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LETTER TO THE EDITOR

Carbon ion radiation therapy in prostate cancer: The importance of dosage

Teeradon Treechairusame, Pahnwat T Taweesedt

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Abstract

In this article, we comment on the article by Ono *et al*. We focus specifically on the carbon ion radiotherapy studies and the method to calculate the dosing schedule. While photon hypofractionated radiotherapy in prostate cancer has demonstrated improvement in tumor control with reduced gastrointestinal toxicity compared to conventional radiotherapy, carbon ion radiotherapy (CIRT) offers additional physical and biological advantages. Recent findings, including those from Ono *et al*, have established new dose constraints of CIRT for prostate cancer treatment and risk factors for rectal bleeding. Due to limited data on CIRT dosing, this study underscores the need for more research to refine dose calculation methods and better understand their effects on clinical outcomes.

Key Words: Prostate cancer; Carbon ion radiotherapy; Bleeding; Toxicity; Dose

Core Tip: Carbon ion radiotherapy (CIRT) is widely implemented for many cancer types, including prostate cancer. Gastrointestinal toxicity, particularly rectal bleeding, is a notable risk of radiotherapy. The knowledge of CIRT dosage is crucial as it may impact the risk of rectal bleeding.

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TO THE EDITOR

The research topic aimed to identify the dosimetric parameters which correlated with the rate of rectal bleeding toxicity after 12 sessions of carbon ion radiotherapy (CIRT)[1].

External radiotherapy is one of the mainstay approaches to treat prostate cancer. Based on the low α/β value[2-5], prostate cancer is sensitive to hypofractionated dosing schedule which can improve the local tumor control rates. Many randomized phase III photon studies in prostate cancer reported similar tumor control outcomes between hypofractionation and conventional radiotherapy[5-8]. The adverse effects associated with hypofractionated radiotherapy are lower than the conventional radiotherapy. Particularly, late gastrointestinal (GI) toxicity exceeding grade 2 in patients undergoing hypofractionated radiation therapy for prostate cancer was observed in 10% to 22.4%. Thus, the hypofractionation approach has been considered a standard dosing schedule for treating prostate cancer due to its comparable efficacy and safety, along with a shorter treatment duration.

Regarding particles used in radiation therapy, heavy ion therapy such as CIRT offers both physical and biological advantages over conventional photon radiotherapy[9,10]. By taking its unique properties, CIRT allows dose escalation to the tumor, while reducing radiation dose to adjacent normal tissues. To date, many studies use the hypofractionation approach for CIRT in nearly every type of cancer. Shanghai Proton and Heavy Ion Center reported 64 patients with localized prostate cancer who were successfully treated with carbon ion therapy at a dosage ranging from 59.2 to 66 Grey (Gy) with relative biological effectiveness (RBE) in 16 to 24 fractions (Fr). Notably, there was a 0% rate of late GI toxicity [11]. Similarly, 3 studies conducted in Japan on patients with high-risk localized prostate cancer who received CIRT at doses of 57.5 to 66 Gy (RBE) in 16 to 20 Fr, and long-term androgen deprivation therapy had a 10-year prostate cancer-specific mortality rate of 4.3%. The 10-year incidence of grade 2 GI toxicity was 6.2% and no reports of grade 3 GI toxicity [12].

A phase I/II clinical trial in 2010 evaluated the CIRT feasibility of 51.6 Gy (RBE) in 12 Fr over 3 weeks, including forty-six patients (protocol 1002)[13]. The result showed both safety and efficacy, with a median follow-up duration of 32.3 months. Nonetheless, there are still a limited number of studies on the clinical usage of 51.6 Gy (RBE) in 12 Fr dose schedule, concerning both clinical outcome and long-term toxicity[13,14]. Based on regimen 1002 and previous studies using a 12-dose regimen, the recommended dose limits for the rectum are as follows: The rectal volume prescribed 53 Gy (RBE), 50 Gy (RBE), and 40 Gy (RBE) should be ≤ 0%, ≤ 7%, and ≤ 16%, respectively. The 5-year incidence rates were 0-0.4% for grade 2 and 0% for grade 3 GI toxicity. Takakusagi *et al*[15] using 52.6 Gy (RBE) in 12 Fr dosing schedule also reported the excellent 5-year overall survival[15]. The 5-year cumulative incidence of grade 2 or more late genitourinary and GI toxicity was 7.4% and 1.2%, respectively. They limited dose constraint for the rectum at the volume (cc) irradiated with 80% of the prescribed dose of < 10 cc.

In a study by Fukata *et al*[16], CIRT was predicted to have lower probability of rectal toxicity than intensity-modulated photon radiation therapy based on dose-volume histogram and normal tissue complication probability (NTCP) models [16]. Based on a treatment dose schedule of 63 to 66 Gy (RBE) in 20 Fr, Zhang *et al*[17] recommended the dose constraint for rectal organ at Dmean < 50 Gy (RBE), Dmax < 66 Gy (RBE), D5cc < 60 Gy (RBE) and D10cc < 50 Gy (RBE)[17]. The D2cc and D5cc were important predictors of rectal toxicity equal or greater than grade 1 and 2 in patients with gynecological carcinoma treated by 52.8 to 74.4 Gy (RBE) delivered in 20 to 24 fractionation schemes, according to 2 retrospective studies[18,19]. Due to the linear-quadratic model being applicable with less certainty in CIRT than photon radiotherapy, the effects of alterations in the dose fractionation schedule for CIRT are difficult to estimate. Furthermore, there is no evidence that α/β value calculated by a photon can be used for CIRT because α and β are functions with depth in the carbon ion beam. Secondly, the α/β value of prostate cancer had a varied range from 1.5 to 4.9. The NCTP parameter calculated by Fukahori *et al*[20] was derived from several dose schedules without accounting for the fractionation factor, leading to uncertainty in the NTCP model[3,5,20]. Fukata *et al*[16] reported several dosimetric factors to prediction of rectal toxicity are lower CIRT compared to intensity-modulated radiotherapy from NTCP model. Conversely, clinical outcome of rectal toxicities was similar for two modalities[16]. Lastly, CIRT relies on RBE-weighted dose calculations. Two different models were used including the microdosimetric kinetic model, predominately used in Japan, and the local effect model which mainly utilized in European centers[21]. These two different model calculations might influence clinical outcomes.

In this study by Ono *et al*[1], 259 localized prostatic cancer patients were treated with CIRT 51.6 Gy (RBE) in 12 Fr at the East Japan Heavy Ion Center[1]. Of these patients, 90.3% of patients received androgen deprivation therapy. Rectal toxicity was assessed using Common Terminology Criteria for Adverse Events version 5.0. The median follow-up time was 31 months (range 14-40 months) which is relatively short to observe long-term toxicity. The cumulative incidence of rectal toxicity in grades 1 and 2 are 5.8%, and 3.5%, respectively. The incidence of rectal toxicity is higher than the previous studies[11-14]. In this cohort, they explored new dose constraints of rectal toxicity from clinical experiences in a 12-fraction dosing schedule. They initiated new cut-off values, which were D6cc = 34.34 Gy (RBE), D2cc = 46.46 Gy (RBE), V10 Gy (RBE) = 9.85 cc, V20 Gy (RBE) = 7.00 cc, V30 Gy (RBE) = 6.91 cc, and V40 Gy (RBE) = 4.26 cc. The D2cc, V10 Gy (RBE), and V20 Gy (RBE) cut-off values are important predictors of grade 2 rectal bleeding[1].

Many studies reported that androgen deprivation therapy, anticoagulants, cirrhosis, and diabetes mellitus are associated with a significantly higher risk of late rectal bleeding toxicity greater than grade 2[22,23]. Moreover, Kim *et al* [22] reported that to minimize the risk of rectal toxicity, attention should be given to doses per fraction and hotspots, especially in patients at high risk of bleeding[22]. Contrary to the other studies, androgen deprivation therapy, anticoagulants, and diabetes mellitus did not increase the risk of rectal bleeding in this study. These findings may be influenced by the number of participants in the studies, especially the ratio of those with and without androgen deprivation therapy. Caution is advised in the use of CIRT in combination with these medications and patients with this co-morbidity until further evidence is available. Regarding dose calculations, there is limited information to compare between different dosing schedules in CIRT. This new dose constraint for the 12-fraction dosing schedule provides insights into the GI toxicity related to this schedule. However, further studies and validations in clinical practice are required to enhance more understanding regarding the dose calculation methods, comorbidities of the patients and their impact on toxicity outcomes.

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FOOTNOTES

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