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Original Article

A feasibility study of sentinel lymph node mapping by cervical injection of a tracer in Japanese women with early stage endometrial cancer

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ABSTRACT

Objective: The aim of this study was to investigate the feasibility of sentinel lymph node mapping characterized by a cervical tracer injection in endometrial cancer.
Materials and methods: This retrospective study was carried out using data for 57 patients with endometrial carcinoma who had undergone intraoperative sentinel lymph node mapping and subsequent surgical staging. Technetium colloid and/or indocyanine green was injected into the uterine cervix and a gamma-detecting probe and/or photodynamic eye camera system was used intraoperatively to locate hot spots.
Results: Of the 57 patients, 52 (91.2%) had FIGO Stage I disease. Successful unilateral or bilateral mapping occurred in 54 patients (94.7%) and 46 (80.7%), respectively. The median number of sentinel lymph nodes detected was two (range, 0–5). Following sentinel lymph node mapping, 41 patients (71.9%) underwent pelvic lymphadenectomy alone and 16 (28.1%) full lymphadenectomy. The median number of lymph nodes resected was 17 (range, 8–110). Sentinel lymph nodes were involved in four patients (7.0%), two with macrometastases and two with low-volume metastases. The sensitivity and negative predictive value for detecting lymph node metastasis were both 100%.
Conclusion: Sentinel lymph node mapping with the use of cervical tracer injection is highly feasible in Japanese women with early stage endometrial cancer.

Introduction

Endometrial cancer is the commonest malignancy of the female genital tract in the USA, with an estimated 61,380 new cases in 2017 [1], the annual number of deaths having increased from 6000 in 1997 [2] to 10,920 in 2017 [1]. Surgery comprising hysterectomy, bilateral salpingo-oophorectomy, and establishing lymph node status is the principle treatment for endometrial cancer. Phase III trials have shown that pelvic lymphadenectomy does not significantly improve outcomes and increases complication rates in patients with clinical stage I endometrial cancer [3,4]. However, combined pelvic and para-aortic lymphadenectomy might improve outcomes in selected, especially high-risk, patients with endometrial cancer [5]. Clinical stage I includes both low- and high-risk patients. Although no consensus has been reached on preoperative identification of patients at low- or high-risk for nodal metastasis, it has been reported that several risk-stratification models including the Mayo criteria can be applied in clinical practice [6–11]. These models provide sufficiently low false-negative rates but cause false-positives, namely lymphadenectomies were frequently performed in patients with no lymph nodal metastasis. For instance, by the Mayo criteria, 68%–79% of women with EC are classified in the high-risk category and therefore require lymphadenectomies; however, 89%–94% of patients who undergo lymphadenectomy are negative for lymph nodal metastasis [7,12]. Sentinel lymph node (SLN) mapping is expected to dramatically reduce false-positives, while controlling false-negatives, and thus can offer a trade-off between systematic lymphadenectomy and no dissection in all patients with clinical stage I disease.

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Whereas SLN mapping in patients with endometrial cancer is increasingly accepted in western countries [13,14], Japan is lagging far behind in this research because of the following concerns. First, it is a demanding and complicated technique involving local injection of a tracer in the vicinity of the affected endometrium. To overcome this concern, an easier tracer injection procedure, namely a cervical injection method has been received favorably in some western countries. The second concern is false-negatives, that is, a decrease in sensitivity of detection of lymph node metastases (LNM) attributable to failure to detect SLNs. Two thirds of false-negatives are caused by failure to detect pelvic SLNs and one third by failure to detect para-aortic SLNs [15]. A leading group in the field of SLN mapping from the Memorial Sloan-Kettering Cancer Center (MSKCC) has proposed an algorithm to overcome the former issue, that is, failure to detect SLNs on hemipelvis; this algorithm includes ipsilateral lymph node dissection in patients in whom no SLN is detected with removal of all suspicious nodes irrespective of SLN mapping findings. The false-negative rate dropped from 15% before to 2% after application of this algorithm [16]. As for the latter issue, that is, failure to detect para-aortic SLNs, some experts consider the effect of this negligible because of the extremely low rate of para-aortic LNMs in patients without pelvic LNMs. However, some physicians, especially Japanese oncologists, are cautious about accepting this contention. Unfortunately, the cervical injection method is closely associated with failure to detect para-aortic SLNs. Although cervical injection is correlated with a higher pelvic SLN detection rate [17], it less effectively detects para-aortic SLNs. Whereas hysteroscopic injection achieved a para-aortic SLN detection rate of 33–84% in previous studies with $n \geq 50$ [18–21], cervical injection resulted in a rate of 5–23% in previous studies with $n \geq 100$ [15,16,22–24]. Additionally, although subserosal injection [25] and hysteroscopic injection [19,20] can reportedly detect para-aortic SLNs above the inferior mesenteric artery, as far as we know, SLNs in the upper para-aortic region have not been detected by cervical injection. Thus, the weakest aspect of cervical injection is that it does not detect para-aortic SLNs above the inferior mesenteric artery.

SLN mapping after cervical tracer injection is gradually becoming a mainstream component of treatment of clinical stage I endometrial cancer. Increasing implementation of this procedure in Japanese women may be a pressing issue. Herein, we present our preliminary data and propose an appropriate method for performing this procedure that minimizes the false-negative rate for LNMs.

Materials and methods

The local institutional review board and the hospital's ethics committee approved the study protocol.

Patients

This retrospective study analyzed data from 57 patients with endometrial carcinoma who had undergone intraoperative sentinel lymph node mapping and subsequent surgical staging including lymphadenectomy in the Department of Obstetrics and Gynecology, Hokkaido University Hospital and Hokkaido Cancer Center from 2011 to 2015.

Injection of tracer for SLN mapping

Technetium 99m (99mTc)-phytate and/or indocyanine green (ICG) were used as tracers for detecting SLNs in this study. Technetium colloid was the preferred option but could not be used for patients undergoing surgery on Mondays because in our institution use of radioactive products is forbidden on Sundays for administrative reasons. Therefore, ICG was exclusively utilized in patients undergoing surgery on Mondays. ICG was also used in combination with technetium colloid when lymphoscintigraphy had failed to identify hot spots on the day before surgery.

Timing of injection and sites for SLN mapping

Twenty hours prior to surgery, 0.2 mL of 99mTc-phytate was injected into the subepithelial area of each of four quadrants of the uterine cervix (at 0-, 3-, 6-, and 9-o'clock or 2-, 4-, 8-, and 10-o'clock). Three hours later, lymphoscintigraphy was performed to detect lymph nodes and assess their distribution preoperatively. On the other hand, ICG was diluted 100-fold and 1 mL injected into each of the aforementioned four quadrants of the uterine cervix immediately before surgery. Additionally, ICG was injected into the subserosa of the uterine fundus during surgery in four patients.

SLN detection

When 99mTc-phytate had been used as a tracer, SLNs were scanned intraoperatively with a gamma probe (Navigator GPS; Furuno Electric, Nishinomiya, Japan) and hot nodes with more than 10-fold counts above background were identified. When using ICG, SLNs were detected with a photodynamic eye camera system.

Ultrastaging for SLNs

Ultrastaging involving multiple slicing, staining, and examination of specimens was performed on all SLNs. The detected SLNs were serially sectioned at 2 mm intervals along their minor axes. Several pairs of 4-μm-thick serial sections were cut at 120-μm intervals. One section of each pair was stained with hematoxylin and eosin (H&E) and the other with AE1/AE3 monoclonal antibody (Nichirei, Tokyo, Japan). Staining was performed using an automated immunostainer (NexES; Ventana, Tucson, AZ, USA). Low-volume metastases were defined as isolated tumor cells ($\leq$0.2 mm in diameter) or micrometastases (0.2–2 mm in diameter).

Subsequent surgical staging

Following SLN mapping, all patients underwent lymphadenectomy. The extent of lymphadenectomy was at the discretion of the attending surgeon. However, removal of the interiliac and obturator lymph nodes bilaterally was a mandated component of surgical staging. Lymph nodes removed at this stage were classified as non-SLNs and routine H&E stained sections of them were examined histopathologically.

Final lymph nodal status

Final lymph nodal status was defined as negative when no cancer cells were identified in both SLNs and non-SLNs and positive when cancer cells, including low-volume metastases, were identified in either SLNs or non-SLNs.

Statistical analysis

Proportional data were compared using the chi-square test or Fisher's exact test. The statistical significance level was set at $P<0.05$. Statistical analyses were performed with StatView J-5.0 (SAS Institute, Cary, NC, USA).

Results

The clinicopathological characteristics of the 57 patients are shown in Table 1. Their median age was 60 years and BMI 22.4 kg/m^2. Fifty-one patients (89.5%) had Type 1 uterine cancer and 52 (91.2%) had FIGO stage I disease. Forty-eight patients (84.2%) were classified in the at-risk category by the Mayo criteria. Two patients (3.5%) had lymph node macrometastases and another two (3.5%) low-volume metastases.

Table 2 shows the patients' surgical outcomes. Fifty-three patients (93.0%) underwent SLN mapping exclusively by cervical tracer injection. The remaining 4 patients (7.0%) had ICG concurrently injected into their uterine fundus. At least one SLN was detected in 54 (94.7%) of the patients. Bilateral mapping was achieved in 46 patients (80.7%). The median number of SLNs detected was two (range, 0–5). Only sixteen patients (28.1%) underwent para-aortic lymphadenectomy. The median number of lymph nodes resected was 17 (range, 8–110).

Table 3 shows the locations of detected SLNs by frequency: right obturator (61.5%), left obturator (59.6%), right internal iliac (33.3%), left internal iliac (29.8%), right common iliac (5.3%), right external iliac (5.3%), left external iliac (3.5%), and left common iliac (1.8%). No para-aortic nodes were identified as SLNs in the 53 patients who had undergone SLN mapping exclusively by cervical tracer injection. Para-aortic SLNs were detected in two patients, both of whom had had ICG concurrently injected into their uterine fundus.

While all affected lymph nodes were SLNs, no tumor cells were identified in any of the non-SLNs resected. SLNs were detected in four patients with affected lymph nodes and were positive for metastatic disease in all four. Fifty patients in whom SLNs were negative for metastatic disease were finally diagnosed as having no lymph node metastases. Three patients in whom no SLNs were detected bilaterally were finally diagnosed of having no lymph node metastasis. The sensitivity and negative predictive value for detecting lymph node metastasis were both 100% (Table 4).

Table 1
Patient characteristics of 57 patients in the study population.

Characteristic	Value
Age (y), median (range)	60 (36–77)
BMI (kg/m^2), median (range)	22.4 (16.8–43.3)
Final pathology, n (%)	
Endometrioid grade 1	39 (68.4%)
Endometrioid grade 2	12 (21.0%)
Endometrioid grade 3	3 (5.3%)
Serous	1 (1.8%)
Carcinosarcoma	1 (1.8%)
Other	1 (1.8%)
Postoperative stage, n (%)	
IA*	48 (84.2%)
IB	4 (7.0%)
II	1 (1.8%)
IIIA	2 (3.5%)
IIIC1	2 (3.5%)
Risk stratification by the Mayo criteria [6]	
NOT at-risk category#	9 (15.8%)
at-risk category	48 (84.2%)
Lymph nodal status, n (%)	
no tumor cells	53 (93.0%)
ITC	1 (1.8%)
micrometastasis	1 (1.8%)
macrometatsasis	2 (3.5%)

BMI body mass index; ITC: isolated tumor cells; * including one patient with lymph node micrometastasis and another patient with ITC; # (1) Endometrioid (G1 or 2), myometrial invasion < 50%, and tumor diameter < 2 cm; (2) Endometrioid and no myometrial invasion (independent of grade and tumor diameter).

Table 2
Surgical outcomes of the 57 study patients.

Characteristic	Value
Surgical approach, n (%)	
open surgery	43 (75.4%)
laparoscopic surgery	14 (24.6%)
Injection tracer, n (%)	
99mTc-phytate	40 (70.2%)
indocyanine green	7 (12.3%)
both	10 (17.5%)
Injection site, n (%)	
cervix	53 (93.0%)
cervix and corpus	4 (7.0%)
SLN detection, n (%)	
bilateral mapping	46 (80.7%)
unilateral mapping	8 (14.0%)
detection failure	3 (5.3%)
Number of SLNs detected, median (range)	2 (0–5)
Type of lymphadenectomy, n (%)	
pelvic lymphadenectomy	41 (71.9%)
pelvic and para-aortic lymphadenectomy	16 (28.1%)
Number of lymph nodes removed, median (range)	
PLN	17 (8–82)
PAN	0 (0–28)
total	17 (8–110)

SLN: sentinel lymph node, PLN: pelvic lymph node, PAN: para-aortic lymph node.

Table 3
Location and rate of detection of sentinel lymph nodes detected.

	n (%)
Right	
Common iliac	3 (5.3%)
Internal iliac	19 (33.3%)
External iliac	3 (5.3%)
Obturator	35 (61.4%)
Circumflex iliac	0 (0%)
Left	
Common iliac	1 (1.8%)
Internal iliac	17 (29.8%)
External iliac	2 (3.5%)
Obturator	34 (59.6%)
Circumflex iliac	0 (0%)

Table 4
Sensitivity and negative predictive value.

	Final lymph nodal status	
	Positive	Negative
SLN positive	4	–
SLN negative	0	50
SLN not detected	0	3

SLN: sentinel lymph node.

Discussion

Despite the concerns of some physicians, SLN mapping with the use of a cervical tracer injection has become popular in western countries. The MSKCC group favor this technique and has reported satisfactory results on the whole [16], these being consistent with those of the first prospective, multicenter trial for assessing this technique, the SENTI-ENDO study, which was conducted in France [15]. Successful mapping on at least one side, successful bilateral mapping, sensitivity for LNMs, and negative predictive values for LNM were 81%, 51%, 85%, and 98%, respectively, in the former [16] and 89%, 62%, 84%, and 97%, respectively, in the latter [15]. These indexes were 95%, 81%, 100%, and 100%, respectively, in our study, suggesting that this technique is feasible for Japanese women. Its

Table 5
Lymphatic spread pattern in endometrial cancer by the number of para-aortic lymph nodes removed.

Author	Year	Number[a] of PLNs removed	Number[a] of PANs removed	N	A	B	C	D	B/A + B (%)
					PLN-/PAN-	PLN-/PAN+	PLN+/PAN-	PLN+/PAN+	
Median (Mean) number of PAN removed: <10									
Fanning [28]	1996	21	7	60	55	0	5	0	0.0%
Yokoyama [29]	1997	14	6	63	45	4	6	8	8.2%
Lee [30]	2009	(22.8)	(9.5)	349	277	7	26	39	2.5%
Abu-Rustum [31]	2009	16	5	847	722	12	52	61	1.6%
Chiang [32]	2011	17	5	171	154	2	12	3	1.3%
Solmaz [33]	2015	22	8.5	516	449	4	37	26	0.9%
		subtotal		2006	1702	29	138	137	1.7%
Median (Mean) number of PAN removed: >10									
Onda [34]	1997	(37.9)	(28.7)	173	143	2	10	18	1.4%
Matsumoto [35]	2002	(36.8)	(30.5)	106	79	2	7	18	2.5%
Mariani [36]	2008	35	17	281	218	10	24	29	4.4%
Fujimoto [37]	2009	42	19	355	306	7	20	22	2.2%
Dogan [38]	2011	(49.5)	(19.0)	161	143	2	11	5	1.4%
Odagiri [39]	2014	62.5	20	266	224	7	16	19	3.0%
Altay [40]	2014	26	12	173	135	7	12	19	4.9%
Tomisato [41]	2014	50	22	260	169	9	34	48	5.1%
Fotopoulou [42]	2015	29	21.5	128	101	4	8	15	3.9%
Sautua [43]	2015	(11.9)	(10.7)	90	77	6	3	4	7.2%
Alay [44]	2015	(44.1)	(24.9)	204	160	8	17	19	4.8%
		subtotal		2197	1755	64	162	216	3.5%
		Total		4203	3457	93	300	353	2.6%

[a] Median (mean); PLN pelvic lymph node; PAN para-aortic lymph node.

good performance may be attributable to our team having achieved an adequate level of proficiency in performing this technique, having begun research on SLN mapping in cervical cancer in 2007.

Of course, our study has some limitations. First, we had too few patients to power conclusive results. Additionally, our study inevitably had selection bias because of its retrospective nature and being a single-institution study. Second, 72% of the patients did not undergo para-aortic lymphadenectomy. Thus, our reported sensitivity applies only to pelvic LNMs and not pelvic and/or para-aortic LNMs. Notwithstanding, the excellent sensitivity in our study would likely not be significantly diminished because our cohort consisted almost exclusively of patients at negligible risk of para-aortic LNMs.

The greatest concern regarding SLN mapping is false-negatives, that is, poorer sensitivity for LNMs attributable to failure to detect SLNs. The cervical injection method has an inherent weak point in that it is relatively ineffective at detecting para-aortic SLNs. In the SENTI-ENDO study, two-thirds of false-negatives with the cervical injection method were caused by failure to detect unilateral pelvic SLNs and the remaining third by failure to detect para-aortic SLNs [15]. Preoperatively identification of patients at negligible risk of para-aortic LNM would minimize concerns about failure to detect para-aortic SLN. The authors and colleagues have previously proposed a protocol for preoperative identification of patients at negligible risk of para-aortic LNMs [11]. This protocol includes histological examination of endometrial biopsies, assessment of tumor volume by magnetic resonance imaging (MRI), and serum cancer antigen (CA)125 concentrations, all of which have been reproducibly confirmed as independent risk factors for LNMs by three different cohort studies [11,26,27]. The rate of para-aortic LNMs is reportedly negligible (0.5%) in patients with none of these factors [11]. In that study, para-aortic lymph nodes above the inferior mesenteric artery were routinely resected and examined pathologically, the median number of resected lymph nodes being 75; thus, the para-aortic LNM rate was accurately determined. We therefore believe that patients at negligible risk of para-aortic LNM can be preoperatively identified by our protocol. In a nutshell, SLN mapping by cervical injection is safe performed in patients subjected to this preoperative protocol.

The rate of para-aortic LNMs in patients without pelvic LNMs seems to be recognized as negligible in western countries. However, this belief should be carefully reviewed. Table 5 shows LNM distribution patterns in patients with endometrial cancer based on published data [28–44]. The rate of para-aortic LNMs in patients without pelvic LNM differs between studies in which $\geq$10 versus <10 para-aortic lymph nodes were resected. Thus, the risk of para-aortic LNMs may not be negligible in certain groups of patients without pelvic LNMs. Indeed, some physicians are concerned about this possibility.

As mentioned in the Introduction, Japan has been slow in researching SLN mapping. Very few institutions are studying SLN mapping. Recently, a multicenter, prospective study for assessing SLN mapping by cervical injection, the FIRES trial, conducted in the USA yielded the excellent sensitivity for LNMs of 97%. This result will likely promote the utilization of this procedure worldwide. In conclusion, SLN mapping by cervical injection has a sufficient detection rate and a high degree of diagnostic accuracy. This procedure is highly feasible among Japanese women with early stage endometrial cancer.

Conflicts of interest statement

No potential conflict of interest relevant to this article was reported.

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