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Original Article

# Therapeutic value of lymphadenectomy and adjuvant radiotherapy in uterine corpus confined endometrioid-type cancer

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**Abstract**

*Background*: To determine the efficacy of lymphadenectomy and adjuvant radiotherapy in patients with endometrioid-type cancer confined to the uterine corpus.
*Methods*: A total of 323 patients were evaluated. Patients were stratified according to depth of myometrial invasion (DMI) and tumor grade.
*Results*: Lymphadenectomy was performed in 83% of the entire cohort. Age (<60 vs. ≥60) and DMI affected disease-free survival. Addition of lymphadenectomy improved the disease-specific survival. The improved effect of lymphadenectomy was only observed in DMI ≥½ and grade 2 tumor (78.5% vs. 95.4%). However, that effect in this group was determined in patients with more than 50 removed lymph nodes. Performing adjuvant radiotherapy and the type of the radiotherapy (vaginal brachytherapy vs. external beam radiotherapy) were not significant for disease-free and disease-specific survival. In the entire cohort, loco-regional recurrence occurred in 3.1% and 4.4% of patients with or without adjuvant radiotherapy, respectively. However, these rates were 2.6% and 13.6% for patients with DMI ≥½ and grade 2 who were older than 60 years, respectively.
*Conclusion*: Lymphadenectomy should be performed in patients with DMI ≥½ and grade 2 to improve survival. Adjuvant vaginal brachytherapy may only be given to patients who are older than 60 years old with moderate differentiation and deep myometrial invasion to reduce loco-regional recurrence.


*Keywords:* Adjuvant radiotherapy; Endometrial cancer; Intermediate-risk group

## 1. Introduction

According to GLOBACAN 2012 data endometrium cancer (EC) is the most common sixth malignancy in women, with 320.000 women diagnosed each year.[1] Disease is usually diagnosed in early stages and is confined to the uterus in 80% of patients at the time of diagnosis.[2] Five-year overall survival (OS) is greater than 80% in these patients.[3] This rate increases to 95% in these patients with disease confined to the uterus and with low-risk, defined as having FIGO grade 1 or 2 disease with depth of myometrial invasion less than half (<½).[4−8]

EC has been staged surgically according to the International Federation Obstetricians and Gynecologists (FIGO) since 1988.[9] FIGO revised the staging system in 2009.[10] Evaluation of the pelvic and para-aortic lymph nodes is needed in this new staging system. Additionally, a National Comprehensive Cancer Network (NCCN) guideline recommends lymphadenectomy for all patients with uterine cancer.[11] Nevertheless, routine lymphadenectomy as a part of surgical procedure in EC is still controversial. Discussion continues not

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only about the indications of lymphadenectomy but also about the definition, limits and sufficiency of the procedure. It was shown that addition of lymphadenectomy to total abdominal hysterectomy and bilateral salpingo-oophorectomy in the low-risk group at early stages did not improve survival.[4−6,12−14] Moreover, the morbidity rate resulting from this surgical procedure is in substantial amounts.[4] Thereby, performing lymphadenectomy on all patients with EC will be over-treatment. In contrast, it is known that lymphadenectomy improves survival in patients with depth of myometrial invasion equal and more than half (≥½), FIGO grade 3 tumor, cervical invasion, and extrauterine spread, all of which were defined as high risk for lymphatic spread.[5,15,16]

Another controversial subject regarding endometrial cancer confined to the uterus is the necessity of adjuvant radiotherapy. However, the group of patients who will take radiotherapy or the technique has not been clarified. Despite that, the necessity of radiotherapy is tried to define according to the clinical situation, pathology, and surgery performed. Reports revealed that external beam radiotherapy (EBRT) decreased loco-regional recurrence in patients with deep myometrial invasion, tumor with poor differentiation, and advanced age, but EBRT couldn't be shown to improve overall survival.[17,18] On the other hand, the costs of loco-regional control obtained with ERBT were an increase in morbidity and poor quality of life.[19] It was shown that vaginal brachytherapy provided almost similar pelvic control and overall survival compared to EBRT; with much lower adverse effects.[20]

The present study investigated the role of lymphadenectomy and adjuvant radiotherapy on recurrence and survival in patients with intermediate risk endometrioid-type endometrial cancer confined to the uterine corpus.

## 2. Methods

The data of 357 patients with endometrioid-type EC who underwent at least total abdominal hysterectomy and bilateral salpingo-oophorectomy and whose definitive pathology report revealed disease confined to the uterine corpus and intermediate risk for recurrence between January 1993−May 2013 in our gynecologic oncology clinic was evaluated from database and patient files retrospectively. Patients with FIGO grade 1 or 2 tumor without myometrial invasion and FIGO grade 3 tumor with myometrial invasion ≥ ½ at final pathology were excluded. Additionally, patients with non-endometrioid type EC, EC including sarcoma components, invasion of glandular or stromal cervix, adnexal spread, involvement of uterine serosa, positive peritoneal cytology, nodal or non-nodal extra-uterine tumor spread, synchronized tumors and patients undergoing systemic adjuvant therapy were not included. Patients were staged according to FIGO criteria. IRB approval (2016/209; 17) was obtained before the study.

Thirty-three patients were excluded due to the following reasons; (i) having synchronized tumor (n:9); (ii) lost to follow-up after surgery (n:17); (iii) death within a month after the surgery (n:3); (iv) undergoing adjuvant chemotherapy (n:4); and (v) undergoing sandwich therapy (n:1). Finally, the study included 323 patients. The patients were stratified into five groups according to FIGO grade and depth of myometrial invasion. The groups were defined as; Group 1; no myometrial invasion and grade 3 tumor, Group 2; depth of myometrial invasion < ½ and grade 2 tumor, Group 3; depth of myometrial invasion < ½ and grade 3 tumor, Group 4; depth of myometrial invasion ≥ ½ and grade 1 tumor and Group 5; depth of myometrial invasion ≥ ½ and grade 2 tumor.

Frozen-section (F/S) consultation is utilized routinely for patients with EC in our clinic, and staging surgery is performed for those patients whose F/S consultation has revealed non-endometrioid adenocarcinoma, FIGO grade 2 or 3 disease, depth of myometrial invasion ≥ ½, cervical involvement, and tumor size >2 cm. Also, patients with a preoperative diagnosis of FIGO grade 3 disease or high-risk cell type undergo staging surgery directly. Lymphadenectomy is performed in most patients by skeletonizing of the pelvic and paraaortic regions. Nevertheless, there are patients treated by sampling of the suspicious lymph nodes at the discretion of the surgeon. Since patients with positive lymph nodes were evaluated, patients who had lymph node sampling were also included in the study. Bilateral pelvic lymphadenectomy was performed to complete skeletonization, with all lymphatic tissue of the common, external and internal iliac vessels and the obturator fossa removed after visualization of the obturator nerve. The superior surgical dissection margin for the pelvic nodes was aortic bifurcation, and the anterior distal surgical dissection margin was the circumflex iliac vein. The presacral lymphatic tissue was harvested separately. The upper limit of paraaortic lymphadenectomy was renal veins.

The decision for adjuvant radiotherapy was made by the senior surgeon and the gynecologic oncology counsel, and the radiotherapy was performed as external beam radiotherapy and/or vaginal brachytherapy. Both the depth of myometrial invasion and grade were considered in making this decision. Patients were followed up quarterly in the first two years, semi-annually up to five years, and annually later on. Pelvic examination, abdomino-pelvic ultrasonography, complete blood count and blood chemistry were performed in the follow-up. Chest X-ray was utilized yearly unless there was clinically suspicious of disease. Thoracic and/or abdominal computerized tomography was used when needed. Pap-smear test and CA125 level were utilized in the follow-up, even though they were not used routinely.

The period from initial surgery to recurrence or last visit was defined as disease-free survival (DFS), and the period from surgery to death because of the disease (except in the first month after surgery) or last visit was defined as disease-specific survival (DSS). The recurrences occurring at sites that were below the level of the linea terminalis; such as vagina, vaginal vault and pelvic side wall, were defined as loco-regional recurrence; the ones occurring between the linea terminalis and diaphragma were defined as upper abdominal, and the remainder were defined as extra-abdominal recurrence. Recurrences in the liver parenchyma and bone were accepted as extra-abdominal, and cytologically defined ascites and peritonitis carcinomatosa were accepted as upper

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