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Survival impact based on the thoroughness of pelvic lymphadenectomy in intermediate- or high-risk groups of endometrioid-type endometrial cancer: A multi-center retrospective cohort analysis

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HIGHLIGHTS

- The number of lymph node is a marker of adequate lymphadenectomy in endometrial cancer.
- Thorough pelvic lymphadenectomy is required for accurate staging and improved survival.
- Thoroughness of pelvic lymphadenectomy matters more than para-aortic lymphadenectomy.

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ABSTRACT

Objective. To investigate whether the number of lymph nodes obtained during lymphadenectomy affects the survival of patients with intermediate- or high-risk endometrioid-type endometrial cancer.

Methods. A total of 476 patients who were diagnosed with FIGO stage IB to IIIC2 endometrioid adenocarcinoma through surgical staging, including hysterectomy and pelvic lymphadenectomy with or without paraaortic lymphadenectomy between 2000 and 2013 were retrospectively enrolled from four tertiary centers in Korea. Sentinel lymph node mapping was not performed in any patient. The number of nodes obtained and positive nodes, was extracted from pathologic report.

Results. Paraaortic lymphadenectomy was performed in 298 (62.6%) patients and 164 (34.4%) had stage IIIC disease. The isolated paraaortic lymph node metastasis rate decreased as the number of pelvic nodes obtained increased. In the total study population, an increase of negative pelvic and paraaortic nodes was associated with improved recurrence-free survival (RFS) and overall survival (OS) independent of other prognostic factors. In the node-positive group, an increase of negative pelvic nodes was an independent prognostic factor for RFS [hazard ratio (HR), 0.946; 95% confidence interval (CI), 0.906–0.988] and OS [HR, 0.907; 95% CI, 0.849–0.968]. In stage IIIC2 patients, 14 or less negative pelvic nodes was associated with poor RFS and OS.

Conclusions. Removing as many pelvic nodes as possible is required to warrant accurate nodal staging and improve survival in patients with intermediate- or high-risk endometrial cancer. Sentinel lymph node mapping can be a resolution to minimize lymph node dissection without compromising staging accuracy.

1. Introduction

The role of a lymphadenectomy in endometrial cancer has been a controversial issue for decades. Accurate identification of nodal status helps tailoring the postoperative adjuvant treatment. Because palpation or gross inspection cannot detect nodal involvement accurately and the nodal involvement rate is reported to be increased by performing a systematic lymphadenectomy [1–3], performing a systematic lymphadenectomy is included in the staging procedure for intermediate- or

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high-risk endometrial cancer. Although the therapeutic effect of a systematic lymphadenectomy has been demonstrated in numerous retrospective studies, two randomized trials conducted in the last decade have failed to prove it in clinically early-stage endometrial cancer [2, 4]. From the results of two landmark trials, it has become evident that a systematic lymphadenectomy has no survival benefit in patients with low-risk endometrial cancer, who have excellent prognosis only by receiving simple hysterectomy and bilateral salpingo-oophorectomy [5]. However, controversy still remains over the indications for, the anatomic extent of, the thoroughness of, and the therapeutic value of a lymphadenectomy in endometrial cancer [6]. Regarding the indication, several preoperative or intraoperative risk scoring systems defining the low-risk group as not requiring a lymphadenectomy have been developed and being used clinically [7–9]. Most of them include a depth of myometrial invasion greater than 50%, which is identical to the current FIGO stage IB.

Regarding the anatomic extent and the thoroughness of lymphadenectomy, practitioners have different strategies for how thoroughly to perform pelvic lymphadenectomy (PLND) and whether to perform a paraaortic lymphadenectomy (PALND). The number of lymph node obtained has been commonly used for assessing the thoroughness of lymphadenectomy [2,10]. Several retrospective studies support the association between an increase of lymph node obtained and improved survival, regardless of node positivity [11–14]. In terms of the extent of a lymphadenectomy, a large-scale retrospective cohort study conducted by a Japanese group demonstrated the survival benefit from a PALND in patients with intermediate- or high-risk endometrial cancer [10]. However, it has not been determined whether the extent or the thoroughness of lymphadenectomy is more important.

To determine the ideal strategy for a lymphadenectomy in endometrial cancer, the therapeutic value, thoroughness, and extent of the lymphadenectomy should be assessed simultaneously in patients requiring a systematic lymphadenectomy. Therefore, we conducted a multicenter retrospective study in intermediate- and high-risk groups of endometrioid-type endometrial cancer.

2. Materials and methods

2.1. Patients

Eligible patients were retrospectively enrolled from four tertiary centers in Korea after institutional review board approval of each center. All patients underwent surgical staging, including hysterectomy and pelvic lymphadenectomy (PLND) with or without PALND, between 2000 and 2013 and were ultimately diagnosed with FIGO stage IB to IIIC2 endometrioid adenocarcinoma. Sentinel lymph node mapping was not performed in any patient. From each center, clinical data were abstracted by a review of patient medical records. Pathology reports were reviewed for grade, depth of myometrial invasion, tumor location, the number of nodes obtained and positive nodes of the pelvic and paraaortic areas. Because the FIGO staging system was revised in 2009, re-staging was conducted using pathologic findings in patients staged with the old staging system. Survival data, including date of first recurrence and date of death, were also collected. A total of 503 patients were retrospectively enrolled from the four centers. Among them, 8 patients who did not received any lymphadenectomy, 15 patients with unreliable data, and 4 patients with no survival data were excluded. The remaining 476 patients were finally enrolled and analyzed.

2.2. Evaluation of the thoroughness and extent of the lymphadenectomy

The number of nodes obtained during lymphadenectomy is used for quality assessment of the thoroughness of the lymphadenectomy [1]. We also used the number of negative nodes indicating the number of non-tumor bearing lymph node. Consequently, the number of negative nodes was equal to the number of nodes obtained in cases with negative nodal status. The number of negative nodes is considered to reflect the thoroughness of lymphadenectomy, regardless of the burden of nodal involvement. The PLND was categorized based on the number of pelvic nodes obtained or the number of negative pelvic nodes. Because the anatomical upper limit of the PALND could not be determined for every patient, the PALND was categorized into three classes according to the number of paraaortic nodes obtained (0, 1–10, and >10).

2.3. Classification of adjuvant treatment

Adjuvant treatment was administered on an individual basis at the discretion of treating physician. Adjuvant treatment used in our cohort includes platinum- and/or taxol-based chemotherapy, pelvic radiotherapy with possible extended field therapy to paraaortic lymph nodes, and brachytherapy, either alone or in combination. This was categorized into four classes: no adjuvant treatment, radiotherapy only, chemotherapy only, and both radiotherapy and chemotherapy. Concurrent chemoradiation was categorized into the class of both radiotherapy and chemotherapy.

2.4. Statistical analysis

Continuous variables, such as age and body mass index (BMI), were categorized using the median as the cut-off value. The difference in nodal status according to the number of pelvic nodes obtained was evaluated using linear-by-linear association. Receiver operating characteristic (ROC) curves were constructed to estimate the optimal cut-off values for the number of negative pelvic nodes and the number of total negative nodes. The Kaplan–Meier method was used to generate survival curves and calculate recurrence-free survival (RFS) and overall survival (OS). The log-rank test was used to assess differences in survival rates. Univariate and multivariable analyses were performed using the Cox proportional hazards model to assess whether the number of nodes has an impact on survival independently. In the multivariate analysis for all patients, age, grade, 2009 FIGO stage, the number of total negative nodes, and adjuvant treatment were included as variables. To identify whether the number of negative pelvic nodes has independent prognostic value, a separate multivariate analysis was conducted in node-positive patients who received a PALND and adjuvant treatment. Statistical analyses were performed using SPSS for Windows, version 18 (SPSS, Inc., Chicago, IL, USA) and MedCalc software program (MedCalc Software, Mariakerke, Belgium).

3. Results

3.1. Baseline patient characteristics

General characteristics of patients are shown in Table 1. Median age and body mass index were 55 years and 24.5 kg/m^2, respectively. The median number of pelvic nodes obtained was 23 (range, 2–74). A PALND was conducted in 298 (62.6%) patients and the median number of paraaortic nodes obtained of those patients was 7 (range, 1–58). FIGO stage IB was diagnosed in 165 (34.7%) patients. In 164 (34.4%) patients with node metastasis (FIGO stage IIIC), the median number of positive pelvic nodes, positive paraaortic nodes, and total positive nodes were 2, 2, and 3, respectively. 70% of them had less than 6 of total positive nodes. Of the patients enrolled in the study, 60 (12.6%) did not receive any adjuvant treatment, and 214 (45%) received postoperative adjuvant radiotherapy.

3.2. Positive node detection rate was affected by the number of nodes obtained

Pelvic and paraaortic node positive rates had a positive correlation with the number of nodes obtained. The pelvic node positive rate was higher in >20 pelvic nodes obtained group than in ≤20 pelvic nodes