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Re-irradiation With Carbon Ion Radiotherapy for Pelvic Rectal Cancer Recurrences in Patients Previously Irradiated to the Pelvis

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Abstract. *Background/Aim:* Re-irradiation of locally recurrent rectal cancer poses challenges due to the proximity of critical organs, such as the bowel. This study aimed at evaluating the safety and efficacy of re-irradiation with Carbon Ion Radiotherapy (CIRT) in rectal cancer patients with local recurrence. *Patients and Methods:* Between 2014 and 2018, 14 patients were treated at the National Center of Oncological Hadrontherapy (CNAO Foundation) with CIRT for locally recurrent rectal cancer. *Results:* All patients concluded the treatment. No G_{≥3} acute/late reaction nor pelvic infections were observed. The 1-year and 2-year local control rates were, 78% and 52%, respectively, and relapse occurred close to the bowel in 6 patients. The 1-year and 2-year overall survival

rates were 100% and 76.2% each; while the 1-year and 2-year metastasis free survival rates were 64.3% and 43%. *Conclusion:* CIRT as re-irradiation for locally recurrent rectal cancer emerges as a safe and valid treatment with an acceptable rate of morbidity of surrounding healthy tissue.

Colorectal cancer (CRC) represents the third most frequent cancer worldwide, leading to the fourth most common cause of cancer deaths (1). Tumor stage is the most important prognostic factor; the five-year survival is about 90% for cancers confined to the primary site, 71% in those with local node involvement, and 14% for Stage IV cancers (2).

The treatment standard for patients with CRC relies upon on the initial staging and encompasses a multimodal approach (surgical resection and radiotherapy in addition to chemotherapy). Complete tumor resection is necessary for a curative treatment approach and consists of trans-anal microscopic surgery for T1 lesions and anterior resection for T_{≥2} tumor (3, 4).

For stage II-III tumors, pre-operative radio-chemotherapy has been shown to be superior to post-operative radiotherapy with a lower rate of local failure (13% vs. 6%) (4, 5).

In both the pre- and post-operative radiotherapy, doses of 45 Gy with a boost of 5.4 to 9 Gy to the macroscopic tumor or tumor bed is delivered. Also, radiotherapy administered

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in a short course (25 Gy, 5 Gy/fraction) has been reported to cause a significant reduction in local recurrence (4, 6).

The risk of local recurrence after a curative treatment depends on pathological tumor/node/metastasis (TNM) stage (3), circumferential resection margin status, number of pathological lymph nodes, extracapsular invasion, extranodal deposits, tumor differentiation, lymph-vascular invasion, extramural vascular invasion, and perineural invasion (4, 7, 8).

The multimodal approach plays a critical role in reducing the risk of locoregional recurrence. Most recurrences occur within the radiation field or at margins of radiation field; 78% of them are typically located in the low pelvic and presacral regions (9).

According to the European Society of Medical Oncology (ESMO) guidelines, the operable local recurrences could be treated with preoperative radiotherapy (standard dose of radiotherapy in not previously irradiated patients; short course of radiotherapy followed by a fluoropyrimidine and oxaliplatin-based chemotherapy; re-irradiation using lower doses in previously irradiated patients) followed by salvage surgery performed by a specialist team because of the complications due to the loss of the normal anatomical planes. If salvage surgery is not an option, to appease the symptoms, ESMO recommends palliative treatment, consisting of re-irradiation at the lowest dose, systemic chemotherapy, brachytherapy, and palliative surgical diversion (4).

However, local recurrences are generally resistant to conventional treatments. For this reason, carbon ion radiotherapy (CIRT) may represent a valid alternative treatment with curative intent. CIRT, in comparison with conventional X-ray radiotherapy, has the advantage of primary physical selectivity in releasing the dose to the tumor with minimal surrounding tissue damage. Moreover, CIRT offers biological benefits by inducing complex double-strand breaks in DNA, leading to irreversible cell devastation despite cell cycle phase or oxygenation status. CIRT provides, with respect to photons, an increased relative biological effectiveness (RBE), which may be estimated amid 2 and 5 depending on the cell line as well as the endpoint analyzed (10-12).

Previous Japanese studies used CIRT for treatment of rectal cancer recurrences in patients not previously irradiated. Such experience highlighted exceptional local control rates superior to conventional radiation therapy, which could be considered a potential alternative to surgery alone (13).

The Heidelberg experience using CIRT for local recurrence of CRC in patients previously irradiated is also promising, and reveals only mild toxicity (14).

Patients and Methods

This retrospective study aimed to evaluate the safety and efficacy of re-irradiation with CIRT in patients with local recurrence of rectal cancer. The records of 14 patients with locally recurrent CRC were

Table I. Patient, tumor and treatment characteristics.

	Value
Number	14
Gender (number)	
Male	12
Female	2
Age, years	
Median (range)	58.5 (34-78)
Dose of prior EBRT (at time of first diagnosis)	
Median (range)	45 Gy (45-76*)
Dose of prior BT boost (at time of first diagnosis)	
Total dose (1 patient)	20 Gy
Dose of prior Re-irradiation (at time of first diagnosis)	
Total dose (1 patient)	30 Gy
Interval between EBRT and CIRT, months	
Median (range)	65 (14 - 139)
Relapse site	
Pre-sacral	10
Perineal	1
Perianal	1
Pre-coccygeal	2
GTV volume, ml	
Median (range)	154.63 (7.21-359.94)
PTV volume, ml	
Median (range)	306.7 (53.55-742.64)
Total dose of CIRT	
Median (range)	60 Gy RBE (35-76.8)
Dose for fraction (CIRT)	
Median (range)	3 Gy RBE (3-4.8)
Number of fraction (CIRT)	
Median (range)	16 (15-20)

EBRT: External beam radiotherapy; BT: brachytherapy; CIRT: carbon ion radiotherapy; RBE: relative biological effectiveness; *76 Gy dose delivered for prostatic cancer.

retrospectively reviewed. All patients underwent CIRT for CRC recurrence at the National Center of Oncological Hadrontherapy (CNAO Foundation) in Pavia, Italy.

The treatment planning of the recurrent disease was defined for each patient following an extensive discussion among the working group. Healthcare professionals involved included surgeons, oncologists and radiation oncologists, within a multidisciplinary team approach (15). All team members ensured effective knowledge translation flows (16), employing tools like in-person meetings (17), electronic medical records (18), evidence-based methods (19), clinical cases and best practices (19) and self-assessment (20).

All patients had inoperable lesions and had previously undergone photon therapy. All patients went through staging with total body computed tomographic (CT) scan to exclude distant metastasis and a pelvic magnetic resonance imaging (MRI) to study local disease extension.

CIRT was delivered using synchrotron-based scanning carbon ion beams (pencil beam scanning and spill-by-spill active energy variation). The technical delivery system details have been previously reported (21-23).

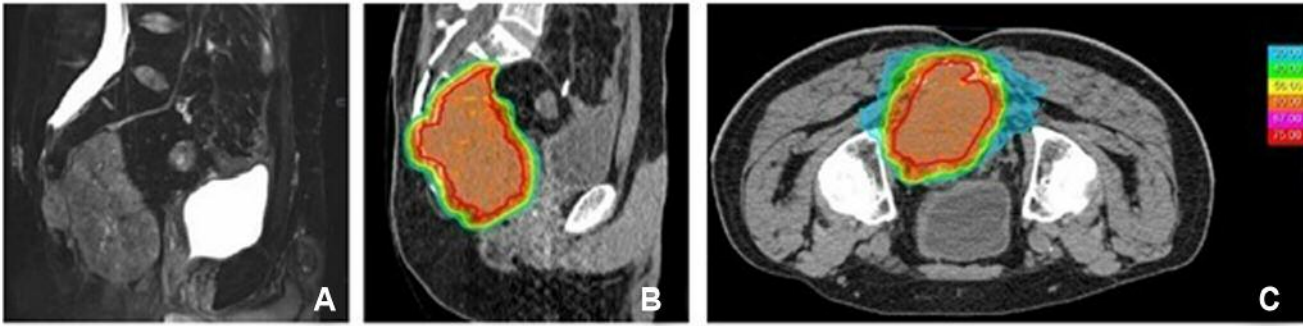


Figure 1. Dose distribution of CIRT. A case of local recurrence of rectal cancer. (A) Tumor extension defined in T2 weighted MRI scan. (B, C). Planning CT scan with typical steep gradient of dose distribution of carbon ion radiotherapy; red area represents the prescription dose of 60 GyRBE, while the light blue area over the edge of the tumour represents the dose of 30 GyRBE.

According to the center's institutional protocol, the following steps were employed (24, 25):

The patient was restrained in the prone position, wearing a customized body thermoplastic mask. In that position, the healthcare professional gathered the planning images (2 mm-thickness CT and contrast-enhanced MRI);

CE-marked Syngo RT treatment planning system (made by Siemens AG Healthcare, Erlangen, Germany; version C13) was used for plan optimization and estimation of RBE-weighted dose distributions;

Following prescription dosage and fractionation scheme in compliance with the National Institute of Radiological Sciences (Chiba, Japan), the dose conversion model mentioned above was applied (18, 19); dose counting was executed in line with the local effect model (LEM) version I exploiting the subsequent parameters: 1) $\alpha/\beta=0.1$ Gy⁻¹; 2) $\beta/\alpha=0.05$ Gy⁻²; 3) $D_t=30$ Gy; and 4) nuclear radius=5 μ m (26-27);

The approved plan was validated by a medical physicist (28);

The set-up was monitored at each treatment session employing two independent custom verification techniques. An infrared optical tracking system and a stereoscopic radiographic verification device were used (29); a six-degrees of freedom set-up correction vector was determined and remotely exerted to the treatment table.

Gross Tumor Volume (GTV) was defined as the area of contrast enhancement on T1-weighted MRI images. To take into account the microscopic spread, the clinical target volume (CTV) included the GTV with an added safety margin (from 5 to 10 mm) depending on the different sites of recurrence and the clinical situation.

The planning target volume (PTV) was dependent on individual factors such as patient positioning or selected beam angles chosen and was CTV+3 and 10 mm of margin (30).

Regular follow-up, including clinical examination with scoring toxicity according to Common Terminology Criteria for Adverse Events version 4.0 (31) took place at our institution. Time-to-event data were calculated from the end of CIRT to last follow-up or death according to the Kaplan-Meier method. Local control (LC) was defined as no evidence of tumor regrowth in the PTV or absence of further tumor regrowth after best-treated lesion response. Local disease-free survival (l-DFS) was defined as the absence of locoregional failure. Metastasis progression-free survival (mPFS) was defined as the absence of distant failure.

Results

Patient and tumors characteristics are shown in Table I. The recurrent disease was presacral in 10 patients, perineal in 1, perianal in 1 and pre-coccygeal in 2 cases. Patients' ages ranged between 34 and 78 years (median: 58.5 years), and the Karnofsky Performance Status was >90. There were twelve males and two females. All patients had a history of surgery and pelvic radiotherapy. Specifically, the dose of the previous radiotherapy ranged from 45 to 50.4 Gy in eleven patients, one of which received a brachytherapy boost up to a total dose of 20 Gy. One patient with a local recurrence of CRC had been previously irradiated with a total dose of 76 Gy for prostate cancer. One patient, at the time of the first recurrence, underwent re-irradiation with stereotactic radiotherapy (30 Gy in six fractions). Before CIRT, four patients received spacer implantation *via* open surgery to create adequate distance between the bowel and the tumor (32). In three cases, an omental flap was used to create space between the tumor and the intestine, and in one case, a polytetrafluoroethylene (PTFE) prosthesis was placed. The median interval between the two courses of radiotherapy was 65 months (range=14-139 months). The median total CIRT dose was 60 Gy RBE (range=35-76.8) and was administered in a median number of 16 fractions (range=15-20 fractions) from 3 to 4.8 Gy RBE per fraction (Figure 1). The GTV ranged from 7.21 to 359.94 cm³, with a median of 154.63 cm³. The PTV ranged from 53.55 to 742.64 cm³ with a median of 306.7 cm³. All patients completed the scheduled treatment course.

The median follow-up was 18 months.

Overall acute toxicity was mild and observed in 3 cases: the most common acute toxicities were grade 2 (G2) (7%) and G1 (14%) neuropathic pain. The major late toxicities consisted of G2 peripheral neuropathy (14%) after a median time of 9 months' post-treatment.

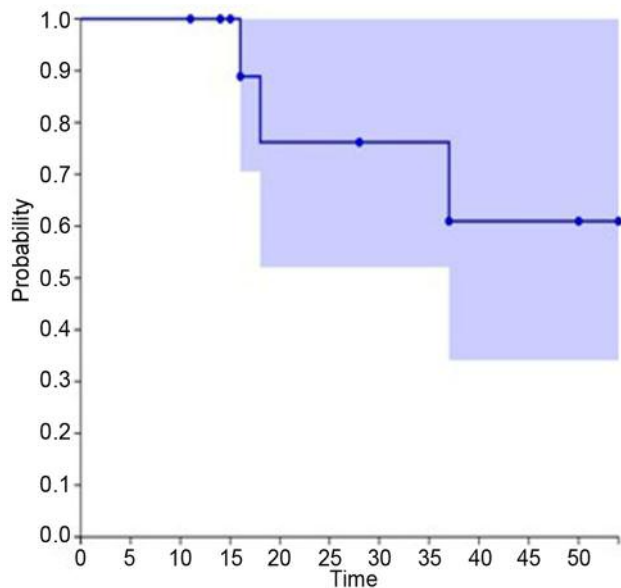


Figure 2. Overall survival. The 1-year and 2-year overall survival (OS) rates were 100% and 76.2%, respectively (Kaplan-Meier plot).

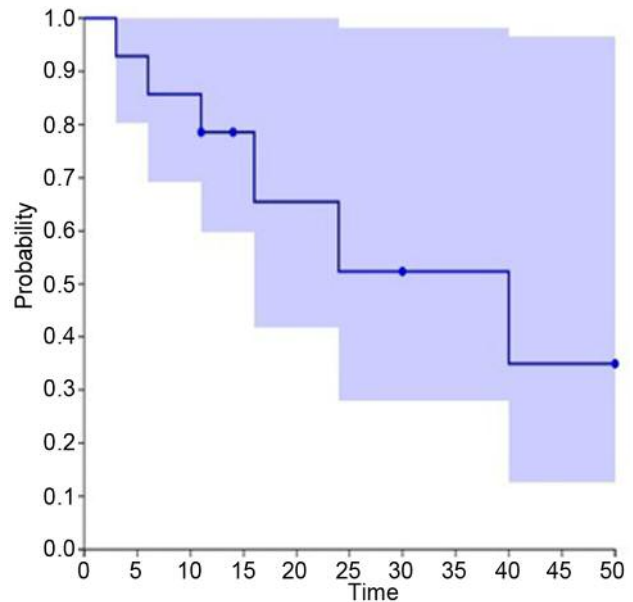


Figure 3. Local disease-free survival. The 1-year and 2-year LC were 78% and 52%, respectively (Kaplan-Meier plot).

Twelve months after CIRT, a sacral asymptomatic insufficiency fracture was observed. No $G \geq 3$ acute/late reaction or pelvic infections were observed. No acute or late $G > 1$ gastrointestinal side effects were reported; two patients complained about a $G2$ intermediate bladder toxicity that resolved with medications. Six patients experienced local progression after CIRT, five of whom in close proximity to the bowel, with a median local control (LC) of 14.5 months (range=2.4-49.5 months); seven patients were diagnosed with systemic progression with a median metastasis-free survival (m-PFS) of 14.4 (range=2-40 months). In the entire series, the 1-year and 2-year LC were 78% and 52%, respectively, the 1-year and 2-year m-PFS rates were 64.3% and 43% and the 1-year and 2-year overall survival (OS) rates were 100% and 76.2%, respectively (Figures 2 and 3).

Discussion

This was a retrospective study to evaluate the clinical outcome of re-irradiation with CIRT for local recurrence of CRC. Surgery, if indicated, is the treatment of choice for locally recurrent CRC. Recurring tumors in previously irradiated CRC areas were often located close to dose-limiting organs such as the intestinal tract. In case of previously high doses to organs at risk (OAR), when it was not possible to deliver doses with curative intent and stay within the OAR dose tolerance constraints, patients were treated with palliative care (chemotherapy or best support care). The palliation offered by

radiotherapy in addition to chemotherapy gives a modest survival benefit and a minimal chance of cure (4). Reports on re-irradiation with photon beam therapy for relapse of CRC are limited, and often radiotherapy is performed concurrently with systemic treatment.

In the Italian multicentric phase II study by the Study Group for Therapies of Rectal Malignancies (STORM), fifty-nine patients with recurrent CRC underwent hyperfractionated chemoradiation (1.2 Gy twice a day up to a total dose of 30 Gy with concomitant infusion of 5-fluorouracil at the dose of 225 mg/m² per day, seven days a week) and, four to six weeks after the end of chemoradiation, surgery was performed in resectable cases. At analysis, acute $G3$ gastrointestinal effects were reported in 5.1% of all cases but no $G4$ gastrointestinal toxicity was documented; the response rate after chemoradiation was 44.1% [95% confidence interval (CI)=29.0-58.9%], in 83.3% of all the cases symptomatic response (pain pelvic control) was observed and the resection was possible in 30 of 59 patients (50.8%) (33).

Also, Tao *et al.* (28) and Sun *et al.* (29) have reported a good tolerance and adequate LC (better in patients who underwent second surgery) using hyperfractionation for the management of local relapse of CRC that had been previously irradiated. In both studies, severe acute grade ≥ 3 gastrointestinal toxicities were described. In the large retrospective series of Tao *et al.* (34), the actuarial 3-year rate of grade 3-4 late toxicities was 34% with a higher rate of $G > 3$ toxicity documented in surgical patients compared to those without surgery (54% versus 16%, $p=0.001$). In the study of

Sun *et al.* (35), acute toxicities, including grade 3–4 diarrhea (9.7%) and late small bowel obstruction (1.4%) were reported.

In the current experience, even though the tumor relapse was closer to the intestinal tract, all patients completed treatment safely, and no episodes of grade ≥ 2 acute or late gastrointestinal toxicity caused by CIRT re-irradiation were experienced.

Besides the favourable dose distribution, CIRT has a variety of documented positive radiobiological features compared to photon radiotherapy, due to the characteristic microscopic distribution of energy deposition. The more considerable energy per particle transferred per unit distance by CIRT determines a higher probability of causing complex double-strand DNA breaks, leading to a more successful cell killing at the tumour site (36–38). The dosimetric and radiobiological properties of CIRT additively define high doses to the tumour saving at-risk adjacent healthy tissues. Therefore, CIRT could be advantageous for patients with radio-resistant CRC not reacted to prior conventional radiotherapy. The same applies when another treatment option is constrained by the adverse effects arising from previous radiotherapy. Different from the above-mentioned studies, in our cohort, temporary treatment interruption due to toxicity or patient lack of compliance was not needed, and all patients completed the scheduled treatment.

At the analysis of the Japanese experience, CIRT was well tolerated and offered a 5-year-LC and survival rates at 73.6 Gy RBE of 88% (95%CI=80–93%) and 59% (95%CI=50–68%), respectively (13).

Regardless, different from the current study, this large cohort of patients (186 treated lesions) did not receive prior radiotherapy, and often the toxicities occurred more frequently in previously irradiated patients. However, the Japanese results concerning LC and toxicity rates were better than those reported in other studies with comparable populations (locally recurrent CRC in patients never previously irradiated to the pelvis) (39). Most likely, the superiority was due to the better dose distribution and higher CIRT-related biological effects.

Habermehl *et al.* have reported the clinical outcome of 19 patients treated with single fractions of 3 Gy (RBE) with CIRT as re-irradiation of locally recurrent CRC. After a median follow-up of 7.8 months, four (21%) local and three (16%) systemic progressions with an estimated local progression of 20.6 months were described. Regarding toxicity, grade 2 gastrointestinal toxicities occurred in two patients, and no grade ≥ 3 toxicities were experienced (14).

In agreement with the above-mentioned study, the CNAO experience showed a functional LC and mild toxicity. When the distance between the relapse and intestinal tract is not enough (at least 5 mm), CIRT may be unsafe. In this case, patients must be evaluated to receive a surgical spacer placement that could create a sufficient distance from the organ at risk allowing tumor treatment with CIRT. In our series, four

patients received spacer implantation by open surgery and a specialized surgical team without any complications.

Despite the limitations of the current study (including the retrospective nature of the data, the limited cohort, and the little follow-up) and considering the impact on clinical outcomes in terms of LC and toxicity, CIRT appears to be a promising, effective, and safe treatment option for the re-irradiation of local recurrent CRC. After considering the mild toxicity, it would be compelling to evaluate concomitant chemotherapy during CIRT for the considered patients.

Conclusion

Re-irradiation with CIRT should be considered in the management of locally recurrent CRC in patients previously irradiated to the pelvis. However, further research is required to identify the long-term safety and efficacy enlarging the sample of treated patients.

Conflicts of Interest

The Authors have no conflicts of interest to declare regarding this study.

Authors' Contributions

All Authors approved the final version of the manuscript. FV conceived the idea for the study. AB: data curation, methodology, writing the original draft and editing; VV data collection and review, LC, AP, AV, FDM review and editing. AM: Methodology and review. AF: data collection and review. MRF, AI, BV, SR, GR, RP, ED, FC, LP: data collection.

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