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Relationship between removal of circumflex iliac nodes distal to the external iliac nodes and postoperative lower-extremity lymphedema in uterine cervical cancer

Hiroyuki Yamazaki [a], Yukiharu Todo [a,*], Sho Takeshita [a], Yoko Ohba [a], Satoko Sudo [a], Shinichiro Minobe [a], Kazuhira Okamoto [a], Katsushige Yamashiro [b], Hidenori Kato [a]

[a] Division of Gynecologic Oncology, National Hospital Organization, Hokkaido Cancer Center, 4-2 Kikusui, Shiroishi-ku, Sapporo 003-0804, Japan
[b] Division of Pathology, National Hospital Organization, Hokkaido Cancer Center, 4-2 Kikusui, Shiroishi-ku, Sapporo 003-0804, Japan

HIGHLIGHTS

- Removal of CINDEIN is associated with lower-extremity lymphedema.
- Removal of CINDEIN can be eliminated in patients with cervical cancer.
- CINDEIN dissection may become obsolete in future treatment of cervical cancer.

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ABSTRACT

Objective. This study aimed to determine if there is a causal relationship between removal of the circumflex iliac nodes distal to the external iliac nodes (CINDEIN) and postoperative lower-extremity lymphedema (POLEL) after systematic lymphadenectomy in patients with cervical cancer.

Methods. A retrospective chart review was performed for all living cervical cancer patients who underwent lymphadenectomy and were managed at Hokkaido Cancer Center between 1993 and 2013. The type of lymphadenectomy gradually shifted from lymphadenectomy with removal of CINDEIN to without CINDEIN dissection during this period. The study period was divided into two phases: from 1993–2007 (first phase) and from 2008–2013 (second phase). We identified patients with POLEL. Logistic regression analysis was used to select the risk factors for POLEL.

Results. Implementation of CINDEIN-dissection lymphadenectomy (94.0% vs. 20.6%, $p < 0.0001$) and adjuvant radiotherapy (26.1% vs. 4.5%, $p < 0.0001$) was significantly higher in the first phase than in the second phase. Of 398 patients evaluated, POLEL was noted in medical records of 80 (20.1%) patients with a median follow-up period of 78.0 months. The occurrence rate of POLEL was significantly higher in the first phase than in the second phase (32.2% vs. 8.0%, $p < 0.0001$), despite no change in the number of dissected lymph nodes between the two phases. Multivariate analysis showed that adjuvant radiation therapy (odds ratio = 2.6, 95% confidence interval = 1.4–4.8) and removal of CINDEIN (odds ratio = 4.6, 95% confidence interval = 2.4–9.0) were independent risk factors for POLEL.

Conclusion. Elimination of CINDEIN dissection is helpful for reducing the incidence of POLEL.

1. Introduction

Among women worldwide, cervical cancer is the third most commonly diagnosed cancer. Cervical cancer is the fourth leading cause of death from cancer, accounting for 8% (275,100) of total cancer deaths among women in 2008 [1]. In the United States, an estimated 12, 900 new cases are expected to be diagnosed and 4100 women are expected to die of cervical cancer in 2015 [2]. Radical hysterectomy with pelvic lymphadenectomy is the preferred treatment for International Federation of Gynecology and Obstetrics (FIGO) stage IA2, IB, and IIA lesions [3]. Postoperative lower-extremity lymphedema (POLEL) is the most frequent complication after pelvic lymphadenectomy [4,5]. POLEL is the accumulation of protein-rich interstitial fluid within the skin and subcutaneous tissue as a result of an obstruction of lymphatic vessels in the lower limbs. Because lymphedema is a chronic, generally

* Corresponding author at: Division of Gynecologic Oncology, National Hospital Organization, Hokkaido Cancer Center, 4-2, Kikusui, Shiroishi-Ku, Sapporo 003-0804, Japan.
E-mail address: yukiharu@sap-cc.go.jp (Y. Todo).

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incurable ailment, it requires life-long care and attention along with psychological support [6]. The median age at diagnosis of cervical cancer is 49 years [7], which means that this disease is associated with younger and middle-aged women. Therefore, POLEL is a severe sequela for cervical cancer survivors because the remaining life-span of these young patients is much longer than those with other malignancies.

Conventional pelvic lymphadenectomy includes removal of the circumflex iliac nodes distal to the external iliac nodes (CINDEIN). CINDEIN are also called circumflex iliac nodes [8], distal external iliac lymph nodes [9], suprafemoral nodes [10], and suprainguinal nodes [11,12] in the literature. Abu-Rustum et al. suggested a causal relationship between CINDEIN dissection and POLEL [8]. Since Abu-Rustum et al.'s report [8], several studies have been conducted to assess this relationship [10,13–15]. Ohba et al. demonstrated that CINDEIN dissection is an independent risk factor for POLEL in cervical cancer [10]. However, their study was too small to power conclusive results.

In this retrospective study, we investigated the relationship between removal of CINDEIN and POLEL in a relatively large number of patients who avoided removal of CINDEIN.

2. Materials and methods

2.1. Patients

A total of 486 patients with cervical cancer underwent lymphadenectomy in the National Hospital Organization, Hokkaido Cancer Center between January 1993 and December 2013. Of these patients, 83 died of cancer or intercurrent disease. Medical records concerning postoperative lower-extremity lymphedema were missing in five patients. Finally, 398 living patients who underwent extensive surgical staging, including lymphadenectomy, were included in this study.

2.2. Surgery and adjuvant therapy

The patients underwent radical hysterectomy/trachelectomy and lymph node dissection (LND). LND included pelvic lymph node dissection (PLND) and para-aortic lymph node dissection (PAND). PAND was performed at the discretion of the surgeon. PLND included dissection of the external iliac nodes, internal iliac nodes, CINDEIN, circumflex iliac nodes to the distal obturator nodes, obturator nodes, sacral nodes, and common iliac nodes. CINDEIN are the most distal external iliac lymph nodes. During the study period, some aspects of the management of cervical cancer shifted at our institution, with the transitional period happening around 2007. Before 2007, PLND included removal of CINDEIN. After this time, the institutional preference gradually started to eliminate CINDEIN dissection from routine PLND. Adjuvant therapy also shifted during the study period. Before 2004, adjuvant radiotherapy or adjuvant chemotherapy had been used for cases with high-risk prognostic factors, including a large tumor size (>4 cm), parametrial involvement, lymph–vascular space invasion, and lymph node metastasis, depending on the patient's preference and physician's discretion. After 2004, adjuvant chemotherapy became the institutional preference for adjuvant therapy in patients with cervical cancer. Radiotherapy was performed using whole pelvic external beam radiation (50 Gy/25 Fr), and chemotherapy consisted of a platinum-based regimen administered for three to six cycles. The study period was divided into two phases. The first phase was from 1993–2007 when standard lymphadenectomy included CINDEIN dissection. The second phase was from 2008–2013 when standard lymphadenectomy did not include CINDEIN dissection.

2.3. Assessment of risk factors for lymphedema and statistical methods

We identified patients with POLEL. POLEL is defined as stage II or III lower-extremity lymphedema related to lymphadenectomy. For determining the stage of lymphedema, we used the consensus document of the International Society of Lymphology [6]. This document contains the following descriptions. Stage I represents early accumulation of fluid with a relatively high protein content (e.g., compared with "venous" edema) and subsides with elevation of the limbs. Pitting may occur in Stage I. Stage II is where elevation of the limbs alone rarely reduces tissue swelling and pitting in manifest. Late in stage II, the limb may or may not pit as tissue fibrosis supervenes. Stage III encompasses lymphostatic elephantiasis where pitting is absent and trophic skin changes, such as acanthosis, fat deposits, and warty overgrowths, develop. We excluded all patients who had leg edema related to recurrent disease, progressive disease, deep vein thrombosis, chronic vascular disease, renal disease, and other medical comorbidities.

We investigated the patient's age (≤47 vs. ≥48 years), FIGO (2009) stage (Ia–IIa vs. IIb–IV), histology (squamous cell carcinoma vs. non-squamous cell carcinoma), neoadjuvant chemotherapy (yes vs. no), type of lymphadenectomy (PLND + PAND vs. PLND alone), adjuvant radiation therapy (yes vs. no), adjuvant chemotherapy (yes vs. no), number of resected lymph nodes (≤60 vs. ≥61), and removal of CINDEIN (yes vs. no). For univariate analysis, the above-mentioned categorical variables were analyzed using the chi-square test. Logistic regression analysis was used to identify risk factors for POLEL. Variables achieving statistical significance in univariate analysis were subsequently included in multivariate analysis. The statistical significance level was set at 0.05. Statistical analyses were performed with R version 3.2.0: A Language and Environment for Statistical Computing (R Core Team 2015).

3. Results

The clinicopathological characteristics of the patients are shown in Table 1. The mean age of the patients was 47.4 years. A total of

Table 1
Clinical background of 398 living patients who underwent surgical treatment including lymphadenectomy.

	Number of patients
Age (years)	
Mean (range)	47.4 (23–79)
≤ 47	219 (55.0%)
≥ 48	179 (45.0%)
FIGO stage (2009)	
1A	25 (6.3%)
1B1	215 (54.0%)
1B2	34 (8.5%)
2A	10 (2.6%)
2B	98 (24.6%)
3	13 (3.3%)
4	3 (0.8%)
Histology	
Squamous cell carcinoma	264 (66.3%)
Non-SCC	
Adenocarcinoma	99 (24.9%)
Adeno-squamous	30 (7.5%)
Others	5 (1.3%)
Neoadjuvant chemotherapy	
No	336 (84.4%)
Yes	62 (15.6%)
Lymph node metastasis	
Negative	325 (81.7%)
Positive	73 (18.3%)
Type of lymphadenectomy	
PLND	224 (56.3%)
PLND + PAND	174 (43.7%)
Adjuvant chemotherapy	
No	244 (61.3%)
Yes	154 (38.7%)
Adjuvant radiation therapy	
No	337 (84.7%)
Yes	61 (15.3%)

SCC: squamous cell carcinoma, PLND: pelvic lymph node dissection, PAND: para-aortic lymph node dissection.