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EJSO
the Journal of Cancer Surgery
ELSEVIER
EJSO xx (2008) 1–5
www.ejso.com

Comparison of chemoradiation with radiation as postoperative adjuvant therapy in cervical cancer patients with intermediate-risk factors

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Accepted 10 April 2008

Abstract

Aims: In cervical cancer patients with intermediate-risk factors, the optimal adjuvant therapy is still controversial. We retrospectively compared the treatment outcome of chemoradiation with that of radiation.
Methods: From 1997 to 2005, 79 consecutive cervical cancer patients received postoperative adjuvant therapy indicated by intermediate-risk factors. Fifty-five women received chemoradiation and 24 women received radiation. Risk factors, recurrence-free survival (RFS), adverse events, and recurrence pattern were investigated and were compared between the chemoradiation and radiation groups. RFS was calculated by the Kaplan–Meier method and was compared by the log-rank test.
Results: Risk factors were well-balanced between the two groups. Four patients recurred in the chemoradiation group and eight patients recurred in the radiation group. RFS rate of the chemoradiation group was significantly higher than that of the radiation group ($P = 0.01$). Hematologic toxicity was more common in the chemoradiation group than in the radiation group ($P < 0.01$). However, non-hematologic toxicity was similar between the two groups and most of the patients (97%) completed postoperative adjuvant therapy. Recurrence pattern was similar between the two groups.
Conclusion: In cervical cancer patients with intermediate-risk factors, chemoradiation was well-tolerated and more effective than radiation as a postoperative adjuvant therapy.

Keywords: Uterine cervical neoplasms; Risk factors; Chemotherapy, adjuvant; Radiotherapy, adjuvant; Combined modality therapy; Recurrence

Introduction

Radical hysterectomy with pelvic lymphadenectomy has been widely accepted as the treatment in patients with early-stage cervical cancer. Because 10–20% of the patients recurred after radical surgery,[1] efforts to identify risk factors for recurrence after radical surgery have been made.[2] Positive or close resection margin, lymph node involvement, and parametrial invasion were recognized as high-risk factors and large tumor size, deep stromal invasion, and lymphovascular space invasion (LVSI) were regarded as intermediate-risk factors.[3]

Radiation has been used as a postoperative adjuvant therapy to reduce recurrences in patients with cervical cancer.[4] A randomized trial on cervical cancer patients with intermediate-risk factors showed that, compared to no further treatment, postoperative radiation reduced the number of recurrences at the cost of more grade 3/4 adverse events.[5] Since Peters et al. showed a significant survival advantage with the use of concurrent chemoradiation rather than radiation in patients with high-risk cervical cancer,[6] concurrent chemoradiation rapidly replaced radiation in the treatment of high-risk cervical cancer. However, the superiority of chemoradiation is still not proven in cervical cancer patients with intermediate-risk factors.

We hypothesized that, like in high-risk cervical cancer, chemoradiation could be more effective than radiation as

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doi:10.1016/j.ejso.2008.04.004

Please cite this article in press as: Kim K et al., Comparison of chemoradiation with radiation as postoperative adjuvant therapy in cervical cancer patients with intermediate-risk factors, Eur J Surg Oncol (2008), doi:10.1016/j.ejso.2008.04.004

a postoperative adjuvant therapy in cervical cancer patients with intermediate-risk factors. We retrospectively compared the treatment outcome of chemoradiation with that of radiation in cervical cancer patients with intermediate-risk factors.

Methods

Patients

From 1997 to 2005, at our institute, 110 patients with cervical cancer received postoperative adjuvant therapy due to intermediate-risk factors. Intermediate-risk factors were defined as follows: large tumor size (longest diameter on surgical specimen $\geq$4 cm), deep stromal invasion (invasion depth $\geq$1/2 of cervical wall), and LVSI. Patients with high-risk factors such as lymph node involvement, parametrial invasion, and positive resection margin were excluded from this study. Among the 110 patients, 27 patients who received adjuvant chemotherapy, three patients with cervical intraepithelial neoplasia at the resection margin, and one patient with neuroendocrine cell type were excluded from this study. Among the remaining 79 patients, 55 patients received adjuvant chemoradiation and 24 patients received adjuvant radiation. From 1997 to 1999, most of the patients received adjuvant radiation (15/16). However, since 2000, over 80% of the patients received chemoradiation (54/63).

Surgery, chemotherapy, and radiation

Clinicopathologic variables were obtained via medical records' review. All patients underwent radical hysterectomy with pelvic/paraaortic lymphadenectomy. Surgeries were performed by five gynecologic oncologists in our department. Specimens were examined at the department of pathology in our institute. Seventeen patients received one to four cycles of neoadjuvant chemotherapy before surgery. Regimens of neoadjuvant chemotherapy were as follows: 5-fluorouracil + cisplatin (11 patients), 5-fluorouracil + carboplatin + interferon gamma (two patients), epirubicin + cisplatin (one patient), paclitaxel + carboplatin (one patient), UFT + cisplatin (one patient), etoposide + cisplatin (one patient). In all 79 patients, the radiation was given on the whole pelvis area using 2- or 4-field techniques. Only one patient received additional intracavitary radiation. Radiation dose ranged from 4500 to 5100 cGy except for a patient with 3600 cGy who did not complete the radiation because of toxicities. Chemotherapy regimens used in chemoradiation were: 5-fluorouracil + cisplatin in three patients and paclitaxel + carboplatin in 52 patients. Chemotherapy was given every three or four weeks. During chemoradiation, 48 patients received two cycles of chemotherapy and seven patients received three cycles of chemotherapy. Additional chemotherapy was not given after radiation. Toxicity was assessed after every cycle of therapy and was graded according to the GOG common toxicity criteria.[7]

Analysis

Between the chemoradiation and radiation groups, the differences of clinicopathologic variables were evaluated using the chi-square test, Fisher's exact test, or linear by linear association method for categorical variables and Mann–Whitney U test for follow-up duration. Recurrence-free survival (RFS) defined as the duration from surgery to recurrence was calculated by the Kaplan–Meier method and was compared by the log-rank test. Adverse event rates of both groups were compared using Fisher's exact test. All analyses were performed using SPSS 11 software (SPSS Inc., Chicago, IL) and P values less than 0.05 were considered significant.

We did not request the approval of the institutional review board due to the retrospective nature of this study.

Results

Clinicopathologic variables

Clinicopathologic variables were well-balanced between the two groups (Table 1). Distributions of age ($P = 0.79$),

Table 1
Clinicopathologic variables in the chemoradiation and radiation groups

Clinicopathologic variables	Chemoradiation ($n = 55$)	Radiation ($n = 24$)	P value
Age			0.79
≤50	27	11	
>50	28	13	
Stage			0.50
1B1	26	14	
1B2	19	6	
2A or 2B	10	4	
Cell type			0.60
Squamous	42	17	
Non-squamous	16	7	
Size of tumor			0.61
<2 cm	7	2	
≥2 cm to <4 cm	25	15	
≥4 cm	23	7	
Stromal invasion			1.00
<1/2	5	2	
≥1/2	50	22	
Lymphovascular space invasion			0.37
−	26	14	
+	29	10	
Neoadjuvant chemotherapy			0.62
−	44	18	
+	11	6	
Recurrence	4	8	
Median follow-up, month (range)	48 (1–92)	54 (6–125)	0.11

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stage ($P = 0.50$), and cell type ($P = 0.60$) in the chemoradiation group were similar with those of the radiation group. The portions of patients with large tumor size ($P = 0.61$), deep stromal invasion ($P = 1.00$), and LVSI ($P = 0.37$) were similar between the two groups. Similar portions of patients received neoadjuvant chemotherapy in the two groups ($P = 0.62$). Four patients recurred in the chemoradiation group and eight patients recurred in the radiation group. Follow-up duration was similar between the two groups ($P = 0.11$). No disease-related death was observed in both groups.

Treatment outcome

RFS rate of the chemoradiation group was significantly higher than that of the radiation group ($P = 0.01$). The estimated 5-year RFS rate of the chemoradiation group was 89% and that of the radiation group was 67% (Fig. 1).

Hematologic toxicity was more severe in the chemoradiation group than in the radiation group ($P < 0.01$). However, non-hematologic toxicity was similar between the two groups ($P = 1.00$). Treatment delay due to toxicities happened in six patients of the chemoradiation group and in one patient of the radiation group ($P = 0.67$). Two patients in the chemoradiation group abandoned treatment due to toxicities but no patient in the radiation group did ($P = 1.00$) (Table 2).

Recurrence pattern

The recurrence pattern of the chemoradiation group was similar with that of the radiation group. In the chemoradiation group, one local recurrence (stump) and three distant recurrences (paraaortic lymph node, lung, vulva) occurred. In the radiation group, three local recurrences (two stump, one pelvis) and five distant recurrences (four lung, one vulva) were observed. Half of the tumors were non-squamous cell type and most of the patients had deep stromal invasion.

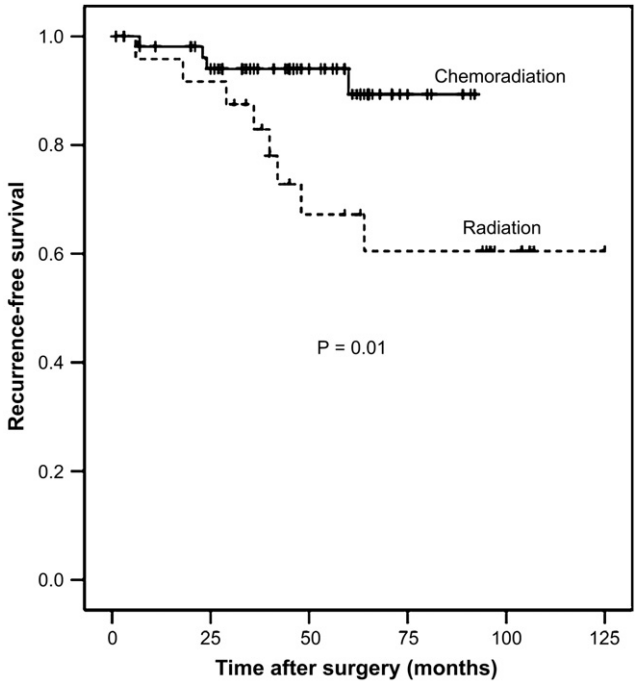

Figure 1. Recurrence-free survival of patients with intermediate-risk factors according to adjuvant therapy.

Table 2
Adverse events in the chemoradiation and radiation groups

Adverse events	Chemoradiation ($n = 55$)	Radiation ($n = 24$)	P value
Hematologic toxicity			<0.01
0–2	35	24	
3–4	20	0	
Non-hematologic toxicity			1.00
0–2	50	22	
3–4	5	2	
Treatment delay due to toxicities	6	1	0.67
Incomplete treatment due to toxicities	2	0	1.00

Discussion

Background and our finding

Since the beneficial effect of adjuvant chemoradiation for patients with high-risk factors was proven in prospective studies,[6] chemoradiation is considered the optimum postoperative adjuvant therapy in patients with high-risk factors. Similarly, since the efficacy of adjuvant radiation for patients with intermediate-risk factors was demonstrated in the trial,[5] radiation is the standard adjuvant therapy in patients with intermediate-risk factors.[4] However, some doctors insisted that chemoradiation may be applicable for patients with intermediate-risk factors.[4] We also believed that chemoradiation will be more effective than radiation in patients with intermediate-risk factors, because, in trials on patients with high-risk factors, women with different stages of cervical cancer all appear to benefit from the use of chemoradiation and there is likely to be a continuum of benefit as suggested by the secondary analysis of GOG 109.[8]

The benefit of adding chemotherapy to radiation in patients with intermediate-risk factors was suggested by previous studies. A retrospective study reported that, in patients with LVSI and deep stromal invasion, the 3-year RFS of the chemoradiation group was significantly greater than that of the radiation group. However, the small number of patients, inclusion of patients with lymph node metastasis, and no difference in 5-year RFS were limitations of that study.[9] Another study reported excellent local control rate with adjuvant chemotherapy in cervical cancer patients with deep stromal invasion.[4] However, due to the lack of randomized trials that specifically address the benefit of

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chemoradiation over radiation in cervical cancer patients with intermediate-risk factors, the optimal adjuvant therapy for these patients is still unclear. Despite being a retrospective study, our study suggested that chemoradiation is more effective than radiation in cervical cancer patients with intermediate-risk factors.

Adjuvant therapy for cervical cancer in our institute

In our institute, before 2000, the postoperative adjuvant therapy for patients with cervical cancer was mostly radiation. However, since the trial demonstrating the superiority of chemoradiation in high-risk patients, even patients with intermediate-risk factors received chemoradiation instead of radiation as the adjuvant therapy.

In this study, the chemotherapy regimen of chemoradiation was mostly paclitaxel + carboplatin. Initially, we used standard regimens such as weekly cisplatin or 5-fluorouracil + cisplatin. However, in our experience, the standard regimens had some disadvantages. To explain further, the weekly cisplatin frequently caused a treatment delay due to hematologic toxicities. In addition, the requirement of a weekly visit to the hospital was inconvenient. Similarly, 5-fluorouracil + cisplatin, a five-day regimen, needed a long hospital stay and sometimes caused intractable nausea and vomiting.

In patients with cervical cancer, we found that paclitaxel + carboplatin is very active and well-tolerated as a chemotherapy regimen of chemoradiation.[10,11] In our institute, paclitaxel + carboplatin has been being used as the primary chemotherapy regimen of chemoradiation in cervical cancer.

The benefit and cost of chemoradiation

To conclude that chemoradiation is the better adjuvant therapy than radiation in patients with intermediate-risk factors, the benefit of chemoradiation should overweigh the cost of adverse effects. Hematologic toxicity was more severe in the chemoradiation group than in the radiation group but non-hematologic toxicity was similar. In addition, the rates of treatment delay or abandonment were minimal and were not different between the two groups. Considering that the hematologic toxicities usually do not leave sequelae and could be managed with supportive treatments, we thought that the benefit of chemoradiation overweighed the cost.

Recurrence pattern

We anticipated less distant recurrences in the chemoradiation group than in the radiation group, but the recurrence pattern of the chemoradiation group was similar with that of the radiation group. Therefore, in patients with intermediate-risk factors, the effect of chemoradiation on reducing distant recurrences is thought to be minimal. This ineffectiveness of chemoradiation in reducing distant recurrences is also true for patients with high-risk factors.[12] Therefore, like in patients with high-risk factors, the main role of a chemotherapeutic agent in the chemoradiation of patients with intermediate-risk factors is thought to be a radiosensitizer.

Limitations

Although our study suggested the superiority of chemoradiation to radiation in reducing recurrences, the overall survival advantage is unclear. As we mentioned in the Results, no disease-related death was observed in both groups. Considering that the survival advantage of adjuvant therapy itself is unclear in patients with intermediate-risk factors,[5] a trial with sufficient size and follow-up duration would be necessary to demonstrate the survival advantage of chemoradiation in patients with intermediate-risk factors.

We admit that there might be some hidden factors which could account for the RFS difference between the chemoradiation and radiation groups. About surgeons, one of the five gynecologic oncologists in our department retired during the study period. However, the number of patients treated by each surgeon was similar between the chemoradiation and radiation groups. About radiation oncologists, the radiation oncologist for cervical cancer was changed during the study period. However, the radiation techniques and doses were not changed significantly during the study period. Certainly, there were many other things that changed such as the residents and fellows, and facilities of the hospital. However, we found no reason to believe that the RFS difference was due to factors other than chemoradiation.

Summary

Postoperative adjuvant chemoradiation reduced recurrences more effectively than radiation at the cost of more hematologic toxicities. However, non-hematologic toxicities were similar between the two therapies and chemoradiation was well-tolerated. The recurrence pattern of the chemoradiation group was similar with that of the radiation group.

Conflict of interest

No potential conflict of interest relevant to this article was reported.

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