficult to detect by H&E.[10,18,19] Thus, on the basis of our previous experience in endometrial cancer and in conjunction with our current findings, we recommend the integration of cytokeratin IHC staining of SLNs for women with negative H&E staining.[10]

Less blood loss and a shorter length of hospital stay were observed in the SLN group than in the pelvic lymphadenectomy group (Table 1). A systematic review of 21 endometrial cancer studies revealed that SLN biopsy was associated with lower estimated blood loss.[20] Another retrospective study involving 621 patients with stage I-III endometrial cancer revealed that SLN biopsy was associated with a significantly shorter mean operative time, shorter length of hospital stay, and lower median estimated blood loss than pelvic lymphadenectomy.[21] During pelvic lymphadenectomy, the retroperitoneal space (such as the paravesical space and obturator fossa) should be thoroughly dissected to remove all lymph nodes in the drainage area where the primary tumor is located. This inadvertently leads to vessel disruption and thus increases intraoperative blood loss. SLN biopsy involves the removal of the first group of lymph nodes that drain the tumor and thus results in less damage than the standard procedure of lymphadenectomy. A shorter length of hospital stay is likely an additional benefit of the lower degree of radicality of the surgery. Although in this study, we did not observe a difference in surgical morbidity between the two groups, the application of SLN mapping and biopsy tended to predict the length of hospital stay (coefficient = −2.16, 95% CI, −4.38 to 0.05, $p = 0.055$), adjusted by blood loss (coefficient = 0.0014, 95% CI, 0.0004-0.0024, $p = 0.005$) according to multivariable linear regression analysis. The shorter hospitalization associated with SLN biopsy potentially reduces surgical costs and improves women's satisfaction.[22]

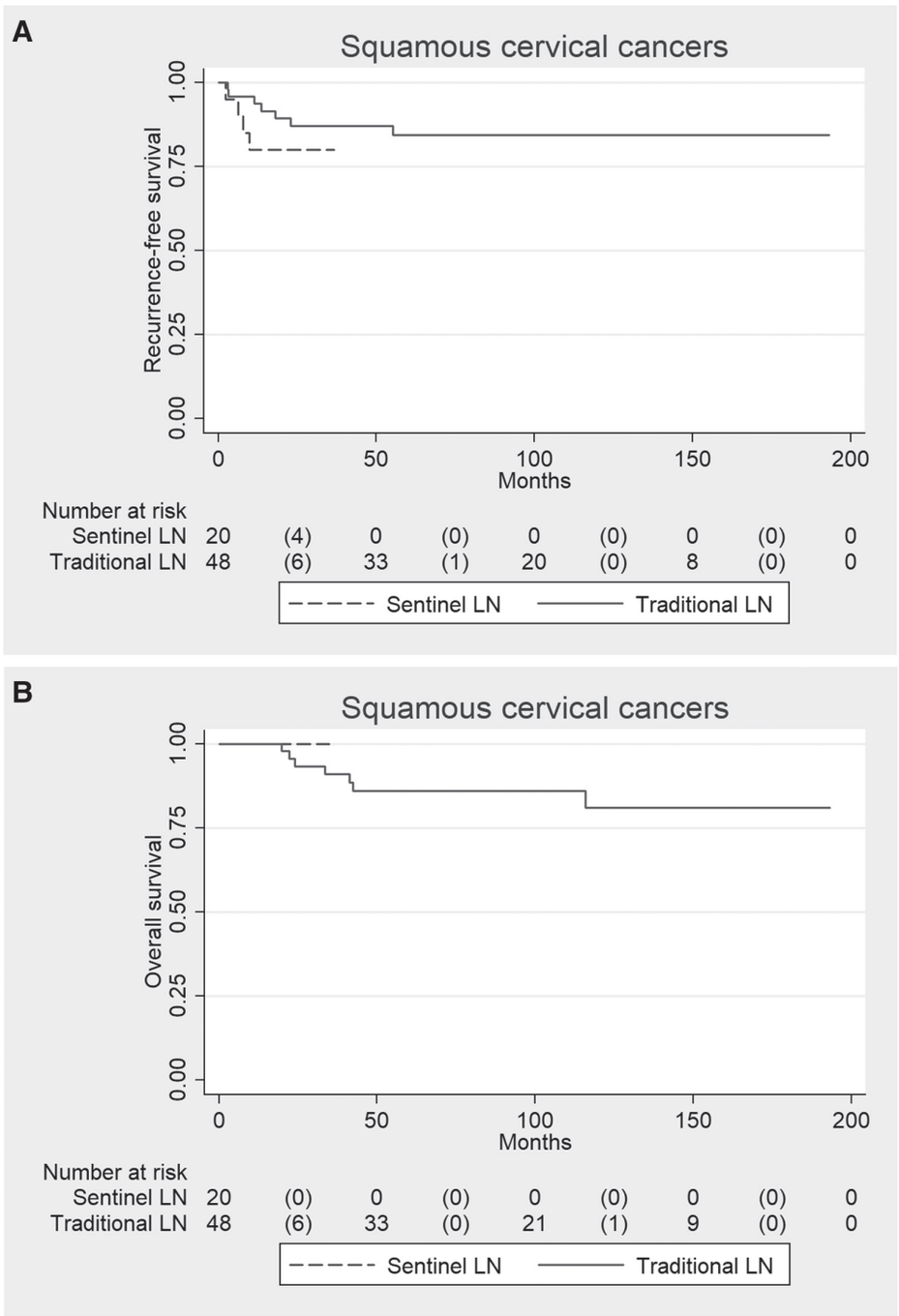

Fig. 3 Probabilities of (A) recurrence-free survival and (B) overall survival in surgically treated early-stage squamous cervical cancer women who received sentinel lymph node mapping and biopsy (n = 20) vs lymphadenectomy (n = 48). LN = lymph node.

In this study, one 30-year-old woman with cervical adenocarcinoma, stromal invasion of 4 mm with negative margins (FIGO stage IA2) and without lymphovascular space invasion in a conization specimen underwent subsequent robotic pelvic SLN mapping and biopsy. The risk of pelvic lymph node involvement is approximately 8% in patients with stage IA2 squamous cervical carcinoma.[23] Koliopoulos et al[24] reported that conization with lymphadenectomy might draw some attention in patients with FIGO stage IA2 squamous cervical carcinoma. From the database of Memorial Sloan Kettering Cancer Center, Andikyan et al[25] reported that cervical conization and SLN mapping seem to be acceptable treatment strategies for select patients with small-volume stage I cervical cancer. NCCN guidelines also indicate that conization with negative margins and pelvic SLN mapping is also an option in FIGO stage IA2 disease without lymphovascular space invasion. Recently, the SHAPE trial reported that in patients with low-risk cervical cancer (that is, FIGO 2009 stage IA2 or IB1 tumors with lesions measuring no more than 2 cm, limited

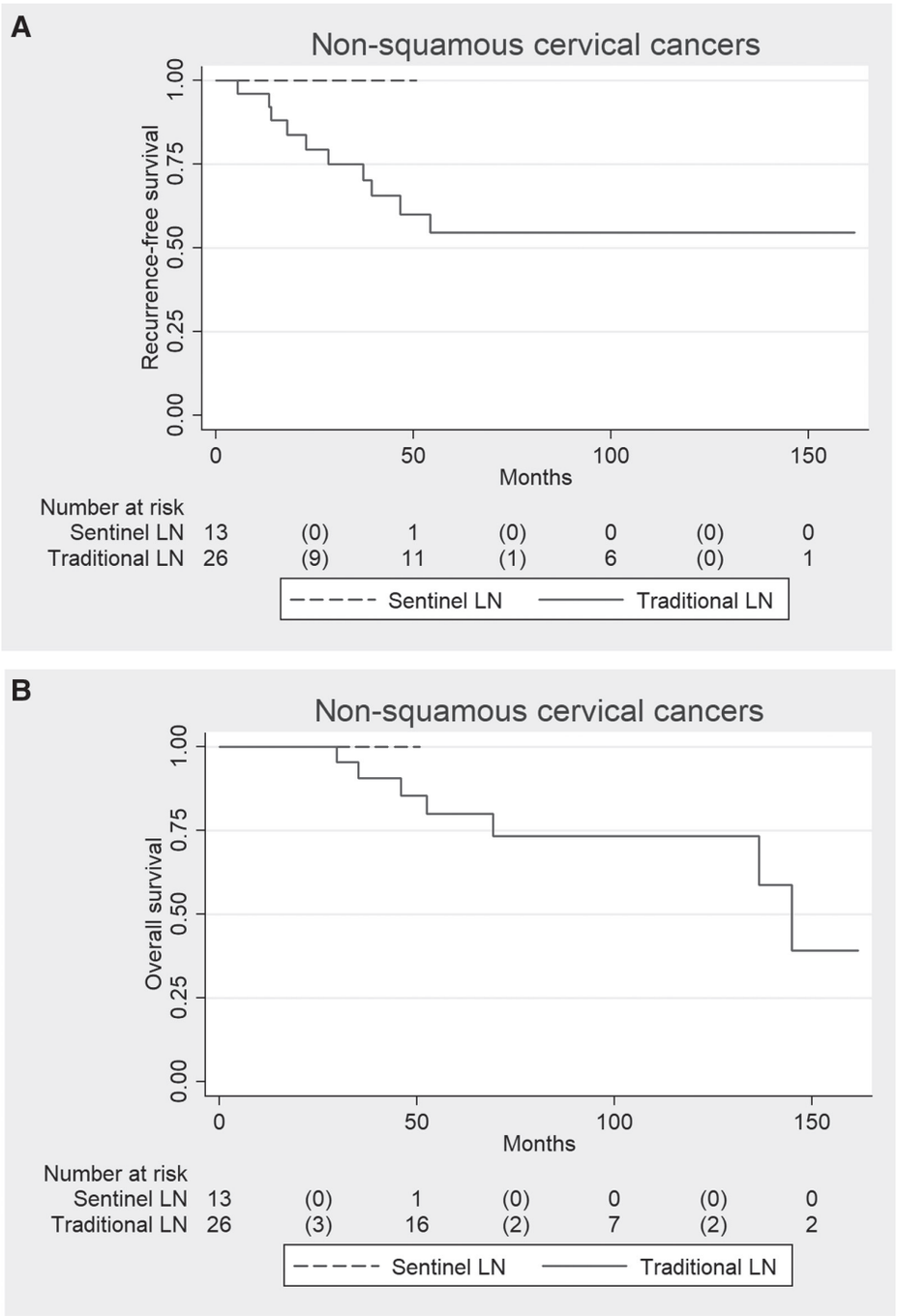

Fig. 4 Probabilities of (A) recurrence-free survival and (B) overall survival in surgically treated early-stage nonsquamous cervical cancer women who received sentinel lymph node mapping and biopsy (n = 13) vs lymphadenectomy (n = 26). LN = lymph node.

depth of cervical stromal invasion by loop electrosurgical excision procedure or conization, or <10% of cervical stromal invasion by perioperative magnetic resonance imaging), simple hysterectomy was not inferior to radical hysterectomy with respect to the 3-year incidence of pelvic recurrence.[26] Thus, removal of the parametrium seems less important in patients with low-risk cervical cancer.

We acknowledge that the clinical evidence of this study is limited by its small sample size and nonrandomized and retrospective nature. We shall anticipate the final results from the three ongoing prospective trials SENTIX, PHENIX, and SENTICOL III.[7–9]

In conclusion, compared with conventional lymphadenectomy, SLN biopsy seems not to be associated with an inferior survival outcome in women with early primary cervical cancer. In addition, SLN biopsy is associated with less blood loss and a shorter length of hospital stay than conventional lymphadenectomy.

Table 3

Comparisons of perioperative outcome of women with early primary cervical cancer who underwent radical hysterectomy between laparotomic and robotic radical hysterectomy (n = 100)

Variables	Laparotomic (n = 93)	Robotic (n = 7)	*p*[a]
Surgical time, min	267 ± 60	301 ± 58	0.134
Blood loss, mL	1089 ± 1085	279 ± 210	<0.001
Bladder perforation	4 (4)	0 (0)	1.000
Vesicovaginal fistulae	2 (2)	1 (14)	0.197
Lymphocyst	10 (11)	0 (0)	1.000
Length of stay, d	9.6 ± 5.6	8.4 ± 3.6	0.576

Data were presented as mean ± SD or number (percentage).
[a]Spearman rank-sum test, Chi-square test, or Fisher exact test.

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