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Clinical Impact of Proton Beam Therapy for Postoperative Lymph Node Oligorecurrence of Esophageal Cancer

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Abstract. *Background/Aim: Radiotherapy is a salvage therapy type for postoperative recurrence of esophageal cancer. Compared to conventional photon-based radiotherapy, proton beam therapy can reduce the irradiated dose to the surrounding organs, facilitating the management of patients who are unfit for radiotherapy. In this study, the outcomes and toxicity of proton beam therapy for postoperative lymph node oligorecurrence of esophageal cancer were investigated. Patients and Methods: We retrospectively evaluated the clinical outcomes and toxicity of 13 sites in 11 patients treated with proton beam therapy for postoperative lymph node oligorecurrence of esophageal cancer. In total, eight men and three women with a median age of 68 years (range=46-83 years) were included. Results: The median follow-up period was 20.2 months. During the follow-up period, four patients died of esophageal cancer. Eight of the 11 patients developed recurrence; of these, seven patients had recurrence outside the irradiated field, and one had recurrence inside and outside the irradiated field. The 2-year overall survival, progression-free survival, and local control rates were 48.0%, 27.3%, and 84.6%, respectively. The median survival time was 22.4 months. There were no severe acute or late adverse events. Conclusion: Proton beam therapy could be a safe and effective treatment method for postoperative lymph node oligorecurrence of esophageal cancer. It may be beneficial even in cases where conventional photon-based radiotherapy is difficult to administer in combination with increased doses or with chemotherapy.*

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Esophageal cancer (EC) is the 10th most common cause of death in Japan, and the incidence of EC patients has been on the rise in recent years (1). The standard treatment for EC is surgery, and research to date has made gradual progress. In recent years, minimally invasive treatments such as endoscopic treatment for early-stage EC and thoracoscopic surgery for advanced cancer have become popular. In order to improve surgical outcomes, docetaxel, cisplatin plus 5-FU regimen for patients in good general condition and neo-adjuvant chemoradiotherapy (NACRT) for patients with more locally-advanced EC are being tried as preoperative treatments (2).

Despite advances in treatment, postoperative recurrence of EC remains a major problem. In the Chemoradiotherapy for Oesophageal Cancer Followed by Surgery Study (CROSS) trial, a prospective study, the recurrence rate was 57.1% in the surgery alone group and 34.7% in the NACRT group (3). In Japan, the standard surgery for advanced EC is subtotal esophagectomy with three-field lymph node dissection after neo-adjuvant chemotherapy (NAC); however, the reported postoperative recurrence rate is high at 43.3% (4). The prognosis of patients with recurrent disease is extremely poor, with a median survival time of 6-8.2 months, and an effective salvage therapy is necessary to improve their prognosis (5, 6).

In recent years, the concept of oligometastasis or oligorecurrence has become widespread (7, 8); even in the field

Table I. *Patient characteristics*.

Pt. No	Age	Sex	Primary site	Time from surgery to Rec (month)	Site of Rec	Total dose/fr	Concurrent CT	CT Regimen
1	83	Male	Mt	22.8	Inside of SD	66/33	With	FP
2	79	Female	Lt	11.6	Inside of SD	60/30	With	FP
3	71	Male	Mt	54.1	Outside of SD	56/28	With	FP
4	46	Male	Mt	20.4	Outside of SD	52/26	With	FP
5	70	Male	Lt	8.4	Outside of SD	54/27	Without	
6	58	Male	Lt	3.1	Inside of SD	66/33	With	FP
7-a1	77	Male	Ce	307.5	Inside of SD	56/28	With	FP
7-a2					Inside of SD	60/30	With	FP
7-b					Outside of SD	54/27	Without	
8	54	Male	Ut	6.1	Inside of SD	56/28	With	FP
9	66	Female	Ae	26.2	Outside of SD	54/27	With	FP
10	49	Female	Lt	5.5	Inside of SD	50/25	With	PTX
11	68	Male	Ae	36.1	Inside of SD	60/30	With	FOLFOX

Pt: Patient; No: number; Rec: recurrence; fr: fraction; RT: radiotherapy; CT: chemotherapy; Ce: cervical esophagus; Ut: upper thoracic esophagus; Mt: middle thoracic esophagus; Lt: lower thoracic esophagus; Ae: abdominal esophagus; SD: surgical dissection; FP: cisplatin and 5-fluorouracil; PTX: paclitaxel.

of EC, where radical surgery and radiotherapy (RT) have been used conventionally (9). RT has become more precise in recent years, and intensity-modulated RT and stereotactic body RT are now commonly used in daily clinical practice (10). Although RT is highly accurate, high doses are delivered to the gastrointestinal tract and anastomosis sites, which are relatively radiosensitive. Of late, proton beam therapy (PBT) is being used to treat various types of cancer. It has facilitated reduction of the dose to the surrounding normal tissues by taking advantage of the Bragg-Peak, a physical property of rapidly accelerated protons, to focus the dose on the target lesion. PBT has the same biological effects as photon RT, so conventional RT methods can be used without modification and with the same risks. In recent decades, the efficacy and feasibility of PBT has been reported for many cancers such as those of the liver, rectum, and pancreas (11-13). In cases of postoperative recurrence of EC, PBT can be used to concentrate high doses on the lesion while avoiding the radiosensitive gastric tube and anastomosis, and the bone marrow, which plays an important role in immunocompetence. This could potentially increase the efficacy of treatment while minimizing adverse events.

To date, there has been no definitive evidence regarding the efficacy of PBT for postoperative recurrence of EC. The purpose of this study was to evaluate the therapeutic efficacy and toxicity of PBT for postoperative lymph node oligorecurrence of EC.

Patients and Methods

Patients. This retrospective study included 11 patients (13 sites) with postoperative lymph node oligorecurrence of EC who received PBT between October 2014 and September 2020. The inclusion criteria for this retrospective study were as follows: 1) radical surgery for EC with R0 resection, 2) 1 to 3 lymph node recurrences, 3) inoperable lesions as judged by a cancer board, 4) PBT for recurrent disease at our institution, and 5) no recurrent lesions outside the irradiated area. The exclusion criteria were as follows: 1) an Eastern Cooperative Oncology Group performance status (PS) of >2, 2) a history of previous RT (other modalities) for the same site, 3) uncontrolled metastases exist outside the irradiation field, 4) the presence of another primary malignancy, and 5) infection involving the irradiated lesion.

Before treatment initiation, the absence of distant metastases other than the lymph node oligometastasis from EC was confirmed by computed tomography (CT) with an intravenous contrast agent and 18F-fluoro-2-deoxy-d-glucose positron emission tomography-CT before treatment. After the examinations were completed, all cases were confirmed to be inoperable by thoracic surgeons on the cancer board.

Proton beam therapy. Using CT images without intravenous contrast agent that were obtained at 2.5-mm intervals, we established an initial clinical target volume (CTV1) to include the lymphatic region relevant to the recurrent lymph nodes that contained the gross tumor volume (GTV). After 40 Gy of irradiation, boost irradiation was performed up to the final dose for the second CTV (CTV2) with a 5-mm margin on the GTV. After determining the CTVs, beam-dependent margins of PBT, such as 0.5-1-cm margins around the CTVs, were added.

Irradiation was performed daily during weekdays and at least four days a week, even on holidays. During treatment, patients were treated with proton beams from 155 to 230 MeV using a passive spreading method. The proton beams were spread out and shaped with ridge filters, double scattering sheets, multicollimators, and a custom-made bolus to ensure that the beams conformed to the planning data. Spinal bones and two sets of orthogonal digital radiographs were used for daily positional confirmation.

Beam directions and the total dose were determined by the tumor location and the distance between the tumor and organs at risk, such as the reconstructed esophagus. The dose constraints were based on

Table II. *Clinical outcomes and toxicities*.

Pt. No	OS (month)	Rec after PBT	Local Rec	Site of re-Rec	PFS (month)	Acute adverse event				Late adverse event
						Non-hematologic adverse event	Leukopenia	Anemia	Thrombo-cytopenia	
1	76.3	N	N		76.3	Dermatitis Gr1	Gr1	Gr2	Gr0	None
2	22.4	Y	N	Inside of SD and outside of IF	8.4	Dermatitis Gr1	Gr3	Gr1	Gr1	None
3	10.9	Y	N	Inside of SD and outside of IF	10.9	None	Gr3	Gr2	Gr1	None
4	18.3	Y	N	Inside of SD and outside of IF	8.1	None	Gr3	Gr1	Gr0	None
5	18	Y	N	Outside of SD and IF	1.8	None	Gr0	Gr1	Gr0	None
6	12.0	Y	N	Outside of SD and IF	4.0	None	Gr2	Gr2	Gr0	None
7-a1	15.8	Y	N	Outside of SD and IF	5.5	None	Gr0	Gr2	Gr0	None
7-a2			N			None	Gr0	Gr2	Gr0	None
7-b		N	N			None	Gr0	Gr2	Gr0	None
8	21.7	Y	Y	Inside and outside of SD and IF	5.7	Dermatitis Gr1	Gr2	Gr1	Gr0	None
9	34.3	N	N		34.3	None	Gr1	Gr2	Gr0	None
10	29.4	N	N		29.4	Radiation pneumonia Gr1	Gr0	Gr1	Gr0	None
11	20.2	Y	N	Outside of SD and IF	11.3	None	Gr2	Gr1	Gr0	Poor appetite Gr1

Pt: Patient; No: number; OS: overall survival; Rec: recurrence; PBT: proton beam therapy; PFS: progression free survival; Y: yes; N: no; SD: surgical dissection; IF: irradiated field; Gr: grade.

QUANTEC, for example, 50 Gy for the reconstructed gastrointestinal tract and 44 Gy for the spinal cord (14). When the tumors were in close proximity to high-risk organs, fractional doses were reduced to avoid severe adverse effects. Irradiated doses were calculated by assuming a relative biological effectiveness of 1.1.

Concurrent chemotherapy. In cases where PBT was considered feasible with chemotherapy based on age, PS, and other factors; chemotherapy was concurrently performed in combination with PBT. However, concurrent chemotherapy was skipped when the absolute neutrophil count was less than 2,000/mm^3 or the platelet count was less than 70,000/mm^3 on a scheduled dosage day, when the PS was poor, when biochemical data were abnormal, or if any diagnosed conditions that contraindicated administration were present.

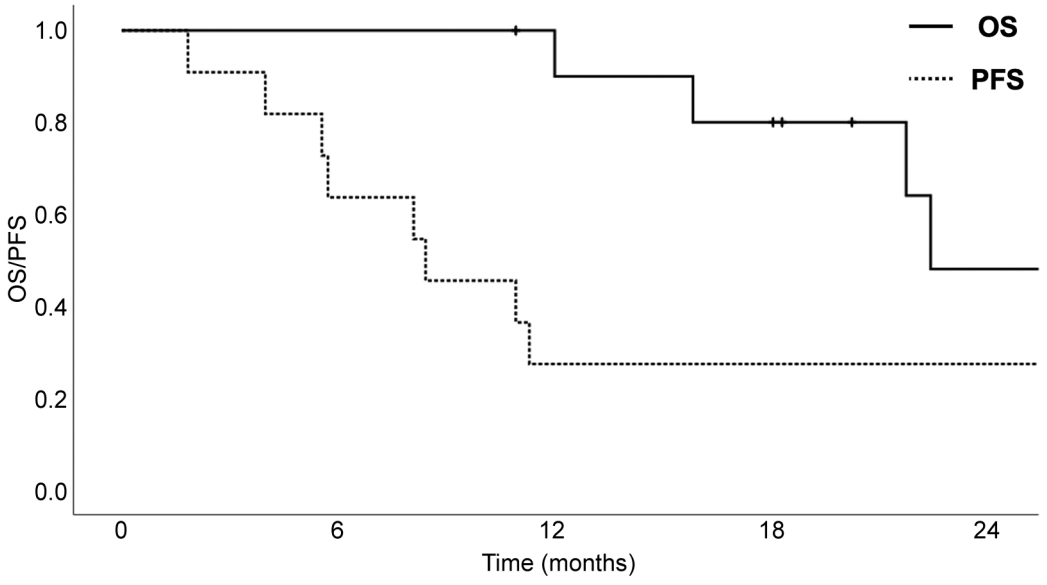
Follow-up procedure. During PBT, acute treatment-related toxicities were evaluated once or twice per week in all patients. All patients were scheduled for clinical examination every three months, and examination of their physical condition, blood sampling, and imaging were conducted prior to their visits after completion of PBT. If the patients were unable to visit our hospital, follow-up examinations were performed at a nearby institute, and the results were sent to our hospital. Adjuvant therapy after PBT was performed at the discretion of the referring physician in accordance with patient's condition.

Evaluation and stastical analysis. Acute and late toxicities were evaluated according to the National Cancer Institute Common Terminology Criteria for Adverse Events (version 4.0) (15), while relapse was evaluated according to the Response Evaluation Criteria in Solid Tumors (version 1.1) (16). In this study, recurrence within the irradiated field was defined as local recurrence. Adverse effects associated with PBT were defined as late adverse events if they occurred after three months of treatment and acute adverse events if they occurred before three months. We examined overall survival (OS), progression-free survival (PFS), and local control (LC) rates using the Kaplan-Meier method. All analyses were performed using SPSS version 25.0 (IBM Inc. Armonk, NY, USA).

Ethics. All procedures involving human participants, including case reviews of treatments, were conducted in accordance with the ethical standards of the 1964 Declaration of Helsinki and its later amendments and approved by the University of Tsukuba Institutional Research Committee (Approval H29-331). All treatments were discussed at an in-hospital cancer board involving thoracic surgeons, gastroenterology physicians, and radiologists. Informed consent was obtained from all participants included in the study; we obtained the consent from either the living patients themselves or legally designated next-of-kin when appropriate.

Results

Patient characteristics. In total, eight men and three women with a median age of 68 years (range=46-83 years) were included. The characteristics of the 11 patients (13 sites) are summarized in Table I. One patient received PBT at two sites at the time of initial salvage treatment; subsequently, the site of recurrence was treated outside the irradiated field (Patient number 7-a1, 2 and -b). There were eight cases of



Number at risk	OS	11	11	9	7	3
	PFS	11	7	3	3	3

Figure 1. *Kaplan-Meier estimates of OS and PFS rates following initiation of proton beam therapy for postoperative oligorecurrence of esophageal cancer. The 2-year OS and PFS were 48.0% and 27.3%, respectively. The median survival time was 22.4 months. OS: Overall survival; PFS: progression free survival.*

intraregional recurrence after the first surgery and five cases of distant metastases. The median total dose was 56 Gy (range=50-66Gy). Eleven of the 13 sites received concurrent chemotherapy with PBT, while the remaining two sites received only PBT. All patients completed their scheduled treatments.

Treatment outcomes. The median follow-up period from the initiation of PBT was 20.2 months (range=10.9-76.3 months). By March 2022, four patients had died of EC. No patient continued chemotherapy after PBT.

Eight of the 11 patients developed re-recurrence after salvage PBT; of these, only one patient developed recurrence both inside and outside the irradiated field. The remaining seven patients developed recurrence outside the irradiated field. The outcome of each patient is listed in Table II.

The 2-year OS, PFS, and LC rates were 48.0% [95% confidence interval (CI)=10.6%-85.4%], 27.3% (95% CI=1.0%-53.6%), and 84.6% (95% CI=65.0%-100%), respectively. The median survival time was 22.4 months (Figure 1).

Toxicities. The most common acute adverse event associated with treatment was hematological toxicity. In particular, grade 3 leukopenia was observed in three (27.3%) patients. No grade 2 or higher nonhematological toxicities were observed, either in the acute or late phase. The treatment-related toxicities are shown in Table II.

Discussion

To date, there has been no definitive evidence for the efficacy of RT *versus* that of other salvage therapies for postoperative recurrence of EC, although chemoradiotherapy (CRT) is recommended as a salvage therapy in several guidelines (17, 18). The National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology recommend CRT for patients who can tolerate the treatment (17). Japanese guidelines for the treatment of EC recommend CRT for postoperative recurrence. Although evidence for this treatment is not well established, 70% of the committee members recommend it (18).

Postoperative recurrence of EC has been reported using follow-up results after the CROSS trial (3). The most common site of recurrence in the NACRT group was outside the irradiated field, accounting for 26.3% cases. Similar results were also reported by Jongh *et al*. (19). These suggest that the option of RT remains available, and it may play an important role as a salvage treatment even for postoperative recurrence of EC treated with NACRT. In the CROSS trial,

squamous cell carcinoma (SCC) is reported to have a significantly higher recurrence rate. Since 87.9% of ECs are reported to be SCC in Japan (20), RT would be useful as a salvage treatment for postoperative lymph node recurrences. Therefore, the benefits of salvage RT for postoperative recurrent EC may be greater in Japan.

Several studies have reported the usefulness of salvage RT for postoperative recurrences of EC (21-23). Jingu *et al*. reported a favorable long-term result after salvage RT, with a 5-year OS rate of 39.2%, PFS rate of 31.0%, and LC rate of 59.9% (23). They mentioned irradiated dose escalation as one of the prognostic factors and their result was supported by another study (22). On the other hand, in a Japanese multicenter study, Yamashita *et al*. showed significantly better outcomes in the CRT group than in the RT alone group (8). Tanaka *et al*. performed a retrospective analysis of cases where chemotherapy, RT/CRT, or surgery were used as salvage therapies for patients with postoperative lymph node recurrences (24), and they found a significant survival advantage of local therapy especially for patients with recurrences limited to ≤2 lymph nodes. These results have not been confirmed by prospective studies, but it is possible that salvage RT for postoperative limited lymph node recurrences from EC not only provides LC but also prolongs survival. Furthermore, a combination of chemotherapy with salvage RT and dose escalation of RT may be desirable. One of the reasons why we obtained favorable results was all of the cases in the present study had two or fewer lymph nodes. On the other hand, a trend toward better OS and LC was observed in the concurrent chemoradiotherapy group *versus* the RT alone group (p=0.363, p=0.093, respectively). These results, as well as these existing reports, may suggest that the combination of chemotherapy and radiotherapy is important for improving treatment outcomes.

The maintenance of systemic immune function plays an important role in oligo metastasis, but it is known that peripheral blood cells, which control immunity, are generally vulnerable to radiation (25). In this context, because of its superior dose distribution, PBT has an advantage over conventional RT, especially in chest irradiation, in that it can reduce the effects on the heart and lungs as well as the spine (26). It has been reported that reducing the dose to the spine *via* PBT results in less loss of blood cells, including lymphocytes, relative to that with RT, and it leads to prolonged survival (27, 28). PBT is also superior to conventional RT in that it can be used in combination with immune checkpoint inhibitors in the future, in which case the risk of radiation pneumonitis is lower than with RT and immunocompetence can be maintained (29). In addition, factors reported to cause hemopenia in cancer treatment include the type of previous treatment, concomitant use of RT or platinum drugs, and volume of RT received (30, 31). PBT allowing treatment completion while reducing the irradiation dose to the bone marrow may be one of the reasons for the lack of severe hemopenia and the improved prognosis. Although the number of cases in the present study is too small to mention, our previous data on radical irradiation also showed a better prognosis in cases with good lymphocyte counts, and moreover, the lymphocyte counts were preserved in cases treated with PBT than in those treated with RT (26).

This study has several limitations. First, the number of patients was small. Second, this was a retrospective study. Third, the median follow-up period was relatively short. In addition, not all patients were treated immediately with PBT for postoperative recurrence; some were treated with chemotherapy. Therefore, the patients' background was not homogeneous. However, to the best of our knowledge, this is the first study to report the results of PBT for postoperative lymph node oligorecurrence of EC. Further studies involving a larger sample size, longer follow-up period, and comparisons with conventional RT are necessary to clarify the benefits of PBT.

Conclusion

The results of the study suggest that PBT for postoperative lymph node oligorecurrence of EC provides good LC with low toxicity. PBT may be beneficial even in cases where conventional RT is difficult to administer in combination with increased doses or with chemotherapy.

Conflicts of Interest

The Authors have no conflicts of interest to declare.

Authors' Contributions

Conceptualization, Yuichi Hiroshima (Y.H.); Methodology, Y.H.; Formal analysis, Y.H. and Motohiro Murakami (M.M.); Investigation, Y.H. and Taisuke Sumiya (T.S.); Resources, Toshiki Ishida (T.I.), Y.H., Masatoshi Nakamura (M.N.), Koichi Ogawa (K.O.) and Katsuji Hisakura (K.H.); Data curation, Y.H.; Writing—original draft preparation, Y.H.; Writing—review and editing, T.S., M.N., Masashi Mizumoto and Hitoshi Ishikawa (H.I.); Visualization, Y.H. and M.N.; Supervision, H.I. Tatsuya Oda, and Toshiyuki Okumura (T.O.); Project administration, Hideyuki Sakurai (H.S.). All Authors have read and agreed to the published version of the manuscript.

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