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Ultrastaging of para-aortic lymph nodes in stage IIIC1 endometrial cancer: A preliminary report

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HIGHLIGHTS

► Occult para-aortic node metastasis is frequently found in stage 3C1 uterine cancer.
► Local treatment of para-aortic area should be considered in stage 3C1 uterine cancer.

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ABSTRACT

Objective. The aim of this study was to determine the rate of occult metastasis, including isolated tumor cells, in para-aortic lymph nodes of patients with stage IIIC1 endometrial cancer who underwent pelvic and para-aortic lymphadenectomy.

Methods. A series of 15 patients who had undergone combined pelvic and para-aortic lymphadenectomy during the period from 2004 to 2010 and who were diagnosed as being positive for pelvic node metastasis but negative for para-aortic node metastasis were included in this study. Ultra-staging by multiple slicing, staining with hematoxylin/eosin and cytokeratin, and microscopic inspection was performed on a total of 242 para-aortic lymph nodes.

Results. Eleven (73.3%) of the 15 patients had occult para-aortic lymph node metastasis. Two patients (13.3%) had macrometastasis and nine patients (60.0%) had isolated tumor cells. Type 2 endometrial cancer tended to have a higher rate of occult metastasis than that of type 1 cancer (90% vs. 40%, $P = 0.07$). The rate of occult para-aortic node metastasis was not related to the number of metastatic pelvic nodes. Five patients suffered recurrence in the lung or in the intraabdomen, but lymph node recurrence was not found in any case.

Conclusion. Patients with stage IIIC1 endometrial cancer have a potentially high rate of occult para-aortic node metastasis. Local treatment of the para-aortic region should be considered in patients with stage IIIC1 endometrial cancer until effective adjuvant therapy is established.

Introduction

In the field of breast cancer, many groups support the systemic theory, which regards lymph node metastasis as an indicator of poor prognosis, and surgical removal of lymph nodes as unimportant for survival [1]. Lymphadenectomy is therefore currently performed less commonly in breast cancer patients than it has been in the past. However, some groups support the spectrum theory, which does not always regard lymph node metastasis as an indicator of poor prognosis, and regards locoregional treatment as important for survival [2]. It is unclear which of these theories applies to the biological behavior of endometrial cancer.

The International Federation of Gynecology and Obstetrics (FIGO) staging system for endometrial cancer has recently been changed [3]. As the data suggest that the prognosis of endometrial cancer is worse if the para-aortic nodes (PANs) are involved, stage IIIC has now been divided into stage IIIC1 (positive pelvic nodes without positive PANs) and stage IIIC2 (positive PANs with or without positive pelvic nodes).

Although two randomized clinical trials failed to show a therapeutic benefit for pelvic lymphadenectomy in endometrial cancer [4,5], we recently reported that systematic lymphadenectomy including

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para-aortic lymphadenectomy has a therapeutic benefit in patients with intermediate- or high-risk endometrial cancer [6]. We also demonstrated that combined pelvic and para-aortic lymphadenectomy has a therapeutic benefit in patients with lymph node metastasis [7]. The para-aortic region has been shown to be a critical site for sentinel nodes in endometrial cancer [8,9]. Therefore, treatment of PANs might be a key factor for successful treatment of endometrial cancer.

Although it is possible that patients with stage IIIC1 endometrial cancer have occult PAN metastasis, a consensus regarding treatment of PANs in such cases has not been reached. The rate of occult disease in PANs for patients with stage IIIC1 endometrial cancer has remained unclear. Ultra-staging including serial sectioning and immunohistochemistry enables detection of occult lymph node metastasis including micrometastasis. In this study, the rate of occult PAN metastasis was assessed in patients with pelvic lymph node metastasis who were previously diagnosed as being negative for PAN metastasis. The importance of locoregional treatment of PANs in patients with stage IIIC1 endometrial cancer should be reconsidered.

Materials and methods

Study population

This study was carried out using data for 280 patients with endometrial carcinoma for whom extensive surgical staging including lymphadenectomy was performed in the Department of Obstetrics and Gynecology, Hokkaido University Hospital and Hokkaido Cancer Center from 2004 to 2010. All patients underwent a work-up with computed tomography and magnetic resonance imaging to detect distant metastases in the preoperative setting and underwent lymphadenectomy in addition to hysterectomy and bilateral salpingo-oophorectomy.

Of those patients, 155 patients (55.4%) were in stage IA (FIGO 2009), 47 (16.8%) were in stage IB, 12 (4.3%) were in stage II, 10 (3.6%) were in stage IIIA, 15 (5.4%) were in stage IIIC1, 30 (10.7%) were in stage IIIC2, and 10 (3.6%) were in stage IV (Table 1). One hundred thirty patients (46.4%) had grade 1 endometrioid adenocarcinoma, 78 patients (27.9%) had grade 2 endometrioid adenocarcinoma, 31 patients (11.1%) had grade 3 endometrioid adenocarcinoma, 24 patients had serous adenocarcinoma, 10 patients had clear cell carcinoma, 5 patients had mixed type adenocarcinoma, and 2 patients had other types of carcinoma. Fifty-three patients (18.9%) had lymph node metastasis. Two hundred sixty-one patients (93.2%) underwent pelvic lymphadenectomy plus para-aortic lymphadenectomy and 19 patients (6.8%) underwent pelvic lymphadenectomy alone. In terms of adjuvant treatment, chemotherapy consisting of a platinum-based regimen has been used for cases with intermediate-/high-risk factors in both institutions.

Fifteen patients who had undergone combined pelvic and para-aortic lymphadenectomy, who were diagnosed as positive for pelvic node metastasis but negative for para-aortic node metastasis (equivalent to the new FIGO stage IIIC1), were included in this study. Seven of these patients were treated at Hokkaido University Hospital and eight were treated at Hokkaido Cancer Center.

Ultrastaging of para-aortic lymph node metastasis

Ultra-staging was performed for a total of 242 PANs diagnosed as negative for metastasis, to assess them for microscopic tumor cells including isolated tumor cells. Ultra-staging was performed by multiple slicing, staining, and inspection of specimens.

The slicing process consisted of cutting five pairs of 4-μm-thick serial sections (10 sections in total) from archival, formalin-fixed, paraffin-embedded blocks containing all para-aortic nodes examined. Pairs of serial sections were cut at 120-μm intervals (Fig. 1). Sixty-eight paraffin-embedded blocks were examined, each containing several para-aortic nodes. A total of 680 sections were prepared.

Table 1
Clinical background of patients with endometrial cancer who underwent extensive surgical staging including lymphadenectomy during the study period.

	Total patients (N = 280)
Age (years)	
Median (range)	59 (14–78)
FIGO surgical stage	
1A	155
1B	47
2	12
3A	10
3B	1
3C1	15
3C2	30
4	10
Tumor grade/histology	
Endometrioid	
G1	130
G2	78
G3	31
Non-endometrioid	
Serous	24
Clear	10
Mixed	5
Others	2
Myometrial invasion	
<1/2	177
≥1/2	103
Adnexal involvement	
Negative	257
Positive	23
Lymph node metastasis	
Negative	227
Positive	53
Lymphadenectomy	
PLX + PALX	261
PLX alone	19

PLX: pelvic lymphadenectomy, PALX: para-aortic lymphadenectomy.

The staining process consisted of hematoxylin and eosin staining of one section from each pair, and AE1/AE3 monoclonal antibody staining (Nichirei, Tokyo, Japan) of the other section from the pair (340 sections were stained with hematoxylin and eosin, and 340 were stained with cytokeratin). Staining was performed using an automated immunostainer (NexES, Ventana, Tucson, AZ).

During the inspection process, microscopic tumors were classified as isolated tumor cells (smaller than 0.2 mm in diameter), micrometastasis (0.2 mm to 2 mm in diameter), or macrometastasis (larger than 2 mm in diameter).

Statistical analysis

Correlations between variables were evaluated using the chi-square test or Fisher's exact test. The statistical significance level was set at 0.05. Statistical analyses were performed with StatView J-5.0 (SAS Institute, Cary, NC).

Results

Table 2 shows the clinicopathological characteristics of the 15 patients included in this study. The median age of those patients was 59 years (range: 42–76 years). Seven patients had endometrioid adenocarcinoma and eight had non-endometrioid carcinoma. Six patients had metastasis in a solitary pelvic lymph node and nine patients had metastasis in two or more pelvic lymph nodes. The median number of pelvic lymph nodes harvested was 55 (range: 25–76), and the median number of PANs harvested was 14 (range: 6–32). All patients had PANs removed, but four patients, including one obese patient and two patients with a preoperative diagnosis of cervical cancer, did not have nodes located