Role of the Internal Iliac Node Dissection in Radical Hysterectomy for Cervical Cancer: A Retrospective Analysis

J.TWMU 2: 14-20, 2018

Original

Role of the Internal Iliac Node Dissection in Radical Hysterectomy for Cervical Cancer: A Retrospective Analysis

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(Accepted September 5, 2018)

(Advance Publication by J-STAGE November 22, 2018)

Objective: This study aims to assess the role of the internal iliac node (IIN) dissection, which is occasionally neglected in radical hysterectomy for uterine cervical cancer.

Methods: We retrospectively reviewed the clinical and pathological records of patients with cervical cancer (stage IB1-IIB) with lymph node metastases, who underwent radical hysterectomy at our institute. We assessed the number and site of lymph node metastases along with history and site of recurrence.

Results: Twenty-three patients who underwent radical hysterectomy reported lymph node metastases and included in this study. Of these, 13 with only one positive node revealed no IIN metastases, whereas 5 of 10 with two or more positive nodes exhibited IIN metastases. While 20 patients, including 4 with positive IIN, received platinum-based chemotherapy, 3 received radiotherapy as adjuvant therapy. Four patients, including 2 with positive IIN, experienced disease recurrence.

Conclusion: Given the high prevalence of IIN metastases in patients with multiple lymph node metastases, the IIN dissection should be performed in radical hysterectomy. IIN metastasis could be one of the important factors for regional recurrence in cervical cancer.

Key Words: cervical cancer, pelvic lymphadenectomy, internal iliac node

Introduction

The number of patients with cervical cancer, especially in younger generation, is increasing in the last two decades in Japan[1]. Recently, fertility-sparing surgery, such as radical trachelectomy, has gained recognition as treatment strategies for early cervical cancer. Meanwhile, lymph node metastasis has been established as one of the crucial prognostic factors in early cervical cancer[2)3)]. In the current clinical practice for early cervical cancer with lymph node metastases, either primary concurrent chemoradiotherapy (CCRT) or radical hysterectomy incorporating the systematic pelvic node dissection followed by CCRT are applied. Although the lymph node dissection is the best method to determine the nodal state, its therapeutic role remains debatable. Conversely, multimodal therapy of node-positive cervical cancer by radical surgery and (chemo) radiation correlates with the augmented risk of severe toxicity, such as radiation colitis, cystitis, or lymphedema. Recently, the European Society of Gynaecological Oncology recommended that the combination of radical surgery and radiotherapy as treatment

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doi: 10.24488/twmuj.2018005

strategy should be avoided because of the highest associated morbidity[4]. They recommended avoiding further pelvic lymph node dissection and radical hysterectomy if lymph node involvement is detected intraoperatively and that these patients should be referred for definitive CCRT.

Meanwhile, radical surgery followed by adjuvant chemotherapy (with or without neoadjuvant chemotherapy: NACT) has emerged as a valid alternative treatment strategy for node-positive patients with early cervical cancer (stage IB1-IIB) in Europe, Latin countries, and Japan[5)-9)]. Höckel et al. reported excellent pelvic control and overall survival rate for node-positive patients with cervical cancer with their modified radical hysterectomy and lymph node dissection without adjuvant radiotherapy[6)]. Angioli et al. reported the validity of adjuvant chemotherapy after NACT and radical hysterectomy as a treatment strategy for node-positive patients with cervical cancer[7)].

However, recent retrospective research in Japan reported that node-positive patients receiving adjuvant chemotherapy following radical surgery were more susceptible to frequent local relapses compared with those receiving adjuvant CCRT[10)11)]. Perhaps, one possible factor of pelvic control disadvantage of adjuvant chemotherapy group could be incompleteness of the pelvic node dissection. Hypothetically, the anticancer drug distribution along the lymphatic system might be obstructed after lymphadenectomy. Consequently, cancer cells in the missing residual lymph nodes easily escape from the attack of chemotherapy agents. For example, the internal iliac node (IIN), located along the internal iliac vessels, is often neglected or abandoned for the pelvic node dissection. The blunt node dissection of this region often causes annoying bleeding. As surgical procedures or techniques have been passed on to younger generations at each institute, the procedures and intensity of lymph node dissection might vary among institutes. In addition, the description of the medial IIN dissection is often missing in the Japanese literature or educational DVD contents explaining the procedure of pelvic lymphadenectomy for radical hysterectomy[12)13)].

Thus, this study aims to elucidate the role of the IIN in the therapeutic pelvic lymphadenectomy. The study retrospectively investigates the clinical and pathological data from node-positive patients with early cervical cancer who underwent radical hysterectomy at our institute.

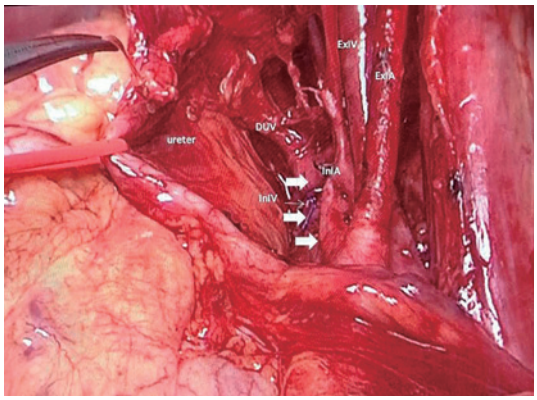

Fig. 1 External iliac vessels and internal iliac vessels after systematic pelvic lymphadenectomy (right side). Arrow, the medial internal iliac node region.
InIA, internal iliac artery; InIV, internal iliac vein; ExIA, external iliac artery; ExIV, external iliac vein; DUV, deep uterine vein.

Patients and Methods

We retrospectively examined the clinical and pathological records of patients with cervical cancer, the International Federation of Gynecology and Obstetrics (FIGO) stage IB1-IIB, with lymph node metastases, who underwent radical hysterectomy between October 2007 and December 2017 at our institute. The study was approved by the institutional Research Ethics Committee (No. 4407).

The Okabayashi-Fujii methods formed the basis of radical hysterectomy[14)], although we preferred the Höckel's procedure for modified radical hysterectomy regarding the sacro-uterine ligament resection and hypogastric nerve preservation[15)]. Pelvic lymphadenectomy with therapeutic intent was performed as described in the Gynecologic Cancer Surgery by Morrow and Curtin[16)]. The medial IIN was cautiously removed from its connection with sacral nodes toward the lymphatic channels entering the parametrium (**Fig. 1**). If node metastases were suspected during surgery, frozen-section was performed for confirmation. In node-positive cases, the node dissection area was extended to the paraaortic region up to the level of the root of the inferior mesenteric artery, at least.

For patients with large tumor size (> 5 cm), 1 or 2 cycles of NACT was administered preoperatively. Regard-

Table 1 Patients' characteristics

Factors (%)	
Age	Median: 45 (range 23-73) years
Clinical Stage	
IB1	12 (52)
IB2	6 (26)
IIA1	1 (4)
IIA2	1 (4)
IIB	3 (13)
Histopathology	
Squamous cell	15 (65)
Adenosquamous	2 (9)
Adenocarcinoma*	6 (26)
pT**	
1b1	6 (26)
1b2	6 (26)
2a2	1 (4)
2b	10 (44)
pN (number)	
1	13 (56)
2 or more***	10 (44)
pMA****	3 (13)

*Endocervical adenocarcinoma (usual type), 2 patients; mucinous carcinoma, 2 patients; endometrioid carcinoma, 1 patient; and serous carcinoma, 1 patient.

**Including 6 patients with neoadjuvant chemotherapy (ypT).

***2: 3 patients, 3: 3 patients, 4: 3 patients, 9: 1 patient.

****Paraaortic lymphadenectomy was performed, up to the inferior mesenteric artery in 16 patients and up to the renal vein in 3 patients.

ing adjuvant therapy, we provided patients with information on chemotherapy as well as (chemo) radiotherapy. Patients could then choose between these two therapies. Adjuvant therapy was administered within 4 weeks postoperatively after obtaining written informed consent from patients. Regarding NACT or adjuvant chemotherapy, we administered irinotecan plus platinum agents every 4 weeks for squamous cell carcinoma and paclitaxel or docetaxel plus platinum agents triweekly for non-squamous cell carcinoma (1 to 2 cycles for NACT, and 5 to 6 cycles for the postoperative adjuvant therapy, respectively). Radiotherapy was given as whole-pelvis external irradiation at 50 Gy, with or without weekly cisplatin administration for 5 cycles.

In this study, we assessed the number and site of positive lymph nodes, site of recurrence, and the progression-free survival (PFS). The nomenclature of the retroperitoneal lymph nodes was determined by the classification by the committee on the classification of regional lymph nodes of the Japan Society of Clinical Oncology (JSCO)[17]. The PFS was evaluated using the Kaplan-Meier method.

Results

Between October 2007 and December 2017, 67 patients with FIGO stage IB1-IIB cervical cancer underwent radical hysterectomy at our institute. Of these, 24 patients exhibited lymph node metastases. We excluded 1 patient with small-cell carcinoma because of its histological specificity; thus, 23 (median age 45 years) patients were enrolled in this study. **Table 1** summarizes the characteristics of node-positive patients in this study. Of all, 12 patients (52%) had stage IB1 cancer, whereas 3 had stage IIB cancer. While 15 patients (65%) had squamous cell carcinoma, the remaining 8 were diagnosed with other histological types. Six patients received 1 or 2 cycles of NACT. While 13 patients (54%) had solitary node metastasis, 10 had 2 or more node metastases. Paraaortic lymphadenectomy was performed, up to the inferior mesenteric artery in 16 patients and up to the renal vein in 3 patients; of these, 3 patients had paraaortic node metastases. In this study, the median number of pelvic nodes removed was 41 (range 25-64). Regarding the distribution of pelvic node metastasis, solitary node metastasis was detected in the obturator node in 6 patients, external iliac node in 5 patients, parametrial node in 1 patient, and common iliac node in 1 patient. We found no IIN metastasis in 13 patients with solitary node metastasis. Regarding patients with multiple node metastases, metastases were detected in the obturator node in 7 patients, external iliac node in 6 patients, IIN in 5 patients, sacral node in 1 patient, and suprafemoral node in 1 patient (**Table 2**).

Twenty patients, including 4 with positive IIN, received platinum-based chemotherapy, and 3 received radiotherapy as adjuvant therapy. The median follow-up period for censored patients was 86 (range 8-127) months. Disease recurrence was experienced by 4 patients, including 2 with positive IIN; these 2 patients with positive IIN had mucinous histology and relapsed with dissemination into the peritoneum and pelvic cavity despite adjuvant chemotherapy. The other 3 patients with positive IIN (2 with squamous cell type and 1 with adenosquamous type) have presented no evidence of disease to date (**Table 3**). The other 2 relapsed patients were

Table 2 The number of patients by the site of lymph node metastases (median number of pelvic nodes removed, 41 [range 25-64])

	The number of patients	
	Patients with a solitary positive node (13 patients)	Patients with 2 or more positive nodes (10 patients)
Parametrial node	1	0
Obturator node	6	7
External iliac node	5	6
Internal iliac node	0	5
Common iliac node	1	0
Sacral node	0	1
Suprafemoral node	0	1
Paraaortic node	0	3

Table 3 Patients with internal iliac node metastasis

No	Stage/pT	Histology	Number of positive node (Pelvic/PA)	Adjuvant therapy	Rec	First site of Rec	Outcome
1	IB2/ yT1b2	Mucinous	3 /1	Chemo	Yes	Regional, IP	23 M DOD
2	IB1/ T2b	Mucinous	3 /0	Chemo	Yes	IP	8 M DOD
3	IB2/ T1b2	Squamous	6 /3	Chemo/Rad*	No	-	102 M NED
4	IB1/ T2b	AdSq	3 /0	Chemo	No	-	57 M NED
5	IB1/ T1b1	Squamous	4 /0	CCRT	No	-	8 M NED

*External-beam radiation to the paraaortic region.

PA, paraaortic; Rec, recurrence; Chemo, chemotherapy; Rad, radiation; CCRT, concurrent chemoradiotherapy; IP, intraperitoneal dissemination; AdSq, adenosquamous; M, months; DOD, died of disease; NED, no evidence of disease.

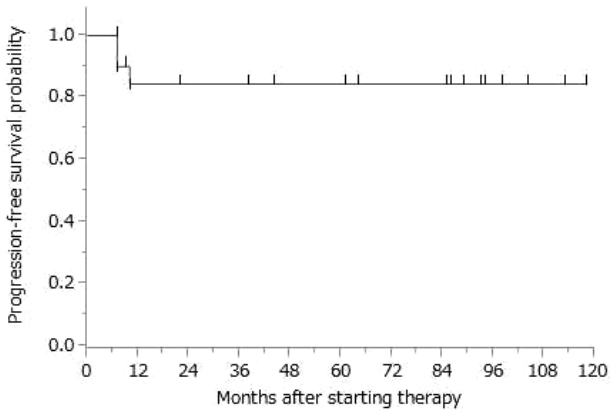

Fig. 2 The progression-free survival of node-positive patients with adjuvant chemotherapy. The median follow-up, 86 (range 10-118) months.

diagnosed with squamous cell type and relapsed with dissemination (1 with adjuvant radiotherapy) and vaginal recurrence (1 with adjuvant chemotherapy), respectively. **Figure 2** shows the PFS of 20 patients with positive nodes who received adjuvant chemotherapy; their 5-year PFS was 84.4%.

Discussion

This study focused on the IIN dissection in radical hysterectomy for cervical cancer and offered the following suggestions. First, the IIN is at risk and frequently involved in multiple nodal metastases; thus, metastasis to this area might be one of the important factors for regional recurrence in cervical cancer. Second, the complete regional node dissection, including the IIN, in radi-

cal hysterectomy might contribute not only to adequate local control but also to disease-free benefit without adjuvant radiotherapy, at least, in squamous-type cervical cancer.

In this study, 13 patients with solitary positive node revealed no IIN metastases, whereas 5 of 10 patients with multiple positive nodes revealed IIN metastases. Previously, several studies have reported the distribution pattern of pelvic node metastasis in patients with cervical carcinoma treated with radical hysterectomy. Panici et al. reported solitary metastasis in the obturator, external iliac, or common iliac nodes. They detected IIN metastasis in 5 (9.6%), all of whom had multiple node metastases, of 52 node-positive patients[18]. Our results corroborate with that of Panici et al., although the positive rate of IIN was higher. Sakuragi et al. reported solitary node metastasis in the obturator, IIN, parametrial, and common iliac nodes, mostly (69.2%) in the obturator[19]. Of note, their results differ from others in the point that no solitary metastasis was observed in the external iliac nodes, whereas 3 of 26 solitary metastases were present in the IIN. Perhaps, these results could be affected by the equivocal definition of the IIN per the JSCO classification, defined as "located in the triangular between the external and internal iliac blood vessels", whereas the external iliac node is defined as "located below the origin of the external iliac blood vessels"[18]. In our study, we classified nodes located along the external iliac vein as the external iliac node, even if these were located between the external iliac vein and the internal iliac artery. In their book, Morrow et al. described that "The hypogastric lymph nodes although seldom involved in early cervical cancer, are at risk and frequently involved when there are multiple nodal metastases"[16]. The term "hypogastric node" is identical to the entire IIN, although some studies have used this term to designate the most cephalic of the IIN[20]. This study is entirely consistent with Morrow's statement. On the basis of previously reported results and our data, we anticipate that the retroperitoneal lymphatic spread in cervical cancer might have, at least, two routes as follows: (1) the first stream, the major one, flows laterally into the obturator nodes and external iliac nodes and (2) the second stream flows medially into the IIN and sacral nodes. In the last decade, sentinel lymph node biopsy (SLNB) in cervical cancer has been assessed as a reliable strategy for identifying patients with negative pelvic lymph nodes to spare the morbidity related to pelvic lymphadenectomy[21]. Perhaps, lymphatic mapping techniques used in SLNB might be useful for providing the definitive evidence of the retroperitoneal lymphatic spread in cervical cancer.

Höckel et al. reported their modified radical hysterectomy based on the ontogenetic anatomy, namely, total mesometrial resection, and the therapeutic lymph node dissection[6]. We attribute the excellent pelvic control and PFS (5-year: 81%) by surgery without adjuvant radiotherapy for patients with node-positive cervical cancer to their therapeutic lymph node dissection. Our study demonstrates comparable survival outcome of node-positive patients receiving adjuvant chemotherapy, especially for patients with squamous cell type. The Japanese Gynecologic Oncology Group (JGOG) 1070s retrospective study compared the outcome of patients with node-positive cervical cancer who received adjuvant chemotherapy and those who received adjuvant CCRT[11]. The 2-year PFS for the former group was 55.5% and significantly lower than not only that of the latter group (73.9%) but also the reported outcome for node-positive patients with adjuvant chemotherapy in the other studies or our study results[5)-10)]. The JGOG 1070s study is unique for that the survey collected 10 consecutive cases per institute from JGOG-designated institutions, implying that the results might not reflect the power of teaching or specialist hospitals. We speculate that one possible factor for the inferiority of the treatment outcome in the study is the quality of surgeries, including therapeutic lymphadenectomy such as IIN dissection, although there are no reliable documents, which demonstrate the outcome of patients with cervical cancer who underwent radical hysterectomy without IIN dissection specifically.

Regarding our study, we cannot explicitly state the therapeutic role of IIN dissection because of the small number of cases. However, the 2 of the 5 IIN-positive patients who relapsed had cervical adenocarcinoma (mucinous histology). Takeshima et al. reported the results of adjuvant chemotherapy for node-positive cervical adenocarcinoma and inferred that the efficacy of chemotherapy alone in node-positive cervical adenocarcinoma was not as high as that in squamous cell type[22]. The remaining 3 IIN-positive patients (squamous- or adenosquamous-

type) in our study have not experienced relapses to date. Thus, perhaps, the complete regional node dissection, including the IIN, in radical hysterectomy might result in adequate local control and survival benefit without adjuvant radiotherapy, at least, in squamous cell type cervical cancer when combined with adjuvant chemotherapy. Currently, the JGOG is planning a prospective randomized study to compare postoperative chemotherapy and CCRT in surgically treated high-risk early-stage cervical cancer, including node-positive patients. Assumedly, this trial might provide the evidence for the efficacy of adjuvant chemotherapy in node-positive cervical cancer; however, rigorous quality control of radical surgery, including node dissection, should be mandatory to obtain reliable evidence, which could change the routine practice.

This study has several limitations. First, the sample size is small. A study with a larger sample size might offer more accurate analysis for the distribution pattern of node metastases. Second, we administered NACT in 6 patients in this study. Panici et al. examined patients with early-invasive cervical cancer and locally advanced disease treated with NACT separately[18] Although they deduced that the pattern of the lymphatic spread was similar to each other, the possibility that the number and distribution of node metastasis were affected by NACT cannot be excluded. Meanwhile, from the perspective of surgical procedure, quality uniformity of node dissection was assured because all surgeries in this study were performed by one surgeon.

Conclusion

Given the high prevalence of IIN metastases in patients with multiple lymph node metastases, the IIN dissection should be performed in radical hysterectomy. IIN metastasis might be one of the important factors for regional recurrence, and pelvic lymphadenectomy without the IIN dissection in radical hysterectomy could be a pitfall for the surgical treatment of cervical cancer.

Conflicts of Interest: The authors indicated no conflicts of interest.

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