A multicenter analysis of adjuvant therapy after surgery for stage IIIC endometrial adenocarcinoma: A Korean Radiation Oncology Group study (KROG 13-17)☆

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HIGHLIGHTS

• Adjuvant CTRT or RT alone showed comparable outcome in stage IIIC1 or IIIC2.
• Patients with stage IIIC1 were more likely to develop an recurrence in the PALNs.
• CTRT did not affect PALN recurrence compared to the RT alone group in stage IIIC1.

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ABSTRACT

Objective. To investigate whether combined chemoradiotherapy (CTRT) confers a benefit for survival outcome over radiotherapy (RT) alone after primary surgery in patients with FIGO stage IIIC endometrial adenocarcinoma.

Methods. We conducted a multicenter retrospective study of patients with surgical stage IIIC endometrial cancer from 1990 to 2011. Adjuvant RT alone was performed in 85 patients (40.3%) and adjuvant CTRT in 126 patients (59.7%). Disease-free survival (DFS) and overall survival (OS) were analyzed using Kaplan–Meier method and Cox proportional hazards model.

Results. Stage IIIC1 and stage IIIC2 accounted for 63% and 37%, respectively. FIGO IIIC2 had a higher recurrence rate than FIGO IIIC1 (38.5% vs. 29.3%, p = 0.172). Five-year OS and DFS were lower in FIGO IIIC2 than FIGO IIIC1 (85.1% vs. 76.9%, p = 0.417; 71.0% vs. 59.2%, p = 0.108, respectively). Eighteen patients (13.5%) in stage IIIC1 developed PALN recurrence, whereas only one (3.3%) in stage IIIC2 had PALN recurrence (p = 0.001). In multivariate analysis, predictors of DFS were parametrial invasion (HR, 3.49; 95% CI, 1.83–6.64; p < 0.001), higher
1. Introduction

Traditionally, postoperative radiotherapy (RT) has been employed in stage IIIC endometrial carcinoma to improve locoregional control and outcome [1–3]. Recently, with advances in chemotherapy (CT), the majority of adjuvant treatment consists of CT with or without RT in high-risk or advanced stage endometrial cancer; in randomized settings, some investigators are trying CT intensification instead of RT [4–6]. Patients with node-positive endometrial cancer, however, have higher locoregional recurrence compared to the RT alone group [7]. Many retrospective studies have reported substantial locoregional recurrence, ranging from 30% to 47% for patients treated with CT alone [5,8].

Several studies have suggested that combined chemoradiotherapy (CTRT) can provide additional benefits for advanced endometrial cancer compared with CT or RT alone [9–12]. A recent meta-analysis showed that the CTRT group in advanced stage endometrial cancer had a more significant survival benefit compared to the RT group [13]. However, advanced endometrial cancer represents a heterogeneous group of patients in terms of histologic grade; extent of nodal involvement; stage IV; uterine serosal, adnexal, vaginal or parametrial involvement; and histologic subtype, such as serous or clear cell carcinoma. This variability has led to a wide range of five-year survival rates for stage IIIC endometrial cancer, ranging between 40% and 80% [14].

The optimal adjuvant therapy in stage IIIC endometrial carcinoma has not yet been determined. Researchers have questioned whether combined CTRT can provide additional benefit to patients who receive adjuvant RT alone for stage IIIC endometrial cancer. Another important question is whether it is reasonable to recommend pelvic or extended-field RT alone without CT in patients with a favorable histologic subtype.

Advanced endometrial cancer with positive lymph node (LN) is classified as stage IIIC based on the staging system of the International Federation of Gynecology and Obstetrics (FIGO), dividing pelvic LN involvement into revised 2009 FIGO IIIC1 and paraaortic LN (PALN) into stage IIIC2. In this study, we evaluated survival outcomes in stage IIIC endometrial adenocarcinoma and sought to determine the benefit of combined modality after surgery in this favorable histologic subtype of FIGO stage IIIC1 or IIIC2.

2. Methods and materials

2.1. Patients

We retrospectively evaluated 407 patients with surgical stage III endometrial cancer treated with curative intent at 18 institutions in Korea between January 1990 and December 2011. Classifying according to the revised FIGO 2009, 109 patients had FIGO stage IIIA, 20 had IIIB, and 278 had FIGO stage IIIC. Patients eligible for analysis had endometrioid adenocarcinoma and positive pelvic LN ± PALN metastasis on imaging or surgery. Patients were excluded if they had non-endometrioid histology (n = 44); CT only (n = 9); no adjuvant therapy (n = 1), previous neoadjuvant therapy (n = 2), incomplete RT (< 40 Gy, n = 5), whole abdominal irradiation (n = 4), vaginal brachytherapy only (n = 1) or double primary cancer (n = 1). Finally, a total of 211 stage IIIC patients with positive pelvic LN or PALN who received radical surgery followed by adjuvant RT alone or combined CTRT were analyzed retrospectively.

All patients underwent physical examination, routine blood cell counts and chemistry, biopsy, chest radiographs, and pelvic magnetic resonance imaging. Most patients (97.2%) performed abdomen/pelvic computed tomography scans. Chest computed tomography or whole-body positron emission tomography-computed tomography was obtained if clinically indicated in each institute policy.

2.2. Treatment

All patients underwent hysterectomy, bilateral salpingooophorectomy with pelvic and/or aortic lymphadenectomy followed by postoperative RT or combined CTRT. Pelvic LN dissection or sampling was performed in 206 patients (97.6%) and paraaortic LN dissection or sampling was performed in 126 patients (59.7%). The median number of pelvic and paraaortic LN dissections was 23 (range, 1–57) and 7 (range, 1–43), respectively. Five patients with only positive PALNs on preoperative image or pathologic-positive PALNs after paraaortic lymphadenectomy were classified as FIGO stage IIIC2, although they did not undergo pelvic lymphadenectomy.

RT consisted of external beam RT and vaginal brachytherapy. External beam RT was delivered with 10–20 MV photons using the four-field box technique to the tumor bed and regional lymphatics. The total dose to the pelvis ranged from 45 Gy to 54 Gy in 1.8 Gy daily fractions, five days per week. Sixty-seven patients (31.8%) were treated with extended field RT encompassing a volume of PALN. The superior border was usually located at the T12–L1 interface but was adjusted based on the position of the positive PALNs. Sixty-seven patients (31.8%) received additional vaginal brachytherapy with Fletcher-Suit after-loading applicators. Two to six fractions of 3–5 Gy were delivered to the vaginal surface or 5 mm from the vaginal surface.

Adjuvant combined CTRT was performed in 126 patients (59.7%). Patients receiving adjuvant CT were treated with platinum-based CT (n = 70, 33.2%), carboplatin plus paclitaxel (n = 25, 11.8%), paclitaxel alone (n = 23, 10.9%), or other (n = 8, 3.8%). One hundred nine patients were treated with concurrent CTRT (86.5%), 10 patients with CT followed by RT (7.9%), and 7 patients with RT followed by CT (5.6%). Adjuvant CT was delivered with a median of 6 cycles (range, 3–12), although 3 patients received only 2 cycles. Six patients did not complete the full course of CT because of G4 hematologic toxicity (n = 2), intravascular hemolysis (n = 1), or no available data on toxicity (n = 3).

2.3. Follow-up and statistical analysis

Regular follow-up of patients was performed monthly for 3 months, at 3-month intervals for 2 years, and every 4–6 months thereafter. Acute toxicity, measured from the initiation of treatment to 3 months after adjuvant treatment, was assessed using the National Cancer Institute Common Terminology Criteria for Adverse Event, version 4.0. Late toxicities were graded according to the Radiation Therapy Oncology Group late toxicity scale. Failure was defined as biopsy-proven recurrence or progression of disease on serial imaging studies. Time to recurrence and death was calculated from the date of surgery until failure or death from any cause. Disease-free survival (DFS) was defined as alive without disease recurrence at the time of censoring. Survival curves were calculated using the Kaplan–Meier method, and comparison of
3. Results

3.1. Patient characteristics

There were no statistically significant differences between the RT alone group and combined CTRT group with respect to age; tumor grade; serosal, adnexal, vaginal or lymphovascular space involvement; or resection margin status (Table 1). A higher proportion of patients in the CTRT group had stage IIIC2 (41.3% vs. 30.6%) and parametrial involvement (8.7% vs. 5.9%) compared to the RT alone group. There was a higher number of positive pelvic LN (3.1 vs. 2.4, p = 0.128) and a larger mean tumor size (5.1 cm vs. 4.6 cm, p = 0.131) in the CTRT group compared to the RT alone group, but the differences did not reach statistical significance. A higher proportion of patients in the CTRT group received paraaortic lymphadenectomy compared to the RT alone group (65.9% vs. 50.6%, p = 0.026). Type of adjuvant RT including extended-field RT and vaginal brachytherapy did not differ significantly in the two groups.

Classifying according to stage, 133 patients had FIGO stage IIC1, and 78 had FIGO stage IIIC2. Of 78 patients with stage IIIC2, 56 (26.5%) had both pelvic and PALN metastasis and isolated PALN metastasis was in 22 patients (10.4%). Patients with stage IIIC2 had higher grade (G3 42.3% vs. 21.1%, p = 0.002), more parametrial involvement (12.8% vs. 4.5%, p = 0.006), more close or positive resection margins (6.4% vs. 3.8%, p = 0.006), larger mean tumor size (5.5 cm vs. 4.6 cm, p = 0.026) and positive pelvic LN (3.9 vs. 2.2, p = 0.001). A higher proportion of patients in the stage IIIC2 groups received paraaortic lymphadenectomy compared to that in the stage IIC1 groups (91.0% vs. 41.4%, p < 0.001). There was no significant difference between the RT alone group and the combined CTRT group for paraaortic lymphadenectomy (32.2% vs. 48.6%, p = 0.056) in stage IIC1. In stage IIIC2, most patients had paraaortic lymphadenectomy; 24 patients (92.3%) in the RT alone group and 47 patients (90.4%) in the CTRT group. Most patients (95.5%) with stage IIC1 received postoperative RT to the entire pelvis, while 61 patients (78.2%) in the stage IIIC2 groups received extended-field RT encompassing PALN region. A higher proportion of patients with stage IIIC2 received CTRT compared to that in the stage IIC1 group (66.7% vs. 55.6%, p = 0.115). Other variables including CT agent, and additional vaginal brachytherapy showed no significant differences between the stage IIC1 and stage IIIC2 groups.

3.2. Toxicities

The data for toxicity was available in 131 patients (Table 2). Forty patients (43%) in the CTRT group experienced grades 3–4 acute toxicity,
while 4 patients (10.5%) in the RT alone group had grades 3–4 acute toxicity \( p < 0.001 \). The most common acute toxicities were hematologic. Grades 3–4 acute hematologic toxicities were observed in 36 patients (38.7%) in the CTRT group and 3 patients (7.9%) in the RT alone groups. Of patients with extended-field RT, 18 patients (40.9%) experienced G3–4 acute hematologic toxicity, and 2 (4.5%) had G3–4 acute gastrointestinal toxicities. In patients treated with pelvic RT, 21 patients (24.1%) had G3–4 hematologic toxicity, and 3 patients (3.4%) had gastrointestinal toxicity.

Four patients in the CTRT group experienced grade 3 late toxicity, two with rectovaginal-vesico fistula and two with leg edema. No patients experienced grades 3–4 late toxicity in the RT alone group.

3.3. Patterns of failure

The median follow-up duration was 52 months (range, 5–184 months). A total of 69 patients (32.7%) relapsed during the follow-up period; 39 patients (29.3%) in the stage IIIC1 group and 30 patients...
(38.5%) in the stage IIIC2 group. The difference was not significant between stage IIIC1 and IIIC2 (p = 0.172). The median period for recurrence was 18 months (range, 3–139 months). There was an excellent pelvic control both the RT alone group and the CTRT group (3.5% vs. 0.8%, p = 0.152). However, there was a statistically significant difference in the pattern of failure between the stage IIIC2 group and the stage IIIC1 group (p = 0.001) (Table 3). In the stage IIIC1 group, 20 patients (51.3%) developed pelvis + extrapelvic LN regions including 14 patients with PALN only and 4 patients with both PALN and supraclavicular LN (SCL), whereas 27 patients (90%) in stage IIIC2 had distant metastasis and three (10%) had pelvic LN ± PALN recurrence including only one with PALN recurrence. In order to explore the role of multimodality therapy in controlling disease in the irradiated volume, we performed subgroup analysis. In the stage IIIC1, 3 patients in the RT alone group developed an in-field recurrence, whereas no patients in the CTRT group had an in-field recurrence (5.1% vs. 0%, p = 0.031). However, combined CTRT did not affect PALN recurrence compared to the RT alone group (14.9% vs. 11.9%, p = 0.218).

### 3.4. Treatment outcomes

The 5-year OS and DFS were 81.9% and 66.3%, respectively. Five-year OS and DFS were lower in stage IIIC2 than stage IIIC1 (85.1% vs. 76.9%, p = 0.417; 71.0% vs. 59.2%, p = 0.108), but the difference did not reach statistical significance. In order to explore the role of multimodality therapy in more advanced stages, we performed subgroup analysis. There was no significant difference between the RT alone group and the combined CTRT group for OS (90.5% vs. 89.0%, p = 0.312) or DFS (73.3% vs. 69.1%, p = 0.523) in stage IIIC1. Also, of the patients with stage IIIC2, combined CTRT did not affect DFS (55.8% vs. 66.5%, p = 0.358) or OS (71.4% vs. 87.4%, p = 0.152) compared with RT alone (Fig. 1). In the combined CTRT group, there was no statistically significant difference in 5-year OS (76.7% vs. 77.8%, p = 0.598) or DFS (60.6% vs. 78.1%, p = 0.218) between the concurrent and sequential CTRT groups.

We analyzed the prognostic factors affecting OS and DFS (Table 4). There was a statistically significant difference in OS (85.4% vs. 41.8%, p = 0.001) and DFS (70.4% vs 22.6%, p < 0.001) for the presence of parametrical invasion regardless of stage. We investigated the relationship between the number of pelvic LN metastasis and the prognosis. Patients were stratified according to the number of pelvic LN metastasis, patients having >3 positive pelvic LN had a worse 5-year OS compared to patient having ≤3 pelvic LN (70.3% vs. 86.3%, p = 0.01). Patients having >1 positive LN had a comparable 5-year OS compared to patients having ≤1 (80.2% vs. 84.2%, p = 0.320). Also, patients having >2 positive LN had a comparable 5-year OS compared to patients having ≤2 (75.6% vs. 85.1%, p = 0.119). In addition, age, histologic grade, and tumor size (>5 cm) were significantly associated with survival on univariate analysis.

On multivariate analysis, predictors of DFS were parametrial invasion (HR, 3.49; 95% CI, 1.83–6.64; p < 0.001), higher grade (HR, 2.78; 95% CI, 1.31–5.89; p = 0.008), and >3 positive pelvic nodes (HR, 1.84; 95% CI, 1.19–2.87; p = 0.004). The presence of parametrial invasion was the strongest predictor of OS (HR, 2.59; 95% CI, 1.33–4.95; p = 0.004) compared to other variables.

### Table 4
Factors affecting overall survival and disease-free survival.

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Overall survival (n = 211)</th>
<th>All (n = 83)</th>
<th>IIIC1 (n = 133)</th>
<th>IIIC2 (n = 78)</th>
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<tr>
<td>Age (years)</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>≤55</td>
<td>88.6%</td>
<td>89.1%</td>
<td>86.4%</td>
<td>81.3%</td>
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<td>&gt;55</td>
<td>70.4%</td>
<td>70.8%</td>
<td>71.5%</td>
<td>68.5%</td>
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<tr>
<td>Grade</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
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<td>94.9%</td>
<td>94.1%</td>
<td>91.9%</td>
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<tr>
<td>Grade 2 or 3</td>
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<td>78.8%</td>
<td>75.9%</td>
<td>72.2%</td>
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<td>FIGO</td>
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<tr>
<td>Overall</td>
<td>81.9%</td>
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<td>79.8%</td>
<td>76.1%</td>
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<td>85.6%</td>
<td>83.8%</td>
<td>83.4%</td>
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<tr>
<td>Other</td>
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<td>40.6%</td>
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<td>Size (diameter, cm)</td>
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<td></td>
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<td>≤5</td>
<td>85.7%</td>
<td>85.0%</td>
<td>78.1%</td>
<td>71.5%</td>
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<td>&gt;5</td>
<td>74.9%</td>
<td>72.9%</td>
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<td>63.4%</td>
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<td>No. of + pelvic LN</td>
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<td></td>
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<tr>
<td>≤3</td>
<td>86.3%</td>
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<td>84.6%</td>
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<tr>
<td>&gt;3</td>
<td>70.3%</td>
<td>73.9%</td>
<td>68.1%</td>
<td>62.6%</td>
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<tr>
<td>Adjuvant treatment</td>
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<tr>
<td>RT alone</td>
<td>89.6%</td>
<td>90.5%</td>
<td>87.4%</td>
<td>86.5%</td>
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<tr>
<td>CTRT</td>
<td>76.7%</td>
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<td>73.3%</td>
<td>69.7%</td>
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<td>CTRT sequence</td>
<td>0.989</td>
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<td>0.479</td>
<td>0.202</td>
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<tr>
<td>Sequential</td>
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<td>77.8%</td>
<td>85.7%</td>
<td>83.3%</td>
</tr>
<tr>
<td>Concurrent</td>
<td>76.7%</td>
<td>81.7%</td>
<td>69.6%</td>
<td>65.1%</td>
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### Table 5
Multivariate analysis.

<table>
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<tr>
<th>Parameters</th>
<th>DFS</th>
<th>OS</th>
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</thead>
<tbody>
<tr>
<td>Age (≤55 vs. &gt;55)</td>
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<td></td>
</tr>
<tr>
<td>Grade (G1 vs. other)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>FIGO (IB vs. IIB2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PM invasion (no vs. yes)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LVI (no vs. yes)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Size (other vs. &gt;5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pelvic LN (≤3 vs. &gt;3)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: FIGO = International Federation of Gynecology and Obstetrics; LVI = lymphovascular space invasion; LN = lymph node; RT = radiotherapy; CTRT = chemoradiotherapy; DFS = disease-free survival; OS = overall survival.
patients with stage IIIC disease. Those treated with CT only were 2 to 7 times more likely to develop a vaginal recurrence (35% vs. 18% vs. 5%), and 2 times more likely to develop a pelvic only recurrence (18% vs. 9% vs. 7%) compared to those treated with RT alone or combined treatments, respectively. In controlling disease in irradiated volume, the present study also showed that only 5.1% patients in the RT alone group in stage IIIC1 developed an in-field recurrence, whereas no patients in the CTRT group had an in-field recurrence (p = 0.031), suggesting that the CTRT may have an additional benefit for the control of irradiated nodal disease compared with RT alone in patients with endometrial cancer with positive nodal disease.

Comparing stage IIIC1 and IIIC2 groups in our study, there was a significant difference in the pattern of failure. Of 39 patients who had recurrence in the stage IIIC1 group, half of the cases (n = 17, 43.6%) were in the unirradiated PALN region, including 4 patients with both PALN and SCL. However, in stage IIIC2 patients, the majority (90%) of the 30 patients who had recurrences developed distant metastasis, and only one patient (3.3%) showed PALN failure. There is ongoing debate on the diagnostic and therapeutic role of paraaortic lymphadenectomy in endometrial cancer [18–20]. A retrospective cohort analysis [20] found that paraaortic lymphadenectomy significantly improved the survival of endometrial cancer patients at intermediate risk/high risk for recurrence. A study from the Mayo Clinic [21] assessed the prevalence of lymphatic dissemination with lymphadenectomy. In 63 (22%) of 281 patients with lymph node metastases, half had metastases in both the pelvic and paraaortic areas. 33% had metastasis only in the pelvic area, and metastasis was isolated to the para-aortic area in 16% of patients. In our study, 133 patients (63.0%) had positive pelvic LN only and 56 (26.5%) had both pelvic and PALN metastasis. Isolated PALN metastasis was in 22 patients (10.4%). Of 133 patients with positive pelvic LN, 82 patients did not undergo paraaortic lymphadenectomy. We hypothesize that, among 82 patients who underwent pelvic lymphadenectomy only, some patients might have micrometastasis to the PALNs, although it is difficult to interpret the diagnostic benefit of lymphadenectomy in this retrospective study.

We also performed subgroup analysis according to paraaortic lymphadenectomy. In contrast with stage IIIC2, less than half of patients in stage IIIC1 underwent PALN dissection or sampling. Of 127 treated with whole pelvic RT in stage IIIC1, those treated with pelvic LN dissection only were developed three times PALN recurrence compared to those treated with paraaortic lymphadenectomy (18.9% vs. 5.7%). There was a very low incidence of PALN recurrence in stage IIIC2, suggesting the possible benefit of paraaortic lymphadenectomy. Among 78 patients in stage IIIC2, all patients except 7 patients underwent paraaortic lymphadenectomy. Of 17 patients treated with whole pelvic RT ± CT in stage IIIC2, all patients except one had paraaortic lymphadenectomy, resulting in no PALN recurrence.

Another possible explanation for the difference in pattern of failure between stage IIIC1 and IIIC2 may be due to CT-related factors. Although combined CTRT did not affect PALN recurrence compared to the RT alone group (15.7% vs. 10.5%, p = 0.207) in stage IIIC1 patients treated with pelvic RT, the CTRT group had no in-field recurrence compared with RT alone (0% vs. 3.5%, p = 0.031). In stage IIIC2, there was a limitation to assess the role of CT, since most of these patients (94.9%) had CT or extended-field RT, showing a low incidence of in-field recurrence. There was a statistical significant difference in 2-year disease-free survivals between those who developed soft tissue metastasis only and those who have nodal and systemic relapse (45.7% vs. 18.8%, p = 0.043). We thought that lower incidence of PALN failure but more common distant metastasis in stage IIIC2 compared to patients in stage IIIC1 might result in comparable survival outcome. It was unclear whether CT or extended-field RT had more impact on clinical outcome in this retrospective study.

In conclusion, the current study showed favorable outcomes in IIIC1 compared to IIIC2, but we did not identify survival benefit with respect to treatment modality in either stage IIIC1 or IIIC2. There was a
significant difference in the pattern of failure, resulting in a higher recurrence rate of PALN in stage IIIC1 compared to stage IIIC2. Further studies in randomized settings are needed to determine the significance of the combined treatment modality in stage IIIC endometrioid adenocarcinoma.

Conflict of interest statement
The authors declare that there are no conflicts of interest.

References


