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Original Article

One-step nucleic acid amplification (OSNA) assay for detecting lymph node metastasis in cervical and endometrial cancer: a preliminary study

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ABSTRACT

Objective: To evaluate the accuracy of the one-step nucleic acid amplification (OSNA) assay for the diagnosis of lymph node (LN) metastasis in uterine cancer.
Methods: A total of 116 LNs from 30 patients with cervical and endometrial cancer, enrolled in this prospective study, were used. Excised LNs were cut into 4 to 6 blocks at 2 mm intervals, and nonadjacent blocks were alternately subjected to either histological examination or the OSNA assay.
Results: The concordance rate between histological examination and the OSNA assay in cervical cancer and in endometrial cancer was 95.9% and 95.2%, respectively. The sensitivity, specificity, and negative predictive value of the OSNA assay were 80%, 97.7%, and 97.7% in cervical cancer, and 85.7%, 93.3%, and 98.2% in endometrial cancer, respectively. In cervical cancer, discordant results were observed in 2 out of 49 LNs (4.1%); 1 was OSNA assay-positive and histological examination-negative, and 1 was OSNA assay-negative and histological examination-positive. In endometrial cancer, discordant results were observed in 5 out of 67 LNs (7.5%); 4 were OSNA assay-positive and histological examination-negative, and 1 was OSNA assay-negative and histological examination-positive.
Conclusion: The OSNA assay showed high concordance rate with histological examination, sensitivity, and specificity in uterine cancer, suggesting that it could enhance the accuracy of conventional pathological examination for the detection of LN metastasis by reducing false negative rate.

Keywords: Cervical Cancer; Endometrial Cancer; One-Step Nucleic Acid Amplification; Sentinel Lymph Node

Synopsis

High concordance rate between the one-step nucleic acid amplification (OSNA) assay and histological examination in uterine cancer. OSNA assay demonstrates high sensitivity and specificity for metastatic lymph node detection. Preoperative confirmation of cytokeratin 19 expression in primary tumors may reduce false-negative results.

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

Author Contributions
Conceptualization: Y.S.; Data curation: T.S., K.M., K.H.; Formal analysis: T.S., U.T., K.M., K.H.; Investigation: T.S., K.I., T.A.; Supervision: K.H.; Writing - original draft: T.S., U.T.; Writing - review & editing: T.S., Y.S., K.M., K.H.

INTRODUCTION

Cervical cancer is one of the most common gynecologic cancers, and its lymph node (LN) metastasis has been identified as an important prognostic factor for survival. Radical hysterectomy with pelvic lymphadenectomy is the standard procedure for patients with cervical cancer. Similarly, pelvic lymphadenectomy results in a favorable prognosis as well as accurate surgical staging in patients with endometrial cancer. However, comprehensive pelvic lymphadenectomy has been associated with numerous morbidities, such as massive bleeding, nerve injury, lower extremity lymphedema, and pelvic lymphocele [1,2]. In our previous study, the occurrence rates of lower extremity lymphedema for cervical and endometrial cancer were 16.6% and 14.9%, respectively [3,4]. Recently, sentinel LN (SLN) mapping was reported as an accepted procedure to avoid comprehensive lymphadenectomy in uterine cancer [5-8]. In recent years, new methods have been developed to improve the accuracy of LN metastasis detection in cancer patients, including the one-step nucleic acid amplification (OSNA) assay. The OSNA assay uses the reverse-transcription loop-mediated isothermal amplification (RT-LAMP) technique for gene amplification, and quantifies the number of tissue cytokeratin 19 (CK19) messenger RNA (mRNA) copies [9,10]. The OSNA assay does not require RNA extraction, and the amplification of marker genes can be performed in as short a time as approximately 15 minutes, making it quick and simple. In addition, this method has the advantage of detecting metastases localized in the LNs because it can screen the entire LN. Several studies have reported the feasibility of the OSNA assay for many malignancies [11-15], but few have examined its feasibility in uterine cancer patients [16-19]. If the high diagnostic accuracy of the OSNA method is proven in uterine cancer, it will reduce the burden on pathologists and enable more accurate staging.

The purpose of this study was to evaluate the accuracy of the OSNA assay in diagnosing LN metastasis of uterine cancer and to verify that this method is an adequate alternative to conventional pathological LN diagnosis.

MATERIALS AND METHODS

1. Patients and LNs

A total of 116 LNs from 30 patients with cervical (12) and endometrial (18) cancer, enrolled in this prospective study at the Department of Obstetrics and Gynecology of Kagoshima University Hospital from July 2018 to March 2019, were used. This prospective study was approved by the Institutional Ethics Committee (approval No. 170316), and informed consent was obtained from all patients. The inclusion criteria were: 1) cervical or endometrial cancer confirmed by histological examination and 2) ages between 20 and 75 years. Patients with pre-treatment chemotherapy or radiotherapy and other active cancers were excluded from this study.

After obtaining informed consent, the patients were registered and anonymized. The surgically removed pelvic or para-aortic LNs were assigned a fixed LN ID. The surgically removed LNs were cut into 4 to 6 blocks at 2 mm intervals depending on their size, and nonadjacent blocks were alternately subjected to either histological examination or the OSNA assay, as shown in **Fig. 1**. The maximum number of LNs removed per patient was 5, and either SLN or non-SLN was acceptable.

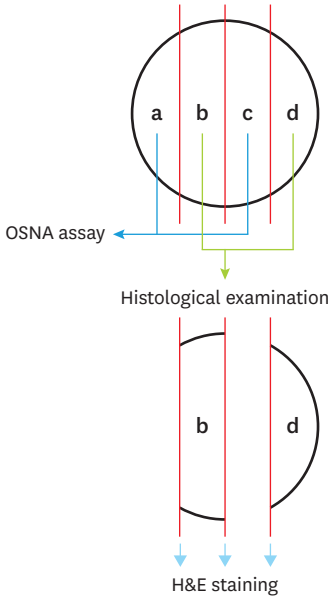

Fig. 1. LN processing. The removed LNs were cut into 4 to 6 blocks at 2 mm intervals with a short axis, and nonadjacent blocks were alternately subjected to either histological examination or the OSNA assay.
LN, lymph node; OSNA, one-step nucleic acid amplification; H&E, hematoxylin and eosin.

2. Histological examination

Histological examination by hematoxylin and eosin (H&E) staining was performed on slides from formalin-fixed, paraffin-embedded LN tissues of all sections adjacent to the OSNA block. The final histological diagnosis was performed by a multiplex pathologist.

3. OSNA assay

Excised LNs were refrigerated (2–8°C) or stored on ice (0–4°C) without drying to avoid RNA degradation. Processing was performed as soon as possible, and the weight of the LNs for homogenization was set within a range of 25 to 600 mg, the recommended weight range for obtaining accurate results by this method. Accordingly, LNs exceeding 600 mg were divided into 2 samples. Homogenization of the LN was performed on ice (0–4°C) using Lynorhag lysis buffer (Sysmex, Kobe, Japan). CK19 mRNA was amplified by reverse-transcription loop-mediated amplification (RT-LAMP) using a reagent kit (Lynoamp; Sysmex). The OSNA assay requires only approximately 30 to 40 minutes from the start to the completion of the test, which is almost the same as that required for conventional pathology tests. The results were expressed as the number of CK19 copies per microliter, and the cut-off value for positive results was set at 250 cCP/μL.

4. Further examination by immunohistochemical staining

For discordant results between pathological examination (H&E staining) and the OSNA assay, the same LN block was analyzed by immunohistochemistry using CK19. From the LN block used for histopathological examination, one-pair (for H&E staining and CK19 immunostaining) of serial sections was prepared at an interval of 200 μm.

When pseudo-negative results were observed, the expression of CK19 was also analyzed in the original cancer tissue.

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5. Statistical analysis

The primary outcome measures were the concordance rate between the histopathological examination and the OSNA assay, sensitivity, and specificity. The JMP software (version 14; SAS Institute Inc., Cary, NC, USA) was used for statistical analysis.

RESULTS

The clinicopathological characteristics of the patients are presented in **Table 1**. In cervical cancer, the median age was 44 years (range=32–62), and the final pathological type distribution was as follows: 5 (41%) patients with squamous cell carcinoma, 5 (41%) patients with adenocarcinoma, and 2 (18%) patients with adenosquamous cell carcinoma. Lymph-vascular space involvement (LVSI) was observed in 8 (66%) patients, and pelvic or pelvic and para-aortic lymphadenectomy was performed in 11 (92%) and 1 (8%) patients, respectively. The International Federation of Gynecology and Obstetrics (FIGO) stage (2018) was as follows: 2 (17%) IB1, 2 (17%) IB2, 2 (17%) IB3, 1 (8%) IIA1, 2 (17%) IIB, and 3 (24%) IIIC1p. In endometrial cancer, the median age was 59 years (range=29–80 years), and the final pathological type distribution was as follows: 12 (67%) patients with endometrioid carcinoma, 1 (6%) patient with serous carcinoma, 3 (16%) patients with carcinosarcoma, and 2 (11%) patients with other types of carcinomas. LVSI was observed in 12 (66%) patients, and pelvic or pelvic and para-aortic lymphadenectomy was performed in 6 (34%) and 12 patients (66%), respectively. The FIGO stage (2008) was as follows: 5 (28%) IA, 1 (5%) IB, 2 (11%) II, 6 (34%) IIIC1, 3 (17%) IIIC2, and 1 (5%) IVB.

The correlations between the OSNA assay and the histological examination are shown in **Table 2**. According to histological examination, 5 out of 49 LNs (10.2%) in cervical cancer were metastatic. The concordance rate between histological examination and the OSNA assay was 95.9%. The sensitivity, specificity, and negative predictive value (NPV) of the OSNA assay were 80%, 97.7%, and 97.7%, respectively. Similarly, 7 out of 67 LNs (10.4%) in endometrial cancer were metastatic according to histological examination. The concordance rate between histological examination and the OSNA assay was 92.5%. The sensitivity, specificity, and NPV of the OSNA assay were 85.7%, 93.3%, and 98.2%, respectively. In cervical cancer, discordant results were observed in 2 out of 49 LNs (4.1%) (**Tables 3** and **4**); one was OSNA-positive and histological examination-negative, and the other was OSNA-negative and histological examination-positive. In endometrial cancer, discordant results were observed in 5 out of 67 LNs (7.5%); 4 were OSNA-positive and histological examination-negative, and 1 was OSNA-negative and histological examination-positive. Details regarding the correlation between the OSNA assay and the histological examination are shown in **Tables S1** and **S2**.

DISCUSSION

Although comprehensive lymphadenectomy is a standard procedure for accurate staging and recurrence risk classification of uterine cancer, it has been associated with numerous morbidities. Therefore, new molecular methods have been developed for the detection of metastatic LNs in cancer patients. This includes the OSNA assay, which is a quick and simple procedure that allows complete screening of the LNs. Although several studies have reported its feasibility for many malignancies [11-15], few have examined its feasibility in uterine

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Table 1. Clinicopathological characteristics in cervical cancer and endometrial cancer

Characteristics	Values
Cervical cancer*	
Median age (yr)	44 (32–62)
Final pathology	
Squamous cell carcinoma	5 (41)
Adenocarcinoma	5 (41)
Adenosquamous cell carcinoma	2 (18)
Tumor size	
<20 mm	1 (8)
20–40 mm	4 (33)
>40 mm	7 (59)
LVSI	
Positive	8 (66)
Negative	4 (34)
Lymphadenectomy	
Pelvic	11 (92)
Pelvic and paraaortic	1 (8)
FIGO stage (2018)	
IB1	2 (17)
IB2	2 (17)
IB3	2 (17)
IIA1	1 (8)
IIB	2 (17)
IIIC1p	3 (24)
Endometrial cancer†	
Median age (yr)	59 (29–80)
Final pathology	
Endometrioid	12 (67)
Grade 1	4 (34)
Grade 2	3 (25)
Grade 3	5 (41)
Serous	1 (6)
Carcinosarcoma	3 (16)
Other	2 (11)
Tumor size	
<20 mm	3 (17)
20–40 mm	4 (22)
>40 mm	11 (61)
LVSI	
Positive	12 (66)
Negative	6 (34)
Lymphadenectomy	
Pelvic	6 (34)
Pelvic and paraaortic	12 (66)
FIGO stage (2008)	
IA	5 (28)
IB	1 (5)
II	2 (11)
IIIC1	6 (34)
IIIC2	3 (17)
IVB	1 (5)

Values are presented as median (interquartile range) or number (%).
FIGO, International Federation of Gynecology and Obstetrics; LVSI, lymph-vascular space involvement.
*Patient (n=12); †Patient (n=18).

cancer patients [16-19]. Thus, we sought to evaluate the accuracy of the OSNA assay for the diagnosis of LN metastasis in uterine cancer by comparing it with standard histological examinations.

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Table 2. Correlations between the results of the OSNA assay and those of histological examination

OSNA	Histological examination		Total
	Positive	Negative	
Cervical cancer*			
Positive	4	1	5
Negative	1	43	44
Total	5	44	49
Endometrial cancer†			
Positive	6	4	10
Negative	1	56	57
Total	7	60	67

OSNA, one-step nucleic acid amplification.
*Concordance rate: 95.9%, sensitivity: 80%, specificity: 97.7%, negative predictive value: 97.7%; †Concordance rate: 92.5%; sensitivity: 85.7%; specificity: 93.3%; negative predictive value: 98.2%.

Table 3. Analysis of OSNA-positive and histological examination-negative cases in cervical cancer and endometrial cancer

Patient	Age	Final pathology	LVSI	Histological examination (maximum diameter) (0.2 mm interval)	OSNA	CK19 mRNA (copies/μL)	Epithelial cell inclusions
Cervical cancer							
1	41	SCC	Positive	Negative	+	3,300	No
Endometrial cancer							
1	51	Endometrioid	Positive	Positive (0.5 mm)	+	2,000	Yes
2	56	Endometrioid	Positive	Positive (0.8 mm)	++	46,000	No
3	56	Endometrioid	Positive	Positive (1.3 mm)	+	2,800	No
4	74	Endometrioid	Positive	Positive (0.8 mm)	+	7,600	No

CK19, cytokeratin 19; LVSI, lymph-vascular space involvement; mRNA, messenger RNA; OSNA, one-step nucleic acid amplification; SCC, squamous cell carcinoma.

Table 4. Analysis of one-step nucleic acid amplification-negative and histological examination-positive cases in cervical cancer and endometrial cancer

Patient	Age	Final pathology	LVSI	Histological examination (maximum diameter) (0.2 mm interval)	CK19 mRNA (copies/μL)	CK19 expression of LN by IHC	CK19 expression of primary tumor by IHC	Epithelial cell inclusions
Cervical cancer								
1	52	Adenosquamous	Positive	Positive (1.4 mm)	170	Positive	Positive	No
Endometrial cancer								
1	80	Endometrioid	Positive	Positive (11.5 mm)	40	Negative	Negative	No

CK19, cytokeratin 19; IHC, immunohistochemistry; LN, lymph node; LVSI, lymph-vascular space involvement; mRNA, messenger RNA.

In this study, the concordance rates between histological examination and the OSNA assay were 95.9% and 92.5% for cervical and endometrial cancer, respectively. The sensitivity, specificity, and NPV were 80%, 97.7%, and 97.7%, and 85.7%, 93.3%, and 98.2% for cervical and endometrial cancer, respectively, confirming that the OSNA assay can be used to detect metastatic LNs and that it is an adequate substitute for histological examination.

The OSNA assay was first used by Tsujimoto et al. [10] to detect metastatic LNs in breast cancer, and since then, the effectiveness of the OSNA assay in diagnosing metastatic LNs has been widely reported in various cancer types. A meta-analysis reported a sensitivity and a specificity in breast cancer of 0.87 (95% confidence interval [CI]=0.81–0.91) and 0.92 (95% CI=0.86–0.95), respectively [15]. In addition, the sensitivity and specificity for head and neck cancers were shown to be 0.85 (0.79–0.89) and 0.96 (0.92–0.98), respectively, while for gastrointestinal cancers, the sensitivity and specificity were 0.90 (0.85–0.94) and 0.96 (0.94–0.98), respectively [20]. Okamoto et al. [18] reported a concordance rate between histopathological examination and the OSNA assay of 96.2%, with a sensitivity of 50% and a specificity of 98.4%. Nagai et al. [17] reported a concordance rate of 99.1%, a sensitivity of 93.3%, and a specificity of 99.5%. Thus, the concordance rate, sensitivity, and specificity

found in our study were comparable to those for gynecological cancers and other cancer types found in previous studies, and confirmed the accuracy of the OSNA assay.

In previous studies [21-23], the SLN metastasis detection rate using the OSNA assay was higher than that by histological examination because the OSNA assay can detect cancer cells in whole tissues. In the present study, OSNA-positive and histological examination-negative discordant results were observed in one LN from cervical cancer and in 4 LNs from endometrial cancer. Histological ultra-staging examination revealed the presence of micro-metastasis in 4 out of the 5 discordant cases. Thus, our findings suggest that the OSNA assay can detect LN metastasis, including micro-metastasis, better than histological examination. Kumagai et al. [12] reported discordant results for 23 out of 394 LNs (5.8%) from patients with gastric cancer. Escalante Pérez et al. [11] reported discordant results in 27 LNs (3%) from patients with lung cancer. In a previous study, discordant results were recorded for 11 out of 94 (11.8%) SLNs from endometrial cancer patients [16]. Therefore, the discordance rate in this study was similar to that reported for other carcinomas. Furthermore, we speculate that the discordance in our study was due to the allocation bias of cancer cells. Bizzarri et al. [24] reported that OSNA detected micro-metastasis in 6/18 (33.3%) patients with cervical cancer. We believe that OSNA can provide a more accurate diagnosis of micro-metastasis in uterine cancer, and further studies are needed.

Similarly, OSNA-negative and histological examination-positive discordant results were found in one case each of cervical cancer and endometrial cancer. The discordant case in cervical cancer may have been due to allocation bias because the pathological examination showed the presence of micro-metastasis. In contrast, we presume that negative CK19 expression in both primary tumors and LN metastases is the reason for the discordant case in endometrial cancer. In previous studies [25-27], 3%–6% of primary breast cancer cases showed absence of CK19 expression.

False-positive SLN diagnosis using the OSNA assay is an issue because it leads to unnecessary lymphadenectomy. Endosalpingiosis is a benign Müllerian lesion that is occasionally observed in pelvic LNs. López-Ruiz et al. [16] reported that in 2 out of 94 LNs, histopathological examination revealed the presence of benign epithelial inclusions that were CK19-positive. In the present study, we did not find any LN in which only benign epithelial inclusions were present.

Unfortunately, there are no reports on prognosis for uterine cancer patients, or any other cancers, with positive OSNA and negative histopathology results. However, in one study, the prognosis of patients with breast cancer who underwent SN biopsy and were negative for metastasis by histopathology and OSNA were compared (prognostic comparison of SN OSNA-negative vs. SN pathology-negative) [28]. When compared to histopathology, distant recurrence-free survival was better in OSNA N0 cases than in pathology N0 cases, suggesting that the OSNA method has high sensitivity and is more accurate than the pathologist's negative judgment.

This study had several limitations. First, it was conducted in a single institute, and the number of LNs analyzed was small. Second, the intraoperative use of the OSNA assay for the detection of SLN metastasis in uterine cancer requires further investigation. For clinical use, the concordance between pathological findings and the OSNA assay for SLN metastatic diagnosis must be analyzed. Third, in this study, we are unable to evaluate whether the

diagnosis of LN metastasis, including micro-metastasis, by OSNA assay improves the prognosis of patients with uterine cancer. In the future, we believe it is necessary to verify these results using SN.

In conclusion, our findings demonstrate that the OSNA assay could enhance the accuracy of conventional pathological examination for the detection of LN metastasis by reducing false negative rate in patients with uterine cancer. We suggest that preoperative confirmation of CK19 expression in primary tumors may reduce false-negative results in the OSNA assay and allow a more accurate diagnosis of LN metastasis.

SUPPLEMENTARY MATERIALS

Table S1

Comparison between OSNA assay results and histological examination for cervical cancer cases

Click here to view

Table S2

Comparison between OSNA assay results and histological examination for endometrial cancer cases

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