Carbon Ion Radiotherapy for Locally Recurrent Rectal Cancer

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Patients with rectal cancer initially treated with short- or long-course radiotherapy followed by total mesorectal excision have a pelvic recurrence rate of about 5–10%.^{1–5} Thus, theoretically, those treated with prior radiation may likely benefit from potentially higher doses of radiation in the setting of pelvic recurrence. Compared with X-ray (photon) radiotherapy, particle radiotherapy has unique physical and biologic properties that allow delivery of higher doses of radiation to the tumor with more normal tissue sparing. While proton radiotherapy has been the mainstay in particle radiotherapy, carbon ion radiotherapy (CIRT) could be even more advantageous.⁶ CIRT causes less lateral radiation scatter, leading to better radiation dose distribution and improved organ sparing. It also produces more dense ionizations, leading to higher relative biological effectiveness (RBE), along with reduced effect of hypoxia, lower deoxyribonucleic acid (DNA) damage repair, and less cell cycle dependence, potentially leading to greater effects on the tumor.⁷ Thus, there has been growing interest in leveraging the physical and radiobiologic properties of CIRT in the setting of re-irradiation of various disease sites such as in abdominal and pelvic malignancies.

In this issue of *Annals of Surgical Oncology*, Yamada et al.⁸ retrospectively reported on the safety and efficacy of CIRT in the setting of locally recurrent rectal cancer in patients with prior pelvic irradiation. In that study, 77 patients with locally recurrent rectal cancer who had previously received a median dose of 50 Gy were treated with CIRT to 70.4 Gy (RBE) in 16 fractions over 4 weeks. The

overall 3- and 5-year LC rates were 69% and 62%, respectively, and the overall 3- and 5-year regional control (RC) rates were 85% and 81%, respectively. The median overall survival was 47 months. The authors also reported that 8 (10%) patients developed acute grade 3 toxicity, of whom 5 were grade 3 pelvic infections. Late grade 3 toxicities occurred in 16 (21%) patients, which included 13 late grade 3 pelvic infections. The authors concluded that re-irradiation with CIRT for locally recurrent rectal cancer is safe and effective with acceptable toxicity.

CIRT has been previously investigated in abdominal and pelvic malignancies. In the setting of recurrent rectal cancer, a dose escalation phase I trial showed 5-year local control and survival rates of 88% and 59%, respectively, with no acute reactions higher than grade 3 in patients treated at the highest dose level of 73.6 Gy (RBE).⁹ In addition to recurrent rectal cancer, CIRT has been evaluated and extensively reviewed in the setting of pancreatic cancer.¹⁰ The efficacy of radiotherapy in pancreatic cancer is often limited by its inherent radioresistance likely secondary to hypoxia¹¹ and the proximity to surrounding normal tissue such as the duodenum. However, several studies have shown CIRT to be a promising treatment option to improve overall survival and local control with limited toxicity in patients with resectable¹² and locally advanced¹³ pancreatic cancer.

Prior studies on X-ray (photon) re-irradiation for recurrent rectal cancer have reported accelerated hyperfractionated approaches involving twice-daily treatment.^{14,15} Valentini et al. reported a phase II trial of 40.8 Gy in 1.2 Gy twice-daily fractions in 59 patients, with 5-year local control of 38.8% in all patients and 69.0% in radically resected patients.¹⁴ Similarly, Tao et al. reported that a median dose of 39 Gy in 1.5 Gy twice-daily fractions in 102 patients resulted in 3-year freedom from local progression of 40% in all patients and 49% in patients undergoing surgical resection.¹⁵ In contrast, Yamada et al. report 3- and 5-year LC rates of 69% and 62%,

respectively, which appear higher compared with that in the prior studies, especially given that patients in the study by Yamada et al. did not undergo surgical resection. Acute and late toxicity from CIRT also appears comparable with what has been previously reported in patients with prior radiation receiving X-ray radiotherapy for recurrent rectal cancer.

Overall, Yamada et al. add to the growing body of literature regarding the use of CIRT in previously irradiated malignancies. However, it is important to note that the patients treated in this cohort were carefully selected. For example, the recurrent tumor edge had to be greater than 3 mm from key structures (bowel, bladder, and urethra); these criteria would exclude many common sites of recurrences, including anastomotic recurrences. Therefore, CIRT would be a viable option only for a subset of patients with locally recurrent rectal cancer. Such selection criteria also make it difficult to compare the results with that in prior studies using other radiation modalities. Furthermore, it is important to note that CIRT has very limited availability, with only 13 centers worldwide. Further studies would be needed to determine if CIRT is a cost-effective option at the patient, provider, and healthcare system level.

In conclusion, Yamada et al. demonstrate that CIRT is a promising radiation modality that provides durable LC control rates with acceptable rates of toxicity in select patients with locally recurrent rectal cancer treated with prior pelvic irradiation. Future studies should aim to further evaluate the role of CIRT for recurrent cancers, ideally through randomized comparisons with other radiation approaches.

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