pISSN 1598-2998, eISSN 2005-9256

Cancer Res Treat. 2015;47(2):298-305

http://dx.doi.org/10.4143/crt.2014.038

Original Article

Open Access

Postoperative Radiotherapy Alone Versus Chemoradiotherapy in Stage I-II Endometrial Carcinoma: An Investigational and Propensity Score Matching Analysis

Jong Hoon Lee, MD[1]
Hyo Chun Lee, MD[1]
Sung Hwan Kim, MD[1]
Mi Joo Chung, MD[1]
Song Mi Jeong, MD[1]
Sung Jong Lee, MD[2]
Joo Hee Yoon, MD[2]
Dong Choon Park, MD[2]

Departments of [1]Radiation Oncology and [2]Obstetrics and Gynecology, St. Vincent's Hospital, The Catholic University of Korea College of Medicine, Seoul, Korea

Correspondence: Dong Choon Park, MD
Department of Obstetrics and Gynecology, St. Vincent's Hospital, 93 Jungbu-daero, Paldal-gu, Suwon 442-723, Korea
Tel: 82-31-249-7560
Fax: 82-31-257-3734
E-mail: dcpark@catholic.ac.kr

Received February 14, 2014
Accepted March 19, 2014
Published online September 15, 2014

*Jong Hoon Lee and Hyo Chun Lee contributed equally to this work.

Purpose

The purpose of this study was to compare the results of postoperative adjuvant radiotherapy (RT) and concurrent chemoradiotherapy (CRT) in stage I-II endometrial carcinoma.

Materials and Methods

We analyzed a total of 64 patients with surgically staged I-II endometrial carcinoma who were treated with postoperative adjuvant RT or concurrent CRT between March 1999 and July 2013. Thirty-two patients who received postoperative RT alone were matched with those who received postoperative CRT (n=32) in accordance to age, stage, and tumor histology. Overall survival and relapse-free survival, as well as toxicity of the RT and CRT arms were evaluated and compared.

Results

The 5-year overall survival rate was 90.0% for the RT arm and 91.6% for the CRT arm. There was no significant difference in overall survival between the two treatment arms (p=0.798). The 5-year relapse-free survival rate was 87.2% in the RT arm and 88.0% in the CRT arm. Again, no significant difference in relapse-free survival was seen between the two arms (p=0.913). In a multivariate analysis, tumor histology was an independent prognostic factor for relapse-free survival (hazard ratio, 3.67; 95% of CI, 2.34 to 7.65; p=0.045). Acute grade 3 or 4 hematologic toxicities in the CRT arm were significantly higher than in the RT alone arm (6.2% vs. 31.2%, p=0.010).

Conclusion

Adjuvant pelvic concurrent chemoradioherapy did not show superior results in overall survival and relapse-free survival compared to RT alone in stage I-II endometrial carcinoma.

Key words
Chemotherapy, Endometrial neoplasms, Radiotherapy

Introduction

Endometrial carcinoma is the second most common gynecological cancer in Korea, accounting for approximately 1.8% of all the cancers diagnosed in women. The annual incidence of endometrial carcinoma is gradually increasing [1]. Total abdominal hysterectomy with bilateral salpingo-oophrectomy and lymph node dissection is essential for staging and treatment of endometrial carcinoma [2]. Adjuvant treatment after surgery is indicated in high-risk endometrial carcinoma, and postoperative radiotherapy has shown relatively good outcomes. In a recent retrospective analysis that evaluated 382 patients, adjuvant radiothrapy significantly improved recurrence-free, disease-specific, and overall survival in patients with early-stage endometrial carcinoma [3]. The National Cancer Comprehensive Network guideline recommends various ways of administering adjuvant therapy according to stage and grade of tumor in endometrial carcinoma. No one single therapy has shown superiority

over the others, leading to no treatment being established as the gold-standard.

Several randomized trials have shown that the use of pelvic radiotherapy in stage I endometrial carcinoma provides a highly significant improvement of pelvic control in patients with selected risk factors, as well as progression-free survival [4-8]. For stage I-III endometrial carcinoma patients with high risk features, the use of adjuvant chemotherapy has been investigated, and no survival benefit has been shown compared to pelvic radiotherapy [9-12]. With the unsatisfactory results of previous trials involving single treatment modality, multi-modality adjuvant treatment has been introduced. There are some trials investigating the roles of concurrent chemoradiotherapy compared to chemotherapy or radiotherapy alone [13]. However, the role of chemoradiotherapy after surgery has not been established definitely in stage I-II endometrial carcinoma.

Thus, this study was designed to compare the overall and relapse-free survival of adjuvant pelvic radiotherapy and concurrent chemoradiotherapy after surgical treatment of stage I-II endometrial carcinoma.

Materials and Methods

1. Patients

From March 1999 to July 2013, a total 83 patients with stage I-II endometrial carcinoma, who underwent curative surgery and postoperative pelvic radiotherapy with or without concurrent chemotherapy, were reviewed retrospectively. However, two patients were excluded from the study due to both patients having lung metastases during the course of radiotherapy, and one patient proved to have uterine sarcoma on examination of the permanent pathologic specimen. Thus, the remaining 80 patients were evaluated in this study.

The patients had histologically proven adenocarcinoma arising from the uterine body, with a tumor stage of pT1N0 with one or more risk factors, such as high grade tumor, old age (> 60), lymphovascular invasion, and outer half of myometrial invasion or T2N0. Low grade represents a well or moderately differentiated histology and high grade represents poorly differentiated, papillary serous or clear-cell histology. There was no distant metastasis (M0) in our patients. This study was approved by the institutional review board of our institution.

2. Treatment

All patients underwent open or laparoscopic hysterectomy with adnexectomy and pelvic and paraaortic lymph node dissection. Surgical staging was based on the American Joint Cancer Staging system 7th edition. External beam radiation therapy was delivered with the standard whole pelvic four-box field technique 2 to 8 weeks (median, 3 weeks) after surgery. Two patients with postoperative pelvic abscess received a delayed radiation therapy, 6 and 8 weeks after surgery, respectively.

A contrast-enhanced computed tomography was scanned for the treatment plan. Patients were in supine position and a candle-shaped cylinder was inserted into the vagina to indicate a stump. The radiation field was designed to cover the whole pelvic cavity. Clinical target volume included distal common and iliac lymph nodes, tumor bed, and vaginal stump. The upper border was defined to be at the L5/S1 interspace. The lower border was at the lower margin of the obturator foramen. The lateral border of the anterior-posterior field was defined to be 1.5 cm from the lateral margin of the bony pelvis. In the lateral field, the anterior border was the anterior aspect of the symphysis pubis, and the posterior border was the S2/S3 interspace.

The median external beam radiation therapy dose was 45 Gy with a daily dose of 1.8 Gy, ranging from 40 Gy to 60 Gy. One patient in the chemoradiotherapy arm was scheduled to receive 45 Gy of radiation. However, she received 40 Gy due to pancytopenia and high fever. All other patients tolerated the treatment well, and the initial planned dose was fully delivered. Midline shielding was done after 45 Gy in the case of stump boost. Intracavitary brachytherapy was recommended to stage I-II endometrial cancer patients, except to those who had toxicity grade 3 or higher during the external beam radiotherapy period. Intracavitary brachytherapy was done in 55 of 64 patients. Fifteen Gray in 3 fractions of intracavitary brachytherapy was delivered with an iridium source. Adjuvant vaginal brachytherapy was delivered with the largest fitting vaginal cylinder (2.5-4.0 cm in diameter). The dose was specified to 0.5 cm from the applicator surface. It included vaginal apex and 5 cm of vaginal vault [14].

A total of 32 patients received six cycles of weekly cisplatin, in which 40 mg/m^2 was delivered concurrently with radiotherapy. Concurrent chemotherapy was given in the first day of every week. Patients received prophylactic hydration and antiemetic agents. Basically, radiotherapy alone after surgery was recommended to patients with stage I-II endometrial cancer. Radiotherapy with concurrent cisplatin was considered in patients with high-grade histology or lymphovascular invasion.

3. Evaluation

During radiotherapy, patients were to have a weekly physical examination and complete blood count for the evaluation of acute toxicity. After radiotherapy, patients were to visit the clinic every 3 months for the first 2 years and 6 months thereafter for surveillance of late complications and recurrence. Adverse effects of chemotherapy and radiotherapy were assessed using the National Cancer Institute Common Terminology Criteria for Adverse Events ver. 3.0. Incidence of toxicity grade ≥ 2 was recorded.

Overall survival was defined as the period from the end date of radiotherapy to the date of death. Relapse-free survival was defined as the period from the end date of radiotherapy to the date of recurrence at any site or death.

4. Statistical analysis

For a prospective and definitive analysis, the trial is designed to have 80% power in detecting a difference in the primary end point, the recurrence-free rate at 3 years, of 85% in radiotherapy alone arm versus 90% in chemoradiotherapy arm using a two-sided test at the 5% level of significance. Thirteen hundred and ninety evaluable patients, with a minimum follow-up of 3 years, were required [15]. However, it is not easy to conduct a randomized controlled trial due to the low incidence of endometrial cancer in Korea [1]. Therefore, we undertook a retrospective and matching study to evaluate the role of concurrent chemoradiotherapy in endometrial cancer. Propensity score matching analyses were used to compensate for the differences in baseline characteristics of age, stage, and histology. Of the 48 patients who received postoperative radiotherapy (RT), 32 were matched with those who received postoperative chemoradiotherapy (CRT). The propensity scores were estimated without regard to the outcome variables, with multiple logistic regression analysis. Prespecified covariates were age, stage, and tumor histology were included in the non-parsimonious models for RT alone versus CRT. The model was well-calibrated (Hosmer-Lemeshowthe test, p=0.141) with reasonable discrimination (c statistic=0.62). Overall and relapse-free survival was a primary endpoint. Toxicity and prognostic factor analyses were secondary end points.

Categorical variables were compared using a chi-square test. The Kaplan-Meier method was used to figure out the overall survival and relapse-free survival rates. Prognostic factors, such patient age, cancer antigen (CA) 125, CA 19-9, pT stage, histologic grade, lymphovascular invasion, and stump boost were analyzed. In a univariate analysis, the log-rank test was used to evaluate the association between survival time and prognostic factors. For the multivariate analysis, Cox proportional hazards regression model was used to estimate the hazard ratio of the prognostic factors for overall survival and relapse-free survival. Statistical significance was evaluated at the 0.05 alpha level. All the tests were two-sided.

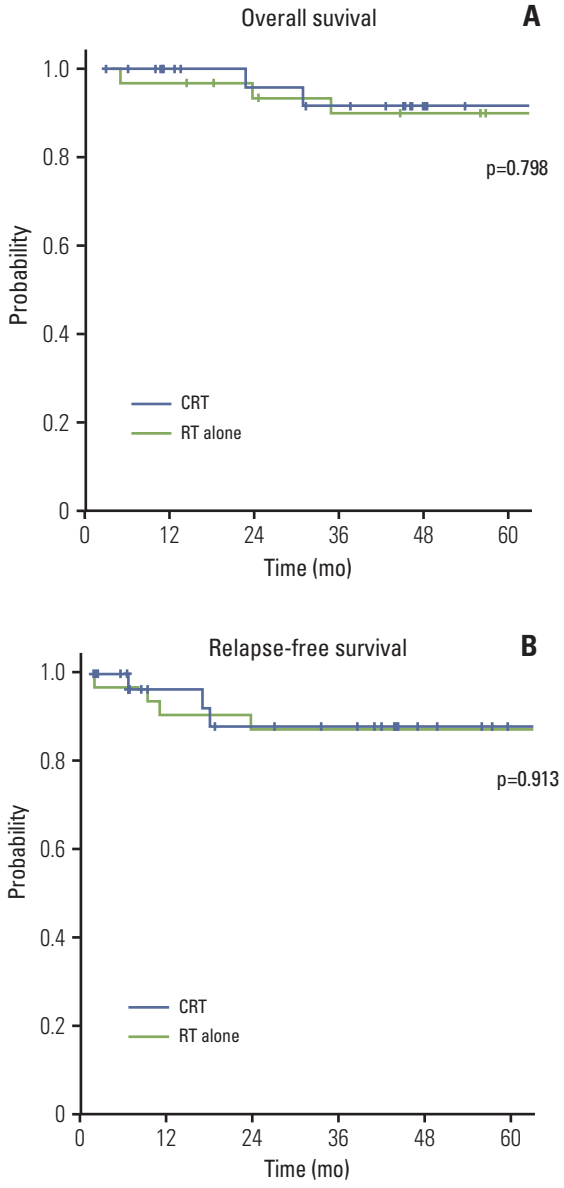

Fig. 1. (A) 5-Year overall survival of the postoperative chemoradiotherapy (CRT) arm is not significantly higher than the postoperative radiotherapy (RT) alone arm (91.6% vs. 90%, p=0.798). (B) 5-Year relapse-free survival of the postoperative chemoradiotherapy arm is not significantly higher than the postoperative radiotherapy alone arm (88.0% vs. 87.2%, p=0.913).

Table 1. Patient and tumor characteristics (n=64)

Characteristic	CRT arm (n=32)	RT arm (n=32)	p-value
Age (yr)	53.5	56.0	0.217
CA 125 (IU/mL)	39.8	41.1	0.514
Pathologic tumor stage			0.491
pT1	26 (48.1)	28 (51.9)	
pT2	6 (60.0)	4 (40.0)	
Tumor differentiation			0.250
Well differentiated	11 (47.9)	12 (52.1)	
Moderately differentiated	12 (41.4)	17 (58.6)	
Poorly differentiated	9 (75.0)	3 (25.0)	
Lymphovascular invasion			0.140
Negative	22 (44.9)	27 (55.1)	
Positive	10 (66.7)	5 (33.3)	
Histopathology			0.627
Adenocarcinoma	27 (46.5)	31 (53.5)	
Adenosquamous carcinoma	2 (66.7)	1 (33.3)	
Papillary serous cancer	1 (100)	0	
Clear cell cancer	2 (100)	0	
Stump boost RT			0.140
Yes	22 (44.9)	27 (55.1)	
No	10 (66.7)	5 (33.3)	

Values are presented as median or number (%). CRT, chemoradiotherapy; RT, radiotherapy; CA 125, cancer antigen 125.

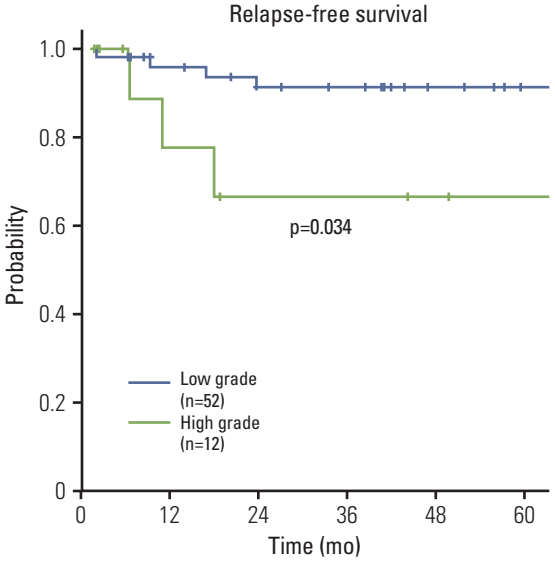

Fig. 2. Relapse-free survival according to the tumor histology is shown. Endometrial cancer patients with high-grade histology has significantly lower 5-year relapse-free survival than patients with low-grade histology (66.6% vs. 91.5%, p=0.034).

Results

The median age of the patient population in this study was 55 years and ranged from 40 to 77 years. All patients were diagnosed with stage I-II (pT1-2N0M0) endometrial carcinoma (54 with stage I and 10 with stage II). The characteristics of the patients and tumor are shown in Table 1. The baseline characteristics of the two arms were more or less skewed in spite of propensity score matching. More patients with pT2, lymphovascular invasion, and poorly differentiated histology have been allocated to the CRT arm, rather than the RT alone arm. The other baseline characteristics of the two arms were relatively well-balanced.

1. Survival

The median follow-up time was 42.5 months, ranging from 6 to 172 months. The 5-year overall survival rate of 64 patients was 90.8%. The 5-year overall survival rates were 90.0% for the radiotherapy arm and 91.6% for the chemoradiotherapy arm. There was no significant difference in overall survival between the two arms (p=0.798) (Fig. 1A). Five patients died during the follow-up period, two in the CRT arm and three in the RT arm.

The 5-year relapse-free survival rate of 64 patients was

Table 2. Univariate and multivariate analyses of factors associated with relapse-free survival

Variable	No. of patients	5-Year survival (%)	Univariate analysis (p-value)	HR (95% CI)	Multivariate (p-value)
Age (yr)			0.032	1.25 (0.58-1.89)	0.349
≤ 55	36	94.0			
> 55	28	75.6			
CA 125 (IU/mL)			0.458	1.12 (0.40-1.80)	0.627
≤ 40	31	87.2			
> 40	33	80.7			
Pathologic T stage			0.257	2.41 (0.88-5.15)	0.490
pT1	54	89.4			
pT2	10	77.7			
Histologic grade[a]			0.034	3.67 (2.34-7.65)	0.045
Low	52	91.5			
High	12	66.6			
Lymphovascular invasion			0.146	1.96 (0.81-3.61)	0.375
Negative	49	90.4			
Positive	15	77.4			
Stump boost radiotherapy			0.231	0.85 (0.54-2.03)	0.417
No	15	72.4			
Yes	49	85.6			
Treatment modality			0.913	1.03 (0.53-1.52)	0.986
Chemoradiotherapy	32	88.0			
Radiotherapy	32	87.2			

HR, hazard ratio; CI, confidence interval; CA 125, cancer antigen 125. [a]Low grade represents well or moderately differentiated histology and high grade represents poorly differentiated, papillary serous, or clear cell histology.

87.6%. The 5-year relapse-free survival rates were 87.2 % in the radiotherapy arm and 88.0 % in the chemoradiotherapy arm. There was no statistically significant difference in relapse-free survival between the two arms (p=0.913) (Fig. 1B). Treatment failure occurred in six patients. In the radiotherapy arm, three patients failed; two failed locoregionally and one failed distantly. In the CRT arm, three patients failed; one had locoregional failure only, one had distant failure, and one had both locoregional and distant failures. There was no statistically significant difference in the failure pattern between the two arms.

2. Prognostic factors for relapse-free survival

Age, CA 125, pathologic T stage, histological grade, lymphovascular invasion, stump boost, and treatment modality were analyzed for relapse-free survival. Table 2 shows the univariate and multivariate analyses of the factors associated with relapse-free survival. In the univariate analysis, age > 55 years (p=0.032) and high-grade histology (p=0.034) (Fig. 2) were significant poor prognostic factors for relapse-free survival. As for the multivariate analysis, high-grade histology (hazard ratio, 3.67; 95% of confidence interval, 2.34 to 7.65; p=0.045) was the only statistically significant prognostic factor for relapse-free survival.

3. Toxicity

Grade 3 or higher acute and chronic toxicities are summarized in Table 3. Acute grade 3 or 4 hematologic toxicities in the chemoradiotherapy arm were significantly higher than the radiotherapy alone arm (12.5% vs. 37.5%, p=0.021). Ten patients in the chemoradiotherapy arm and 2 patients in the radiotherapy arm had acute grade 3 or higher hematologic toxicities. Non-hematologic grade 3 or higher acute toxicities were as follows: four patients with diarrhea, three patients with pelvic abscess, and one patient with cystitis in the chemoradiotherapy arm; two patients with diarrhea and one patients with pelvic abscess in the radiotherapy alone arm.

Chronic grade 3 or higher toxicity was not significantly different between the two arms. One patient in the radiother-

Table 3. Grade 3 or higher treatment toxicities

Toxicity	RT arm (n=32)	CRT arm (n=32)	p-value
Acute			
Hematologic	2 (6.2)	10 (31.2)	0.010
Cystitis	0	1 (3.1)	0.314
Diarrhea	2 (6.2)	4 (12.5)	0.391
Pelvic abscess	1 (3.1)	1 (3.1)	1.000
Any acute toxic effect	4 (12.5)	12 (37.5)	0.021
5-Year actuarial chronic toxicity			
Chronic diarrhea	0	0	1.000
Small bowel obstruction	0	0	1.000
Bladder problom	0	1 (3.4)	0.314

RT, radiotherapy; CRT, chemoradiotherapy.

Table 4. Randomized trials comparing radiotherapy alone and chemoradiotherapy in endometrial cancer

Trial	Kuoppala et al. [15] (n=156)	SGO-9501/EORTC-55991 [17] (n=383)	MaNGO ILIADE-III [17] (n=157)
Eligibility	Stage IA-B with grade 3 or stage IC-IIIA with grade 1-3	Stage I-III	Stage II-III
Treatment arm	Radiotherapy alone, 56 Gy vs. sequential chemoradiotherapy	Radiotherapy alone vs. sequential chemoradiotherapy	Radiotherapy alone vs. sequential chemoradiotherapy
Locoregional recurrence	3.2% vs. 3.2%	Joint analysis: 4.1% vs. 1.9%	-
Distant recurrence	13.8% vs. 20.2%	Joint analysis: 19.4% vs.13.1%	-
5-Year survival	84.7% vs. 82.1% (p=0.14)	76% vs. 83% (p=0.10)	73% vs. 78% (p=0.41)

apy alone arm had small bowel obstruction 2 years after the end of radiotherapy and she received a reoperation, and three patients in the chemoradiotherapy arm had long-term grade 3 or higher toxicities of diarrhea, cystitis, and small bowel ileus. Patients with grade 3 cystitis and small bowel ileus in the chemoradiotherapy arm were cured after medical and surgical treatment. However, grade 3 cystitis was observed in one patient 5 years after chemoradiotherapy.

Discussion

Pelvic radiotherapy still remains as an indispensible treatment option for high-risk or advanced stage endometrial carcinoma. Several retrospective studies have shown significantly higher rates of locoregional recurrence if high-risk patients were not treated with radiotherapy after curative surgery. Mundt et al. [12] reported a retrospective analysis of high-risk pathologic stage I-IV endometrial carcinoma patients who were treated with chemotherapy alone. Of the 43 patients, 67% relapsed, 40% had pelvic recurrence, and 56% had distant relapse. The 3-year pelvic relapse rate was 47%, and the pelvic cavity was the first or the only site of relapse in 31% of patients. In a study conducted by Klopp et al. [16], 71 endometrial carcinoma patients treated with or without radiotherapy were analyzed. Patients who were treated with regional radiotherapy had a significantly better 5-year relapse-free survival compared to those who received chemotherapy only (98% vs. 61%, p=0.001). Patients who received regional radiotherapy at the same time showed a better outcome in disease-specific survival (78% vs. 39%, p=0.01) and overall survival (73% vs. 40%, p=0.03). In patients who received chemotherapy alone, the pelvis was the most common site of relapse.

Therefore, it has come down to the theory that combining chemotherapy and radiotherapy might be the optimal treatment modality to reduce both locoregional and distant relapse. In our study, both the radiotherapy alone and the chemoradiotherapy arms showed excellent outcomes as adjuvant therapy in surgically treated stage I-II endometrial carcinoma. In our retrospective analysis, overall survival and relapse-free survival of the chemoradiotherapy arm was not significantly higher than the radiotherapy alone arm. However, acute treatment hematologic toxicities were

significantly higher in the chemoradiotherapy arm than in the radiotherapy alone arm. Some randomized trials tested the efficacy of concurrent or sequential chemoradiotherapy in endometrial carcinoma. The first randomized clinical trial to evaluate the benefit of chemoradiotherapy was designed and tested by the Gynecologic Oncology Group (GOG). However, this study was closed early due to protocol violations, small sample size, and loss of follow-up. Hence, it was unable to determine whether the use of chemoradiotherapy as adjuvant therapy would have a significant effect on recurrence, progression, and survival [13]. Randomized trials comparing radiotherapy alone and chemoradiotherapy in endometrial cancer are shown in Table 4. Kuoppala et al. [15] randomized 156 patients to receive radiotherapy or sequential chemoradiotherapy. However, adjuvant chemoradiotherapy failed to show an improvement in the overall survival and recurrence rates. Grade 3 or 4 bowel toxicity in the sequential chemoradiotherapy arm was higher than that of the radiotherapy alone arm (9.5% vs. 2.8%). In the NSGO 9501/EORTC-55991 trial [17], 382 patients were randomized to receive radiotherapy with or without sequential chemotherapy. The combined treatment modality showed a 7% increase in progression free survival (79% vs. 72%, p=0.03), but not in overall survival. Currently, trials are ongoing to evaluate the role of concurrent chemoradiation or radiotherapy followed by adjuvant chemotherapy. The PORTEC-3 trial compares pelvic radiotherapy alone with two cycles of concurrent chemotherapy during radiation, followed by four cycles of chemotherapy in stage I-II endometrial carcinoma. This trial was designed to see if chemoradiotherapy improves the overall and relapse-free survival rates. This trial is expected to address the concerns of chemoradiotherapy and its impact over radiotherapy alone on survival [18].

In our series, high-grade tumor histology was found to be a poor prognostic factor for relapse-free survival. Prognostic factors for survival, such as tumor histology, surgical stage, depth of myometrial invasion, and presence of lymphovascular invasion in endometrial carcinoma, have been reported by other studies [19-21]. In the results of a retrospective study conducted by Irwin et al. [22], high tumor grade, lower uterine segment involvement, and old age were independent poor prognostic factors for disease-free survival in a multivariate analysis. Yalman et al. [23] reported a retrospective analysis of 440 patients who were treated with postoperative radiotherapy. In a multivariate analysis, histologic type, myometrial invasion, and histologic grade were the prognostic factors for disease-free survival.

We reported no significant impact on relapse-free survival of chemoradiotherapy over radiotherapy alone for patients with stage I-II endometrial cancer in our study. However, we acknowledged that our series had a number of limitations. First, our study should be understood with the consideration of inherent biases due to the nature of a retrospective study design. We evaluated just 64 cases of both chemoradiotherapy and radiotherapy alone arm. As a result, our study may have a low statistical power. There also might be a selection bias which allocated more patients with risk factors, such as pT2, lymphovascular invasion, and poorly differentiated histology to the CRT arm rather than the RT alone arm. Although we executed a matching analysis to minimize selection bias of our study, we admitted that our result could be just preliminary. Second, we had a shortage of patient information in our analysis and did not conduct quality of life assessments, such as sexual dysfunction and depressive disorder [24,25]. Third, the overall follow-up period was less than 5 years. Therefore, a long-term follow-up of more than 5 years is indicated for the exact survival analysis in the chemoradiotherapy and radiotherapy alone arms.

Conclusion

In our investigational matching study, postoperative adjuvant chemoradiotherapy after curative surgery did not show higher overall survival and relapse-free survival than radiotherapy alone in stage I-II endometrial carcinoma. Hence, postoperative radiotherapy alone rather than chemoradiotherapy is a standard treatment in patients with stage I-II endometrial cancer.

Conflicts of Interest

Conflict of interest relevant to this article was not reported.

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