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Impact of lymphadenectomy on survival after recurrence in patients with advanced ovarian cancer without suspected lymph node metastasis

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HIGHLIGHTS

- Lymphadenectomy group showed longer survival in advanced ovarian cancer patients without suspected lymph node metastasis.
- Lymphadenectomy during primary debulking surgery was associated with longer survival, especially survival after recurrence.
- Patients with more number of removed lymph nodes showed tendency for better survival outcomes.

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ABSTRACT

Objective. To investigate the impact of pelvic and para-aortic lymphadenectomy during primary debulking surgery (PDS) on recurrence pattern and survival after recurrence in patients with advanced epithelial ovarian cancer (EOC) without suspected lymph node (LN) metastasis in preoperative imaging studies and intraoperative findings.

Methods. A retrospective review of patients with FIGO stage III and IV EOC without suspected lymph node metastasis was performed. Patients with stage III EOC due to LN metastasis without peritoneal disease were excluded from this study. Survival comparisons for progression-free survival (PFS), overall survival (OS), and survival after recurrence were performed between patients with or without lymphadenectomy.

Results. Of the 261 EOC patients fulfilling inclusion criteria, 194 (74.3%) experienced relapse and a further 132 (50.6%) died within a median follow-up period of 48 months (range, 6–139 months). Patterns of recurrence and CA-125 level at recurrence were not different between patients with lymphadenectomy and without lymphadenectomy; however, patients with lymphadenectomy showed longer survival after recurrence than those without lymphadenectomy (43 vs. 32 months, $p = 0.013$). This difference was pronounced in the group with residual tumor <1 cm (48 vs. 30 months, $p = 0.010$). The survival advantage of lymphadenectomy after recurrence remained significant in multivariate analysis (HR 0.57, 95% CI 0.38–0.84, $p = 0.005$).

Conclusions. Lymphadenectomy during PDS was associated with longer survival, especially survival after recurrence. The underlying mechanism should be elucidated in future studies.

Introduction

Epithelial ovarian cancer (EOC) is one of the most lethal malignancies [1] and has a relatively high incidence in developed countries [2]. The standard primary surgical treatment consists of hysterectomy, bilateral salpingo-oophorectomy, omentectomy, retroperitoneal (pelvic and paraaortic) lymphadenectomy, and tumorectomy of any metastatic lesions with the goal of complete cytoreduction of disease. Prognosis of ovarian cancer patients is influenced by the surgical outcomes of primary treatment, which can be categorized into subgroups according to the largest residual tumor diameter. Of the many prognostic factors for survival in ovarian cancer patients, residual tumor at primary surgery is widely known to be a powerful predictor of outcome [3–5].

Regarding lymphadenectomy in primary surgery, the current National Comprehensive Cancer Network (NCCN) guideline suggests systemic pelvic and paraaortic lymph node (LN) dissection for early-stage EOC, and resection of suspicious and enlarged LN for advanced-stage disease. In cases with tumor nodules outside the pelvis ≤2 cm (presumed stage IIIB), bilateral pelvic and para-aortic LN dissection is

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recommended. The prognostic role of comprehensive lymph node staging in early-stage disease has been established both by an exploratory analysis of a prospective trial and in a large epidemiologic series [6,7]. In advanced-stage EOC with enlarged LN, lymphadenectomy should be performed to complete debulking of disease. However, the purpose of lymphadenectomy in advanced-stage disease without suspected LN metastasis is unclear since lymphadenectomy does not play a role in diagnosis or debulking in these cases.

Although lymphadenectomy during the treatment of EOC is known to be feasible, surgical morbidity such as higher blood loss, increased transfusion rate, and lymphocele or lymphedema [8–10] should be considered because the value of the procedure remains controversial. In this study, we conducted analysis to determine whether pelvic and paraaortic lymphadenectomy improves survival outcomes in patients with advanced stage EOC without suspected LN metastasis in preoperative imaging studies and intraoperative findings.

Patients and methods

Patients

After obtaining IRB approval (IRB file no. 2016–04-114), we performed a retrospective review of all EOC patients who underwent primary treatment at Samsung Medical Center between January 2002 and December 2013. Data were obtained from electronic medical records. Patients were included according to the following inclusion criteria: (1) FIGO stage III and IV disease: (2) patients without suspected LN metastasis in preoperative imaging studies (computed tomography (CT), pelvis magnetic resonance imaging (MRI), or positron emission tomography (PET)-CT); and (3) patients who had undergone primary debulking surgery (PDS) and adjuvant chemotherapy as primary treatment. Patients who had neoadjuvant chemotherapy (NAC) and interval debulking surgery (IDS) and patients with enlarged LN during surgery were excluded from the study. Patients were categorized into two groups: with and without lymphadenectomy. Patients with pelvic and/or paraaortic lymphadenectomy were considered as lymphadenectomy group in this study.

Treatment

Before starting primary treatment for EOC, patients were routinely evaluated by abdominal/pelvic CT, MRI, or PET—CT. Imaging studies were evaluated by a radiologist to designate cancer metastatic lesions and decide treatment plans. On preoperative imaging, shortest diameter of visible LN <1 cm was considered negative for LN metastasis.

The standard primary surgical treatment consisted of hysterectomy, bilateral salpingo-oophorectomy, omentectomy, retroperitoneal (pelvic and paraaortic) lymphadenectomy, and tumorectomy of any metastatic lesions. Peritoneal washing was routinely performed. Peritoneal biopsies were performed if any abnormalities were identified. After PDS, either abdominopelvic CT or MRI was routinely performed to confirm the disease status. Optimality of surgery was defined by the largest diameter of residual disease as follows: optimal residual (<1 cm), and suboptimal residual (≥1 cm) disease.

In our institution, patients routinely started their first cycle of taxane/platinum combination chemotherapy within 2 weeks of surgery. As routine protocol, chemotherapies were repeated every 3 weeks for 6 cycles, but the number of cycles may have been adjusted depending on patient's condition and response. The CA-125 level was routinely checked to determine whether CA-125 was in the normal range between cycles.

Follow-up

After primary treatment, patients were assessed by physical examination and complete blood count and chemistries, including CA-125 levels, every 3 months for the first 3 years and twice a year thereafter. Chest radiography and abdominopelvic CT scan (or alternatively abdominopelvic MRI) were performed every 6 months for the first 3 years, and every 12 months thereafter. Additional diagnostic procedures were performed according to specific clinical suspicions. If recurrence was suspected on the basis of symptoms or CA-125 elevation, additional imaging studies were performed. Recurrence was detected by imaging studies in the presence or absence of CA-125 elevation. After detection of recurrence, patients were treated mainly with chemotherapy, or secondary cytoreductive surgery with additional chemotherapy.

Overall survival (OS) was described as the time between diagnosis and the patient's death or loss to follow-up. Progression-free survival (PFS) was described as the time between diagnosis and the patient's recurrence/progression or loss to follow-up. Survival after recurrence was described as the time between diagnosis of recurrence and the patient's death or loss to follow-up.

Statistical analysis

Summary statistics were used to describe the data. Continuous variables are presented as means (standard deviation) or medians (range). Mann-Whitney test was used to compare medians and Student's *t*-test was used to compare mean values after confirmation of non-normal or normal distributions with the Shapiro-Wilks test. Categorical variables are presented as frequencies (percentages). Fisher's exact test or χ^2 test was used to analyze the distribution of recurrence patterns according to lymphadenectomy. Survival analyses and curves were established via the Kaplan-Meier method and compared via the log-rank test. Univariate and multivariate analyses were performed with the Cox proportional hazards model to evaluate the importance of lymphadenectomy and other clinicopathological features as prognostic factors. Multivariate *p* values were used to characterize the independence of these factors. A 95% confidence interval (CI) was used to quantify the relationship between survival time and each independent factor. All *p*-values were two-sided and *p* values <0.05 were considered statistically significant. Statistical analyses were performed using *R*3.0.3 (Vienna, Austria; http://www.R-project.org).

Results

We investigated 261 patients who were diagnosed with stage III and IV EOC and without suspected lymph node metastasis in preoperative imaging studies. Among EOC patients treated in Samsung Medical Center between 2002 and 2013, 587 patients were stage III and IV. Fifty-nine patients who received neoadjuvant chemotherapy and 260 patients with suspected LN metastasis in preoperative imaging studies were excluded. Additionally, seven patients with bulky/suspicious lymph node described in the operation record were also excluded.

At the time of this analysis, 194 patients (74.3%) had experienced relapse, 132 (50.6%) had died and 129 (49.4%) were still living after a median observation period of 48 months (range, 6–139 months). The clinical characteristics of the patients are listed in Table 1; 87.4% of patients had FIGO stage III disease, and 78.5% had high grade serous type. Residual disease was <1 cm in 159 patients and ≥1 cm in 102 patients. There were no significant differences in clinicopathological characteristics between patients with and without lymphadenectomy except for age in all patients and the suboptimal residual disease group, but not in the optimal residual disease group. Median number of removed lymph nodes was 17 (range 8–51) for all patients and 18 (range 8–51) for optimal residual patients.

Comparison of characteristics between recurrent patients with and without lymphadenectomy is shown in Supplementary material 1. There were no significant differences in age, stage, and histology between patients with and without lymphadenectomy. Recurrence pattern, number of recurrence lesions, and CA-125 level at recurrence

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