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Salvage Carbon-ion Radiotherapy for Isolated Lymph Node Recurrence Following Curative Resection of Esophageal Cancer

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Abstract. *Aim: Evaluation of the therapeutic efficacy of carbon-ion radiation therapy for isolated lymph node recurrence following curative resection of esophageal cancer. Materials and Methods: Ten cases with lymph node recurrence after esophageal cancer surgery were treated with carbon-ion radiation therapy. A total of 48.0 Gy [relative biologic effectiveness (RBE)] was delivered over 3 weeks with a daily dose of 4.0 Gy (RBE). Results: The median follow-up duration was 27.1 months (range=3-92.0 months) after carbon-ion radiation therapy. The local control rates at 2, 3 and 5 years were 92.4%. The overall survival rates at 2, 3 and 5 years were 70.0%, 58.3% and 21.9%. The median survival period was 45.3 months after carbon-ion radiation therapy. There were no toxicities of grade 3 or higher. Conclusion: Carbon-ion radiation therapy may be a safe and effective treatment option for isolated lymph node recurrence after radical surgery for esophageal cancer.*

Esophageal cancer is a particularly malignant form of digestive disease, and the eighth most common cancer worldwide (1). Esophagectomy remains the standard treatment for patients with resectable disease, but is complicated by a high rate of postoperative recurrence and poor survival, even when preliminary investigation suggests that surgery will be curative. According to previous reports, 27-52% of patients who undergo esophagectomy in the setting of esophageal cancer will go on to develop recurrence (2-9).

It was revealed that lymphadenectomy for lymph node recurrence following curative resection achieved locoregional disease control and offered a favorable outcome, especially for cervical node recurrence (10, 11). Several articles showed the clinical usefulness of chemoradiotherapy (CRT) for patients with isolated lymph node recurrence (2, 11).

In 1994, clinical studies of carbon-ion radiotherapy (CIRT) began at the National Institute of Radiological Sciences (NIRS), Japan (12). Carbon-ion beams have a high relative biological effectiveness (RBE) with high linear-energy transfer compared to proton or photon beams (13). They are also superior to photon beams in terms of dose distribution and minimization of dose to surrounding normal tissues (13).

The first phase I/II clinical trial for short-course preoperative CIRT for resectable esophageal carcinoma was a dose escalation study carried out between 2004 and 2008 (14, 15). Our results suggested that CIRT could be both a highly effective and less toxic therapy (14). A second-phase I/II clinical dose-escalation study of preoperative short-course irradiation combined with concurrent chemotherapy was started from 2012 and is currently ongoing (14, 15).

To further contribute improvement to the prognosis of esophageal cancer, CIRT for isolated lymph node recurrence after curative resection of esophageal cancer was conducted at a single institution. We retrospectively evaluated the effectiveness and safety of this treatment.

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Key Words: Esophageal cancer, lymph node recurrence, carbon-ion radiotherapy.

Table I. *Patient clinical characteristics are shown. Four patients had already received radiotherapy for irradiation field.*

Case	Age (years)	Gender	Location	Pathology	pT	pN	Adjuvant therapy	Resection	DFI (months)	Site of recurrence	Tumor size (cm)	Radiation field
1	64	M	Lt	SCC	3	3	NACRT	Esophagectomy	23.3	Abdominal	1.1	Local
2	65	M	Mt	SCC	2	3	NACRT	Esophagectomy	14.9	Lt recurrent nerve	3.5	Local
3	67	M	Ce	SCC	4	2	NAC	Esophagectomy	9.1	Thoracic	2	Regional
4	60	F	Ut	SCC	1b	2	NAC	Esophagectomy	19.7	Lt supraclavicular	1.5	Regional
5	66	F	Mt	SCC	3	0	NACRT	Esophagectomy	33.6	Thoracic	2.5	Local
6	61	M	Mt	SCC	U	U	AC	Esophagectomy	19.2	Lt recurrent nerve	1.6	Regional
7	71	M	Mt	SCC	1b	1	NAC	Esophagectomy	15.1	Rt recurrent nerve	3.5	Regional
8	60	M	Mt	SCC	U	U	--	Esophagectomy	21	Upper mediastinal	4.6	Regional
9	68	M	Mt	SCC	3	3	NAC	Esophagectomy	17.3	Upper mediastinal	8	Regional
10	72	F	Mt	SCC	1b	0	Prophylactic radiation	Endoscopic resection	84.5	Rt recurrent nerve	1.8	Local

Ce: Cervical, Ut: upper thoracic, Mt: middle thoracic, Lt: lower thoracic, SCC: squamous cell carcinoma, NACRT: neoadjuvant chemoradiotherapy, NAC: neoadjuvant chemotherapy, AC: adjuvant chemotherapy, DFI: disease-free interval from resection to lymph node recurrence, Lt: left, Rt: right, U: unknown.

Materials and Methods

Patient eligibility. From March 2000 to August 2016, 10 cases of isolated lymph node recurrence after curative resection for esophageal cancer received CIRT. Eligibility criteria included: i) Confirmed heterochronic isolated lymph node recurrence after curative resection for esophageal cancer, ii) no findings of other metastasis, iii) an expected prognosis of more than 6 months, iv) performance status (PS) 0-2, v) no other serious complications. Exclusion criteria included: i) patients with another primary malignancy, ii) an infection at the tumor site.

Isolated lymph node recurrence was defined as recurrence of a resected primary esophageal carcinoma in one or multiple lymph nodes within a single en-bloc region, within one irradiation field, with no other metastasis at time of presentation. Disease was diagnosed and evaluated with contrast-enhanced computed tomography (CT) scans, positron-emission tomography (PET), ultrasonography and physical findings.

Informed consent was obtained from all patients and the present study was approved by the Institutional Review Board of the NIRS (9404, 9905, 0801G).

Carbon-ion radiotherapy. The carbon ion beam irradiation system has previously been described (16). To reproduce exact body position at the time of treatment, patients were positioned in customized cradles and immobilized with a low-temperature thermoplastic sheet. Using CT images, three-dimensional treatment planning was performed using the Xio software program (ELEKTA, Stockholm, Sweden, and Mitsubishi Electric, Tokyo, Japan), which was developed specifically for CIRT treatment planning.

CIRT was performed once per day, 4 days per week. A total dose of 48.0 Gy (RBE) was delivered to the planning target volume, with a daily dose of 4.0 Gy (RBE). The target volume was verified by contrast-enhanced CT and PET. For the first six cases treated, the initial target volume was defined as the lymph node recurrence and the nodal region (including the bilateral superclavicular, mediastinal or abdominal regions). After a total dose of 36 Gy (RBE), the field was limited to only macroscopic lesions with an added margin of 1.0 cm (Figure 1A). For the remaining four patients, who were previously irradiated, local fields with a margin of 1.0 cm around the macroscopic tumor were used (Figure 1B).

The irradiation dose was calculated for the target volume and surrounding normal tissue and was expressed in Gy (RBE), defined as the carbon physical dose (Gy) multiplied by the RBE value of 3.0 for carbon-ion beams (12,17).

Treatment results and evaluation of adverse events. After treatment, patients were followed-up every 1-3 months for 2 years and then every 3-6 months thereafter using CT and PET scans. Changes in the tumor diameter before and after treatment were evaluated in accordance with the Response Evaluation Criteria in Solid Tumors: Revised guidelines (RECIST version 1.1) (18). The first site of failure was evaluated in terms of local (recurrent lymph node) recurrence, regional field (regional lymph nodes) failure, and distant failure.

The local control, survival, and relapse-free survival rates were calculated using the Kaplan–Meier method. Acute toxicity within 3 months was classified according to the National Cancer Institute Common Toxicity Criteria Version 4.0 (19). Late toxicity was evaluated using the Radiation Therapy Oncology Group/European Organization for Research and Treatment of Cancer scoring system (20).

Results

Clinical characteristics of patients. Patient clinical characteristics are shown in Table I. The median age was 65 (range=60-72) years, with seven males and three females. The disease-free interval between curative resection and diagnosis of recurrence ranged from 9.1 to 84.5 months. The lymph node recurrences were within the supraclavicular field in one patient, mediastinal field in eight patients, and abdominal field in one patient. Four patients had already received radiotherapy to the irradiation field. The median maximal coronal diameter of the tumor was 2.3 cm (range=1.1-8.0 cm). Figure 1 shows

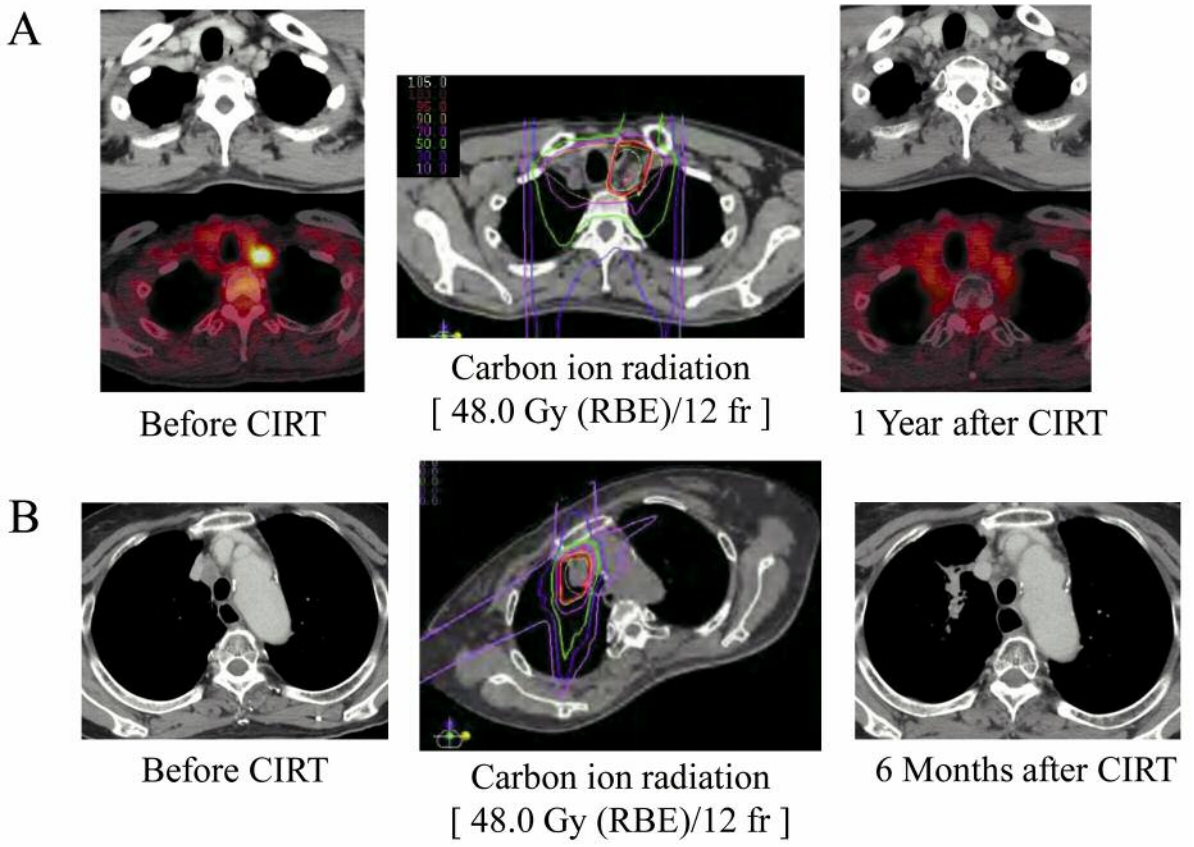

Figure 1. *A: Computed tomography (CT) scan and positron-emission tomography (PET) imaging of the first case treated before and after treatment. The middle figure shows the dose distribution. The initial target volume was defined as the lymph node recurrence and the nodal region. After a total dose of 36 Gy, the field was limited to only the macroscopic lesions with an added margin of 1.0 cm. B: CT scan and PET imaging of the patient, who was previously irradiated, before and after treatment. The middle figure shows the dose distribution. Local fields with a margin of 1.0 cm around the macroscopic tumor were used.*

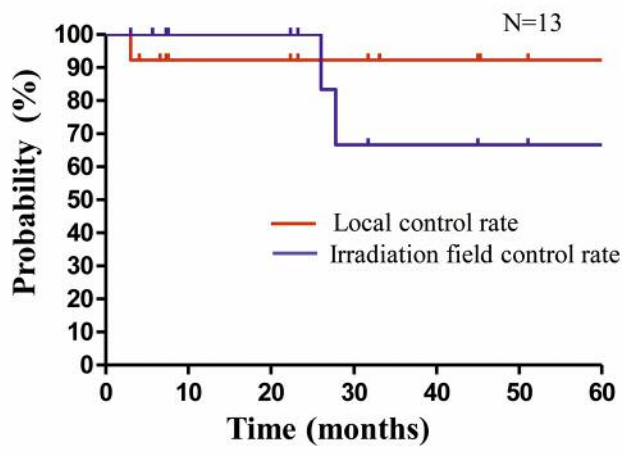

Figure 2. *The local control rate and irradiation field control rate curves are illustrated. The 2-, 3-, and 5-year local control rates of these 13 lesions, including salvage re-irradiation, were 92.4% throughout. The 1-,3-, and 5-year irradiation field control rates were 100.0%, 66.7%, and 66.7%, respectively.*

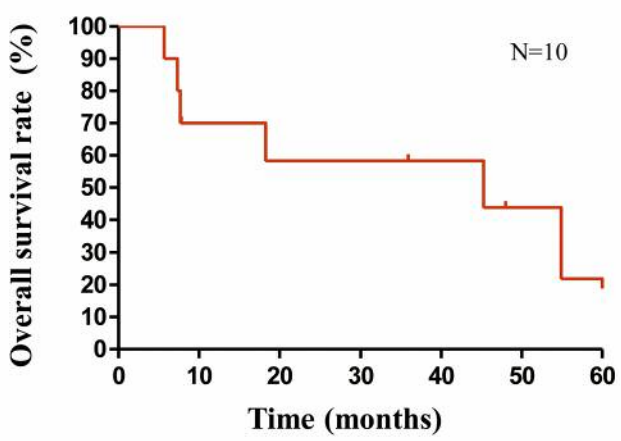

Figure 3. *The overall survival rate curves are illustrated. The 1-, 3-, and 5-year survival rates were 70.0%, 58.3%, and 21.9%, respectively. Four out of the 10 patients were alive at time of publication. The median survival time was 45.3 months.*

Table II. *Clinical outcomes are shown. One patient experienced local recurrence and two patients experienced regional lymph node recurrences within the prophylactic irradiation field. Two patients experienced regional lymph node recurrences out of irradiation field. These two patients received repeat salvage carbon-ion radiotherapy (CIRT).*

Case	Radiation field	Tumor response	Recurrence: Local	Recurrence: Prophylactic irradiated field	Recurrence: Outside of irradiated field	Survival (months), outcome
1	Local	PR				7.7 Dead from cancer
2	Local	PR				92.1, Dead from pneumonia
3	Regional	PR			+ (Salvage re-irradiation CIRT)	54.9, Dead from cancer
4	Regional	SD		+		45.3, Dead from cancer
5	Local	PR			+ (Salvage re-irradiation CIRT×2)	48.0, Alive with disease
6	Regional	CR		+		35.9, Alive with disease
7	Regional	PD	+			18.3, Dead from cancer
8	Regional	PR				7.3, Dead from cancer
9	Regional	PR				5.7, Dead from cancer
10	Local	PR				7.8, Relapse-free survival

CR: Complete response, PR: partial response, SD: stable disease, PD: progressive disease.

example dose distributions with CT images from before and after CIRT in patients 6 and 10.

Tumor response. The median follow-up duration for all patients and surviving patients was 27.1 (range=5.7-92.1) months and 35.9 (range=35.9-48.0) months, respectively.

Clinical outcomes are shown in Table II. One patient experienced local recurrence and two patients experienced regional lymph node recurrences within the prophylactic irradiation field. Two patients experienced regional lymph node recurrences outside of the irradiation field. These two patients received repeat salvage CIRT. One patient out of the two received salvage CIRT twice, since heterochronic recurrences were detected in para-aortic lymph node and inferior mediastinum after initial CIRT.

Treatment response was complete in one patient, partial in seven, stable one, and with disease progression in one. We analyzed the tumor response including these three salvage lesions. There were eight cases (62%) out of 13 cases including salvage cases that achieved complete or partial response after treatment.

The 2-, 3-, and 5-year local control rates of these 13 lesions, including salvage re-irradiation, were 92.4% throughout. The 1-, 3-, and 5-year irradiation field control rates were 100.0%, 66.7%, and 66.7%, respectively. The local control rate and irradiation field control rate curves are illustrated in Figure 2.

The 1-, 3-, and 5-year survival rates were 70.0%, 58.3%, and 21.9%, respectively. Four of the 10 patients were alive at time of publication. The median survival time was 45.3 months. The curves for overall survival are illustrated in Figure 3. Five out of the 10 patients (50.0%) demonstrated survival of greater than 3 years.

Table III. *Acute and late toxicity of the lesions including repeat salvage carbon-ion radiotherapy are listed. No toxicities of grade 2 or more were observed.*

	Acute (NCI-CTC)			Late (RTOG/EORTC)		
Toxicity	n	Grade 0	Grade 1	n	Grade 0	Grade 1
Skin	13	6	7	13	10	3
GI tract	13	8	5	13	13	0
Heart	13	13	0	13	13	0
Lung	13	13	0	13	9	4
Spinal cord	13	13	0	13	13	0
Other	13	13	0	13	13	0

NCI-CTC: National Cancer Institute-Common Terminology Criteria, RTOG: Radiation Therapy Oncology Group, EORTC: European Organization for Research and Treatment of Cancer, Gr: grade; GI: gastrointestinal.

Toxicity. All patients completed their CIRT course without interruption. Acute and late toxicity of the 13 lesions including repeat salvage CIRT are listed in Table III. No grade 3 or more acute toxicities were observed.

Discussion

Our study showed the efficacy and safety of CIRT for patients with isolated lymph node recurrence after curative resection of esophageal cancer. In 10 patients, with a median follow-up of 27.1 months, the 3-year local control rate and overall survival rate were 92.4% and 58.3%, respectively. CIRT achieved favorable local control and survival, comparable with surgery. Simultaneously, there were no

grade 3 or higher toxicities reported. This suggests that CIRT is a safe technology providing favorable outcomes in the setting of oligometastatic lymph node recurrence following curative-intent resection of esophageal cancer.

Recent data suggests that chemoradiation (CRT) can improve patient survival in this disease setting (2, 11, 21, 22). Lymphadenectomy tends to be the treatment of choice for isolated lymph node recurrence, and shows good local disease control (10, 11). However, challenges remain for achieving favorable long-term outcomes, except in the case of cervical node recurrence (10, 11). Nakamura *et al*. reported a comparison of clinical outcomes with multimodal treatment for recurrent lymph node metastasis, such as lymphadenectomy, conventional CRT and chemotherapy (11). The survival rate at 3 years for groups treated with conventional CRT *versus* lymphadenectomy were 26.6% (n=21) and 50.7% (n=19), respectively. Lymphadenectomy tended to offer more favorable survival in comparison with conventional CRT, although no statistically significant difference in survival was noted. The patients who underwent R1 resection did not survive long term, and it was suggested that CRT might be indicated for lymph node recurrences for which there is a risk of residual disease.

Previous CRT studies for postoperative lymph node recurrence from esophageal cancer demonstrate a median overall survival rate at 3 years of 24% (range=11-50.6%), with a median survival time of 17 (range=7-43.4) months (2, 11, 22-27). Grade 3-5 acute or late toxicities were observed in 0-9% of patients in these previous studies (2, 11, 21-26). The clinical outcomes of our study appeared to achieve favorable survival with less toxicity, comparable or superior to other CRT studies.

There were several differing points between our study and previous chemoradiation studies. Firstly, our study included patients who had already received radiotherapy. During the past few decades, preoperative CRT has been actively performed, and a fair number of patients received preoperative radiation (14, 27). Generally, re-irradiation is challenging because radiosensitive organs may have already received near-tolerance dose during prior treatments. This makes salvage conventional CRT particularly difficult. CIRT, however, offers a superior dose distribution due to the nature of particulate irradiation, with dose asymptotically concentrated in the Bragg peak (12). This produces a more conformal dose distribution with steeper dose gradients, without an increase in normal tissue integral dose compared with photon. These characteristics enable good local control while diminishing the likelihood of adverse events. Furthermore, two patients with new lymph node recurrence following CIRT were able to receive repeat salvage CIRT with good tolerability and little toxicity.

There are a few limitations to this study. This was a retrospective analysis with a small sample size. Prospective evaluation of a larger cohort will be needed to further verify the results found here.

A number of important issues were defined by our study that will need to be elucidated prior to treatment progression. The control rate within the prophylactic irradiation field at 3 years was limited to 66.7%, with two patients out of 10 developing new regional lymph node recurrences within the prophylactic field. The role of prophylactic irradiation for regional lymph nodes is controversial, and re-evaluation of prophylactic CIRT in this setting may be warranted. To further mitigate locosystemic progression, chemotherapy should be included.

To our knowledge, this is the first study to evaluate the use of CIRT for isolated lymph node recurrence following curative resection of esophageal cancer. Our results were comparable or superior to those for conventional CRT, with no severe toxicities being observed. In particular, CIRT may be a good option for patients who have received prior irradiation to the area of a recurrence. We recommend continued investigation into further CIRT indications and techniques so as to further improve disease response and survival.

Ethical Statement

The present study was performed at the Hospital of the National Institute of Radiological Science, National Institutes for Quantum and Radiological Science and Technology in accordance with the Declaration of Helsinki and the protocol was approved by the Ethics Committee of the Hospital of the National Institute of Radiological Science, National Institutes for Quantum and Radiological Science and Technology.

Conflicts of Interest

The Authors declare that they have no conflicts of interest in regard to this study.

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