Systematic Lymphadenectomy Improves Survival in Patients with Advanced-Stage Primary Fallopian Tube Cancer

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Primary fallopian tube cancer (PFTC) is a rare tumor (< 1% of all female genital tract cancers) and remains poorly characterized. Histologically and clinically, PFTC resembles epithelial ovarian cancer (EOC). The similarities in pathological features and patterns of spread between EOC and PFTC have led clinicians to treat these two malignancies in a similar manner. However, these malignancies may be biologically distinct and may follow different clinical courses. Lymphadenectomy is of crucial importance in patients with EOC, because it improves disease-free survival even in advanced stages. The lymph node metastasis is relatively frequent even in early-stage PFTC. We therefore hypothesized that lymphadenectomy could improve the prognosis in PFTC, as observed in EOC. The purpose of this study is to evaluate the prognostic role of lymphadenectomy in PFTC with a special focus on advanced-stage PFTC. The medical records of 18 patients treated in a single institute from April 1997 to August 2004 were reviewed retrospectively. For advanced stages (III and IV, 10 patients), mean overall survival for patients with positive lymph node involvement is 62.00 ± 4.00 months, while the patients with negative lymph node involvement were alive at last follow-up performed in July 2008 (log-rank; $P < 0.05$). Furthermore, the mean disease-free survival for patients with positive lymph node involvement is 46.67 ± 5.14 months. Based on our analysis, lymphadenectomy could improve overall survival and disease-free survival in patients with advanced-stage PFTC.

Primary fallopian tube cancer; epithelial ovarian cancer; Lymphadenectomy; Survival.

Materials and Methods

Twenty-four patients with the diagnosis of PFTC treated from
April 1997 to August 2004 at Asan Medical Center in Korea. Two who were initially operated on at other institutions were excluded and 4 patients were also excluded due to their probable reclassification as primary ovarian adenocarcinoma. The original histology slides were reviewed again by a specialist in gynecological histopathology to confirm the diagnosis according to the diagnostic criteria proposed by Hu et al. (1950) and modified by Sedlis (1978). Staging was performed using a modification of the FIGO surgical staging of ovarian carcinoma. Differences in proportions were evaluated by the Fisher exact test. All data obtained and research methodologies used in this study were approved by the Institutional Review Board of the Asan Medical Center.

Overall survival (OS) and disease-free survival (DFS) were calculated using the method of Kaplan-Meier. The log rank test was used for univariate analysis. The Statistical Package for Social Science (SPSS, Inc., Chicago, IL) was used for the statistical analysis. Statistical significance was considered as \( P < 0.05 \).

Results

The median age of the patients was 59.5 years (range, 38-72). The clinicopathologic characteristics of the patients are shown in Table 1. Four patients (22.2%) were nulliparous and thirteen patients (72.2%) were postmenopausal at the time of diagnosis. Fourteen patients (77.8%) were poorly differentiated. Bilateral tubal involvement was seen in 4 (22.2%) patients. The primary procedures employed at the initial operation consisted of a total abdominal hysterectomy, bilateral salpingooophorectomy, omentectomy, and routine pelvic and para-aortic lymph node dissection, peritoneal washings, and multiple peritoneal biopsies in patients with early disease and cytoreductive surgery in those patients with advanced disease. Mean number of dissected lymph nodes was 39.1 ± 19.8 and lymph node involvements were seen in 6 patients. Following initial surgery, all 18 patients were treated with paclitaxel-platinum combination chemotherapy for 7.3 ± 2.4 cycles. A clinical complete response was obtained in 15 patients (83.3%) and a partial response in 3 (16.7%). Stable and progressive disease was not observed. None was underwent postoperative radiotherapy.

Median follow-up from time of initial surgery was 56.50 months (range, 10 - 97 months). Three patients had died at the time of review. The mean OS was 89.22 ± 4.89 months (95%CI 79.64 - 98.81) and OS was significantly related to FIGO stage, extent of residual tumor and lymph node involvement \( (P < 0.05) \). The DFS was significantly related to lymph node involvement \( (P < 0.05) \) but not to FIGO stage and extent of residual tumors. For advanced-stage (III and IV, 10 patients), the OS for suboptimal patients is 62.00 ± 4.00 months (95%CI, 54.16 - 69.84 months), but mean OS for patients with optimal cytoreduction has not been reached, as all patients were alive at last follow-up performed in July 2008 (log-rank; \( P < 0.05 \) (Fig. 1). The mean OS for patients with positive lymph node involvement is 62.00 ± 4.00 months (95%CI, 54.16 - 69.84 months), while mean OS for patients with negative lymph node involvement has not been reached as all patients were alive at last follow-up (log-rank; \( P < 0.05 \) (Fig. 2).

The mean disease-free survival (DFS) for patients with suboptimal cytoreduction is 34.50 ± 4.60 months (95%CI, 25.49 - 43.51 months), while mean DFS in patients with optimal cytoreduction has not been reached as all patients were not recurred at last follow-up (log-rank; \( P > 0.05 \) (Fig.

### Table 1. Clinicopathologic characteristics of the patients with primary fallopian tube cancer.

<table>
<thead>
<tr>
<th>Age</th>
<th>Parity</th>
<th>Menopause</th>
<th>Stage</th>
<th>RD after surgery</th>
<th>OS</th>
<th>DFS</th>
<th>Outcome</th>
<th>Recurrence</th>
<th>CC</th>
<th>No. of LN</th>
<th>No. of positive LN</th>
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<td>2</td>
<td>No</td>
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<td>34</td>
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<td>12</td>
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<tr>
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<td>13</td>
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<tr>
<td>7</td>
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<td>6</td>
<td>Yes</td>
<td>IIb</td>
<td>&gt; 1 cm</td>
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<td>22</td>
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<td>62</td>
</tr>
<tr>
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<tr>
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<td>8</td>
<td>Yes</td>
<td>IV</td>
<td>&gt; 1 cm</td>
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<td>28</td>
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</table>

RD, Residual disease; OS, Overall survival; DFS, Disease-free survival; CC, Chemotherapy cycles; No, Number; LN, Lymph node.
The mean DFS for patients with positive lymph node involvement is 46.67 ± 5.14 months (95%CI, 36.59 - 56.74 months), while mean DFS in patients with negative lymph node involvement has not been reached as all patients were not recurred at last follow-up (log-rank; \( P < 0.05 \)) (Fig. 4). Two patients had evidence of recurrent disease and received additional chemotherapy. They were all initially suboptimally cytoreduced. One patient was treated with paclitaxel-carboplatin and one with topotecan chemotherapy. All recurred patients are alive without evidence of disease.

**Discussion**

The etiology of PFTC is unknown. Hormonal, reproductive, and possibly genetic factors that are thought to increase EOC risk might also increase PFTC risk (Pectasides et al. 2006). High parity has been reported to be protective, and a history of pregnancy and the use of oral contraceptives decreases the PFTC risk significantly (Pectasides et al. 2006). It has been reported that there is no statistically significant correlation between PFTC and age, race, weight, education level, pelvic inflammatory disease, infertility, pre-
vious hysterectomy, endometriosis, lactose intolerance, or smoking (Pectasides et al. 2006).

The FIGO EOC staging system has been adapted to apply to PFTC (Ajithkumar et al. 2005). PFTC is often diagnosed at an earlier stage compared to EOC. In general, 20%-25% of patients have stage I, 20% have stage II, 45%-50% have stage III, and 5%-10% have stage IV (Ajithkumar et al. 2005).

Surgery is the treatment of choice for PFTC. Surgical principles are the same as those used for EOC. Aggressive cytoreductive surgery with removal of as much tumor as possible is warranted in patients with advanced disease. Anatomically, lymphatic drainage from the fallopian tubes to pelvic nodes occurs through lymphatic channels located near the proximal part of the uterus and drainage to para-aortic nodes is ensured through lymphatic channels in the distal part of tubes and fimbria (Deffieux et al. 2005). Recent report showed that left para-aortic chain above the

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Fig. 3. Kaplan-Meier analysis of disease-free survival for patients with PFTC at stages III and IV. Disease-free survival is shown for patients with optimal cytoreduction (7 patients) and suboptimal cytoreduction (3 patients). Optimal cytoreduction group showed significantly longer disease-free survival ($P < 0.05$).

Fig. 4. Kaplan-Meier analysis of disease-free survival for patients with LN (+) and LN (−) at stages III and IV. Disease free survival is shown for patients with positive lymph node involvement (6 patients) and negative lymph node involvement group (4 patients). Negative lymph node involvement group showed significantly longer disease-free survival ($P < 0.05$).

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level of the inferior mesenteric artery is the most frequently involved in patients with PFTC and unlike patients with EOC, lymph node involvement is observed even in patients with disease confined to one tube (stage IА) and in patients with an early stage endometrioid tumor (Deffieux et al. 2005). As a result, lymphadenectomy should be performed routinely whatever the disease stage (provided a complete surgical resection of the intraabdominal tumor is feasible) and whatever the histologic type of PFTC considering the strong tendency for the lymphatic spread. (Klein et al. 1999; Gadducci et al. 2001; Deffieux et al. 2005; Konishi et al. 2008)

Some reports showed that patients with PFTC that have optimal primary cytoreduction have been noted to have improved outcomes compared to those patients with suboptimal cytoreduction (Gemignani et al. 2001; Chi et al. 2004).

Chemotherapeutic agents administered for the management of EOC have generally been used in the management of patients with PFTC. Outcomes are thought to be similar to those of women with EOC, although a population-based series has suggested improved outcomes based on stage for women with PFTC as compared to EOC (Kosary andTrimble 2002). The current gold standard chemotherapy for EOC is a paclitaxel-platinum combination and there are very few data that are extractable from the literature with regard to PFTC. The combination chemotherapy with paclitaxel and platinum appears to be superior, in terms of OS, compared to earlier agents used for this malignancy, including melphalan and platinum-based combinations(Leath et al. 2007).

In a large population-based tumor registry study of 416 women with PFTC, the reported 5-year survival rate by stage was as follows: stage I, 95%; stage II, 75%; stage III, 69%; and stage IV, 45% (Kosary and Trimble 2002). Compared with 9,032 women treated for EOC during the same study period, patients with PFTC showed better survival stage by stage. PFTC is more likely to present at an early stage and have an overall more favorable outcome even when matched for other known prognostic variables. The improved survival for PFTC is most pronounced for patients with advanced-stage (Wethington et al. 2008). As in EOC, residual disease after initial surgery is also a significant prognostic factor (Gadducci et al. 2001).

Systematic lymphadenectomy has a diagnostic value in early-stage EOC, thanks to the possibility of accurate clinical staging and helps to avoid unnecessary adjuvant chemotherapy (Angioli et al. 2008). In patients affected by advanced-EOC, systematic lymphadenectomy statistically significantly improves DFS and reduces recurrence rates but improvement of OS is not statistically significant (Chan et al. 2007; Angioli et al. 2008).

Although limited by small numbers, our data show that lymph node involvement is associated with poor OS and DFS in advanced-stage PFTC and that optimal cytoreduc-


References


