International Journal of Radiation Oncology biology • physics

www.redjournal.org

Clinical Investigation

A Phase 2 Trial of Radiation Therapy With Concurrent Paclitaxel Chemotherapy After Surgery in Patients With High-Risk Endometrial Cancer: A Korean Gynecologic Oncologic Group Study

Hanbyoul Cho, MD, PhD,[*,†] Byung-Ho Nam, PhD,[‡] Seok Mo Kim, MD, PhD,[§] Chi-Heum Cho, MD, PhD,[||] Byoung Gie Kim, MD, PhD,[¶] Hee-Sug Ryu, MD, PhD,[#] Soon Beom Kang, MD, PhD,[**] and Jae-Hoon Kim, MD, PhD[*,†]

Department of Obstetrics and Gynecology, Gangnam Severance Hospital, and †Institute of Women's Life Medical Science, Yonsei University College of Medicine, Seoul; ‡Cancer Biostatistics Branch, Research Institute for National Cancer Control and Evaluation, National Cancer Center, Goyang; §Department of Obstetrics and Gynecology, Chonnam National University School of Medicine, Gwangju; ||Department of Obstetrics and Gynecology, Keimyung University School of Medicine, Daegu; ¶Department of Obstetrics and Gynecology, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul; #Department of Obstetrics and Gynecology, Ajou University School of Medicine, Suwon; and **Department of Obstetrics and Gynecology, Konkuk University School of Medicine, Seoul, Republic of Korea

Received Jan 13, 2014, and in revised form May 12, 2014. Accepted for publication May 16, 2014.

Summary

This prospective study evaluated the efficacy and toxicity of concurrent chemoradiation with weekly paclitaxel in patients with high-risk endometrial cancer.

Purpose: A phase 2 study was completed by the Korean Gynecologic Oncologic Group to evaluate the efficacy and toxicity of concurrent chemoradiation with weekly paclitaxel in patients with high-risk endometrial cancer.

Methods and Materials: Pathologic requirements included endometrial endometrioid adenocarcinoma stages III and IV. Radiation therapy consisted of a total dose of 4500

Reprint requests to: Dr Jae-Hoon Kim, MD, PhD, Department of Obstetrics and Gynecology, Gangnam Severance Hospital, Yonsei University College of Medicine, 146-92 Dogok-Dong, Gangnam-Gu, Seoul 135-720, Republic of Korea. Tel: (+82) 2-2019-3430; E-mail: jaehoonkim@yuhs.ac

Presented at the Society of Gynecologic Oncology (SGO) 45th Annual Meeting on Women's Cancer, Tampa, FL. on March 22-25, 2014.

This study is registered at ClinicalTrials.gov (no. NCT00373620).

Conflict of interest: none.

Acknowledgments—This study was made possible by the help of the following subinvestigators: St. Mary's Hospital (Seog Nyeon Bae, Woong Shick Ahn), Cheil General Hospital and Women's Healthcare Center (Ki-Heon Lee), Kyungpook National University Hospital (Yoon Soon Lee), Kyung Hee University Medical Center (Min Hyung Jung), Keimyung University Dongsan Medical Center (Soon-Do Cha), Korea University Guro Hospital (Jae-Kwan Lee), National Cancer Center (Sang-Yoon Park), Dong-A University Hospital (Moon Seok Cha), Seoul National University Hospital (Noh-Hyun Park), Samsung Medical Center (Duk-Soo Bae, Jeong-Won Lee), Soonchunhyang University Chunan Hospital (Dong-Han Bae), Ajou University Hospital (Suk-Joon Chang), Severance Hospital (Young Tae Kim, Sunghoon Kim, Sang Wun Kim), Yeungnam University Medical Center (Seung Ho Lee), Asan Medical Center (Yong Man Kim), Korea Cancer Center Hospital (Sang-Young Ryu), Hanyang University Seoul Hospital (Joong Sub Choi).

Int J Radiation Oncol Biol Phys, Vol. 90, No. 1, pp. 140–146, 2014
0360-3016/$ - see front matter
http://dx.doi.org/10.1016/j.ijrobp.2014.05.024

paclitaxel after surgery in patients with high-risk endometrial cancer. Toxicities were not excessive, and 91.2% of the enrolled patients completed the planned courses of concurrent chemotherapy with minimal delays. We also demonstrated a favorable outcome in 5-year disease-free and overall survival. This approach produced favorable results and appears reasonable to be evaluated for efficacy in a prospective, randomized controlled study.

to 5040 cGy in 5 fractions per week for 6 weeks. Paclitaxel 60 mg/m^2 was administered once weekly for 5 weeks during radiation therapy.

Results: Fifty-seven patients were enrolled between January 2006 and March 2008. The median follow-up time was 60.0 months (95% confidence interval [CI], 51.0-58.2). All grade 3/4 toxicities were hematologic and usually self-limited. There was no life-threatening toxicity. The cumulative incidence of intrapelvic recurrence sites was 1.9% (1/52), and the cumulative incidence of extrapelvic recurrence sites was 34.6% (18/52). The estimated 5-year disease-free and overall survival rates were 63.5% (95% CI, 50.4-76.5) and 82.7% (95% CI, 72.4-92.9), respectively.

Conclusions: Concurrent chemoradiation with weekly paclitaxel is well tolerated and seems to be effective for high-risk endometrioid endometrial cancers. This approach appears reasonable to be tested for efficacy in a prospective, randomized controlled study. © 2014 Elsevier Inc.

Introduction

Endometrial cancer is the most common malignant cancer among women in developed countries, and the number of patients diagnosed with endometrial cancer continues to increase in countries such as Korea and the United States (1). Although patients with early stages of endometrial cancer can be cured by surgery alone, those with advanced endometrial cancer commonly experience local or distant recurrence (2). Often, adjuvant chemotherapy or radiation therapy is applied to reduce the rate of recurrence, but an optimal adjuvant therapy for advanced endometrial cancer remains to be determined.

Not long ago, postoperative radiation therapy was the most commonly used and effective adjuvant treatment for high-risk endometrial cancer. Although whole pelvic irradiation with or without extended fields can efficiently reduce the risk of local and regional recurrence, its inability to reduce the risk of distant recurrence outside the irradiation field thwarts its effectiveness in improving long-term survival (3). As a result, whole abdominal irradiation (WAI) is applied to overcome this limitation, but many patients with stage III/IV disease still experience local/regional or distant recurrence. By contrast, adjuvant chemotherapy has been shown to be more effective in preventing distant metastasis (4), although the efficacy of chemotherapy alone remains inconclusive because of its association with a high risk of pelvic recurrence (5). Because of these differences, the combination of chemotherapy and radiation therapy after surgery is used to eradicate local/regional residual disease and to prevent distant metastasis among patients with high-risk endometrial cancer (6).

At present, a weekly prescription of cisplatin is the primary approach in concurrent chemoradiation in numerous settings. However, various agents, including paclitaxel, have been recognized as potent radiosensitizers (7). Concomitant radiation therapy and weekly single-agent paclitaxel 60 mg/m^2 have been evaluated in patients with high-risk endometrial cancer (8). Experience in treating cervical cancer also suggests that applying paclitaxel concurrently with pelvic radiation is both active and tolerable (9). Given the activity of paclitaxel as a single agent against endometrial cancer and its radiosensitizing properties, we hypothesized that combining paclitaxel with radiation therapy might reduce the toxicity of systemic chemotherapy without compromising the treatment efficacy for patients with high-risk endometrial cancer. Here, we describe a phase 2 trial undertaken by the Korean Gynecologic Oncology Group to evaluate the survival rate, incidence of local/regional and distant relapse, and toxicity of concomitant weekly paclitaxel and radiation therapy treatment in patients with stage III/IV endometrial cancer.

Methods and Materials

Patient selection and eligibility criteria

Patients aged $\geq$20 and $\leq$80 years with histologic diagnoses of International Federation of Gynecology and Obstetrics (FIGO) (1988) stage III or IV endometrioid adenocarcinoma and without having had any prior surgery, chemotherapy, or radiation therapy for the treatment of any other cancers were enrolled in this study. Patients were given a staging laparotomy, including a total abdominal hysterectomy, bilateral salpingo-oophorectomy, pelvic and paraaortic lymphadenectomy, and peritoneal washing cytology, and they were required to have an Eastern Cooperative Oncology Group performance status of 0 to 2. Patients with diagnoses of other cancers or severe infection requiring parenteral antibiotics; those with a history of cardiac arrhythmia, congestive heart failure, or myocardial

infarction within the previous 6 months; or those with uncontrolled infection, diabetes or hypertension, or compromised cardiac, renal, liver, or bone marrow functions were not enrolled. All patients provided informed consent to participate in a randomized study, and all institutions participating in the protocol obtained the approval of their institutional review boards. A central pathology review was not conducted. Registration and initiation of treatment were performed mandatorily within 6 weeks of surgery, with radiation therapy beginning 2 days before or after the first chemotherapy.

Radiation therapy

All eligible patients completed a course of external pelvic radiation comprising a total dose of 4500 to 5040 cGy given in 5 fractions per week (180-200 cGy per day) for a total of 25 to 28 fractions. Pelvic radiation was performed using a standard 4-field box technique with x-ray energy magnitude >10 MV. Extended field irradiation was performed on the patients with positive para-aortic lymph nodes. Radiation therapy was delayed up to 2 weeks in patients whose absolute neutrophil count was $<500/mm^3$ or who experienced radiation-related gastrointestinal or genitourinary toxicity.

Chemotherapy

Paclitaxel (60 mg/m^2) diluted in 500 mL of 5% dextrose in water was administered intravenously for 3 hours once per week for a total of 6 weeks. Standard anaphylaxis premedication was also administered. Unless the patient had febrile neutropenia or persistent grade 4 neutropenia, colony-stimulating agents were not used during the periods of radiation therapy.

Treatment modifications

Dose modification of paclitaxel was based on the greatest toxicity grade using the National Cancer Institute Common Toxicity Criteria for Adverse Events, version 3.0. Chemotherapy was repeated every week, providing that the patient's absolute neutrophil count recovered to $\geq 1500/mm^3$ and the platelet count was $\geq 75{,}000/mm^3$. The paclitaxel dose was reduced by 20% (48 mg/m^2) if the patient's nadir absolute neutrophil count of $<1500/mm^3$ and/or the nadir platelet count of $<75{,}000/mm^3$ persisted between 1 to 2 weeks or if febrile neutropenia occurred. Chemotherapy was also delayed up to 2 weeks in patients who experienced grade 3 or 4 nonhematologic adverse events.

Follow-up

All patients were followed up for 5 years after surgery. Radiologic assessments of disease were conducted by chest x-ray and by abdominal-pelvic computed tomography (CT) or magnetic resonance imaging (MRI), both of which were conducted every 6 months in the first 2 years and annually thereafter until 5 years after surgery. In addition, patients were evaluated by pelvic examination, serum CA125 level, and Papanicolaou tests at an outpatient clinic every 3 months in the first 2 years and every 6 months thereafter for 5 years after surgery. Disease progression was identified when any of the following criteria were met: (*1*) biopsy-proven metastasis in newly detected lesion(s) on physical examination, chest x-ray, or CT/MRI scan; (*2*) notable increase in size of para-aortic nodes (≥ 2 cm) as shown on a CT/MRI scan (a separate biopsy was not necessary to confirm the recurrence); (*3*) elevated serum CA125 level to >3 times the upper normal limit accompanied by lesions suggestive of recurrence on CT/MRI scan; or (*4*) lesions that had increased in size progressively on CT/MRI scans performed at 1-month intervals.

Study endpoints

The primary endpoints included the 5-year disease-free survival (DFS) and overall survival (OS), which were defined as the interval between the date of entry into the study to the date of the first documentation of disease recurrence, death, or last follow-up visit. The secondary endpoint was the toxicity of paclitaxel during concurrent radiation therapy. The frequency and severity of toxicity to the combined treatment were also analyzed.

Statistical analysis

This was a single-arm phase 2 study of weekly paclitaxel with radiation therapy. Statistical analyses were performed for all eligible patients on an intent-to-treat principle. The primary endpoints of the study were DFS and OS. The 2-year DFS rate of patients with stage III/IV endometrial cancer was assumed to be 50% after a conventional modality such as radiation therapy after surgery and 70% after chemoradiation. Based on these considerations, our accrual goal was 56 patients, which would provide a statistical power of 90% in the detection of a 20% increase in DFS. Pelvic failure and extrapelvic failure rates were estimated using the cumulative incidence method. DFS and OS curves were calculated using the Kaplan-Meier method, and the significance was calculated by the log-rank test. Univariate and multivariate analyses for relevant clinical covariates associated with recurrence were conducted using the Cox proportional hazards model. Statistical analyses were performed using SPSS, version 18.0 (SPSS Inc, Chicago, IL). Significance was set at $P<.05$, and all P values were determined from 2-sided tests.

Table 1 Characteristics of patients (n = 57)

Characteristic	N	%
Age, y		
Mean (SD; range)	52.2 (6.8; 36-72)	
31-40	3	5.3
41-50	20	35.1
51-60	27	47.3
>60	7	12.3
Stage		
IIIA	12	21.1
IIIB	0	0
IIIC	40	70.1
IVA	3	5.3
IVB	2	3.5
Tumor grade		
1	14	24.6
2	27	47.3
3	16	28.1

Results

Patient characteristics

Between January 2006 and March 2008, 57 eligible patients were enrolled in 20 institutes. The characteristics of the patients included in this study are described in Table 1. The patients' ages were 36 to 72 years (mean, 52.2 years). All patients had a histologic diagnosis of endometrioid adenocarcinoma. Twelve patients (21.1%) had FIGO stage IIIA, 40 (70.1%) had stage IIIC, and 5 (8.8%) had stage IV disease. No patients in this study had FIGO stage IIIB disease. Fourteen patients (24.6%) had grade 1, 27 (47.3%) had grade 2, and 16 (28.1%) had grade 3 tumors.

Chemotherapy was suspended because of adverse toxic effects in 2 patients; 1 patient experienced septic shock, and the other had persistent grade 4 neutropenia for more than 2 weeks. One patient refused treatment after enrollment, and 2 patients withdrew from treatment without completing all 6 cycles of chemotherapy. There was no major violation during the protocol therapy. Overall, 52 patients completed the treatment protocol without major violations and were evaluated for the final analysis (Fig. 1).

Toxicity

The toxicities observed during the protocol therapy are shown in Table 2. Among 52 patients who underwent toxicity evaluation, severe toxicity pertained primarily to hematologic toxicity. Of the 312 cycles given to 52 patients, 35 episodes (11.2%) of grade 3 or 4 neutropenia were observed, and 98 cycles were delayed by 1 week because of hematologic toxicity. Paclitaxel dose reduction was required for 8 patients (15.3%) because of persistent neutropenia for more than 1 week.

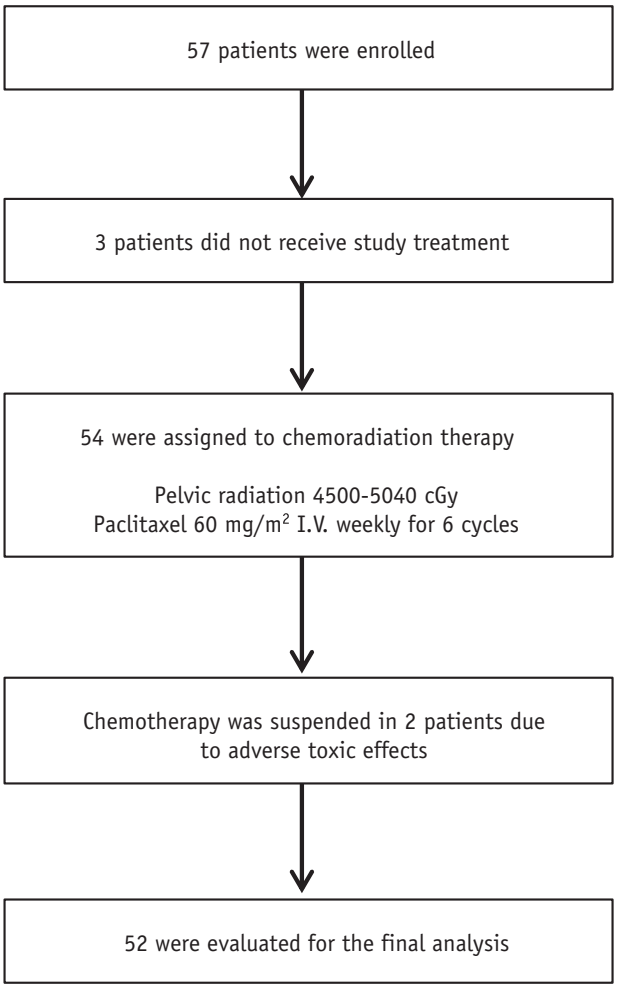

Fig. 1. Enrollment, treatment, and follow-ups of the study patients. After enrollment, 1 patient refused treatment and 2 patients withdrew from the study. Chemotherapy was suspended in 2 patients (1 for septic shock, 1 for persistent grade 4 neutropenia). I.V. = intravenous.

Recurrence sites

The median follow-up period of these patients was 60.0 months (95% CI, 51.0-58.2). Recurrences occurred in 19 of 52 patients (36.5%) (Table 3). The cumulative

Table 2 Major toxicities

Toxicity	Grade 0/1	Grade 2	Grade 3	Grade 4
Leukopenia	0	86	47	5
Neutropenia	3	63	30	5
Anemia	0	32	0	0
Neuropathy	1	1	0	0
Diarrhea	14	18	0	0
Constipation	5	12	0	0
Nausea/vomiting	16	11	0	0
Cystitis	1	1	0	0
General weakness	2	1	0	0

Table 3 Sites of recurrence

Patient	Stage	Site of recurrence	Time to recurrence (months)
1	IIIC	Vaginal vault	12
2	IIIC	Extrapelvic LN	12
3	IVA	Liver	12
4	IIIA	Peritoneal seeding	24
5	IVB	Peritoneal seeding	20
6	IIIA	Lung	20
7	IIIC	Lung	16
8	IIIC	Bone	20
9	IIIC	Bone	8
10	IVA	Liver	4
11	IIIC	Lung, para-aortic LN	4
12	IIIC	Lung, brain, bone	7
13	IIIC	Lung, para-aortic LN	10
14	IIIC	Lung, extrapelvic LN	6
15	IIIC	Liver	3
16	IIIC	Para-aortic LN	19
17	IIIC	Extrapelvic LN	3
18	IIIC	Peritoneal seeding	4
19	IVA	Bone	24

Abbreviation: LN = lymph nodes.

incidence of intrapelvic recurrence, such as in the vaginal vault or pelvis, was 1.9% (1/52), and the cumulative incidence of extrapelvic recurrence, such as in the lung, liver, bone, para-aortic lymph node, or other sites, was 34.6% (18/52). The median time to the detection of recurrence was 12.0 months (range, 3-24 months).

Survival analysis

Survival data were available for all 52 patients. By the end of the follow-up period, 9 patients (17.3%) had died of endometrial cancer, and 19 patients (36.5%) experienced recurrence. The estimated 5-year DFS and OS rates were 63.5% (95% CI, 50.4-76.5) and 82.7% (95% CI, 72.4-92.9), respectively. Figure 2 shows the 5-year DFS and OS data. In subgroup analyses, the estimated 5-year DFS and OS rates for patients with stage III disease (n = 48) were 68.7% (95% CI, 56.1-81.3) and 87.5% (95% CI, 55.5-81.8), respectively.

Discussion

This study by the Korean Gynecologic Oncology Group was a prospective phase 2 trial conducted to determine both the efficacy and the toxicity of radiation therapy when applied concurrently with paclitaxel chemotherapy to patients with a high risk of endometrial cancer. Thus, the eligibility criteria for this study were restricted primarily to patients with FIGO stage III/IV endometrioid adenocarcinoma. In our study, most of the enrolled patients had stage III lesions, and only 8.8% had stage IV lesions. More importantly, all patients enrolled in our study completed the 60-month follow-up. Because the pool of patients was homogeneous and well within the eligibility criterion of this study, we strongly believe that the efficacy of chemoradiation as an adjuvant treatment for advanced-staged

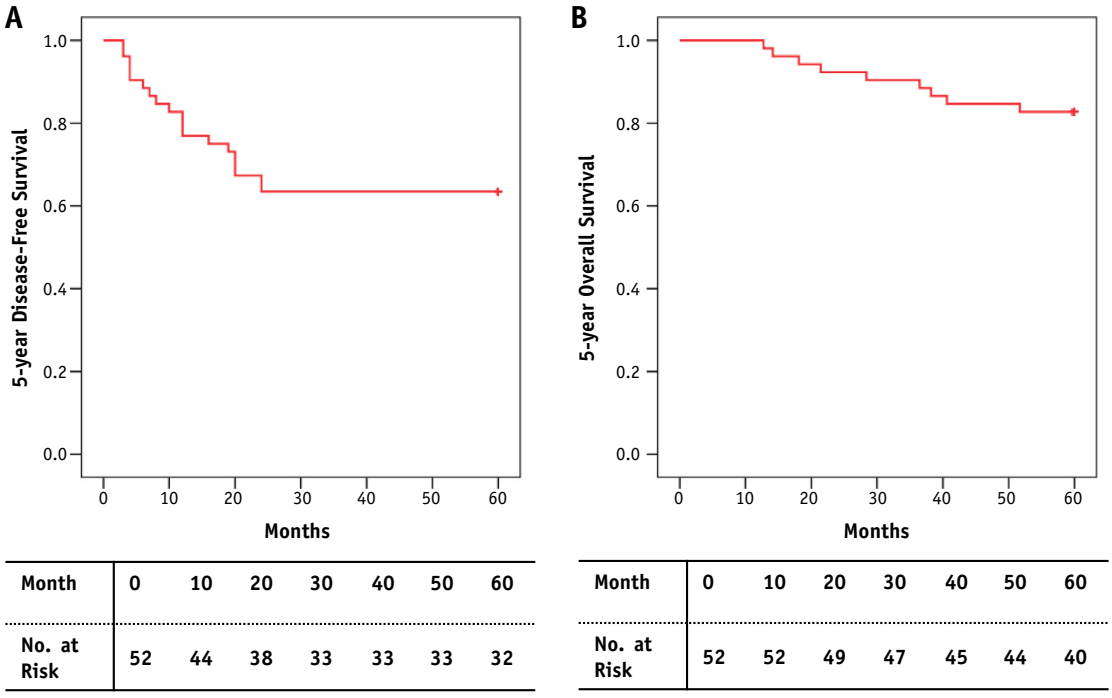

Fig. 2. Kaplan-Meier estimates of 5-year disease-free (A) and overall survival (B) of patients in the Korean Gynecologic Oncology Group 2001 study.

endometrial cancer was evaluated appropriately with due consideration.

Advanced endometrial cancer has a poor long-term prognosis if treated with surgery only. Therefore, numerous postoperative adjuvant therapies have been proposed to reduce the risk of recurrence. However, the standard treatment regimen for advanced endometrial cancer has not been determined, and recurrence rates remain unacceptably high. Such difficulty may reflect the fact that most recurrences of advanced endometrial cancer involve a distant and/or upper abdominal location (10, 11). Thus, systemic chemotherapy has been investigated to improve the outcome of advanced endometrial cancer, and several active chemotherapy candidates have been identified (4, 12).

The Gynecologic Oncology Group 122 study was the first randomized multi-institutional trial comparing WAI and doxorubicin-cisplatin chemotherapy in 422 patients with stage III or IV endometrial cancer with optimal postoperative residual disease (10). In their study, chemotherapy significantly improved both PFS and OS compared with its WAI counterpart. The stage-adjusted death hazard ratio was 0.68 (95% CI, 0.52-0.89; $P<.01$) in favor of chemotherapy. Such noticeable efficacy of chemotherapy in high-risk patients is partly explained by the fact that distant recurrence cannot be prevented with pelvic irradiation. The pattern of recurrence between the 2 treatment groups also differed; chemotherapy was much more effective than WAI in reducing the rate of distant recurrence, although it also led to higher pelvic recurrence rates than did WAI, in which case additional radiation had to be used to reduce such a shortcoming (10). Nonetheless, other studies have also reported higher rates of pelvic recurrence when chemotherapy was used as the sole adjuvant therapy for advanced endometrial cancer (4, 13). Taken together, these results suggest that, although systemic chemotherapy may be effective in improving the rate of distant recurrence, pelvic recurrence remains a problem.

To control both pelvic and distant recurrence more adeptly, the combination of chemotherapy and radiation therapy was evaluated. The Radiation Therapy Oncology Group (RTOG) 9708 study assessed the feasibility and patterns of recurrence and survival when cisplatin-paclitaxel chemotherapy was combined with adjuvant radiation for patients with high-risk endometrial cancer (14). At 4 years, pelvic, regional, and distant recurrence rates were 2%, 2%, and 19%, respectively. Similarly, the DFS and OS rates were 81% and 85%, respectively. Although distant recurrence continued to occur, pelvic control showed noticeable improvements after combined modality treatment in the patients with advanced disease.

In our study, we assessed the feasibility of radiation therapy with concurrent weekly paclitaxel chemotherapy (60 mg/m^2) in patients with stage III or IV endometrial cancer. We chose to administer paclitaxel weekly because of its efficacy as a single agent in endometrial cancer and its radiosensitizing action (7, 15, 16). It is well known that the response rate to combination chemotherapy is greater than that to a single agent. However, especially in chemoradiation therapy, we must always consider toxicity as an important factor. In the previous experiences, the toxicities of combination agents with radiation therapy were approximately twice that of a single agent (4, 17). This high toxicity was the major reason for treatment termination. Thus, when designing our study, we hoped to minimize the toxicity level as much as possible, and we believed that selecting the paclitaxel single-agent regimen for concurrent chemoradiation would do just that.

Overall, weekly paclitaxel with concurrent pelvic radiation was well tolerated, and the types and incidence of acute toxicity were not excessive (11.2% with grade 3 or 4 neutropenia). Consistent with our findings, previous studies have also reported negligible toxicity when paclitaxel is given at a dosage of 40 to 80 mg/m^2 with radiation (18, 19). In contrast to our study, Jhingran et al (20) recently reported that the rate of grade $\geq$3 severe diarrhea during radiation therapy was 43% and the rate of grade $\geq$3 severe late bowel toxic effects was 13%. There may be many reasons for the observed difference. One possible reason is that the mean patient age of 52 years in our study is much younger than that of 63 years in the study by Jhingran et al Another potential reason is that both studies selected radiation therapy with concurrent weekly paclitaxel as the treatment regimen, but in the study by Jhingran et al, 4 cycles of adjuvant paclitaxel (135 mg/m^2) were administered at the end of the chemoradiation regimen.

The rates of pelvic and distant recurrence in our study were 1.9% and 34.6%, respectively, and these rates are similar to those of other series that used multimodality therapy (14, 21). These findings all indicate that weekly administration of paclitaxel together with pelvic irradiation can adequately control and reduce pelvic recurrence. However, almost all recurrences in our study occurred outside the radiation field, suggesting that concurrent paclitaxel successfully enhanced the impact of radiation therapy as a radiation sensitizer but did not have much systemic effect. Therefore, the administration of a higher dosage of paclitaxel in consolidation cycles or the addition of another active agent with a different toxicity profile could be considered to ensure better systemic control and improve survival in patients with high-risk endometrial cancer.

In terms of survival, our results showed that the 5-year DFS and OS rates were 63.5% and 82.7%, respectively, in all patients and 68.7% and 87.5%, respectively, in patients with stage III disease. Our survival results of patients with stage III disease were either similar to, or slightly better than, those in the RTOG 9708 study. De Marzi et al (22) recently reported on their clinical experience of adjuvant treatment with concomitant radiation therapy and weekly paclitaxel at a dosage of 60 mg/m^2 in 47 patients with high-risk endometrial cancer. In their study, no life-threatening toxicity was identified, and the 5-year DFS and OS rates were 81.8% and 88.4%, respectively. Comparison of the

5-year DFS rates reveals that the De Marzi results were superior to ours, whereas comparison of the 5-year OS rates shows little difference between them. We believe that the difference in the 5-year DFS occurred not only because patients with stage I and II disease constituted 23.4% and 25.5% of the total patients in the De Marzi study but also because those authors administered 3 additional doses of consolidation therapy after the radiation therapy. Nevertheless, our findings and those of De Marzi et al suggest that radiation with concurrent weekly paclitaxel is a reasonable treatment regimen for patients with advanced-stage endometrial cancer and that this regimen has some unique advantages that should be evaluated further. However, it should be noted that there were important differences between our study design and theirs. First, unlike in the study by De Marzi et al, in which patients were enrolled for 8 years, our study was conducted with patients enrolled for only 2 years, mainly because this was a multi-institutional trial. Second, although the study by De Marzi et al included patients with stage IC (23.4%) or stage II (25.5%) disease, our research focused primarily on patients with either stage III or IV disease to enable us to gain more insight into high-risk endometrial cancer. Thus, our study sample can be said to have been more homogeneous. Taken together, our findings and those by De Marzi et al suggest that radiation with concurrent weekly paclitaxel is a reasonable treatment regimen for patients with advanced-stage endometrial cancer and that this regimen has some unique advantages that should be evaluated further.

References

1. Jemal A, Bray F, Center MM, et al. Global cancer statistics. *CA Cancer J Clin* 2011;61:69-90.
2. Kuwabara Y, Susumu N, Banno K, et al. Clinical characteristics of prognostic factors in poorly differentiated (G3) endometrioid adenocarcinoma in Japan. *Jpn J Clin Oncol* 2005;35:23-27.
3. Aalders J, Abeler V, Kolstad P, et al. Postoperative external irradiation and prognostic parameters in stage I endometrial carcinoma: Clinical and histopathologic study of 540 patients. *Obstet Gynecol* 1980;56:419-427.
4. Thigpen JT, Brady MF, Homesley HD, et al. Phase III trial of doxorubicin with or without cisplatin in advanced endometrial carcinoma: A Gynecologic Oncology Group study. *J Clin Oncol* 2004;22:3902-3908.
5. Mundt AJ, McBride R, Rotmensch J, et al. Significant pelvic recurrence in high-risk pathologic stage I-IV endometrial carcinoma patients after adjuvant chemotherapy alone: Implications for adjuvant radiation therapy. *Int J Radiat Oncol Biol Phys* 2001;50:1145-1153.
6. Alvarez Secord A, Havrilesky LJ, Bae-Jump V, et al. The role of multi-modality adjuvant chemotherapy and radiation in women with advanced stage endometrial cancer. *Gynecol Oncol* 2007;107:285-291.
7. Choy H, Rodriguez FF, Koester S, et al. Investigation of taxol as a potential radiation sensitizer. *Cancer* 1993;71:3774-3778.
8. Frigerio L, Mangili G, Aletti G, et al. Concomitant radiotherapy and paclitaxel for high-risk endometrial cancer: First feasibility study. *Gynecol Oncol* 2001;81:53-57.
9. Vogt HG, Martin T, Kolotas C, et al. Simultaneous paclitaxel and radiotherapy: Initial clinical experience in lung cancer and other malignancies. *Semin Oncol* 1997;24(4 Suppl 12):S12-S101. S112-105.
10. Randall ME, Filiaci VL, Muss H, et al. Randomized phase III trial of whole-abdominal irradiation versus doxorubicin and cisplatin chemotherapy in advanced endometrial carcinoma: A Gynecologic Oncology Group study. *J Clin Oncol* 2006;24:36-44.
11. Sutton G, Axelrod JH, Bundy BN, et al. Whole abdominal radiotherapy in the adjuvant treatment of patients with stage III and IV endometrial cancer: A Gynecologic Oncology Group study. *Gynecol Oncol* 2005;97:755-763.
12. Hoskins PJ, Swenerton KD, Pike JA, et al. Paclitaxel and carboplatin, alone or with irradiation, in advanced or recurrent endometrial cancer: A phase II study. *J Clin Oncol* 2001;19:4048-4053.
13. Aoki Y, Kase H, Watanabe M, et al. Stage III endometrial cancer: Analysis of prognostic factors and failure patterns after adjuvant chemotherapy. *Gynecol Oncol* 2001;83:1-5.
14. Greven K, Winter K, Underhill K, et al. Final analysis of RTOG 9708: Adjuvant postoperative irradiation combined with cisplatin/paclitaxel chemotherapy following surgery for patients with high-risk endometrial cancer. *Gynecol Oncol* 2006;103:155-159.
15. Lissoni A, Zanetta G, Losa G, et al. Phase II study of paclitaxel as salvage treatment in advanced endometrial cancer. *Ann Oncol* 1996;7:861-863.
16. Woo HL, Swenerton KD, Hoskins PJ. Taxol is active in platinum-resistant endometrial adenocarcinoma. *Am J Clin Oncol* 1996;19:290-291.
17. Aapro MS, van Wijk FH, Bolis G, et al. Doxorubicin versus doxorubicin and cisplatin in endometrial carcinoma: Definitive results of a randomised study (55872) by the EORTC Gynaecological Cancer Group. *Ann Oncol* 2003;14:441-448.
18. Choy H, Akerley W, Safran H, et al. Phase I trial of outpatient weekly paclitaxel and concurrent radiation therapy for advanced non-small-cell lung cancer. *J Clin Oncol* 1994;12:2682-2686.
19. Wolf M, Faoro C, Goerg C, et al. Paclitaxel and simultaneous radiation in the treatment of stage IIIA/B non-small cell lung cancer. *Semin Oncol* 1996;23:108-112.
20. Jhingran A, Ramondetta LM, Bodurka DC, et al. A prospective phase II study of chemoradiation followed by adjuvant chemotherapy for FIGO stage I-IIIA (1988) uterine papillary serous carcinoma of the endometrium. *Gynecol Oncol* 2013;129:304-309.
21. Fowler JM, Brady WE, Grigsby PW, et al. Sequential chemotherapy and irradiation in advanced stage endometrial cancer: A Gynecologic Oncology Group phase I trial of doxorubicin-cisplatin followed by whole abdomen irradiation. *Gynecol Oncol* 2009;112:553-557.
22. De Marzi P, Frigerio L, Cipriani S, et al. Adjuvant treatment with concomitant radiotherapy and chemotherapy in high-risk endometrial cancer: A clinical experience. *Gynecol Oncol* 2010;116:408-412.