

# Radiation therapy is a treatment to be considered for recurrent epithelial ovarian cancer after chemotherapy

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## ABSTRACT

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**Aims and background.** Radiation therapy provides a safe and effective alternative treatment option for recurrent epithelial ovarian cancer, although it has not been a treatment of choice. We evaluated the efficacy and toxicity of radiation therapy for recurrent epithelial ovarian cancer after chemotherapy according to the disease status.

**Methods.** This was a retrospective study of 38 patients with recurrent epithelial ovarian cancer treated with radiation therapy at the Asan Medical Center, Seoul, Korea, between January 1997 and December 2007. We analyzed their clinical characteristics and the outcome of radiation therapy.

**Results.** Thirty-eight patients were treated with radiation therapy. Their median age was 51.5 years. Most patients were FIGO stage III (27/38) with serous adenocarcinoma (26/38). All patients had received at least one regimen of platinum-based chemotherapy; 24 patients were sensitive to the first chemotherapy and the others were resistant. Lymph node and abdominopelvic wall were the most common sites of radiation therapy. The response rate was 65.0% (16 complete remissions and 10 partial remissions), and the median regression rate was 78.8% (range, -66.6 to 100.0). Median progression-free survival was 7.2 months (range, 1.0-66.6). In 28 patients who had a solitary relapsed site from the radiographic finding at the time of radiation therapy, it was 10.7 months (range, 1.8-66.6). Neither hematologic nor intestinal toxicity of grade 3-4 was observed. Prognostic factors were sensitivity to platinum and the site treated with radiation therapy.

**Conclusions.** Radiation therapy is a treatment that should be considered for recurrent epithelial ovarian cancer, especially in good responders to platinum or patients with solitary relapsed lesions.

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## Introduction

Epithelial ovarian cancer (EOC) is the leading cause of cancer death in women. Although the treatment modalities for EOC have improved in past decades<sup>1-3</sup>, long-term disease-free survival in advanced stage disease is possible in less than one third of patients, and there is no curative therapy for persistent or recurrent disease. The current standard treatment is the optimal debulking operation with postoperative chemotherapy with a taxane and platinum combination for advanced EOC<sup>1,2</sup>. Among women who subsequently develop recurrent disease, the treatment option for those who are platinum sensitive still remains platinum-based chemotherapy, whereas those who are platinum resistant should select another available therapy<sup>4-8</sup>. However, the response rates of second- or third-line chemotherapy are between 10% and 26%<sup>9-16</sup>. As a result, such efforts have not been shown to improve survival after relapse<sup>9</sup>.

**Key words:** radiation therapy, recurrent epithelial ovarian cancer, regression rate, survival, prognostic factor.

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Although radiation therapy (RT) for patients with EOC has not been predominantly used, it provides a safe and effective alternative treatment option for recurrent EOC. Actually, palliative RT has determined a response rate of 50–80% and an acceptable response duration for symptomatic patients with recurrent EOC<sup>17–25</sup>. However, the literature provides limited information regarding the benefits of RT in women with recurrent EOC<sup>18,19,21</sup>.

We evaluated the efficacy and toxicity of RT for recurrent or persistent EOC after chemotherapy according to the disease status.

## Patients and methods

### Patient eligibility

Thirty-eight patients with EOC were treated with RT at the Asan Medical Center, Seoul, Korea, between January 1997 and December 2007. The EOC was confirmed pathologically and was treated with initial debulking surgery followed by postoperative platinum-based chemotherapy. The patients all had proven relapses of ovarian cancer. We reviewed medical records and pathologic reports. We followed all guidelines for experimental investigation with human subjects required by the Institutional Review Board in the Asan Medical Center, and informed consent was obtained.

### Radiation therapy

Patients were treated with RT at the discretion of the treating gynecologic and radiologic oncologists. The radiation fields were tailored to the appropriate treatment for the relapsed sites of disease with whole abdominopelvic or involved-field radiation therapy to the tumor bed. The most common dose fractionation was 50 Gy. All fields were treated daily, 5 days a week, over a 2-week period.

### Response evaluation

Response was assessed by Response Evaluation Criteria in Solid Tumors (RECIST). The response to RT was classified as complete or partial disappearance of the relapsed lesions. Regression rates of tumors and progression-free survival were obtained to evaluate the efficacy of RT. Regression rates of the tumor were calculated by the following equation:

$$\text{Regression rate (\%)} = 100 \times [1 - (\text{maximum diameter after RT}) / (\text{maximum diameter before RT})]$$

Documented side effects were evaluated according to NCI Common Toxicity Criteria, version 3.0. Mild and moderate degrees of severity were classified as grades 1 and 2 respectively, whereas severe and life-threatening side effects were graded as 3 and 4, respectively. We analyzed the prognostic factors for long progression-free survival based on the clinical and pathologic factors.

### Statistical analysis

Response was compared in several patient groups with the chi squared test, and progression-free survival was estimated using the Kaplan-Meier survival and log-rank test. To identify prognostic factors following treatment, a Cox proportional hazards model was performed according to stage, initial histology, chemosensitivity to platinum and treated site/size. All analyses were conducted using SPSS v. 15.0 and considered statistically significant when  $P$  was <0.05.

## Results

### Patient characteristics

The 38 patients with recurrent EOC were treated with RT after chemotherapy, including 2 patients who received RT as two separate cycles. The median age was 51.5 years (range, 29.0–78.0), and the median follow-up was 24.5 months (range, 1.0–66.6). Of the patients, 89.5% (34/38) had advanced EOC (FIGO stage III and IV) and 10.5% (4/38) had early EOC (FIGO stage I and II). The predominant histopathologic type at diagnosis was serous adenocarcinoma (26/38). All patients had received a debulking operation and at least one regimen of postoperative platinum-based chemotherapy. Twenty-four patients were sensitive to the first chemotherapy and the others were resistant. Fourteen of the 38 patients (36.8%) had been heavily treated with more than two regimens of chemotherapy. Twenty-eight patients (70.0%) had only one solitary lesion from the radiologic evaluation at the time of RT (Table 1). The sites treated with RT were as follows: 14 in lymph nodes, 14 in the abdominopelvic wall, 5 in the brain, 5 in the thorax (including pleura and chest wall), and 2 in the liver (Table 2).

### Outcomes

The overall response rate was 65.0%, including 16 complete and 10 partial remissions. The median regression rate of tumors was 78.8% (–66.6 to 100.0). Median progression-free survival was 7.2 months (range, 1.0–66.6) after RT. Patients who had a solitary relapsed lesion from the radiographic finding at the time of RT showed significantly longer progression-free survival than those who had multiple recurred sites (median, 10.7 *vs* 2.9 months) ( $P < 0.05$ ) (Figure 1).

Prognostic factors were sensitivity to platinum and the site treated with RT. Patients who had been resistant to platinum showed a poor outcome and those who were treated for sites other than lymph node showed a poor outcome (hazard ratio, HR, 2.584 *vs* 2.347,  $P < 0.05$ ) (Table 3). Median progression-free survival was 10.9 months (range, 1.8–66.6) in patients who were sensitive to platinum and was 5.4 months (range, 1.0–28.8) in those who were resistant to platinum ( $P < 0.05$ ). When only lymph nodes were treated, median progression-

**Table 1 - Clinical characteristics of 38 patients treated with radiotherapy for recurrent epithelial ovarian cancer**

Characteristic	No. patients	
Age (yr)	Median (range)	51.5 (29.0-78.0)
Follow-up duration (mo)	Median (range)	24.5 (1.0-66.6)
Stage at diagnosis	I	3 (7.9%)
	II	1 (2.6%)
	III	27 (71.1%)
	IV	7 (18.4%)
Histology	Serous	26 (68.4%)
	Endometrioid	3 (7.9%)
	Mucinous	1 (2.6%)
	Mixed	6 (15.8%)
	Other <sup>a</sup>	2 (5.3%)
Previous chemotherapy (no. regimens)	1 or 2	24 (63.2%)
	>2	14 (36.8%)
Response to initial chemotherapy	Sensitive to platinum	24 (63.2%)
	Resistant to platinum	14 (36.8%)
Relapsed lesion at radiotherapy	Single site	28 (70.0%)
	Multiple sites	12 (30.0%)

<sup>a</sup>Squamous cell carcinoma, 1 case; transitional cell carcinoma, 1 case.

**Table 2 - Sites of radiotherapy for recurrent epithelial ovarian cancer**

Sites of radiotherapy	No. patients	
Lymph node	14	35.0%
Para-aortic LN	6	
Supraclavicular LN	3	
Neck LN	2	
Paratracheal LN	2	
Inguinal LN	1	
Abdominopelvic wall	14	35.0%
Brain	5	12.5%
Thorax	5	12.5%
Chest wall	2	
Pleura	2	
Bronchus	1	
Liver	2	5.0%

free survival was 13.2 months (range, 2.3-47.6) and was 6.0 months (range, 1.0-66.6) when other sites were treated ( $P < 0.05$ ) (Figure 2).

### Toxicity

Diarrhea was the most common side effect in the patients treated with whole abdominopelvic irradiation, but it was usually tolerable. Other toxicity such as nausea and vomiting, alopecia, and myelosuppression was not common in the patients treated with the RT. There were both neither hematologic nor intestinal toxicity of grade 3 and 4.

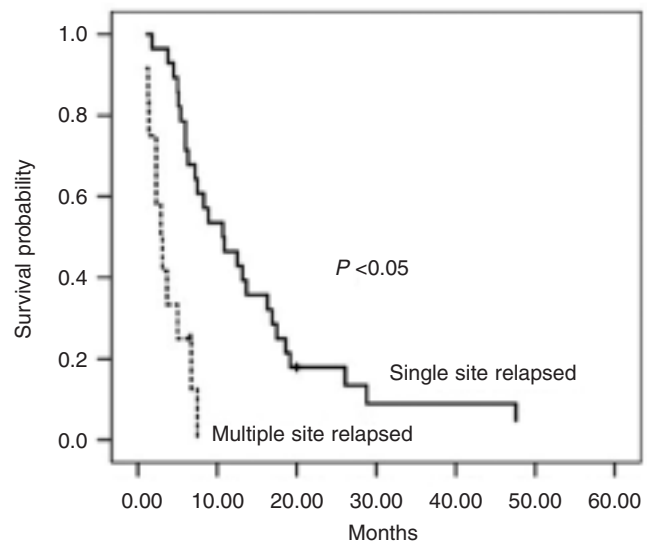


Figure 1 - Progression-free survival of patients treated with radiation therapy for recurrent epithelial ovarian cancer according to the relapsed extent.

### Discussion

Platinum-based combination chemotherapy following optimal cytoreductive surgery is a standard treatment for EOC patients. Nevertheless, most patients with advanced EOC show recurrent disease within several years. A lot of recurrent patients suffer from pain and dysfunction because of the growth of the tumor that is resistant to the chemotherapeutic regimens. Furthermore, secondary cytoreductive surgery improves the survival only in selected patients with tumors within the pelvis and progression free survival  $\geq 12$  months<sup>26</sup>. Therefore, RT should be considered as a treatment option even though limited data are available from the literature concerning the efficacy of RT in women with advanced or recurrent EOC.

Table 4 summarizes the literature of retrospective studies on RT for ovarian cancer. Although patients with ovarian cancer comprise a heterogeneous study population due to the complexity of symptoms, long clinical course, diverse chemotherapy histories and extent of disease, these retrospective studies have the power to confirm the previous experiences and design the principles of the treatment for cancer patients.

There are very few reports that RT has been used as salvage or a consolidation treatment. Cmelak *et al.*<sup>27</sup> have suggested that patients with platinum-refractory persistent or recurrent ovarian cancer limited to the pelvis or to the retroperitoneum may benefit from salvage RT; the 5-year actuarial disease-specific survival was 47% in all 41 patients and 50% in the 22 platinum-refractory patients. Fuks *et al.*<sup>28</sup> analyzed 38 patients with stage III ovarian carcinoma who were treated with initial combination chemotherapy with cyclophos-

**Table 3 - Univariate and multivariate analysis of progression-free survival based on clinical and pathologic factors**

Variable		Univariate		Multivariate	
		HR (95% CI)	P	HR (95% CI)	P
Stage	Stages I-II	0.653 (0.173-2.463)	0.530	-	-
	Stages III-IV				
Histology	Serous carcinoma	1.431 (0.569-3.594)	0.446	-	-
	Non-serous carcinoma				
Chemosensitivity	Sensitive to platinum	2.207 (1.039-4.686)	0.039	2.584 (1.265-5.279)	0.009
	Resistant to platinum				
Site treated	Lymph node	2.074 (0.922-4.663)	0.048	2.347 (1.118-4.927)	0.024
	Non-lymph node				
Size treated		1.065 (0.897-1.265)	0.474	-	-

HR, hazard ratio; CI, confidence interval.

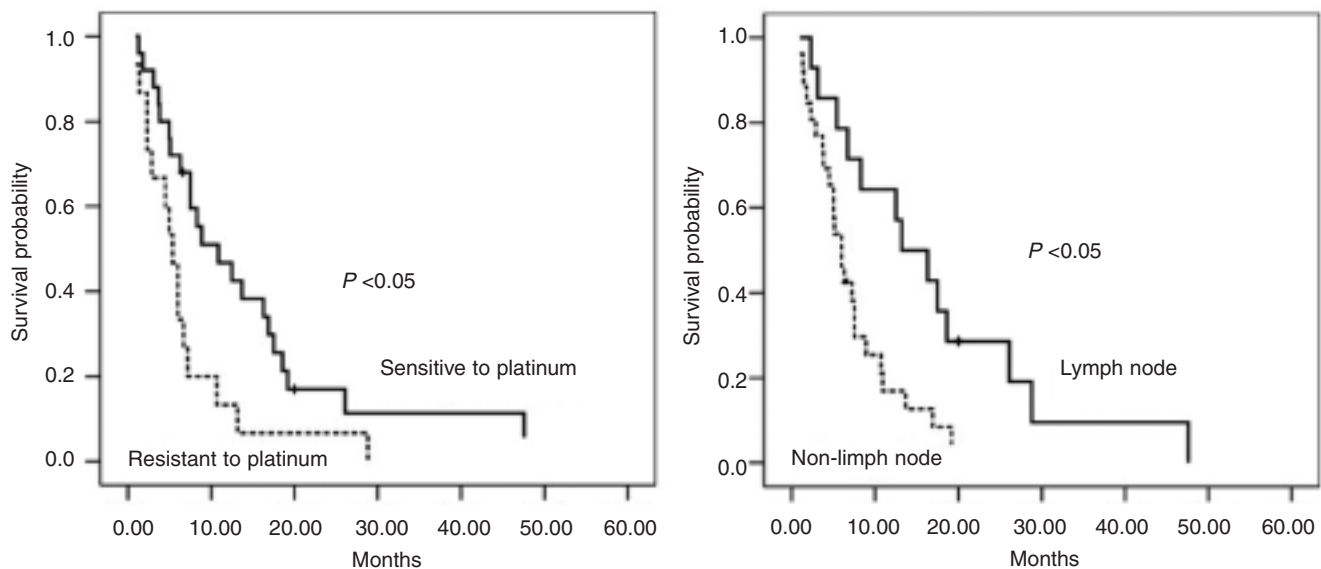


Figure 2 - Progression-free survival of patients treated with radiation therapy for recurrent epithelial ovarian cancer according to chemosensitivity (left) and treated site (right).

phamide, hexamethylmelamine, doxorubicin and cisplatin and a second laparotomy and then followed by RT. However, the long-term results suggested that whole abdominal irradiation for consolidation failed to enhance the cure of stage III ovarian carcinoma.

Palliative RT for selected ovarian cancer patients has been reported as an effective palliative treatment. In particular, excellent response rates have been reported for the symptoms of bleeding and pain. May *et al.*<sup>19</sup> reported the results of palliative RT given to 35 women with EOC who had residual disease which presented existing complaints including dyspnea, vaginal bleeding, mental status changes, symptoms related to gastrointestinal obstruction, pain, and edema. The median duration of symptom relief in patients symptomatic at presentation was 7.2 months. The authors concluded that RT was an effective method of symptom control.

Corn *et al.*<sup>21</sup> reported the overall symptomatic response rate of 70% with palliative RT in recurrent symptomatic EOC. Gelblum *et al.*<sup>22</sup> reported a complete symptomatic response rate of 70%, indicating that palliation was possible. The symptomatic relief attained in a strictly platinum-refractory group of patients lasted for a median of 11 months, similar to the median survival of 11.2 months for the entire group of patients. Furthermore, in 40% of our patients palliation was durable for more than 12 months. Lately, Choan *et al.*<sup>29</sup> reviewed 53 patients treated with palliative RT for symptomatic recurrent or residual ovarian cancer. The overall response rate was 100%, with complete response rates of 88%, 65% and 36% for the symptoms of bleeding, pain, and others, respectively ( $P < 0.05$ ).

In our study, we did not classify RT for EOC into salvage or palliative treatment. The response rate was

**Table 4 - Retrospective studies of the palliative radiotherapy for the recurrent epithelial ovarian cancer**

Study	Year	No. pts	Type of treatment	Response rate	Prognosis	Prognostic factors
Fuks <sup>28</sup>	1988	29	Consolidation (postchemo & op)	-	5 yr OS & PFS, 35% & 20%	Histology, grade
May <sup>19</sup>	1990	35	Palliative (recurrent)	61.5% (symptomatic)	PFS, median 7.2 mo	-
Corn <sup>21</sup>	1994	33	Palliative (recurrent)	70% (symptomatic)	-	-
Cmelak <sup>27</sup>	1997	41	Salvage (persistent)	-	5 yr PFS, 47%	Stage, residual disease
Gelblum <sup>22</sup>	1998	33	Palliative (recurrent)	69.7% (symptomatic)	PFS, median 11.2 mo	-
Firat <sup>23</sup>	2001	28	Palliative and salvage (recurrent)	79% (symptomatic)	1- & 5-yr OS, 50% and 35%	-
Tinger <sup>24</sup>	2001	80	Palliative (recurrent)	73% (RECIST and/or CA-125 level)	PFS, median 9 mo	-
Fujiwara <sup>25</sup>	2002	20	Palliative and salvage (recurrent)	50% (symptomatic)	2- & 5- yr OS <sup>a</sup> , 73% & 33%	Size, site (lymph node)
Choan <sup>29</sup>	2006	53	Palliative (recurrent)	100% (symptomatic)	Duration of response, median, 4.8 mo	Symptom (bleeding), stage

<sup>a</sup>OS, overall survival, was evaluated from the initial diagnosis.

Pts, patients; op, operation; PFS, progression-free survival; OS, overall survival

65.0% (16 complete remissions and 10 partial remissions) by RECIST and the median regression rate was 78.8% (-66.6 to 100.0). The median progression-free survival was 7.2 months (1.0-66.6). Fujiwara *et al.*<sup>25</sup> reviewed palliative and salvage RT in 20 patients with symptomatic recurrent or residual ovarian cancer. However, they evaluated the response rate with only symptomatic relief, which was obtained in approximately 50% in patients with symptoms. Smaller lesions and lymph nodes demonstrated better responses than larger lesions or other sites, respectively.

Tinger *et al.*<sup>24</sup> reviewed 80 patients who received RT for ovarian carcinoma and analyzed the response by RECIST and/or CA-125 level. The overall response rate was 73%, and only 11% suffered progressive disease during therapy that required discontinuation of the treatment. The median time to recurrence of symptoms in this group was 9 months. Such data were a little better than ours. However, the response rate of 65.0% and the progression-free survival of 7.2 months in our study were sufficient to consider RT as a part of treatment for recurrent EOC, compared with the response rates of second- or third-line chemotherapy, which were between 10% and 26%<sup>10-16</sup>. Interestingly, in our study, there was a significant difference in progression-free survival according to disease status at the time of RT. Median progression-free survival was 10.7 months (range, 1.8–66.6) in patients with solitary relapsed lesions and 2.9 months (range, 1.0-7.5) in patients with multiple recurred sites. This result means that RT could be an effective salvage treatment for patients with recurrent EOC when they have a solitary relapsed lesion.

Fujiwara *et al.*<sup>25</sup> reported that smaller lesions (less than 5 cm in diameter) and lymph nodes showed better

responses than larger lesions or other sites, respectively. However, most lymph node metastases were smaller than 5 cm so it is difficult to suggest which determined the response to RT. We confirmed the treated site as a significant prognostic factor of RT in the present study. In multivariate analysis, patients treated at a non-lymph node site showed significantly unfavorable prognoses (HR 2.347; 95% CI, 1.118-4.927;  $P < 0.05$ ).

The other prognostic factor in our study was sensitivity to platinum. Patients who were resistant or refractory to platinum showed a significantly unfavorable prognosis (HR 2.584; 95% CI, 1.265-5.279;  $P < 0.05$ ). These results could be explained by the development of chemoresistance and cross-resistance to RT. They have been proposed as the reason for the poor results of salvage RT or chemotherapy in patients with persistent or recurrent EOC. Interestingly, the effectiveness of radiotherapy in providing a palliative benefit in platinum-refractory ovarian carcinoma was studied by Gelblum *et al.*<sup>22</sup> In their study, a 70% complete symptomatic response rate was achieved in platinum-refractory ovarian carcinoma patients. Thus, further discussions are necessary to confirm the development of cross resistance to RT in platinum-resistant patients.

Most studies that used conventional dose fractionation schemes reported acceptable complication rates, with grade 3 complication risks between 0 and 5%<sup>21,23-25</sup>. Two studies that used a high-dose fractionation scheme (three 10-Gy fractions delivered monthly) reported serious treatment-related morbidities: rectovaginal fistula, bowel obstruction, hemorrhagic cystitis or proctitis. In our study, there was neither hematologic nor intestinal toxicity of grade 3 or 4.

In conclusion, our study showed that RT is a treatment to be considered for recurrent EOC, especially in good responders to platinum or patients with solitary relapsed lesion, even though we were not able to analyze the dose-response relationship and the effect of RT patterns. Large-scale, controlled studies are necessary to definitively validate the efficacy of RT in recurrent EOC.

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