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Proton beam therapy achieves excellent local control for recurrent epithelial ovarian cancer: a single-center retrospective study

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Abstract

Background Previous studies have demonstrated the benefit of radiation therapy for patients with recurrent epithelial ovarian cancer; however, the effects of proton beam therapy in these patients remain unelucidated. This study aimed to evaluate the use of proton beam therapy in recurrent epithelial ovarian cancer and to identify factors predictive of local control.

Results This retrospective study included 13 patients with a total of 30 lesions who underwent proton beam therapy for recurrent epithelial ovarian cancer at our institution between October 2008 and March 2021. The median age of the patients at the initial proton beam therapy was 62 (range, 42–82) years. Eight patients had stage III or IV disease, and seven had serous carcinoma; ten patients exhibited platinum resistance. The irradiated sites included 16 lymph nodes and 9 pelvic or abdominal masses. The median tumor size and maximum standardized uptake value (SUVmax) of fluorine-18-fluorodeoxyglucose-positron emission tomography/computed tomography (^{18}F-FDG-PET/CT) were 25 (range, 9–83) mm and 12.6 (range, 3.9–25.1), respectively. The median total dose was 65 (range, 45–72) Gy (relative biological effectiveness). The 1- and 2-year local control were 91.5% and 71.3%, respectively. The SUVmax of ^{18}F-FDG-PET/CT was a significant predictor of local control (cutoff value, 17.7). The median progressing-free and overall survival after proton beam therapy initiation were 9.6 and 21.5 months, respectively. No grade 3 or higher proton beam therapy-induced adverse events were observed.

Conclusion Proton beam therapy demonstrated excellent local control of recurrent epithelial ovarian cancer, with tolerable toxicity, suggesting that this modality may represent a promising treatment option. The SUVmax of ^{18}F-FDG-PET/CT performed prior to proton beam therapy may serve as a predictor of local control.

Clinical trial number Not applicable.

Keywords Recurrent epithelial ovarian cancer, Proton beam therapy, Local control, Radiation therapy, Oligometastasis

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Background

Epithelial ovarian cancer (EOC) is the most lethal among the gynecological cancers, as most patients are diagnosed at an advanced stage with the disease already widely disseminated throughout the abdominal cavity [1]. Standard treatment for EOC combines surgical cytoreduction with platinum-based chemotherapy, followed by systemic maintenance therapy with either bevacizumab, polyadenosine 5'-diphosphoribose polymerase inhibitor (PARP-I), or a combination of the two [2–6]. However, most patients experience relapse, and the management of recurrent EOC (REOC) remains challenging. Chemotherapy is the mainstay of REOC treatment, as the disease is generally considered systemic. Local therapies such as surgery or radiotherapy (RT) have therefore traditionally been viewed as palliative, with limited impact on survival. However, secondary cytoreduction has a demonstrated survival benefit in patients with platinum-sensitive REOC who are suitable for complete resection [7, 8]. Moreover, in platinum-resistant cases, for which effective systemic treatments are lacking, local control (LC) of isolated recurrences may delay symptom onset and disease progression [9]. These findings suggest a potential role for local therapies in selected patients with REOC.

RT, which is less invasive than surgery, has been used to treat isolated recurrent gynecological cancers, and several studies have demonstrated its efficacy [10–15]. Recently, the use of various RT strategies, including intensity-modulated RT (IMRT) and stereotactic body RT (SBRT), has been investigated in REOC [16–20]. However, photon-based RT involves the exposure of adjacent healthy tissues to radiation, which may increase the risk of gastrointestinal and other toxicities, particularly in patients with an extensive treatment history. Proton beam therapy (PBT) offers an advantage over conventional photon-based RT by exploiting the physical properties of protons, notably the Bragg peak, allowing for high-dose delivery to the tumor while minimizing radiation exposure to surrounding normal tissues. This is particularly beneficial in REOC, which often occurs near radiosensitive structures such as the bowel. Despite these theoretical advantages, evidence for the clinical efficacy and safety of PBT in REOC is scarce, with only isolated case reports published to date [21]. In this study, we retrospectively evaluated the use of PBT in REOC. Additionally, we investigated the predictors of LC by PBT.

Methods

Patients

This single-center retrospective cohort study analyzed the data of patients with REOC who had undergone PBT at our proton beam center between October 2008 and March 2021. Before starting PBT, the presence of three or less metastatic lesions was verified using computed tomography (CT) or fluorine-18-fluorodeoxyglucose-positron emission tomography/CT (^{18}F-FDG-PET/CT). Patients who received multiple courses of PBT were included if each course involved three or fewer lesions. The exclusion criteria were as follows: (1) PBT on four or more recurrent lesions in a single course, (2) adjuvant PBT after salvage surgery, (3) PBT combined with photon beam therapy, (4) PBT for recurrence in the irradiated field after photon beam therapy or PBT, and (5) lack of follow-up imaging data. REOC was categorized as platinum-sensitive or -resistant at the time of PBT initiation. Platinum sensitivity was defined as disease recurrence or progression more than six months after the last administration of platinum-based chemotherapeutics, whereas platinum-resistant was defined as disease recurrence or progression within six months of the last administration of platinum-based chemotherapeutics.

PBT

CT conducted at 2.0-mm slice intervals was used for PBT planning. PBT was performed using the Hitachi Proton Type Particle Therapy System (Hitachi, Kashiwa, Japan), with planning executed via XiO-M (Hitachi). Gross tumor volume was defined as that of the recurrent tumor. To establish the clinical target volume, a median margin of 5 (range, 2–7) mm was applied around the gross tumor volume. An additional median margin of 5 (range, 3–10) mm was added to the clinical target volume to form the planning target volume. PBT was administered four or five times a week using the passive scattering method. The standard PBT protocol at our institution aimed to deliver a dose of >2.0 Gy (relative biological effectiveness [RBE]) per fraction and a total dose of >60 Gy (RBE) when feasible. The maximum permissible doses for the small and large bowels were 50 and 60 Gy (RBE), respectively. This study applied an RBE value of 1.1. The maximum doses for the urethra, bladder, pelvic bones, and skin were planned not to exceed 100% of the prescribed dose. However, the responsible radiation oncologist tailored the final dose and fractionation plan based on factors such as tumor location, proximity of tumors to critical organs, and the overall health of the patient.

Outcomes

Treatment responses were assessed using the first CT or ^{18}F-FDG-PET/CT performed after PBT completion. All ^{18}F-FDG-PET/CT scans were performed following a standardized institutional protocol: patients fasted for at least 4 h prior to the intravenous injection of 3.7 MBq/kg ^{18}F-FDG; scans were initiated 90 min post-injection. PET/CT scans were acquired using the Discovery IQ (GE HealthCare, Chicago, IL, USA). The response criteria for CT and ^{18}F-FDG-PET/CT were in accordance

with the Response Evaluation Criteria in Solid Tumors 1.1 [22] and the criteria of the European Organisation for Research and Treatment of Cancer [23], respectively. Complete resolution of FDG uptake by all lesions was considered a complete metabolic response (CMR); a decrease of ≥ 25% in the sum of maximal standardized uptake values (SUVmax) after PBT was considered a partial metabolic response (PMR); an increase of ≥ 25% in the SUVmax or the appearance of new FDG-positive lesions was considered progressive metabolic disease (PMD); and not qualifying as CMR, PMR, or PMD was defined as stable metabolic disease (SMD).

LC was defined as the absence of in-field progression. Progression-free survival (PFS) was defined as the time interval from the initiation of PBT to disease progression or death. Overall survival (OS) was defined as the period from the initiation of PBT to death or last follow-up. The one- and two-year LC rates, median PFS, and OS were determined. The follow-up period began on the date of PBT initiation. PBT-associated toxicity was assessed using the Common Terminology Criteria for Adverse Events version 5.0. Acute and late toxicities were defined as adverse events occurring within and more than 28 days after PBT completion, respectively.

Statistical analysis

The Kaplan–Meier method was used to calculate the rates of LC, PFS, and OS. Univariate Cox regression analysis was used to identify predictors of LC, examining potential factors including irradiated site, tumor size, histology of the primary site, platinum sensitivity, SUVmax of ^{18}F-FDG-PET/CT before PBT, irradiation dose, and PBT response. Receiver operating characteristic curves were plotted and analyzed to determine the optimal cutoff values for the factors predictive of LC. The final cutoff value was selected as the point where the sum of the sensitivity and specificity was maximized when the AUC was > 0.5 or the median when the AUC was < 0.5. Statistical analyses were performed using SPSS software version 28.0 (IBM, Armonk, NY, USA), and a p-value of < 0.05 was considered to indicate statistical significance.

Results

Patients and irradiated sites

Between October 2008 and March 2021, 16 patients with a total of 40 sites underwent PBT. Three patients with a total of 10 sites were excluded: (1) one patient underwent PBT at four sites simultaneously, (2) one site in one patient received PBT as an adjuvant therapy, (3) one site in one patient received PBT combined with photon beam therapy, (4) one site in one patient previously received PBT, and (5) three patients with three sites lacked follow-up imaging data. Finally, 13 patients with a total of 30 irradiated sites were included in the analysis. Patient characteristics at PBT initiation are summarized in Table 1. All patients were referred to our PBT center after undergoing treatment at other hospitals. The median age at the initial PBT was 62 (range, 42–82) years. The median time from treatment initiation to first recurrence was 17.5 (range, 6.2–42.4) months, and the median time from initial treatment to first PBT was 29.0 (range, 14.9–129.5) months. Staging of patients at the time of initial diagnosis, according to the International Federation of Gynecology and Obstetrics 2014 identified two, two, six, and two patients at stages I, II, III, and IV, respectively; the stage of the remaining patient was unknown. The most common histological type was serous carcinoma (seven patients, 53.8%). At PBT initiation, three patients were platinum-sensitive and 10 were platinum-resistant. The median numbers of surgeries and chemotherapy regimens before PBT was 1 (range, 0–5) and 3 (range, 1–7), respectively. The numbers of sites treated with PBT per patient were as follows: three patients had one site, six patients had two sites, and four patients had three or more than sites. The median follow-up period was 21.5 (5.0–64.0) months.

The characteristics of the irradiated sites are summarized in Table 2. The most common sites were the lymph nodes: seven in the para-aortic regions, five in the pelvic regions, and four in other areas. The median tumor size was 25 (range, 9–83) mm. Histology of the primary sites revealed serous tumors at 19 sites and non-serous tumors at 11 sites. Three sites showed adenocarcinoma, and their detailed histologic characteristics were unknown. At PBT initiation, lesions at six sites were platinum-sensitive and those at 24 sites were platinum-resistant. ^{18}F-FDG-PET/CT was used to assess 22 sites (73.3%) before PBT; the median SUVmax was 12.6 (range, 3.9–25.1). The total median PBT dose was 65 (range, 45–72) Gy (RBE). No patients received concurrent or adjuvant chemotherapy with PBT.

SUVmax, maximum standardized uptake value; ^{18}F-FDG-PET/CT, fluorine-18-fluorodeoxyglucose-positron emission tomography/computed tomography; RBE, relative biological effectiveness.

Treatment response and survival outcomes

The median interval from PBT completion to imaging was two months. CT was performed on 14 sites, with a complete response observed at all sites. ^{18}F-FDG-PET/CT was conducted on 16 sites, with two showing CMR, 13 showing PMR, and one showing SMD; no sites showed PMD. The one- and two-year LC rates were 91.5% and 71.3%, respectively (Fig. 1). Univariate Cox regression analysis revealed that of the factors analyzed, only the SUVmax of ^{18}F-FDG-PET/CT before PBT (cutoff value, 17.7) was significantly associated with LC (hazard

Table 1 Patient characteristics at proton beam therapy initiation

		n **= 13**
Age (years)	Median (range)	62 (42–82)
Stage (FIGO 2014)		
	I	2
	II	2
	III	6
	IV	2
	unknown	1
Histological type		
	Serous carcinoma	4
	High-grade serous carcinoma	3
	Endometrioid carcinoma, G2	2
	Carcinosarcoma	2
	Clear cell carcinoma	1
	Adenocarcinoma	1
Platinum sensitivity		
	Sensitive	3
	Resistant	10
Number of pre-PBT surgeries		
	0	1
	1	9
	2	1
	≥ 3	2
Number of pre-PBT chemotherapies		
	1	4
	2	2
	3	3
	≥ 4	4
Number of sites treated with PBT		
	1	3
	2	6
	3	2
	4	1
	5	1
Time to first recurrence (months)	Median (range)	17.5 (6.2–42.4)
Time to first PBT (months)	Median (range)	29.0 (14.9–129.5)

FIGO, Federation of Gynecology and Obstetrics; PBT, proton beam therapy

ratio, 13.309; 95% confidence interval, 1.359–130.355; $p = 0.026$) (Supplementary Table S1 and Fig. 1).

The median PFS and OS were 9.4 and 30.1 months, respectively (Fig. 2). At the final follow-up, three out of the 13 patients were alive without disease, five were alive with disease, and five had died of the disease. The three patients alive without disease experienced recurrence at a median of 21.3 (range, 15.7–21.3) months. Two of the three patients experienced out-of-field recurrence (one with a single lesion and one with two lesions) and again underwent PBT, remaining disease-free for 30.3 and 41.1 months after recurrence, respectively. The one remaining patient who was alive without disease at the final follow-up experienced in-field recurrence and was treated with secondary cytoreduction; this patient then remained disease-free for 49.8 months. A representative case in which PBT was effective is shown in Fig. 3. Among the five patients who were alive with disease at the last follow-up, the median PFS and OS were 9.6 (range, 3.6–13.5) and 10.9 (range, 5.0–64.0) months, respectively. The median PFS and OS of the five patients who died of the disease were 5.3 (range, 3.6–10.0) and 21.5 (range, 18.8–30.1) months, respectively. Among the three patients with platinum-sensitive recurrence, the PFS was 20.3 (range, 13.5–21.3) months, and all were alive at the last follow-up. In contrast, the 10 patients with platinum-resistant recurrence had a median PFS of 8.0 (range, 3.6–15.7) months and a median OS of 23.7 (range, 5.0–56.8) months.

Table 2 Irradiated site characteristics

		n **= 30**
Irradiated site	Lymph nodes	16
	Para-aortic	7
	Pelvic	5
	Other	4
	Pelvic mass	6
	Abdominal mass	3
	Spleen	3
	Liver	2
Tumor size (mm), median (range)		25 (9–83)
Histology of primary site	Serous	19
	Non-serous	11
Platinum sensitivity	Sensitive	6
	Resistant	24
SUVmax of ^{18}F-FDG-PET/CT, median (range)		12.6 (3.9–25.1)
Total dose [Gy, (RBE)], median (range)		65 (45–72)

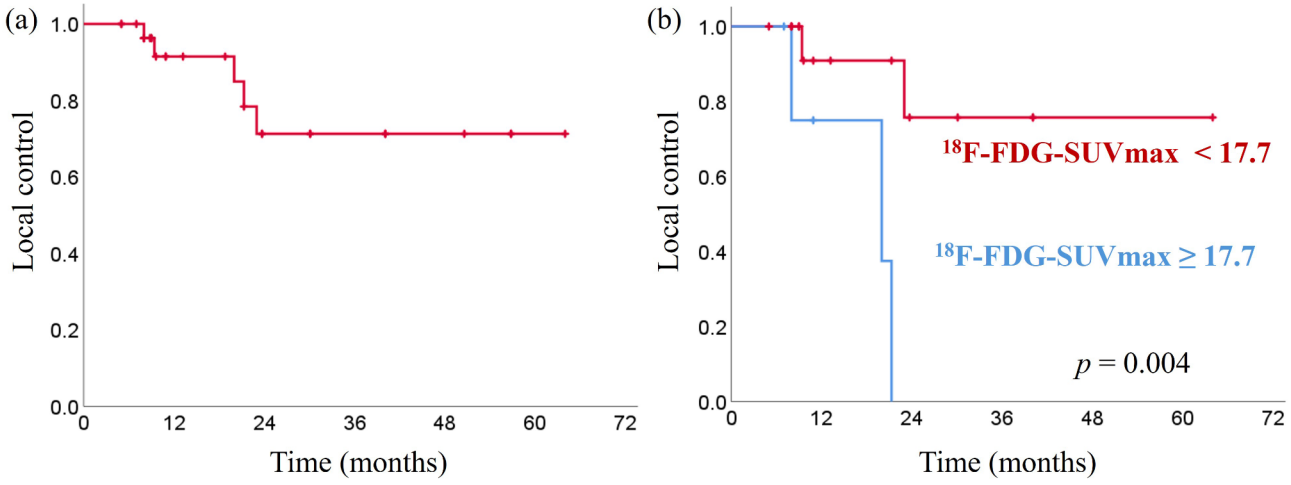

Fig. 1 Kaplan–Meier analysis of local control. Local control of recurrent epithelial ovarian cancer following proton beam therapy (**a**). Patients with an SUVmax ≥ 17.7, as determined prior to proton beam therapy, experienced worse local control than those with an SUVmax < 17.7 (**b**)

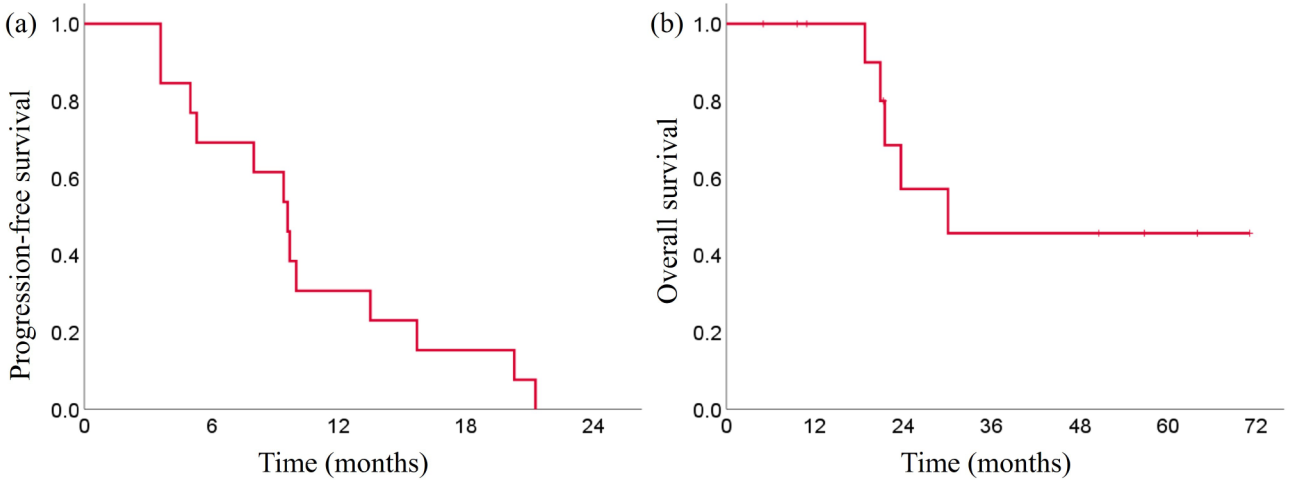

Fig. 2 Kaplan–Meier analysis of patient survival. Progression-free (**a**), and overall (**b**) survival of patients with recurrent epithelial ovarian cancer following proton beam therapy

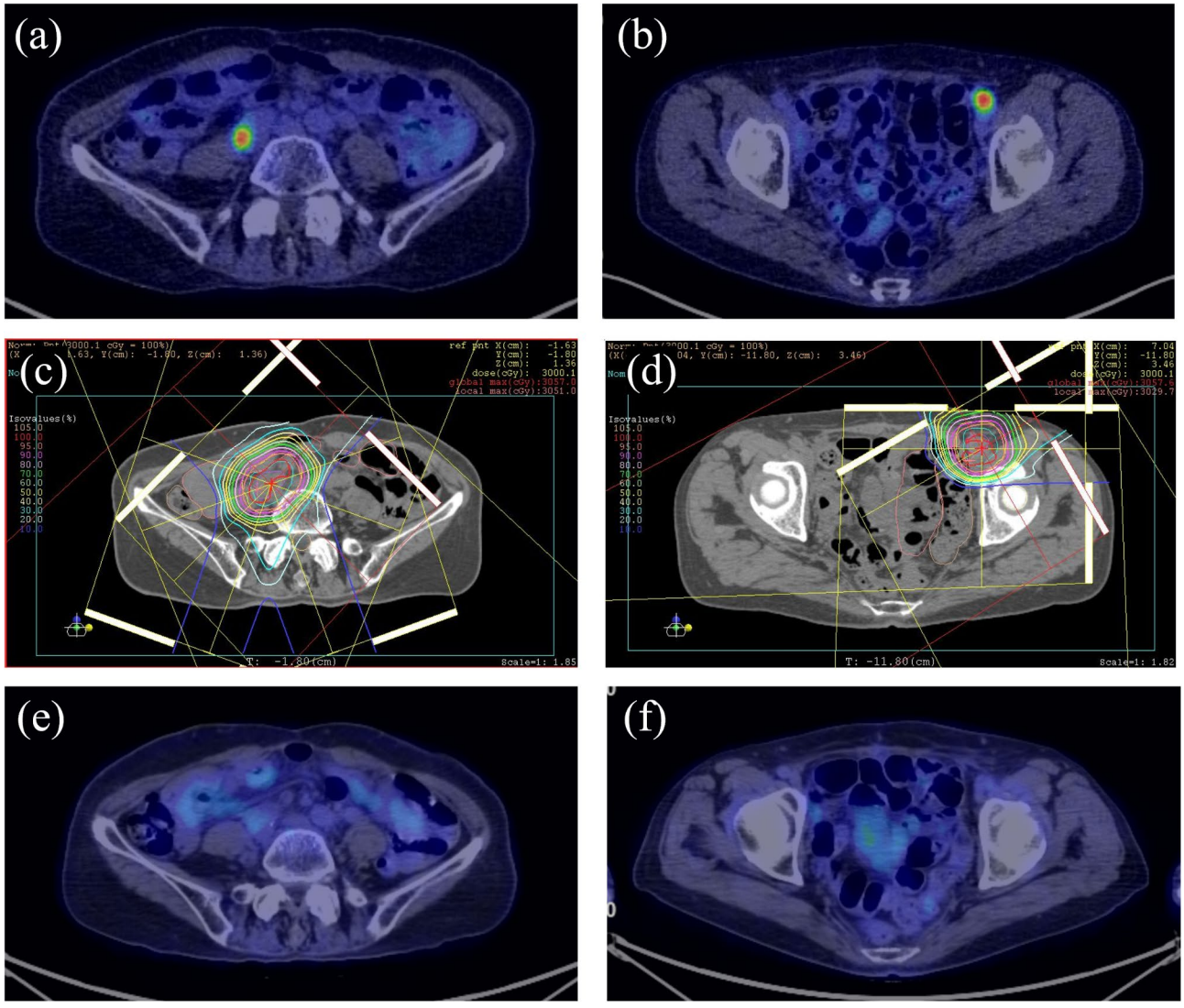

Fig. 3 A representative case in which PBT was effective. ^{18}F-FDG-PET/CT images of the PALN (**a**) and LEILN (**b**). Images of the dose distribution in initial proton beam therapy planning for the PALN (**c**) and LEILN (**d**), both of which received a dose of 70 Gy (RBE). ^{18}F-FDG-PET/CT images two months after PBT of the PALN (**e**) and LEILN (**f**), showing a complete metabolic response. ^{18}F-FDG-PET/CT, fluorine-18-fluorodeoxyglucose-positron emission tomography/computed tomography; PALN, para-aortic lymph node; LEILN, left external iliac lymph node; RBE, relative biological effect

Toxicity

Grade 1 acute radiation dermatitis developed in 13 sites of the 30 irradiated sites, and grade 2 acute radiation dermatitis developed in three sites. No acute grade 3 or higher PBT-induced acute toxicities, or any PBT-induced late toxicities were observed. No acute or late adverse events related to the gastrointestinal or urinary tracts were observed.

Discussion

The present study demonstrates the potential of PBT to achieve excellent LC with minimal toxicity in patients with REOC. The one- and two-year LC rates were 91.5% and 71.3%, respectively, while the median PFS and OS were 9.4 and 30.1 months, respectively, indicating that the SUVmax of ^{18}F-FDG-PET/CT before PBT may be a predictor of LC.

Several previous studies have shown the efficacy of RT in REOC, with reported two-year LC rates of 42.7–100%, PFS rates of 10.6–66.6%, and OS rates of 68.4–78.9% [10–20]. While our two-year LC rate was within this previous reported range at 71.3%, the PFS and OS rates in the present study were lower than those previously reported, at 0% and 21.5%, respectively. However, direct comparisons are difficult owing to the varying patient selection criteria, irradiation techniques, and treatment settings used in these studies. For example, Smart et al. demonstrated the efficacy of salvage RT in a study of 40 patients with localized disease, reporting three-year LC, PFS, and OS rates of 71.3%, 18%, and 80%, respectively [14]. Of the

40 patients, 63% had first-time recurrence and 68% had platinum-sensitive recurrence. Treatment modalities consisted of three-dimensional conformal RT (3D-CRT), two-dimensional (2D) RT, or SBRT. Another retrospective study of salvage RT by Bae et al., involving 79 patients and 114 treatments, reported a one-year LC rate of 86% and a two-year LC rate was 80%, comparable to our findings [10]. This study included patients with fewer than three metastatic lesions treated with photon-beam RT (IMRT, 3D-CRT, or SBRT) or PBT. Importantly, while this study included a small subset (4.4%, five patients) treated with PBT, no details of the PBT protocol were provided, making it difficult to determine its specific contribution. Most patients in the present study were platinum-resistant, heavily pretreated, and received PBT at multiple sites. Given this challenging patient population, the outcomes observed in our study suggest the potential of PBT to achieve LC with minimal toxicity.

The results of the present study highlight the low toxicity profile of PBT in patients with REOC. No grade 3 or higher toxicities were observed among the 30 treatments administered, with toxicities limited to grade 1 or 2 dermatitis in 16 treatments; notably, no acute or late gastrointestinal toxicities were reported. PBT therefore appears to be a safer alternative to photon-based RT. For example, Smart et al. reported grade 3 acute and late bowel obstruction in 3% and 5% of patients, respectively, after treatment with 2D-RT or 3D-CRT [14]. Additionally, a retrospective study on REOC refractory to chemotherapy detected acute and late gastrointestinal toxicities in 6% and 12% of patients, respectively, after treatment with IMRT, despite improved radiation dosimetry and reduced doses to organs at risk [16]. The ability of PBT to deliver high radiation doses to the target lesion while minimizing exposure to adjacent tissues likely contributed to the lower toxicity profile observed in our study. Given that patients with REOC are often heavily pretreated and at a higher risk of treatment-related toxicities, PBT may represent a safer and more tolerable option in this patient population.

In the present study, two patients remained disease-free for 30.3 and 41.1 months after salvage PBT for out-of-field recurrences, suggesting the potential of PBT under these circumstances. Brown et al. investigated the efficacy of involved-field RT in 102 patients with locoregional REOC, and reported five-year LC, PFS, and OS rates of 71%, 40%, and 24%, respectively [15]. Interestingly, 25 of these patients remained recurrence free for a median of 61 months. Additionally, 10 patients who relapsed at a median of 4.5 (range, 3–39) months after involved-field RT underwent successful salvage treatment such as RT, or secondary cytoreduction followed by RT, or adjuvant chemotherapy; these patients remained disease free for a median of 39 months.

Recently, PARP-Is have become the new standard treatment for EOC maintenance therapy. An ad hoc subgroup analysis of the PRIMA trial demonstrated that the majority (93.2%) of patients with advanced EOC who had no residual disease at the start of niraparib maintenance therapy had only one to three lesions at initial progression [24]. Several studies have demonstrated the efficacy of local treatment targeting the oligometastatic progression of EOC during PARP-I maintenance therapy [25, 26]. SBRT has been shown to achieve a median next-line systemic therapy-free interval of 12.4 months with tolerable toxicity when used to manage ovarian cancer oligoprogression during PARP-I therapy [27]. PBT may also represent a potential method of managing oligoprogressive REOC during PARP-I treatment.

The present study identified the SUVmax of ^{18}F-FDG-PET/CT before PBT as the only significant predictive factor for LC. Several reports have demonstrated that platinum sensitivity, a total dose of >50 Gy, and lower serum CA125 levels before RT are favorable prognostic factors. However, the efficacy of the ^{18}F-FDG-PET/CT SUVmax before PBT as a prognostic factor remains to be undetermined. Kowalchuk et al. reported that a higher SUVmax before SBRT was predictive of poor LC in patients with REOC [20]. However, consistent with our findings, recent reports have demonstrated that the SUVmax of ^{18}F-FDG PET/CT prior to PBT serves as a valuable indicator of tumor response and outcomes in cases of locally recurrent rectal cancer [28]. The present study found that tumor size, irradiated site, platinum sensitivity, irradiated dose, and treatment response were not significant predictors of LC. Therefore, different predictors of LC may be required for PBT and photon beam therapy. Several studies have demonstrated that the total dose is predictive of LC, with a total dose of <50 Gy associated with increased risk of local failure [12, 13]. The median total dose in the present study was 65 (range, 45–72) Gy (RBE), with all sites but two being treated with a total dose greater than 50 Gy (RBE).

This study had several limitations. First, the retrospective design of the study introduces potential biases, as patient records were reviewed after treatment and follow-up may have been inconsistent. Second, the small sample size limits the generalizability of the findings. Third, the treatment regimen, including PBT dose and fractionation, was determined by physicians on a case-by-case basis, introducing variability into the treatment protocol. Fourth, selection bias may have occurred because patients with certain characteristics may have been more likely to receive PBT. Fifth, it is possible that physiologic accumulation may be involved because pathological recurrence was not confirmed. In particular, the data showing that lesions with a lower SUVmax were more likely to disappear may be subject to this bias.

Despite these limitations, this may be the largest study to date to evaluate PBT in REOC. The results provide valuable data on its effects, contributing to the growing body of evidence supporting the use of PBT in patients with REOC.

Conclusions

PBT may offer favorable LC with minimal toxicity in patients with REOC, particularly in patients with a limited number of recurrent lesions. The pre-treatment SUVmax of ^{18}F-FDG PET/CT was associated with local control and may serve as a potential imaging biomarker. Prospective studies are warranted to confirm these findings.

Abbreviations

CT	Computed tomography
CMR	Complete metabolic response
EOC	Epithelial ovarian cancer
^{18}F-FDG-PET/CT	Fluorine-18-fluorodeoxyglucose-positron emission tomography/computed tomography
IMRT	Intensity-modulated radiotherapy
LC	Local control
OS	Overall survival
PARP-I	Polyadenosine 5′-diphosphoribose polymerase inhibitor
PBT	Proton beam therapy
PFS	Progression-free survival
PMD	Progressive metabolic disease
PMR	Partial metabolic response
RBE	Relative biological effectiveness
REOC	Recurrent epithelial ovarian cancer
RT	Radiotherapy
SBRT	Stereotactic body radiotherapy
SMD	Stable metabolic disease
SUVmax	Maximal standardized uptake values
2D	Two-dimensional
3D-CRT	Three-dimensional conformal radiotherapy

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s13048-025-01695-2.

Supplementary Material 1: **Supplementary Table S1**. Univariate analysis results of local control. LN, lymph node; SUVmax, maximum standardized uptake value; ^{18}F-FDG-PET/CT, fluorine-18-fluorodeoxyglucose-positron emission tomography/computed tomography; CR, complete response; CMR, complete metabolic response; CI, confidence interval; AUC, area under the curve; HR hazard ratio; ref, reference.

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Author contributions

Yuta Endo, Yoshiaki Takagawa and Shu Soeda conceived the study. Yuta Endo, Yuki Yoshimoto, Masanori Machida, Yuntao Dai, Yusuke Azami, Ichiro Seto, Kanako Takayama, Motohisa Suzuki, Tatsuhiko Nakasato, Yasuhiro Kikuchi, Takahiro Kato, Akiko Yamaguchi, and Keiya Fujimori acquired, analyzed, and interpreted the data. Yuta Endo performed the statistical analysis and wrote the first draft of the manuscript. Yoshiaki Takagawa and Shu Soeda critically revised the manuscript for intellectual content. Masao Murakami supervised the project. All authors read and approved the final manuscript.

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Data availability

The datasets used and/or analyzed in the current study are available from the corresponding author upon reasonable request.

Declarations

Ethics approval and consent to participate

This study was approved by the Ethics Committee of Southern TOHOKU Research Institute for Neuroscience (No. 565) and was announced on the website of Southern TOHOKU Proton Therapy Center and Southern TOHOKU General Hospital. The research was conducted in accordance with the 1964 Helsinki Declaration. This study was conducted using the opt-out method approved by the ethics committee. Patients or their representatives were provided the opportunity to decline participation through the information disclosed on the institutional website. Individual informed consent was therefore not required.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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