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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).