Editorial

Rectal cancer: do protons have prospects?

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Preoperative chemoradiation and preoperative short course radiotherapy have widely been accepted as standards of care for stage II and III rectal cancer. However, pelvic radiotherapy can lead to significant rates of acute and late toxicity. Advances in radiation therapy technique and newer radiation therapy modalities could potentially reduce acute and late toxicity rates, by limiting radiation exposure to normal tissues. In this issue, Colaco *et al.* report a dosimetric study comparing proton therapy with 3-dimensional conformal radiotherapy (3D-CRT) and intensity modulated radiation therapy (IMRT), in an effort to lower treatment-related toxicity (1).

Colaco *et al.* report that proton therapy reduced bone marrow exposure and small bowel exposure, compared to both IMRT and 3D-CRT. Proton therapy also reduced bladder exposure, compared to 3D-CRT, but not compared to IMRT. Their findings are similar to that reported by previous studies on proton therapy for rectal cancer, which also showed that proton therapy reduced normal tissue exposure compared to 3D-CRT and IMRT (2-4). However, all of these studies have been dosimetric analyses and not clinical evaluations. While proton therapy does appear to reduce normal tissue exposure, it remains unknown whether this reduction will lead to differences in acute and late toxicity.

Clinical studies, ideally prospective trials, will be necessary to evaluate the role of proton therapy in the neoadjuvant treatment of rectal cancer. However, it will be difficult to design such studies. Treatment-related toxicity in rectal cancer patients is multifactorial, arising from the combination of chemotherapy, radiation therapy and surgery. Hence, it may be difficult to discern the contribution of radiation therapy to toxicity. If the use of proton therapy leads to only a modest-sized reduction in toxicity, then a large sample size will be required to demonstrate the benefit of proton therapy. Furthermore, long follow-up will be required to evaluate late toxicity. Similar challenges have made it difficult to evaluate the role of IMRT for rectal cancer. While multiple dosimetric studies have shown that IMRT reduces normal tissue exposure, only a limited number of retrospective studies have shown reductions in acute toxicity; furthermore, a prospective study did not show a significant difference in acute toxicity with the use of IMRT compared to conventional radiotherapy (5-8).

Proton therapy for rectal cancer may be associated with certain technical challenges. For example, proton range is highly dependent on the stopping power of different substances; proton range is much higher in air than in tissue. Changes in rectal gas volume may therefore affect proton range, leading to either undercoverage of the target or overexposure of normal tissues. In Colaco *et al.*'s study, Hounsfield units were overridden for air in the rectum. Hence, this study did not account for uncertainties arising from rectal gas. Further studies are needed on such technical factors.

Proton therapy may have a potential role in some specific clinical situations. Proton therapy may reduce the risk of second malignancies in patients undergoing radiation therapy for rectal cancer at a young age. Proton therapy may also have a role in reirradiation for rectal cancer, in patients previously treated with pelvic radiation therapy. While it is difficult to develop clinical trials for such uncommon indications, retrospective studies may help us better understand the role of proton therapy in these situations.

Studies on proton therapy have explored one way of decreasing radiation-related toxicity: reduction in the dose

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to normal tissues. However, another way of decreasing toxicity could be patient selection, i.e., reduction in the number of patients treated with radiation therapy. A large phase II/III trial (PROSPECT) is currently comparing standard preoperative chemoradiation versus induction chemotherapy and selective radiotherapy for rectal cancer. A prospective European trial (MERCURY) has indicated that MRI could be used to identify patients likely to have a good outcome with surgery alone without preoperative radiotherapy (9). In the future, more selective use of radiation may help lower treatment-related toxicity in rectal cancer patients.

In summary, Colaco *et al.* have presented an intriguing dosimetric study on the role of proton therapy for the treatment of rectal cancer. Clinical studies will be needed to further elucidate the potential role of proton therapy.

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