

A retrospective analysis of endometrial carcinoma cases surgically treated with or without para-aortic lymph node dissection followed by adjuvant chemotherapy

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Summary

Purpose: To analyze the efficacies of para-aortic node (PAN) dissection for patients undergoing surgery and adjuvant chemotherapy for endometrial carcinomas. **Methods:** At the Osaka University Hospital and the Kaizuka City Hospital in Osaka, Japan, either pelvic lymph nodes (PLN) plus para-aortic lymph nodes (PAN) or PLN-only dissections were performed for endometrial carcinomas. An adjuvant chemotherapy using paclitaxel, epirubicin, and carboplatin was conducted for all such patients. A retrospective comparison of the efficacy of PAN dissection was conducted. **Results:** Disease-free and overall survivals and frequency of PAN involvement at the first recurrence did not exhibit a statistically significant difference between the PLN-only group and the PLN + PAN group. Operation time was significantly longer in the PLN + PAN group than the PLN-only group, and the total blood loss was also significantly greater in the PLN+PAN group. **Conclusion:** PAN dissection may be omitted, without adverse effect on prognosis, for endometrial carcinoma patients with recurrence risks who undergo adjuvant chemotherapy using platinum, anthracycline and taxane derivatives.

Key words: Endometrial carcinoma; Para-aortic lymph node dissection; Adjuvant chemotherapy; Prognosis.

Introduction

The incidence of endometrial cancer is already the most common gynecological cancer in the United States and has increased significantly over the last three decades. Surgical endometrial cancer therapy consists in a hysterectomy, bilateral salpingo-oophorectomy, and retroperitoneal lymph node dissection [1, 2]. Aggressive cytoreductive surgery for advanced cases with extra-pelvic and distant metastatic diseases has been demonstrated to possibly improve the prognosis [3, 4]. However, the prognostic significance of routine dissection of the retroperitoneal para-aortic lymph nodes (PAN) has been unclear. Several recent randomized studies have indicated that systematic dissection of the pelvic lymph nodes (PLN) was of little therapeutic significance for early-stage endometrial carcinoma [5, 6]. On the other hand, for endometrial carcinoma cases with intermediate or high risk factors of recurrence, a retrospective Science Education Partnership and Assessment Laboratory (SEPAL) cohort study suggested that there was a therapeutic role to be gained for a combined dissection of PLN and PAN [7]. In this study, overall survival (OS) was significantly longer in the PLN + PAN dissection group than in the PLN-only dissection group. However, the confounding issue was that the rates of the use of adjuvant chemotherapy were significantly different in the two groups. In the PLN-only group, chemotherapy was performed in only 45% of the cases; however, in the PLN +

PAN dissection group, chemotherapy was performed in 77% of the cases. A subgroup analysis did not demonstrate prognostic significance of additional PAN dissection in patients with intermediate risks in which adjuvant chemotherapy was performed. A cisplatin-based regimen was used for the adjuvant chemotherapy; however, details of the regimen were not given.

A randomized study by the Gynecologic Oncology Group (GOG) gave strong evidence that a combination chemotherapy of AP (doxorubicin and cisplatin) was superior to the traditional use of whole abdominal irradiation as an adjuvant therapy (GOG #122) [8]. Platinum and anthracycline drugs have long been used as the gold standards for advanced or recurrent endometrial carcinomas [9, 10]. Recently, taxane-related drugs have been added to this cocktail [11, 12]. A recent study showed an even better survival rate following TAP therapy (paclitaxel, doxorubicin, and cisplatin) than for AP (GOG #177) [13].

Lissoni *et al.* reported that a modified TAP, called TEP (paclitaxel, epirubicin, and cisplatin), exhibited superior anti-tumor activity against advanced endometrial carcinoma [14]. Another modified TAP, TEC (paclitaxel, epirubicin and carboplatin) also showed to improve treatment against difficult metastatic and recurrent endometrial carcinomas [15]. In the authors' own recent phase I / II prospective studies of TEC, the optimal dose of TEC therapy in the Japanese population was analyzed and resulted in 150 mg / m² paclitaxel, 50 mg / m² epirubicin, and AUC 4 carboplatin [16]. Based on these findings, TEC has become this institutions' new standard for endometrial carcinoma treatment.

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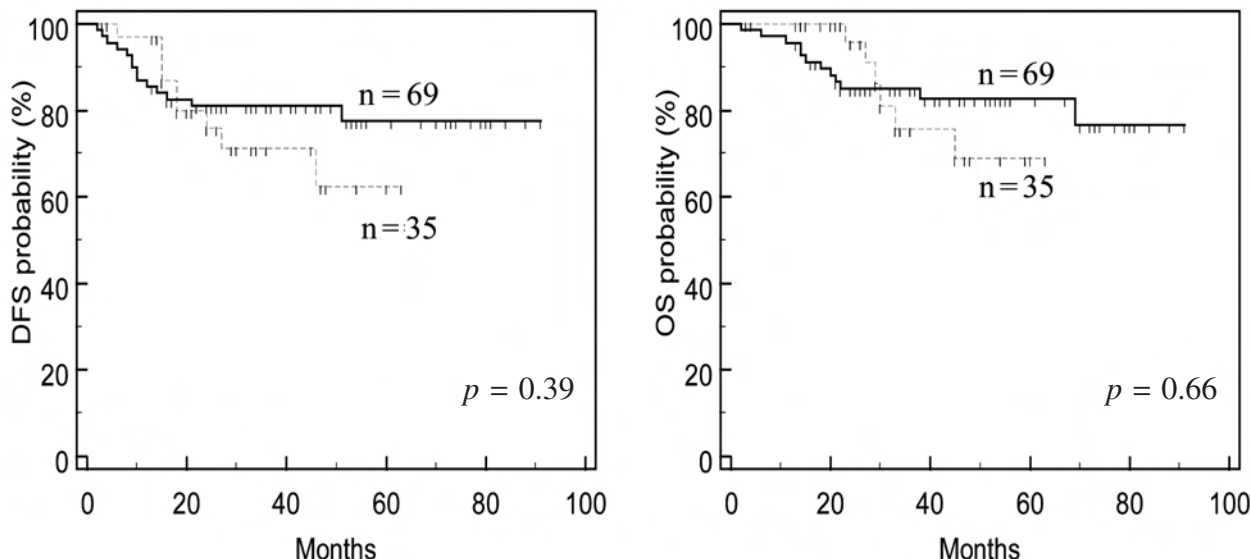


Figure 1. — DFS and OS in the patients treated with or without PAN dissection. Neither DFS nor OS demonstrated significant differences between the patients treated with or without PAN dissection ($p = 0.39$ and $p = 0.66$, respectively, by the log-rank test). Solid line: the cases in which PLN + PAN dissection were performed. Broken line: the cases in which PLN-only dissection was performed.

In the present study, the authors also performed a retrospective comparison of PLN dissection versus PLN + PAN dissection in endometrial carcinoma cases with intermediate or high risk factors for recurrence, all of whom received TEC chemotherapy as an adjuvant therapy.

Materials and Methods

A retrospective comparison of the efficacies of PLN-only versus PLN + PAN dissection was conducted in the endometrial carcinoma cases treated from 2002-2009 at the Osaka University and Kaizuka City hospitals. Both types of dissections were performed under the same indications, including a myometrium invasion depth of > one-half of total thickness and / or an atypical histology (such as endometrioid adenocarcinoma grade 3, clear cell carcinoma, or serous papillary carcinoma). In these cases, a regimen of TEC (150 mg / m² paclitaxel, 50 mg / m² epirubicin, and AUC 4 carboplatin) was administered every three to four weeks for three courses. For more advanced Stage III and IV cases, six courses of TEC therapy were given.

The approved protocol for TEC administration was that it was only to be given to patients who were 70 years of age or less; the present comparative analysis was thus somewhat artificially limited to those under 70 years of age. In addition, chemotherapy was performed only in those patients who were expected to have an estimated remaining survival rate greater than three months.

The cases in which a PAN swelling occurred that was already easily detectable by computed tomography (CT) or magnetic resonance imaging (MRI), and that were therefore strongly suspicious for metastasis, were excluded from the present study. Advanced cases with a tumor that could not be completely excised were also removed from the study. Eligibility for TEC chemotherapy required that the patients had adequate findings in the following: hematology (WBC $\geq 3,000$ / μ l, platelets \geq

100,000 / μ l, granulocytes $\geq 1,500$ / μ l and hemoglobin > 10 g / dl), renal (creatinine ≥ 2 mg / dl) and hepatic (bilirubin ≥ 3 mg / dl, aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≥ 2 times the international normal value). A relative performance status of zero to two was needed. The tumors needed to be histopathologically diagnosed as an endometrial carcinoma. The histological diagnoses were made by authorized pathologists from the Departments of Pathology of the Osaka University and Kaizuka Hospitals, who were all trained at the Osaka University Hospital. The gynecologic surgeons who performed the surgical treatments were also all trained at the Osaka University Hospital, and the surgical procedures and indications for retroperitoneal lymph node dissection were identical in the two hospitals. Moreover, adjuvant chemotherapy was performed using similar indicators.

In the current study, the clinicopathological features of the cases, including age of the patient, histology, stage of the disease, metastatic status of PLN and PAN, frequency of PAN involvement at the first recurrence, operation time, and intraoperative blood loss, were all retrospectively reviewed through their clinical records including: physical examination notes, radiological reports, operative records, and histopathology reports. Disease-free survival (DFS) and overall survival (OS) were calculated. DFS was measured from the administration of chemotherapy to the date of the radiologic or pathologic diagnosis of recurrence, or to the date of the last follow-up. OS was defined as the period from the beginning of chemotherapy to the patient's disease-related death, or to the date of the last follow-up.

Statistical analysis

MedCalc (MedCalc Software, Mariakerke, Belgium) was used for the statistical analyses. The distribution of patients' age, operation time, and blood loss during surgery was analyzed by the Mann-Whitney U-test. Tumor histology and Stage and the frequency of PAN involvement at the first recurrence, were analyzed by the Fisher's exact test. DFS and OS curves were

Table 1. — Characteristics of patients treated with or without PAN dissection.

Characteristic	PLN	PLN + PAN	<i>p</i> value
Number (cases)	35	69	—
Median age (years)	58 (40 - 69)	58 (44 - 70)	0.83
Histology			0.24
endometrioid	22	51	
non-endometrioid	13	18	
Stage			0.062
I/II	22	32	
III/IV	13	37	

Background characteristics of the two groups, PLN-only and PLN + PAN, were not significantly different.

PLN: patients in which only PLN dissection was performed (Kaizuka City Hospital cases).

PLN + PAN: patients in which both PLN and PAN dissection were performed (Osaka University Hospital cases).

Table 2. — Frequency of PLN and PAN metastases in the patients who underwent PLN and PAN dissection.

Metastasis	PAN		Total
	negative	positive	
PLN			
negative	46 (67%)	6 (9%)	52 (75%)
positive	6 (9%)	11 (16%)	17 (25%)
Total	52 (75%)	17 (25%)	69 (100%)

Number of the cases with or without metastasis to PLN and PAN in the patients who underwent PLN + PAN dissection are shown.

constructed using the Kaplan-Meier method and were evaluated for statistical significance by the log-rank test. Results were considered to be significant when the *p* value was less than 0.05.

Results

Clinical characteristics of the cases in which PLN dissection and those in which both PLN and PAN dissections were performed

Under the same indications of retroperitoneal lymph node dissection and adjuvant TEC chemotherapy, 35 patients underwent PLN dissection followed by TEC therapy at the Kaizuka City Hospital, and 69 patients underwent PLN and PAN dissection followed by TEC therapy at the Osaka University Hospital during the study period. Clinical characteristics, including the age distribution of the patients and the histology and Stage of the disease, did not demonstrate a significant difference (Table 1); however, the cases in which dissection of both PLN and PAN was performed tended to be in more advanced stages (*p* = 0.062 by Fisher's exact test).

Frequency of metastasis at PLN and PAN among the patients with an indication of retroperitoneal lymph node dissection

The status of metastasis to the PLN and PAN was analyzed (Table 2). Among the 69 women with risk factor indications who received both PLN and PAN dissections

Table 3. — Comparison of the first recurrent site between the cases in which only PLN was dissected and those in which both PLN and PAN were dissected.

First recurrent site	PLN	PLN+PAN
PAN	3	4
Others	6	10

The frequency of PAN involvement at the first recurrence between the two groups was not different significantly (*p* = 0.81).

PLN: patients in which only PLN dissection was performed.

PLN + PAN: patients in which both PLN and PAN dissection were performed.

Table 4. — Comparison of operation time and blood loss during surgery between the cases in which only PLN was dissected and those in which both PLN and PAN were dissected.

Characteristic	PLN	PLN+PAN	<i>p</i> value
Operation time (min)	214 (167 - 389)	385 (184 - 670)	<i>p</i> < 0.001
Blood loss (ml)	590 (150 - 2590)	770 (200 - 3300)	<i>p</i> = 0.015

Operation time was significantly longer in the PLN + PAN group than the PLN-only group (*p* < 0.001 by Mann-Whitney U test), and total blood loss was also significantly more in the PLN+PAN group than the PLN group (*p* = 0.015 by Mann-Whitney U test).

PLN: patients in which only PLN dissection was performed.

PLN + PAN: patients in which both PLN and PAN dissection were performed.

followed by TEC therapy, 46 patients (67%) had no metastasis at either their PLN or PAN, and 11 patients (16%) had metastasis in both PLN and PAN. There were six cases (9%) without PLN metastasis but with PAN metastasis. Because these cases did not have any other metastasis, it was the PAN dissection that detected the PAN metastasis, which led to an upgrade of the cases to a higher Stage. If these patients had received only a PLN dissection without a PAN dissection, they would have been incorrectly classified as Stage I / II. This is the primary reason why the cases in which dissection of both PLN + PAN performed numerically tended to be in more advanced Stages (Table 1).

Survival effect of PAN dissection in patients with an indication of retroperitoneal lymph node dissection

The DFS and OS curves of the PLN-only and PLN + PAN dissection groups are shown in Figure 1. The median follow up period was 29 months (3 - 63 months) and 36 months (3 - 91 months), respectively. DFS and OS did not exhibit a statistically significant difference between the PLN group and the PLN + PAN group (*p* = 0.39 by the log-rank test, Hazard Ratio: 1.4316; 95% CI: 0.5916 - 3.4643; and *p* = 0.66 by the log-rank test, Hazard Ratio: 1.2473; 95% CI: 0.4488 - 3.4665, respectively).

Frequency of the first recurrence to the PAN

The frequency of PAN involvement during the first recurrence of the tumor was compared between the two study groups (Table 3). In the PLN-only group, the first recurrence at PAN was detected in three (33%) of nine cases, and on the other hand, it was observed in four (29%) of 14 cases in the PLN + PAN group. A statistically significant difference was not detected (*p* = 0.81 by Fisher's exact test).

Adverse effects of PAN dissection

The total operation time and total blood loss during surgery were compared between the PLN group and the PLN + PAN group (Table 4). As would be expected for the more extensive surgery required, the operation time was significantly longer in the PLN + PAN group than the PLN-only group ($p < 0.001$ by Mann-Whitney U test), and the total blood loss was also significantly more ($p = 0.015$ by Mann-Whitney U test).

Discussion

Chemotherapy following surgery has superseded radiotherapy in the treatment of endometrial carcinoma. However, both the significance of PAN dissection and the optimal regimen of chemotherapy have been controversial issues. Although improved survival rate has been shown following TAP therapy, a number of severe toxicities were observed [13]. In the authors' own recent phase I / II prospective studies in the Japanese population, it was shown that TEC therapy was a safer and more effective regimen.

Although a few randomized studies have demonstrated that systematic dissection of the PLN has little therapeutic value for early-stage endometrial carcinoma [5, 6], a retrospective SEPAL cohort study showed that there was a possible therapeutic role for a combined dissection of PLN and PAN in those endometrial carcinoma cases with intermediate or high risk factors of recurrence [7]. However, even after the Todo *et al.* study, the significance has remained unclear for PAN dissection in women who had received adjuvant chemotherapy, especially those using platinum, anthracycline, and taxane derivatives (which are regarded as gold standard drugs for treatment of advanced or recurrent endometrial carcinomas) [9, 10, 12].

In the present study, the authors undertook a retrospective comparison of PLN versus PLN + PAN dissection in endometrial carcinoma cases with intermediate or high risk factors for recurrence, all of whom received TEC chemotherapy as an adjuvant therapy. Among the 69 women with adverse indications who received PLN + PAN dissections followed by TEC therapy, there were six cases (9%) without PLN metastasis, but with PAN metastasis (Table 2). This result suggests that PAN dissection is important for accurate staging of the disease. This upgraded staging led to a higher frequency of Stage III / IV cases in the PLN + PAN group than in the PLN group (Table 1). However, even including these cases, it was demonstrated that PAN dissection did not improve the prognosis of the endometrial carcinoma patients with intermediate or high risk factors for recurrence who underwent adjuvant TEC chemotherapy (Figure 1). The present results might imply that the role of PAN dissection is currently limited to staging of the disease. PAN dissection may not be required for patients with sufficient known adverse risk factors for recurrence, as they would receive adjuvant chemotherapy regardless, and especially

when the regimen is going to be one of the more advanced combinations of platinum, anthracycline, and taxane derivatives.

The current study also includes additional evidence that PAN dissection was unnecessary. The frequency of PAN recurrence after surgery followed by adjuvant TEC chemotherapy was 33% (three of nine cases) in the PLN-only group and 29% (four of 14 cases) in the PLN + PAN group, suggesting that initial PAN dissection did not guarantee later reduced PAN recurrence (Table 3). Moreover, PAN dissection led to more adverse effects. The operation time was significantly longer (with its associated risks) and total blood loss was significantly more in the PLN + PAN group than the PLN group (Table 4).

In this retrospective study, the authors showed that PAN dissection did not reduce PAN recurrence and did not improve the overall prognosis of patients with recurrence risks in cases where they received adjuvant chemotherapy using platinum, anthracycline, and taxane derivatives. It was also shown that PAN dissection was accompanied with a surgical burden. Further prospective studies that analyze the necessity of PAN dissection, followed by current modalities of chemotherapy, are still required.

Conclusion

PAN dissection may be omitted without having an adverse effect on prognosis, in endometrial carcinoma patients with recurrence risks also receiving an adjuvant chemotherapy using platinum, anthracycline, and taxane derivatives.

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