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Mini Review

Online MR guided radiotherapy for rectal cancer. New opportunities

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Rectal cancer might not be the first entity that comes into one's mind when potential indications for online magnetic resonance guided radiotherapy (MRgRT) with a MRI-linac are discussed. The treatment of the primary tumor and the pelvic lymphatics is relatively simple and even the benefit of intensity modulated radiotherapy over three-dimensional radiotherapy is a matter of debate [1]. However, as soon as we move beyond standard treatment protocols rectal cancer appears to be an indication for online MRgRT that teases out the full potential of MRI-linac hybrid devices.

For organ preservation in rectal cancer ("wait & see"), various strategies to increase the clinical complete response rate have been tested in clinical trials [2]. Dose escalation with external beam radiotherapy is possibly the most intuitive approach, however various ongoing clinical trials rather favour alternative strategies such as total neoadjuvant therapy (NCT03561142) [3]. The reason for this is two-fold: first, very high doses are required in order to substantially increase the likelihood to achieve a complete response. Appelt et al. modelled that doses clearly beyond 70 Gy are required to achieve a complete response in 50% of patients [4]. In a systematic review and meta-analysis of clinical trials that applied doses higher than 60 Gy a pooled pCR rate of 20.4% is reported which equals only a moderate increase compared to standard treatments [5]. Second, rectal primaries can only – if at all – poorly be visualized on cone-beam imaging. For this reason and due to considerable day-to-day inter-fractional motion, margins greater 10 mm to ensure adequate tumor coverage are not uncommon in trials that applied a boost [6,7]. The superior image quality of MRI-Linac hybrid devices over cone-beam CT based linear accelerators permits the visualization of these tumors on a daily basis. Furthermore, the concept of online MR guided radiotherapy includes the daily adaptation of the treatment plan to the current anatomy and therefore has the potential to reduce doses in organs at risk, such as the bowel, the anal sphincter, the bladder or the normal rectal mucosa. Particularly patients with tumors in the mid rectum, who are candidates for sphincter sparing surgery, might benefit most from such daily online MR guided adaptive workflow via lower doses to the anal sphincter. Furthermore, in the setting of re-irradiation of recurrent rectal cancer a benefit of the daily adaptive strategy with reduced margins can be hypothesized.

Innovative strategies with MRI-linac hybrid devices are however not limited to the superior visualization of soft tissues and the possibility of daily plan adaptation. Functional MR imaging, such as diffusion weighted imaging (DWI), can provide information about the biology of the target of interest. It has been shown previously that changes on DWI can be applied as an early predictor of response to radiotherapy and outperform volume changes [8,9].

In most of the studies that evaluated the predictive value of apparent diffusion coefficients (ADC) changes a single time point for re-assessment was chosen. Hybrid devices will permit the acquisition of functional imaging on a daily base during treatment. This data can be used to refine response prediction and generate response prediction models that do not rely on individual time points but include the changes over the entire course of treatment [10].

While the acquisition of functional imaging *per se* does not require a hybrid device, novel adaptive strategies that define subvolumes for dose escalation based on functional imaging do require the online visualization of these areas for precise dose escalation. The hypothesis of such a so called "bio-boost" concept, is that areas with persistent diffusion restriction on functional imaging during treatment, harbor tumor cells, that do need a higher dose to overcome their radioresistant phenotype. It has been shown before that functional imaging from an MRI-linac is capable to detect such persistent areas of restricted diffusion [11].

One of the challenges in the future will be to define optimal acquisition timepoints and ADC cut-offs for the definition of these areas and to implement this information in an online adaptive workflow. Even though phantom based studies showed favourable data in terms of accuracy and reproducibility of quantitative MRI data acquired at an MRI-Linac, more patient based data that confirms this is warranted [12].

Self-evidently, the above mentioned strategies will have to be developed and tested within well-designed clinical trials, that are currently under development.

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References

[1] Lawrie TA, Green JT, Beresford M, Wedlake L, Burden S, Davidson SE, et al. Interventions to reduce acute and late adverse gastrointestinal effects of pelvic radiotherapy for primary pelvic cancers. Cochrane Database Syst Rev 2018;1:CD012529.

[2] Gani C, Bonomo P, Zwirner K, Schroeder C, Menegakis A, Rodel C, et al. Organ preservation in rectal cancer – challenges and future strategies. Clin Transl Radiat Oncol 2017;3:9–15.

[3] Smith JJ, Chow OS, Gollub MJ, Nash GM, Temple LK, Weiser MR, et al. Preservation in Rectal Adenocarcinoma: a phase II randomized controlled trial evaluating 3-year disease-free survival in patients with locally advanced rectal cancer treated with chemoradiation plus induction or consolidation chemotherapy, and total. BMC Cancer 2015;15:767-.

[4] Appelt AL, Ploen J, Vogelius IR, Bentzen SM, Jakobsen A. Radiation dose-response model for locally advanced rectal cancer after preoperative chemoradiation therapy. Int J Radiat Oncol Biol Phys 2013;85:74–80.

[5] Rödel C, Liersch T, Becker H, Fietkau R, Hohenberger W, Hothorn T, et al. Preoperative chemoradiotherapy and postoperative chemotherapy with fluorouracil and oxaliplatin versus fluorouracil alone in locally advanced rectal cancer: initial results of the German CAO/ARO/AIO-04 randomised phase 3 trial. Lancet Oncol 2012;13:679–87.

[6] Appelt AL, Ploen J, Harling H, Jensen FS, Jensen LH, Jorgensen JC, et al. High-dose chemoradiotherapy and watchful waiting for distal rectal cancer: a prospective observational study. Lancet Oncol 2015;16:919–27.

[7] Kleijnen JJE, van Asselen B, Van den Begin R, Intven M, Burbach JPM, Reerink O, et al. MRI-based tumor inter-fraction motion statistics for rectal cancer boost radiotherapy. Acta Oncol 2019;58:232–6.

[8] Lambrecht M, Vandecaveye V, De Keyzer F, Roels S, Penninckx F, Van Cutsem E, et al. Value of diffusion-weighted magnetic resonance imaging for prediction and early assessment of response to neoadjuvant radiochemotherapy in rectal cancer: preliminary results. Int J Radiat Oncol Biol Phys 2012;82:863–70.

[9] Joye I, Deroose CM, Vandecaveye V, Haustermans K. The role of diffusion-weighted MRI and (18)F-FDG PET/CT in the prediction of pathologic complete response after radiochemotherapy for rectal cancer: a systematic review. Radiother Oncol 2014;113:158–65.

[10] Boldrini L, Cusumano D, Chiloiro G, Casa C, Masciocchi C, Lenkowicz J, et al. Delta radiomics for rectal cancer response prediction with hybrid 0.35 T magnetic resonance-guided radiotherapy (MRgRT): a hypothesis-generating study for an innovative personalized medicine approach. Radiol Med 2019;124:145–53.

[11] Shaverdian N, Yang Y, Hu P, Hart S, Sheng K, Lamb J, et al. Feasibility evaluation of diffusion-weighted imaging using an integrated MRI-radiotherapy system for response assessment to neoadjuvant therapy in rectal cancer. Br J Radiol 2017;90:20160739.

[12] Kooreman ES, van Houdt PJ, Nowee ME, van Pelt VWJ, Tijssen RHN, Paulson ES, et al. Feasibility and accuracy of quantitative imaging on a 1.5 T MR-linear accelerator. Radiother Oncol 2019;133:156–62.