

Prognostic factors in patients with recurrent ovarian cancer treated with radiation therapy

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Objectives: Radiation therapy (RT) for recurrent ovarian cancer may be considered not only for palliation of symptoms, but also to prolong survival in selected patients. Herein, we investigated the efficacy of RT and associated prognostic factors. **Methods:** The relationship between clinicopathological factors including age, PS, FIGO stage at initial diagnosis, histological type, number of relapsed lesions (solitary or multiple), aim of RT (curative or palliative intent), and treatment-free interval (TFI) and progression-free survival (PFS) and overall survival (OS) was investigated in 17 patients with recurrent ovarian cancer treated with RT. **Results:** The median age was 58.5 years. Eight patients (three with solitary and five with multiple relapsed lesions) were treated with curative-intent RT, and nine patients (all with multiple relapsed lesions) were treated with palliative RT. Response to RT was as follows: CR: 3 patients, PR: 5 patients, SD: 3 patients, and PD: 6 patients. The response rate (CR + PR) and disease control rate (CR + PR + SD) were 47.1% and 64.7%, respectively; neither were associated with TFI. The 2-year PFS and OS rates after RT were 11.8% and 29.4%, respectively. In univariate analysis, solitary relapsed lesions and curative-intent RT were judged as favorable prognostic factors for PFS and OS. However, in multivariate analysis, only curative-intent RT was identified as an independent favorable prognostic factor for OS (hazard ratio: 3.65, 95% confidence interval: 1.03–12.00, $P=0.045$). **Conclusions:** This retrospective study indicated that curative-intent RT may be an effective treatment method for patients when clinically indicated, regardless of whether recurrent tumors are sensitive to chemotherapy.

Keywords

Recurrent ovarian cancer; Radiation therapy; Curative-intent RT; Palliative RT; Prognostic factors

1. Introduction

In the National Comprehensive Cancer Network (NCCN) clinical practice guidelines for ovarian cancer, chemotherapy is the mainstay of treatment for patients with recurrent disease [1]. The combination of chemotherapy with cytotoxic agents and/or molecularly targeted therapies, or occasionally with surgery, has been evaluated in many clinical trials. The efficacy of chemotherapy primarily depends on platinum sensitivity, and for patients who experience platinum-resistant

relapses, progression-free survival (PFS) and overall survival (OS) are remarkably shorter compared with those of patients with platinum-sensitive relapses.

Radiation therapy (RT) for recurrent ovarian cancer is primarily considered to relieve symptoms, such as pain and bleeding, and may also be considered to improve quality of life and prolong survival; it may even be considered to have a key role in the treatment of selected patients. However, the actual role of RT for recurrent ovarian cancer, with the exception of brain metastases, remains uncertain. The NCCN guidelines state that palliative localized RT can be considered for recurrent tumors; however, the role and actual indications for this are not specified in detail [1]. Several reports regarding the efficacy of and lower toxicities associated with RT for recurrent ovarian cancer patients have been published [2–9]; however, many important unresolved issues remain.

Therefore, herein we investigated the clinical efficacy of and toxicities associated with RT, as well as prognostic factors in recurrent ovarian cancer patients treated with RT.

The present retrospective study aimed to evaluate the clinical benefits of RT and to identify which recurrent ovarian cancer patients would have the greatest benefit.

2. Materials and methods

Among 144 patients with radiologically confirmed recurrent ovarian cancer who were treated between Jan 2007 and Dec 2018 at Dokkyo Medical University Hospital, 17 patients (11.8%) with recurrent ovarian cancer treated with RT were enrolled. Patients treated with secondary cytoreductive surgery prior to RT and patients receiving RT for brain metastases were excluded. Recurrent tumors in all patients were diagnosed by computed tomography (CT), and in some patients by [10] F-fluorodeoxyglucose positron emission tomography/CT or magnetic resonance imaging.

The relationship between clinicopathological factors, including age, Federation of Gynecology and Obstetrics (FIGO) stage at initial diagnosis, Eastern Cooperative Oncology Group (ECOG) performance status (PS), histological type,

number of relapsed lesions (solitary or multiple), aim of RT (curative vs. palliative intent), use of concurrent chemotherapy, and treatment-free interval (TFI), and prognosis with respect to PFS and OS was evaluated by uni- and multivariate analyses.

The aim of RT (curative vs. palliative intent) was determined following discussion between gynecologic oncologists and radiation oncologists, considering factors such as comorbidities, performance status (PS), organ reserve, radiological imaging, prognosis, and patient wishes. Then, doses of external-beam RT, fractions, and schedules were selected for each patient. In general, curative-intent RT requires high doses of radiation, and when patients present with multiple relapsed lesions or locally advanced disease, for which the chance of cure is low, achievement of adequately high doses of radiation for eradication of bulky disease without severe toxicity may be difficult. When curative-intent RT may not be feasible due to either tumor or patient factors, palliative RT is offered instead to quell disease symptoms and minimize treatment-related toxicities. Therefore, palliative RT usually involves lower doses and fewer treatment sessions than curative-intent RT. The planning target volume (PTV) was defined taking into account tumor and surrounding organs movements, deformations, and volume changes. Indeed, for irradiation to whole pelvic region, PTV included the clinical target volume (CTV) plus a 1.0–2.0 cm margin for daily set-up variation, and for irradiation for nodal metastasis, CTV was defined as the gross tumor volume (GTV) and LN area plus a 0.5 cm margin.

Response to RT was evaluated by CT, and responses were classified as complete response (CR), partial response (PR), stable disease (SD), or progressive disease (PD) as defined in the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 guideline [11]. Primary outcomes included overall response rate (RR; CR + PR), disease control rate (DCR; CR + PR + SD), PFS, and OS. PFS was defined as the period from the completion of RT to documented disease progression, while OS was defined as the period from completion of RT to documented death. A secondary outcome was safety; severity of adverse events was graded using the Common Terminology Criteria for Adverse Events (CTCAE) v. 4.0.

The current study was approved by the institutional ethical committee of Dokkyo Medical University. Informed consent was obtained in the form of opt-out on the web-site of the Dokkyo Medical University Hospital.

2.1 Statistical analysis

The Kaplan-Meier method was used to evaluate the OS rate, and the log-rank test was used to assess differences. A Cox proportional hazards regression analysis was used to identify prognostic factors (SPSS software, version 12.0). A value of $P < 0.05$ was defined as statistically significant.

3. Results

The clinicopathological characteristics of all 17 patients are shown in Table 1 and Table 2. The median age was 58.5 years (range, 38 to 82 years). The median follow-up duration was 11 months (range, 1 to 85 months). ECOG PS included 0 (n = 7), 1 (n = 5), 2 (n = 4), and 3 (n = 1). Patients had disease of the following FIGO stage at initial diagnosis: stage I/II (n = 4) and stage III/IV (n = 13); and of the following histological subtype: high grade serous carcinoma (n = 5), clear-cell carcinoma (CCC; n = 3), mucinous carcinoma (n = 2), endometrioid carcinoma (n = 1), and others (n = 6, including 2 with adenocarcinoma [not otherwise specified] and 1 each with squamous cell carcinoma derived from mature teratoma, carcinosarcoma, undifferentiated carcinoma, and transitional cell carcinoma). The median number of chemotherapy regimens administered before RT was 3 (range, 1 to 4), primarily consisting of platinum-based regimens. Sites of recurrent tumors included the lymph nodes (n = 7), intra-pelvic region (n = 6), bone (n = 3), and abdominal wall (n = 1); 3 patients had solitary relapsed lesions and 14 patients had multiple relapsed lesions. Eight patients (three with solitary lesions and five with multiple relapsed lesions) were treated with curative-intent RT, and 9 patients (all with multiple relapsed lesions) received palliative RT (Table 1). The median TFI was 1 month (range, 1 to 49 months); only 3 patients, who were considered to have chemosensitive disease, had a TFI ≥ 6 months. Three patients were treated with 2 cycles of concurrent platinum-containing chemotherapy as follows: paclitaxel with carboplatin in 2 patients (case no. 1 and 16, Table 1), gemcitabine with carboplatin in one patient (case no. 17), and only former one of whom experienced a TFI ≥ 6 months (case no. 1). The indications for palliative RT for 9 patients included abdominal discomfort (n = 3), pain due to bone metastases (n = 3), and abdominal pain, buttock pain, and intestinal bleeding (n = 1 each). The median total dose of external-beam RT administered was 50 Gy (range, 20 to 60 Gy), with a daily dose of 2 Gy (Table 1).

The following responses to RT were observed: CR, 3 patients; PR, 5 patients; SD, 3 patients; and PD, 6 patients. The RR and DCR were 47.1% (8 of 17 patients) and 64.7% (11 patients), respectively, and were not associated with TFI.

Six patients (case no. 3, 4, 5, 6, 16 and 17, Table 1) received chemotherapy after completion of RT. The regimens of chemotherapy were non-platinum monotherapy, such as gemcitabine. Pegylated liposomal doxorubicin and paclitaxel. The patients whose responses to RT were PD, and whose ECOG PS 3 or 4 with severe symptoms due to recurrent tumors did not receive any chemotherapy. There was no relationship between the prognosis (PFS and OS rates) and whether receiving or not receiving chemotherapy after RT (data not shown).

The 2-year PFS and OS rates after RT were 11.8% and 29.4%, respectively, and median PFS and OS were 5 and 11 months, respectively (Fig. 1). One patient with solitary para-aortic lymph node recurrence of CCC was alive 40 months

Table 1. Profile of seventeen recurrent ovarian cancer patients treated with RT.

Cases	Age	FIGO stage	Histological subtype	Recurrence sites	Aim of RT	RT dose (Gy)	Response (RECIST)	PFS (Ms)	OS (Ms)	Outcome
1	65	IIIC	serous	LN (multiple)	curative	60	CR	12	52	DOD
2	57	IIIC	mucinous	LN (mediastinum)	curative	50	CR	53	85	DOD
3	62	IIIC	CS	pelvic cavity	curative	50.4	SD	4	8	DOD
4	52	IC1	CCC	LN (multiple)	curative	45	PR	20	44	DOD
5	40	IIIC	serous	LN (multiple)	curative	40	PR	23	33	DOD
6	63	IIC	SCC	pelvic cavity	curative	50.4	PR	10	13	DOD
7	82	IC2	CCC	LN (para-aorta)	curative	50	CR	40	40	alive
8	53	IC1	CCC	LN (mediastinum)	palliative	50	SD	4	8	DOD
9	64	IVB	AD (NOS)	pelvic cavity	palliative	50.4	PD	0	4	DOD
10	38	IIIC	AD (NOS)	pelvic cavity	palliative	50.4	PD	0	4	DOD
11	58	IIIC	UDC	Inguinal, abdominal wall	palliative	45	PD	0	1	DOD
12	59	IVB	endometrioid	pelvic cavity	palliative	50	PD	0	2	DOD
13	44	IVB	mucinous	pelvic bone	palliative	20	PD	0	2	DOD
14	51	IIIC	TCC	spine	palliative	30	PD	0	2	DOD
15	65	IVA	serous	spine	palliative	30	SD	5	5	DOD
16	70	IVB	serous	pelvic cavity	palliative	30	PR	9	11	DOD
17	44	IIIC	serous	LN (supraclavicular)	palliative	40	PR	22	22	DOD

CS, carcinosarcoma; CC, clear cell carcinoma; SCC, squamous cell carcinoma; AD, adenocarcinoma; NOS, not otherwise specified; UDC, undifferentiated carcinoma; TSC, transitional cell carcinoma; LN, lymphnode; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; Ms, months; DOD, dead of disease.

after curative-intent RT. In the palliative RT setting, relief from recurrent tumor-related symptoms was obtained in 4 of 9 patients (44.4%) (case no. 14-17, Table 1). Toxicities due to RT were generally mild; Grade 3 anemia occurred in only 1 patient, and no other Grade 3 or higher hematological or non-hematological toxicities were observed.

Univariate analysis of various factors for PFS and OS revealed solitary relapsed lesions and curative-intent RT as favorable prognostic factors (Tables 3,4). However, in multivariate analysis, only curative-intent RT was identified as an independent favorable prognostic factor for OS after RT (hazard ratio: 3.65; 95% confidence interval: 1.03–12.00; $P = 0.045$) (Table 4). The RR and DCR in patients treated with curative-intent RT vs. palliative RT were 75.0% vs. 22.2%, respectively, and 100% vs. 33.3%, respectively (Table 1). Median PFS and OS after RT in patients treated with curative-intent RT vs. palliative RT were 12 months (range, 4–53 months) vs. 0 month (0–22 months) ($P = 0.029$), respectively, and 38.5 months (range, 8–85 months) vs. 4.0 months (range, 1–34 months) ($P = 0.007$), respectively (Fig. 2).

4. Discussion

Median survival for patients after recurrence of ovarian cancer has previously been reported to be approximately 2 years [12]. Cure is generally difficult to achieve, so the goals of treatment are primarily palliation of symptoms, improvement of quality of life, and prolonged survival [1]. However, selected patients can experience disease-free survival after multidisciplinary treatment.

Treatment strategies for patients with recurrent ovarian cancer are determined based on age, symptoms, PS, histopathological features, organ reserve, sites and numbers

of relapsed lesions, and particularly the platinum-free interval (PFI), which can indicate platinum sensitivity. Treatment algorithms for recurrent tumors are provided in the NCCN [1] and ESMO-ESGO guidelines [13]. Secondary cytoreductive surgery may be effective in selected patients who have a high probability of complete resection [14, 15]; however, the definitive role of surgery remains controversial and is under investigation [16]. For most patients, chemotherapy is indicated and may be essential.

Recently, molecularly targeted therapies with or without chemotherapy have been introduced, based on significant prolongation of PFS. The anti-angiogenesis agent bevacizumab is approved in combination with platinum-based combination therapy (gemcitabine or paclitaxel) and then as maintenance therapy in patients with a PFI of > 6 months [17], and with non-platinum single-agent chemotherapy (weekly paclitaxel, pegylated liposomal doxorubicin, topotecan) in patients with a shorter PFI [18]. Maintenance treatment with the Poly (ADP-ribose) polymerase (PARP) inhibitor, olaparib following platinum-based chemotherapy in patients with a *BRCA* mutation led to an improvement in PFS in Study 19 [10] and in the SOLO-2 trial [19]. In Study 19, patients without a *BRCA* mutation also derived a significant PFS benefit. However, no significant OS benefit was observed in Study 19, and OS data for SOLO-2 are not yet mature. Toxicities associated with molecularly targeted therapies are generally manageable; however, severe hematological and non-hematological complications are sometimes reported in association with these therapies. Notably, bevacizumab is associated with a risk of gastrointestinal perforation, which can be life-threatening, so clinicians should be aware of this serious complication.

Table 2. Characteristics of patients.

Characteristics (n = 17)		
Age, median, years (range)		58.5 (38–82)
Follow-up, median, months (range)		11 (1–85)
FIGO stage at initial treatment, n (%)	I/II	4 (24)
	III/IV	13 (76)
ECOG PS, n (%)	0/1	12 (71)
	2/3	5 (29)
Histology, n (%)	high grade serous ca.	5 (29)
	clear cell ca.	3 (18)
	mucinous ca.	2 (12)
	endometrioid ca.	1 (6)
	others	6 (35)
Sites of relapsed lesions, n (%)	lymph nodes	7 (41)
	Intra-pelvic lesion	6 (35)
	bone	3 (17)
	abdominal wall	1 (6)
Numbers of relapsed lesions, n (%)	solitary	3 (18)
	multiple	14 (82)
Aim of RT, n (%)	curative intent	8 (47)
	palliative	9 (53)
TFI, n (%)	TFI ≥ 6 months	3 (18)
	TFI < 6 months	14 (82)

ECOG, Eastern Cooperative Oncology Group; PS, performance status; ca, carcinoma; TFI, treatment-free interval; RT, radiation therapy.

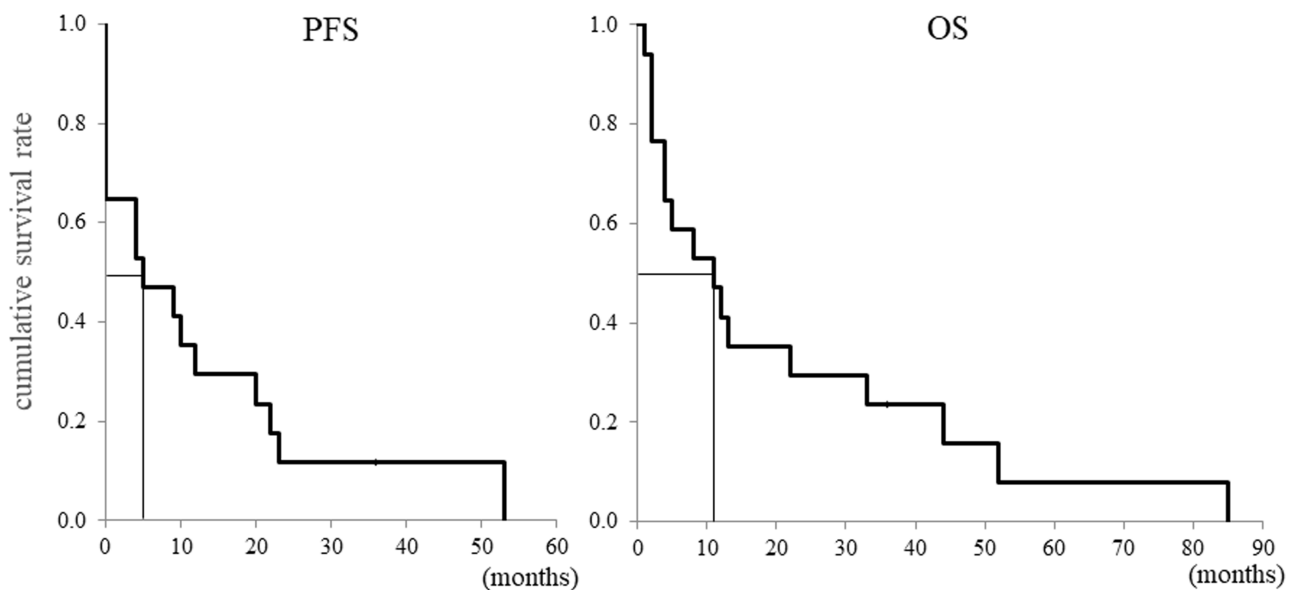


Fig. 1. Progression-free survival (PFS) and overall survival (OS) in 17 patients with recurrent ovarian cancer.

While palliative localized RT can be considered for recurrent tumors according to the NCCN guidelines [1], the role of RT for recurrent tumors is not mentioned in the ESMO-ESGO guidelines [13]. Several studies have reported that local external-beam palliative RT could resolve various symptoms caused by recurrent tumors [2–4]. Tinger *et al.* reported that the overall RR of palliative RT for symptomatic lesions in 80 patients was 73% (CR, 28%; PR, 45%) [4]. These au-

thors also reported relatively longer OS after completion of RT; the 1-, 2-, 3-, and 5-year actual survival rates were 39%, 27%, 13%, and 10%, respectively, which are favorably comparable to those reported for current second- and third-line chemotherapy [4].

However, several studies of curative-intent RT have been conducted in patients with limited ovarian cancer recurrence [5–9]. Firat *et al.* indicated that local pelvic RT may be ef-

Table 3. The clinicopathological factors and prognostic factors for PFS.

		n	Univariate analysis		Multivariate analysis	
			HR (95% CI)	P	HR (95% CI)	P
Age	< 58 y	8	1.0			
	≥ 58 y	9	1.38 (0.48–3.92)	0.55		
FIGO stage	I/II	4	1.0			
	III/IV	13	1.79 (0.50–6.39)	0.37		
ECOG PS	0/1	12	1.0			
	2/3	5	2.57 (0.73–9.06)	0.14		
Histological subtype	serous	5	1.0			
	others	12	1.78 (0.55–5.75)	0.34		
Relapsed lesion	solitary	3	1.0		1.0	
	multiple	14	8.36 (1.05–66.4)	0.045	5.98 (0.68–52.49)	0.11
Aim of RT	curative intent	8	1.0		1.0	
	palliative	9	3.65 (1.15–11.56)	0.028	2.15 (0.66–7.00)	0.20
Chemotherapy	presence	3	1.0			
	absence	14	1.17 (0.32–4.27)	0.80		
TFI	≥ 6 Ms	3	1.0			
	< 6 Ms	14	6.59 (0.83–52.43)	0.075		

PFS, progression free survival; RT, radiation therapy; TFI, treatment free interval; Ms, months; HR, hazard ratio; CI, confidence interval.

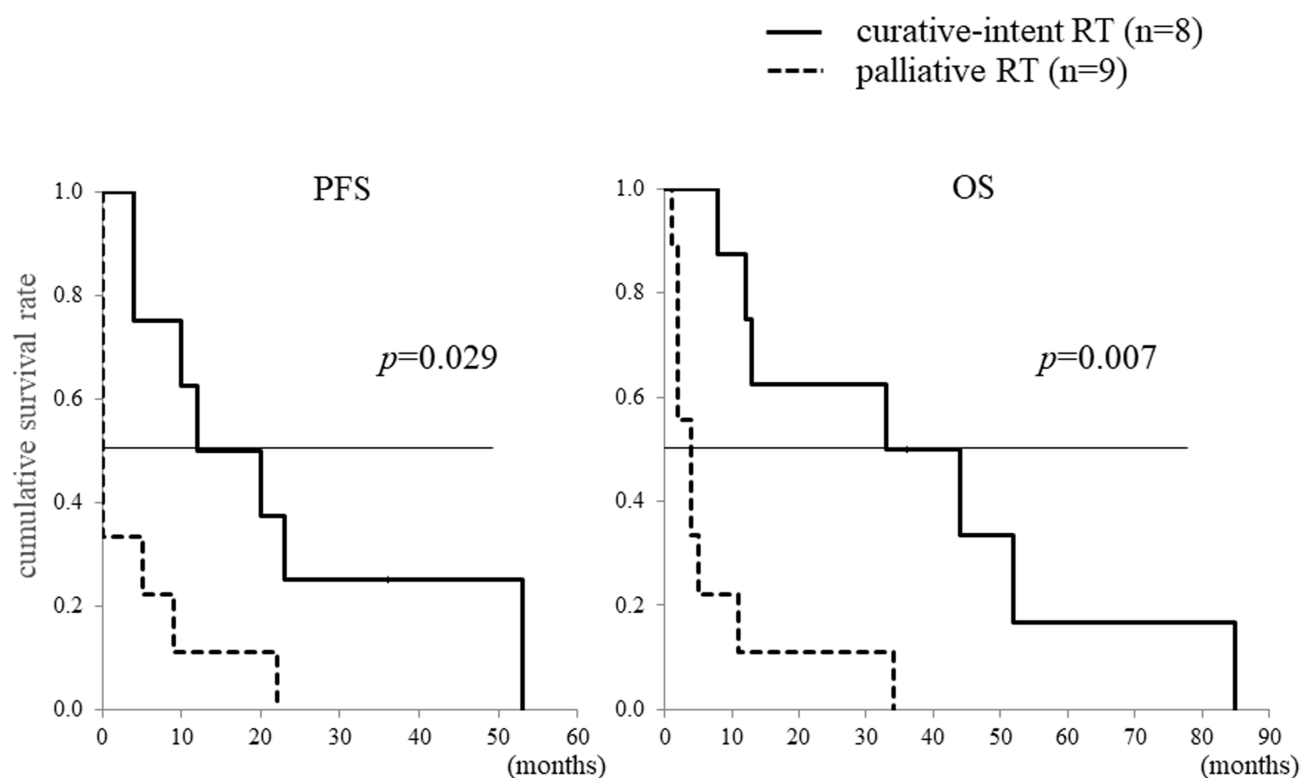


Fig. 2. Progression-free survival (PFS) and overall survival (OS) in patients treated with curative-intent RT vs. palliative RT.

fective as salvage therapy, and that cure was possible in some patients [9]. Smart *et al.* also reported that salvage RT for localized recurrent ovarian cancer patients was effective [5], and these researchers stated that the 3-year disease-free survival and OS rates were 18% and 80%, respectively. Komura *et al.* also reported that in 24 patients with isolated recur-

rent ovarian cancer treated with RT, the in-field overall RR was 58.3% (14/24), the median survival time after RT was 17 months, and 1-year PFS and OS were 45.8% and 66.7%, respectively [6].

Table 4. The clinicopathological factors and prognostic factors for OS.

		Nivariate analysis			Multivariate analysis	
		n	HR (95% CI)	P	HR (95% CI)	P
Age	< 58 y	8	1.0			
	≥ 58 y	9	1.33 (0.48–3.70)	0.59		
FIGO stage	I/II	4	1.0			
	III/IV	13	1.95 (0.54–7.08)	0.31		
ECOG PS	0/1	12	1.0			
	2/3	5	2.06 (0.76–5.58)	0.16		
Histological subtype	serous	5	1.0			
	others	12	1.40 (0.75–2.59)	0.29		
Relapsed lesion	solitary	3	1.0		1.0	
	multiple	14	8.65 (1.09–68.35)	0.041	5.40 (0.62–47.40)	0.13
Aim of RT	curative intent	8	1.0		1.0	
	palliative	9	5.88 (1.70–20.29)	0.005	3.65 (1.03–12.00)	0.045
Chemotherapy	presence	3	1.0			
	absence	14	1.58 (0.44–5.73)	0.48		
TFI	≥ 6 Ms	3	1.0			
	< 6 Ms	14	5.33 (0.69–41.22)	0.11		

OS, overall survival; RT, radiation therapy; TFI, treatment free interval; Ms, months; HR, hazard ratio; CI, confidence interval.

According to the reports described above, PFS and OS rates in patients treated with curative-intent RT are relatively higher than those in patients treated with palliative RT. In the current study, the RR and DCR in patients treated with curative-intent RT were remarkably higher than those in patients treated with palliative RT. Moreover, median PFS and OS after RT in patients treated with curative-intent RT were significantly longer than those in patients who underwent palliative RT. The present results demonstrate obvious differences in efficacy and survival between patients treated with curative-intent vs. palliative RT; such differences have not previously been investigated in detail.

Several previous studies about palliative RT after chemotherapy failure have reported benefits regardless of chemoresistance, suggesting that resistance to chemotherapy is not correlated with poor response to radiation [2, 3]. Recently, it was reported that regardless of resistance to platinum-based chemotherapy, RT can be a feasible treatment modality for patients with persistent or recurrent ovarian cancer [20]. Komura *et al.* also reported that platinum sensitivity at the time of RT was not associated with tumor response to RT or survival after RT [6]. However, several studies have reported higher efficacy of RT in patients with platinum-sensitive recurrence [5, 21, 22]; therefore, the association between the efficacy of RT and platinum sensitivity is uncertain. Further studies with larger numbers of patients are required to resolve this critical issue.

Several studies have evaluated the association between histological subtype and efficacy of RT. Smart *et al.* reported that five patients with clear-cell histology receiving salvage RT had not experienced relapse at the time of last follow-up [5]. Brown *et al.* also reported that clear-cell histology was a favorable prognostic factor, as patients with clear-cell histol-

ogy experienced longer PFS and OS after RT than those with other histologies [23]. In the present study, 1 patient with solitary para-aortic lymph node recurrence of CCC experienced prolonged progression-free survival (for 40 months) after curative-intent RT (Table 1). Therefore, salvage RT should be considered as a treatment option in addition to salvage chemotherapy for solitary recurrence of ovarian CCC, which is generally presumed to be a platinum-resistant histology. However, Jiang *et al.* reported the contradictory result that among patients treated with palliative RT, those with clear-cell histology had significantly lower RRs compared with those with serous, endometrioid, or other histologies [24]. Therefore, the relationship between histological subtype and the efficacy of RT remains controversial, and further studies with more patients are also required in this setting to confirm any association.

Eifel *et al.* indicated that the challenge was to determine the select few who stand to benefit from RT in their review article of the role of RT [25]. Several investigators have reported various prognostic factors for RT for recurrent ovarian cancer. Lee *et al.* reported a RR of 65% (16 CR, 10 PR) in 38 patients treated with salvage or palliative RT [21], and noted platinum sensitivity and solitary relapsed lesions to be prognostic factors [21]. Smart *et al.* reported that non-serous histology and platinum sensitivity were associated with a lower relapse rate in multivariate analysis, and platinum sensitivity was also associated with OS [5]. Yahara *et al.* reported that in univariate analysis of 27 patients with limited recurrence treated with curative-intent RT, tumor size (< 3 cm), TFI (≥ 2 years), objective tumor response (CR) after RT, and chemotherapy sensitivity were significant prognostic factors for OS, while tumor size (< 3 cm) and objective tumor response were significant prognostic factors for

PFS [8]. Moreover, Komura *et al.* reported that tumor size (< 25.5 mm) and number of prior chemotherapy regimens (≤ 1) were predictors of longer survival after RT [6]. In the current study, solitary relapsed lesions and curative-intent RT were determined to be favorable prognostic factors for PFS and OS in univariate analysis. Moreover, curative-intent RT was the only independent favorable prognostic factor for OS after RT identified in multivariate analysis. Based on the results described above regarding prognostic factors of RT for recurrent ovarian cancer, various factors were subjected to uni- or multivariate analysis; however, no universally consistent factors for all investigations were identified. Nevertheless, limited recurrence (i.e., solitary relapsed lesions) has been identified as a relatively favorable factor in several studies, including the present study.

Recently, improvement in RT techniques has increased efficacy and decreased adverse effects in patients with recurrent ovarian cancer compared with external-beam RT. For example, volume-directed involved-field radiation therapy (IFRT) showed possible benefit and favorable locoregional control in carefully selected patients with locoregional recurrent ovarian cancer [7, 22, 23, 26, 27]; with this advanced technique, unnecessary irradiation of normal tissue can be avoided and can thus allow for dose escalation and a relatively low toxicity rate. Brown *et al.* reported that 102 patients treated with definitive IFRT at a dose ≥ 45 Gy experienced a 5-year in-field DCR of 71%, and 35% of patients had no evidence of disease at 28 months after IFRT [23]. Albuquerque *et al.* reported that survival after locoregional IFRT, with a median dose of 50 Gy in 25 fractions, for localized extraperitoneal recurrences was superior compared with that of salvage chemotherapy [7]. Kim *et al.* demonstrated that IFRT can yield excellent treatment outcomes in patients with recurrent ovarian cancer, irrespective of the administration of chemotherapy. Moreover, patients with a normal CA-125 level and/or platinum-sensitive tumors may be good candidates for IFRT [22]. Intensity-modulated radiation therapy (IMRT), a type of IFRT used for recurrent chemo-refractory ovarian cancer, was reported to be associated with excellent local control and limited radiation-related toxicity [26]. Furthermore, stereotactic body radiotherapy (SBRT) demonstrated activity with a good safety profile for oligometastatic ovarian cancer in a retrospective, multicenter study [28]. A large-scale prospective study should be conducted to confirm the efficacy and safety of these techniques for recurrent ovarian cancer patients with a limited number of relapsed lesions.

The current study has some limitations. It was conducted at a single institution, and the number of patients enrolled was small, which could have led to incorrect conclusions and interpretation. In particular, other clinicopathological factors in addition to aim of RT (curative-intent RT) could potentially be identified as independent prognostic factors in uni- and multivariate analyses if the number of recruited patients was larger. Another limitation is the doses of curative-

intent and palliative RT, which varied not only between sites but also between patients, because they were scheduled based on individual patient clinical characteristics. Therefore, a possibility of bias in the schedule of RT and patient selection exists.

Despite these limitations, the present study identified curative-intent RT as an independent favorable prognostic factor associated with the a possibility of prolonged survival in selected patients, particularly those with solitary relapsed lesions.

In conclusion, curative-intent RT in ovarian cancer patients with limited recurrence (solitary relapsed lesions) may be used to achieve local control without severe toxicity, and is a promising treatment strategy that may result in long-term survival in selected patients. These results justify further evaluation with detailed treatment protocols to clarify whether curative-intent RT can improve survival in selected patients. The appropriate selection of patients with recurrent ovarian cancer who would most likely benefit from RT could yield achievement of long-term control without requiring further chemotherapy. The role of RT for patients with recurrent ovarian cancer requires reassessment in prospective studies with sufficient statistical power.

Author contributions

These should be presented as follows: NK: drafting of the manuscript and first author. KH: corresponding author, supervision. KK & EM: acquisition of data, especially clinical data and course. YE: radiological diagnosis, radiation therapy and interpretation. All authors read and approved the final manuscript.

Ethics approval and consent to participate

The current study was approved by the institutional ethical committee of Dokkyo Medical University. Informed consent was obtained in the form of opt-out on the web-site of the Dokkyo Medical University Hospital.

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Conflict of interest

The authors declare no conflict of interest.

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