Postoperative Recurrence of Rectal Cancer

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Abstract

To improve long-term local control and survival of locally recurrent rectal cancer, we have initiated a radiation dose-escalation trial using carbon ion beams. The purpose of this study is to evaluate the tolerance for and effectiveness of carbon ion radiotherapy in patients with locally recurrent rectal cancer.

Between April 2001 and August 2012, 198 lesions at 189 patients were treated with C-ion RT. The dose was determined as 67.2 GyE and escalated to 70.4 GyE and 73.6 GyE. The local control rates in 197 lesions are 94 % at 3 years and 89 % at 5 years. Local control rate and survival rate at 5 years were 97 % at 73.6 GyE and 51 % at 73.6 GyE. In the literature, the reported 5-year survival rates for locally recurrent rectal cancer treated with resection were 20–40 %. Carbon ion radiotherapy seems to be a safe and effective modality in the management of locally recurrent rectal cancer, providing good local control and offering a survival advantage without acceptable morbidity.

In this chapter, the treatment methods and the up-to-date outcomes of carbon ion radiotherapy (C-ion RT) for the recurrent rectal cancer at the NIRS are introduced.

Keywords

Carbon-ion • Rectal cancer • Recurrence

24.1 Introduction

The large intestine starts at the ascending colon, which is connected to the small bowel, and ends at the rectum, which extends from the sacral promontory to the anal canal. In 2008, approximately 43,000 patients died of colorectal cancer in Japan, which is the third most common cause of cancer deaths, after lung and stomach cancers. Approximately 100,000 patients were diagnosed with colorectal cancer in 2004, thus making it the second most common type of cancer after stomach cancer. The analysis of the postoperative recurrence rates of colorectal cancer indicates a higher rate for rectal cancer than colon cancer. When compared by the site of recurrence, rectal cancer had a more than three times higher local recurrence rate than colon cancer.

With the recent advances in surgical techniques and procedures, the pelvic recurrence rate of rectal cancer has been decreasing; however, the postoperative recurrence rate is still 5–20 % today. Surgical resection is the first choice for locally recurrent rectal cancer, although total pelvic exenteration or another highly invasive procedure is often required. In many cases, locally recurrent rectal cancers are not completely resectable so generally surgical resections are not selected. The comparison of resection rates by the type of tumors shows that the resection rates were in the range of 40–50 %

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Table 24.1 Resection rates and survival rates by recurrence sites

	Resc rate (%)	5-year survey (%)
Local rec	10–30	30–45
Liver meta	40–50	35–45
Lung meta	20–30	40–50

for liver metastases and 20–40 % for lung metastases, whereas the rate was 10–40 % for locally recurrent colorectal cancers (Table 24.1) [1, 2]. Curative resection of these tumors will lead to a survival rate similar to those for other types of recurrences and metastases.

24.2 Significance of C-Ion Radiotherapy

Improvements in tumor response and control have been sought through efforts to overcome the radioresistance of the hypoxic tumor cells identifiable in rectal cancers. These aspects might give high-LET particles a particular advantage, independent of whether this is due to a lower oxygen enhancement ratio (OER) or other intrinsic factors. Therefore, high-LET particle radiotherapy such as carbon ion or neutron radiotherapy may possess an advantage in the treatment of radioresistant and hypoxic, recurrent tumors. Twenty patients with recurrent rectal cancer were treated using the neutron generator in Munster by combined neutron radiotherapy [3].

The radiation schedule most often used for palliation involved giving 40 Gy photon and 10 Gy neutron doses (14 MeV). Initiation of pain relief appeared to occur faster with neutrons than with photons alone. Pain relief was achieved in 11–15 patients (73 %), and the probability for a pain-free period was 46 % at 9 months. It remains to be proven if a higher degree of pain relief, longer period of absence of pain, and length of progression-free period are improved with neutrons in comparison to photons. The incidence of acute toxicity was 30 % and late toxicity 10 %, with all reported toxicity occurring in the skin. A higher neutron dose may give better results, but its utility is potentially limited by well-recognized local radiation side effects. In contrast to neutrons, where escalation to tumoricidal doses is limited by potential normal tissue complications, carbon ion therapy offers the potential for an increase in biologically effective dose delivery in the target tissue relative to normal tissues through its superior dosimetric and radiobiological properties [4].

24.3 Clinical Trial in Recurrent Rectal Cancer at NIRS

The first clinical trial of the C-ion RT at the National Institute of Radiological Sciences (NIRS) for the recurrent rectal cancer was started in 2000. It was a phase I/II dose-searching study and the dose was escalated from the starting dose of 67.2 to 73.6 GyE in 16 fractions. A total of 38 patients were treated and the results indicated that the C-ion RT could be a sufficiently safe and effective treatment for the recurrent rectal cancer. This study was finished in 2004 and the second trial with the recommended dose determined by the first trial was initiated immediately. One hundred and fifty-two patients were treated in the second study until 2004 and the satisfactory results could be obtained as well. In November 2003 the approval of the Japanese government for the advanced medicine was given to the C-ion RT at the NIRS, and after the end of the second trial, the recurrent rectal cancer was added to the indication of the advanced medicine.

24.4 Methods of Carbon Ion Radiation Therapy at NIRS

24.4.1 Patient Immobilization

The patient needs to be immobilized for the C-ion RT as well as other tumor sites. The C-ion RT at the most heavy-ion therapy facilities is performed with fixed beam directions of vertical, horizontal, or 45-degree oblique. On the other hand, the recurrent tumor of the rectal cancer locates anywhere in the pelvis, at the presacral region, iliac lymph node, or mesenteric lymph node, and therefore the proper direction of the carbon ion beam is varied. Moreover, more than two ports are usually necessary to obtain satisfactory dose distribution in terms of avoidance of high dose to the bowels and the skin. Consequently, rather complicated immobilization is an everyday occurrence.

At the NIRS, it could be realized by using relatively thick low-temperature thermoplastic (Shellfitter; Keraray Co., Ltd., Osaka, Japan), sufficient amount of customized cradle (Moldcare; Alcare, Tokyo, Japan), and rotatable couch on the treatment bed.

Management of the respiratory motion is also essential in the most case of the recurrent rectal cancer (see Chaps. 4, 5, 6, 7, 8, and 9 Motion Management). There are plenty of methods for motion management. At the NIRS, synchronization with respiration is adopted at both CT acquisition and every session of the C-ion RT irrespective of direction of the beam. Although the influence of the respiratory motion on the session with the vertical beam is less than that with horizontal beam in the treatment of pelvic tumor, that is, mainly difference in the length of air gap, it is desirable to irradiate the tumor with similar condition to dose calculation using CT images taken at the expiratory phase.

24.4.2 Target Delineation

A set of 2.5–5.0-mm-thick CT images throughout the pelvis was taken for treatment planning, with the patient placed in immobilizing devices and with respiratory gating.

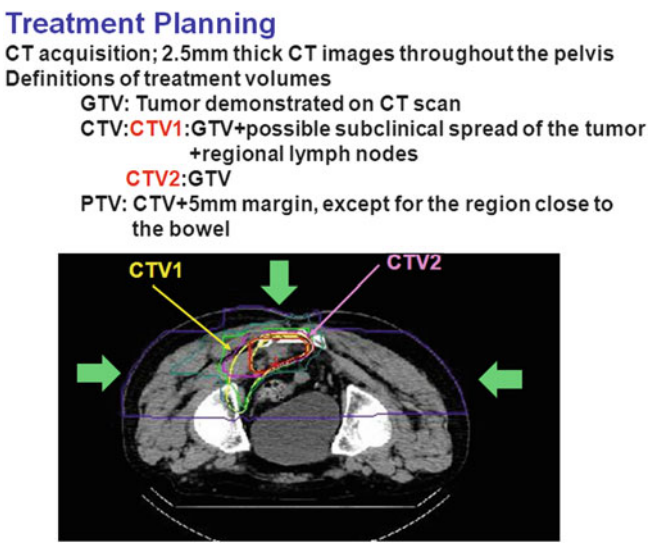

Fig. 24.1 The method of treatment planning for recurrent rectal cancer. *Yellow line* indicates the clinical target volume CTV) and *red line* indicates the planning target volume (PTV). The margins for the PTV is intentionally reduced to spare the bowels

Clinical target volume (CTV) was determined by setting the margin 5 mm outside the GTV and included the regional lymph nodes (LN). The LN areas that should be considered the target volume include the internal iliac, the external iliac, and the presacral node. The dose constraints of the maximum dose for the intestine and bladder were 30 GyE in 9 fractions and 60 GyE in16 fractions, respectively. Prophylactic nodal areas of risk are usually treated to 37.8–41.4 GyE in 9 fractions of 4.2–4.6 GyE before irradiation field is reduced in size. The target volume includes the primary tumor, adjacent lymph nodes, and presacral region. Target volumes are based on known pattern of local recurrence in locally recurrent rectal cancer. MRI and methionine PET are useful to distinguish the tumor from postoperative fibrosis and the bowels.

Planning target volume (PTV) is defined as the CTV plus at least 5 mm margin in all directions; however, the margins are modified if the critical organs, such as skin or bowels, exist near the tumor (Fig. 24.1).

24.4.3 Dose Prescription

The current recommended dose was 73.6 GyE/16 fractions as described above. One hundred percent of the prescribed dose is given at the maximum dose point of each portal. The treatment planning is performed so that the PTV is covered with at least 90 % of the prescribed dose. For this purpose, additional margins are necessary to determine the shape of collimator and compensation bolus. Figure 24.1 shows the representative dose distribution of current C-ion RT at the NIRS.

Major organs at risk (OAR) for this treatment are the bowels, sciatic nerve, urinary bladder, ureter, and skin. It is particularly important to spare the bowels from the high-dose area of the carbon ion beam. At the NIRS, dose constraints of the digestive tract are established based on the treatment results in the prostate, uterine cervical cancer, and the recurrent rectal cancer, where the maximum dose to the colon should not exceed 83 % of the prescribed dose. The sciatic nerve is also important OAR and the dose should be reduced as much as possible; however, control of the local tumor is much more important not only for the survival but also for the quality of life (QOL) of the patient. If the tumor is located close to the skin surface, the dose to the skin should also be taken into account. Selecting proper direction of the beam and using more than two ports are desirable, particularly in the treatment of big-sized lesion.

24.4.4 Field Positioning and Irradiation at NIRS

At the NIRS, the C-ion RT is carried out once a day, four fractions per week (from Tuesday to Friday). Verification of the field is carried out at every treatment session with a computer-aided online positioning system to maintain a positioning error of less than 2 mm. Fluoroscopic image is taken at the expiration phase of the patient respiration and compared with the reference images, such as the image taken at the preceded simulation or the digitally constructed radiograph (DRR). The C-ion RT is performed under respiration gating as described above, where the carbon ion beam is delivered only during the expiration phase.

24.5 Up-to-Date Results of the C-ion RT at NIRS

24.5.1 C-Ion Therapy for Patients with Pelvic Recurrence of Rectal Cancer

Between April 2001 and August 2012, 198 lesions at 189 patients were enrolled onto this study. Criteria for trial eligibility include confirmation of locally recurrent rectal cancers without distant metastases based on CT, MRI, and PET findings. The dose was determined as 67.2 GyE and escalated to 70.4 and 73.6 GyE. The predominant sites of relapse were 75 presacral, 77 lymph nodes, 28 perineal, and 9 anastomosis.

Ten patients received radiation dose at 67.2 GyE, 18(+3) at 70.4 GyE, and 161(+6) at 73.6 GyE. All toxicities in the 198 lesions at 189 patients were relatively few and mild in these patients. No grade 3–5 acute toxicity was observed. The local control rates in 197 lesions are 94 % at 3 years and 89 % at 5 years. Local control rates at 5 year were 97 % at 73.6 GyE. In terms of symptomatic response within 3 months after treatment, pain improved in 97 % of the symptomatic cases. The 3- and 5-year overall survival rates in 188 patients

Table 24.2 The results on the radiation therapy of locally recurrent rectal cancer reported by other studies

Study and reference	Year	Number	Rad dose(Gy)	Survival rate 2 years (%)	5 years (%)	Local control (%)
Lybeert et al. [5]	1992	76	6–66	61 (1 year)	3	28 (3 years)
Knol et al. [6]	1995	50	60	27	8	–
Murata [7]	1997	18	12–60	44 (1 year)	–	46 (2 years)
Hu et al. [8]	2006	23	55–66	50 (2 years)	18 (3 years)	
Kim et al. [9]	2008	23	30–51/3f	82	23	74 (5 years)
Lee et al. [10]	2011	22	54–66	66	40	56 (5 years)
NIRS	2012	136	73.6	87	45	93 (5 years)

Table 24.3 The results of the surgical treatment reported by other studies

Study and reference	Year	Number of patients	Survival rate 1 year (%)	2 years (%)	5 years (%)
Garcia-Aguilar et al. [12]	1999	42	88	62	35
Wanebo et al. [13]	1999	53	91	62	31
Salo et al. [14]	1999	71	88	75	31
Saito et al. [15]	2003	43	91	78	39
Moriya et al. [16]	2004	48	95	76	36
Melton et al. [17]	2007	29	92	65	20
NIRS	2012	136	99	87	45

were 72 % and 47 %, respectively. Survival rates at 5 years were 20 % at 67.2 GyE, 24 % at 70.4 GyE, and 51 % at 73.6 GyE. In the literature, the reported 5-year survival rates for locally recurrent rectal cancer treated with conventional radiation and with resection were 0–40 % (Table 24.2) and 20–40 % (Table 24.3), respectively. Most of our patients were inoperable, so our results seem to be better than surgery.

Carbon ion radiotherapy seems to be a safe and effective modality in the management of locally recurrent rectal cancer, providing good local control and offering a survival advantage without acceptable morbidity.

24.5.2 Indication of Spacer in the C-Ion RT for the Recurrent Rectal Cancer

Pelvic recurrent tumors are often located in close proximity to the digestive tract. Consequently, a significant proportion of patients were often judged as ineligible for carbon ion radiotherapy, because the digestive tract could not be excluded from the irradiation field. At our hospital, therefore, we adopted a surgical preparatory procedure, to place a spacer between the target tumor and the digestive tract before conducting carbon ion radiotherapy, when the tumor was located close to a sensitive organ.

The tumor locations are classified into three groups according to distance between tumor and intestine. They are penetration type, contact type, and separation type. Contact type is defined by the shorter than 5 mm distance between the tumor and intestine. Previously contact type was not eligible for carbon ion therapy. We have tried to treat these types of tumors by using spacer. To exclude the small intestine and colon from the clinical target volume (CTV) and reduce the exposure of them, we use expanded polytetrafluoroethylene (Gore-Tex soft-tissue patch, W. L. Gore & Assoc Inc, Flagstaff, Ariz) which is a strong and easy-to-use material and does not need to be removed after the conclusion of radiotherapy (Fig. 24.2). Mesenterium, muscle cutaneous flap, or omentum instead of Gore-Tex sheet is used at infectious lesion.

From 2003, 73 patients are treated with the spacer. Most of tumor sites were the sidewall or presacrum. Eight of grade 3 acute toxicities were observed. This rate is higher than without spacer. All patients completed the scheduled treatment course. Local control rate is 96 % at 2 years and 88 % at 5 years. This is almost the same as without spacer. The survival curves of patients with locally recurrent rectal cancer are similar between with and without spacer.

The case was of a 59-year-old Japanese female and referred to the NIRS hospital with a diagnosis of postoperative recurrence of the rectal cancer (Fig. 24.3). CT scan revealed a tumor mass in the sidewall of the pelvis and in contact with the intestine. After placing Gore-Tex sheet, this dose distribution revealed the dose of the surrounding intestine is extremely low. She did not experience any major toxicity. The tumor size on CT scan decreased 24 M after treatment.

24.6 Carbon Ion Radiotherapy for Locally Recurrent Rectal Cancer in Patients with Prior Pelvic Irradiation

Among gastrointestinal malignancies, many studies have shown the safety and efficacy of pelvic reirradiation for rectal cancer [10–14]. Reirradiation to the pelvis could potentially play a role in palliation of symptoms or local control. Local recurrences are located close to critical organs such as the small intestine, colon, and bladder, and in these patients reirradiation would be expected to be associated with a higher risk of acute and late toxicity at these organs than primary irradiation.

Fig. 24.2 The photograph of Gore-Tex soft-tissue patch and operative findings using it. Gore-Tex is made of expanded polytetrafluoroethylene (PTFE). It is widely applied to medical materials such as vascular grafts or hernia repair materials. This is operative finding. The spacer was fixed with the retroperitoneum and peritoneum

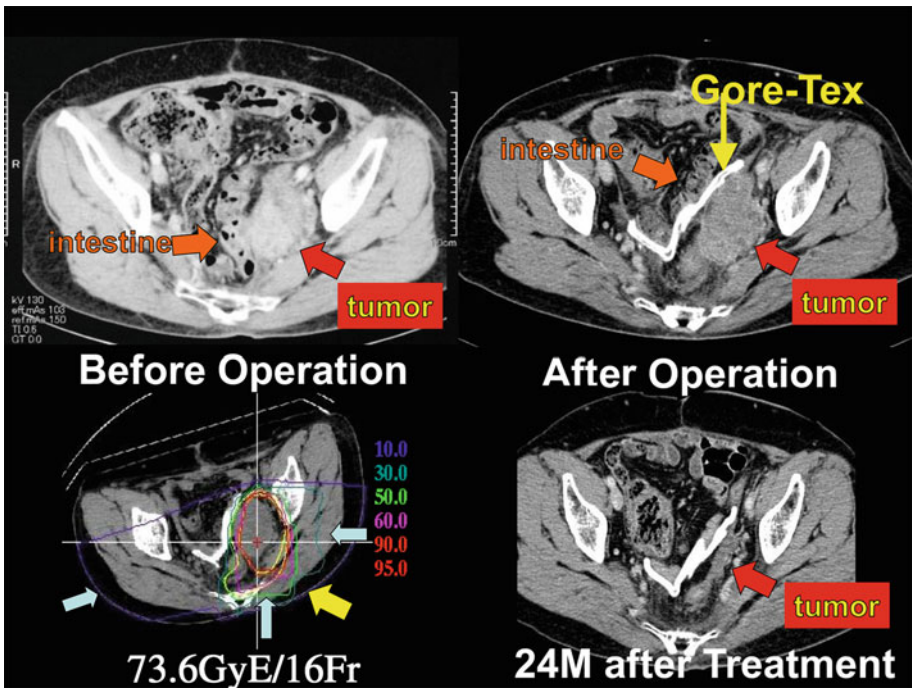

Fig. 24.3 This patient is a 59-year-old female with locally recurrent rectal cancer. CT scan revealed a tumor mass in the sidewall of the pelvis and in contact with the intestine. After placing Gore-Tex sheet, the dose distribution revealed the dose of the surrounding intestine is extremely low. The tumor size on CT scan decreased 24 M after treatment. She did not experience any major toxicity

The purpose of this study was to assess carbon ion radiation therapy performed as reirradiation in patients with locally recurrent rectal cancer. Twenty-three patients were treated with carbon ion RT as reirradiation for locally recurrent rectal cancer. Nine relapses originated in the presacral region, 8 in the pelvic sidewalls and 6 in the perineal region. The total dose range of 70.4 Gy equivalent (GyE) was administered in 16 fixed fractions over 4 weeks (4.4 GyE/fraction).

All patients completed the scheduled treatment course. Grade 3 toxicities occurred in 6 (26 %) patients. The major late toxicities were peripheral neuropathy and infection. No other severe acute reactions (grade ≥3) were observed at this study (Table 24.4).

The 1- and 3-year overall survival rates were 83 % (95 % CI, 68–98 %) and 65 % (95 % CI, 43–87 %), respectively. The 1- and 3-year disease-free survival rates were 71 % (95 % CI, 51–91 %) and 51 % (95 % CI, 27–75 %), respectively.

Carbon ion radiotherapy as reirradiation appears to be a safe and effective modality in the management of locally recurrent rectal cancer, providing good local control and offering a survival advantage without unacceptable morbidity.

24.7 Future Perspectives

24.7.1 Scanning Irradiation

In 2011, the beam delivery using spot scanning became available at the NIRS. It has been applied to the lesion without significant motion due to the respiration until April 2013. However, the spot scanning irradiation for the mobile target is being developed and will be realized in the near future. Therefore, the scanning irradiation will also be performed for the recurrent rectal cancer as well as lung cancer or liver cancer.

The scanning irradiation can offer even better dose distribution than the passive method in the treatment of various lesions because it is much more flexible. In the passive irradiation, uniform length of the spread-out Bragg peak (SOBP) must be used in each field and it often gives unnecessary high dose to the normal tissue. While, there is no unnecessary high-dose area in the dose distribution with the scanning and it is additionally possible to reduce the dose to the normal tissue even more by means of accepting the high-dose spot inside the target if desirable.

Moreover, the improvement of treatment efficiency can be obtained by the scanning. It does not require a collimator or compensation bolus, so the preparation time between CT acquisition and the start of treatment can be shortened and the cost for each treatment can be less expensive.

Furthermore, it is possible for the scanning irradiation to realize rotating gantry of the carbon ion beam. With the gantry, the patient need not be immobilized in the uncomfortable, inclined position as the current C-ion RT with passive irradiation.

Table 24.4 Comparison between maximum normal tissue damage by primary CIRT and CIRT as reirradiation

	Neuropathy					Gastrointestinal				
Toxicity	No	G0	G1	G2	G3	No	G0	G1	G2	G3
Primary CIRT	17	6	6	4	1	17	10	4	3	0
Reirradiation	23	8	7	6	2	23	17	1	2	3[a]

[a]All of the three grades were attributed to operations for spacer before treatment

24.8 Case Study

The case was of a 65-year-old Japanese male referred to the NIRS hospital with a diagnosis of postoperative recurrence of rectal cancer. He underwent the surgery 4 years before and the initial stage was IIIa. The CT scan and PET scan revealed a tumor mass in the right sidewall of the pelvis and infiltrated pelvic bone (Fig. 24.4).

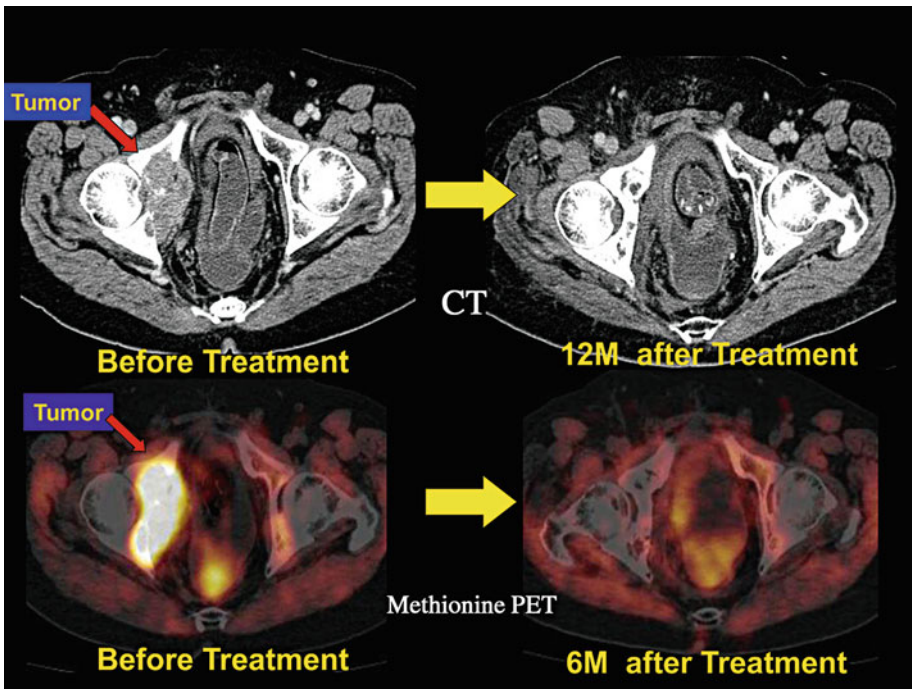

Fig. 24.4 This patient is a 65-year-old male with locally recurrent rectal cancer. A CT scan and PET scan revealed a tumor mass in the right sidewall of the pelvis and infiltrated pelvic bone

The C-ion RT was performed with three ports of left oblique lateral, right oblique lateral, and oblique posterior, and the total dose was 73.6 GyE in 16 fractions.

Twelve months later, the CT and the methionine accumulation after treatment demonstrated disappearance of the tumor and osteogenesis in the osteolytic lesion.

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