Launch of the National Rectal Cancer IMRT Guidance

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Abstract:

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Randomised trials have demonstrated that pre-operative radiotherapy in rectal cancer reduces the risk of locoregional recurrence when delivered either in the form of a one-week short course, or a long course of treatment combined with concurrent chemotherapy [1-6]. However, radiotherapy may also be associated with long-term, treatment-related toxicity [7-10]. Compared to 3D conformal radiotherapy (3D-CRT), intensity modulated radiotherapy (IMRT) has the potential to deliver superior target dose conformality and homogeneity and dose escalation including delivery of a Simultaneous Integrated Boost (SIB) whilst decreasing doses to organs at risk (OAR), especially small bowel, which might result in a reduction in early and late toxicities [11-20].

The majority of studies that have examined IMRT in rectal cancer have reported dosimetric endpoints or early toxicities [11-13, 15-17, 20, 21]. Early gastrointestinal toxicity has been shown to have a close dose-volume relationship with the volume of small bowel irradiated [22, 23]. However, no phase III studies directly comparing IMRT with 3D-CRT for either toxicity or efficacy outcomes have been reported. Despite this absence of high-level evidence, the uptake of IMRT in rectal cancer in the UK and internationally is increasing [24, 25].

As well as theoretical advantages and preliminary evidence of improved toxicity compared with 3D-CRT, IMRT or volumetric modulated arc therapy (VMAT) may deliver efficiencies in the radiotherapy workflow. Compared with 3D-CRT and delivery of a sequential boost, IMRT has potential resource/patient convenience benefits, including reduced planning time, shorter treatment delivery time and shorter overall treatment time. It may, however, be associated with an increased time for target and OAR definition [13, 14, 17-19].

The radiotherapy modernisation programme in the UK also played a major role in the increased use of IMRT [26-31]. Its overarching aims were to improve access to modern, advanced and innovative radiotherapy technologies including IMRT, to improve the patient experience/provision of holistic care, to reduce variation in quality by adopting standardised best practice protocols, to increase participation in research and clinical trials and to undertake an equipment modernisation

programme [31]. In 2012, the Department of Health in the UK recommended that IMRT should be offered to all patients where they could benefit from reduced treatment toxicities, stating a percentage of patients in any department who should be treated with IMRT [32]. This resulted in an increase in the uptake of IMRT in the UK. However the landscape of IMRT utilisation for rectal cancer and how it has been implemented has up to now been unknown. Data collected from the Radiotherapy Dataset and National Cancer Data Repository, in the era before IMRT was widely adopted in the UK, was recently examined [33]. The authors concluded that even without the additional complexity of IMRT, there was a wide variation in both the use and type of radiotherapy to treat rectal cancer.

This heterogeneity in UK practice demonstrates the need for a national strategy to harmonise implementation and delivery of IMRT for rectal cancer. An exemplar that informed the working group was the National Anal Cancer IMRT Guidance [34]. These recommendations for best practice have been widely adopted and have been successful in providing a national dataset for further research [35-37]. The harmonisation in practice has also helped establish a platform for current clinical trials [38]. It is known that the use of guidelines and protocols also correlates with improved radiotherapy delivery and patient outcomes including improved survival [39-45]. In summary, we consider the potential benefits for patient outcomes and the harmonisation of UK practice to be justification for development of robust and comprehensive rectal IMRT guidance.

Given the potential complexities associated with an IMRT workflow relating to rectal cancer treatment in the UK, a national multicentre, multidisciplinary working group was convened. The intention was to bring together clinicians, physicists and radiographers experienced in the treatment of rectal cancer using IMRT, to review and discuss the available evidence and to produce rectal cancer IMRT guidance. The overarching aim of the guidance was to encourage harmonisation of practice and to support the implementation of IMRT for the treatment of rectal cancer throughout the UK. The guidance was to provide specific recommendations regarding patient selection, pre-treatment investigations, target volume and OAR delineation, treatment planning, verification and IMRT delivery. It is hoped that this will increase adoption of IMRT and develop and standardise practice in those centres already using the technology leading to better outcomes for our patients. **Figure 1** illustrates the timeline and individual projects performed in the development of the guidance.

The National Rectal Cancer IMRT Guidance was developed by the working group through an iterative process which included face to face meetings at the Royal College of Radiologists (RCR) and, later, videoconference meetings. Throughout the process, in addition to synthesising the available evidence to inform our recommendations, we aimed to consider the views of the radiotherapy

community in the UK regarding what was practical and implementable in all centres. We reached out to all radiotherapy centres in the UK in the form of a survey of IMRT practice [XX]. We consider that a response rate of 70% represents a good return especially given the COVID-19 pandemic, although we remain mindful that this is not necessarily representative of the views and practice at all centres. The full results from the survey, including areas of consensus and heterogeneity in current UK practice, are outlined in an accompanying paper by XX and XX et al [XX]. These results informed multiple guidance recommendations and were especially useful where there were uncertainties within the working group concerning the feasibility of particular recommendations in UK clinical practice.

The working group also undertook several additional projects to inform specific aspects of the guidance. Our recommendations regarding target volume delineation depending on the extent of T and N staging was informed by a survey of 30 clinicians in 11 centres performed by O'Cathail et al [46]. A project was undertaken in several centres to identify the most reliable method of determining the superior border of the elective volume and this work helped inform our recommendation that the S1/2 vertebral interspace be taken as the superior border. Although this represents a departure from the superior border of S2/3 in ARISTOTLE, in this trial the superior border was deliberately lower than S1/2 because of concerns regarding excess toxicity with the addition of irinotecan [47]. Appelt et al performed a comprehensive literature review that informed our recommendations regarding target volume margins, considering published measurements of internal organ motion and whether image guidance is to be performed daily or via a 'no action limit' protocol [48]. Multiple test plans were delineated and planned in two centres to quality assure our recommendations regarding planning objectives and OAR constraints. Prior to publication of the guidance, we requested external moderation of the document by several reviewers and the group reflected on this feedback and further modified the guidance as a result.

There are likely to be contentious aspects of the guidance which were also encountered by the group during its development. These reflect areas of uncertainty in clinical practice and ongoing discussion within the wider community. As an example, the most obvious manifestation of this concerned the delineation of individual small bowel loops versus a peritoneal cavity/'bowel space' structure. As with all controversial areas within the guidance, we used the results of the survey to aid our decision making concerning the recommendations contained within the guidance. We do accept that there may be some recommendations that do not align completely with individual clinician or radiotherapy centre current preferences for practice. However, we do emphasise that we have made considerable efforts to obtain the input of the wider community and considered their feedback in the framing of our recommendations. We also sought the input of several external

reviewers and further modification of the guidance was performed following this moderation. Many members of both the development group and the wider review panel have accepted that the benefits of a national guidance that harmonises clinical practice across the UK are likely to outweigh firmly held individual views concerning particular aspects of practice where there exists limited high level evidence as to the optimum approach.

The guidance is now available on the RCR website at [insert guidance web address once available]. The launch of the guidance was timed to coincide with the rectal IMRT workshop at RCR20 in October 2020 and was accompanied by the publication of the results of the survey [XX]. We intend to publicise the guidance at the workshop, via RCR member e-mail and social media platforms. The success of the guidance will depend on its use by the radiotherapy community. We would consider the guidance to have been a success if it encourages further adoption of IMRT and development of practice within centres already using IMRT. We hope it will help establish a platform for the next generation of clinical trials in rectal cancer. We plan to repeat our survey in 1-2 years to investigate whether our recommendations have been adopted and seek specific feedback from centres. The guidance will be housed on the RCR website and should be seen as a work in progress.

In summary, we hope the National Rectal Cancer IMRT Guidance will improve the delivery of radiotherapy for patients with rectal cancer. We have aimed to make its development a collaborative effort with the whole UK radiotherapy community, especially with regards to the survey and external review of the guidance. Moving forward, we strongly encourage feedback from centres to inform subsequent versions. Specific comments can be addressed to: publications@rcr.ac.uk. By calling on all centres to embrace this guidance, the ambition is to harmonise and strengthen radiotherapy practice in the UK and to continue to lead on the international stage.

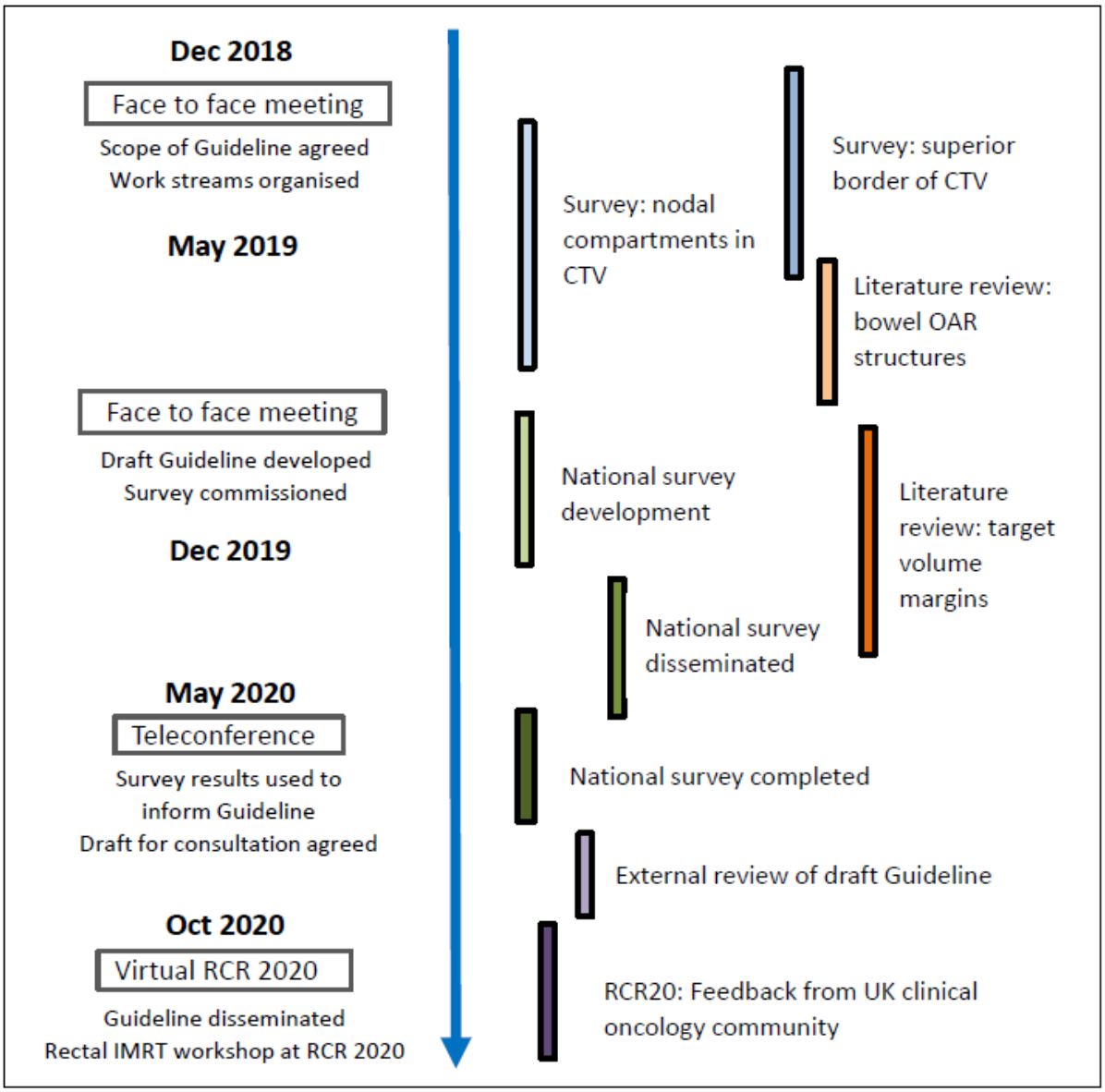

Figure caption:

Figure 1: A flow diagram illustrating the timeline for the National Rectal Cancer IMRT Guidance and the individual projects and milestones during its development

CTV, clinical target volume; OAR, Organs At Risk; RCR, Royal College of Radiologists; RCR20, Royal College of Radiologists annual conference 2020

References

1. Bosset, J.F., L. Collette, G. Calais, et al., *Chemotherapy with preoperative radiotherapy in rectal cancer.* N Engl J Med, 2006. **355**(11): p. 1114-23.

2. Erlandsson, J., T. Holm, D. Pettersson, et al., *Optimal fractionation of preoperative radiotherapy and timing to surgery for rectal cancer (Stockholm III): a multicentre, randomised, non-blinded, phase 3, non-inferiority trial.* The Lancet Oncology, 2017. **18**(3): p. 336-346.
3. Kapiteijn, E., C.A. Marijnen, I.D. Nagtegaal, et al., *Preoperative radiotherapy combined with total mesorectal excision for resectable rectal cancer.* N Engl J Med, 2001. **345**(9): p. 638-46.
4. Martling, A., T. Holm, H. Johansson, et al., *The Stockholm II trial on preoperative radiotherapy in rectal carcinoma: long-term follow-up of a population-based study.* Cancer, 2001. **92**(4): p. 896-902.
5. Sebag-Montefiore, D., R.J. Stephens, R. Steele, et al., *Preoperative radiotherapy versus selective postoperative chemoradiotherapy in patients with rectal cancer (MRC CR07 and NCIC-CTG C016): a multicentre, randomised trial.* Lancet (London, England), 2009. **373**(9666): p. 811-820.
6. van Gijn, W., C.A. Marijnen, I.D. Nagtegaal, et al., *Preoperative radiotherapy combined with total mesorectal excision for resectable rectal cancer: 12-year follow-up of the multicentre, randomised controlled TME trial.* Lancet Oncol, 2011. **12**(6): p. 575-82.
7. Birgisson, H., L. Påhlman, U. Gunnarsson, et al., *Adverse effects of preoperative radiation therapy for rectal cancer: long-term follow-up of the Swedish Rectal Cancer Trial.* J Clin Oncol, 2005. **23**(34): p. 8697-705.
8. Birgisson, H., L. Påhlman, U. Gunnarsson, et al., *Late adverse effects of radiation therapy for rectal cancer – a systematic overview.* Acta Oncologica, 2007. **46**(4): p. 504-516.
9. Marijnen, C.A.M., C.J.H.v.d. Velde, H. Putter, et al., *Impact of Short-Term Preoperative Radiotherapy on Health-Related Quality of Life and Sexual Functioning in Primary Rectal Cancer: Report of a Multicenter Randomized Trial.* 2005. **23**(9): p. 1847-1858.
10. Stephens, R.J., L.C. Thompson, P. Quirke, et al., *Impact of Short-Course Preoperative Radiotherapy for Rectal Cancer on Patients' Quality of Life: Data From the Medical Research Council CR07/National Cancer Institute of Canada Clinical Trials Group C016 Randomized Clinical Trial.* 2010. **28**(27): p. 4233-4239.
11. Arbea, L., L.I. Ramos, R. Martínez-Monge, et al., *Intensity-modulated radiation therapy (IMRT) vs. 3D conformal radiotherapy (3DCRT) in locally advanced rectal cancer (LARC): dosimetric comparison and clinical implications.* Radiation Oncology, 2010. **5**(1): p. 17.
12. Mok, H., C.H. Crane, M.B. Palmer, et al., *Intensity modulated radiation therapy (IMRT): differences in target volumes and improvement in clinically relevant doses to small bowel in rectal carcinoma.* Radiation oncology (London, England), 2011. **6**: p. 63-63.
13. Ng, S.Y., K.L. Colborn, L. Cambridge, et al., *Acute toxicity with intensity modulated radiotherapy versus 3-dimensional conformal radiotherapy during preoperative chemoradiation for locally advanced rectal cancer.* Radiother Oncol, 2016. **121**(2): p. 252-257.
14. Owens, R., S. Mukherjee, S. Padmanaban, et al., *Intensity-Modulated Radiotherapy With a Simultaneous Integrated Boost in Rectal Cancer.* Clin Oncol (R Coll Radiol), 2020. **32**(1): p. 35-42.
15. Parekh, A., M.T. Truong, I. Pashtan, et al., *Acute gastrointestinal toxicity and tumor response with preoperative intensity modulated radiation therapy for rectal cancer.* Gastrointestinal cancer research : GCR, 2013. **6**(5-6): p. 137-143.
16. Patel, S., T. Vuong, O. Ballivy, et al., *Phase II trial of pelvic intensity-modulated radiotherapy (IMRT) with concurrent chemotherapy for patients with rectal cancer.* International Journal of Radiation Oncology*Biology*Physics, 2004. **60**(1, Supplement): p. S424-S425.
17. Samuelian, J.M., M.D. Callister, J.B. Ashman, et al., *Reduced acute bowel toxicity in patients treated with intensity-modulated radiotherapy for rectal cancer.* Int J Radiat Oncol Biol Phys, 2012. **82**(5): p. 1981-7.

18. Stuyck, C., M. Wegge, P. Bulens, et al., *Moderate dose escalation with volumetric modulated arc therapy improves outcome in rectal cancer.* Acta Oncologica, 2017. **56**(11): p. 1501-1506.
19. Teoh, S. and R. Muirhead, *Rectal Radiotherapy--Intensity-modulated Radiotherapy Delivery, Delineation and Doses.* Clin Oncol (R Coll Radiol), 2016. **28**(2): p. 93-102.
20. Urbano, M.T.G., A.J. Henrys, E.J. Adams, et al., *Intensity-modulated radiotherapy in patients with locally advanced rectal cancer reduces volume of bowel treated to high dose levels.* International Journal of Radiation Oncology*Biology*Physics, 2006. **65**(3): p. 907-916.
21. David, J.M., G. Gresham, S.K. Jabbour, et al., *Neoadjuvant PET and MRI-based intensity modulated radiotherapy leads to less toxicity and improved pathologic response rates in locally advanced rectal cancer.* J Gastrointest Oncol, 2018. **9**(4): p. 641-649.
22. Robertson, J.M., D. Lockman, D. Yan, et al., *The Dose–Volume Relationship of Small Bowel Irradiation and Acute Grade 3 Diarrhea During Chemoradiotherapy for Rectal Cancer.* International Journal of Radiation Oncology*Biology*Physics, 2008. **70**(2): p. 413-418.
23. Tho, L.M., M. Glegg, J. Paterson, et al., *Acute small bowel toxicity and preoperative chemoradiotherapy for rectal cancer: Investigating dose–volume relationships and role for inverse planning.* International Journal of Radiation Oncology*Biology*Physics, 2006. **66**(2): p. 505-513.
24. Reyngold, M., J. Niland, A. Ter Veer, et al., *Trends in intensity modulated radiation therapy use for locally advanced rectal cancer at National Comprehensive Cancer Network centers.* Adv Radiat Oncol, 2018. **3**(1): p. 34-41.
25. Wegner, R.E., S. Abel, R.J. White, et al., *Trends in intensity-modulated radiation therapy use for rectal cancer in the neoadjuvant setting: a National Cancer Database analysis.* Radiat Oncol J, 2018. **36**(4): p. 276-284.
26. Cancer Research UK and NHS England, *A Vision for Radiotherapy, 2014-2024*. 2014.
27. NHS England, *Achieving World-class Cancer Outcomes – A Strategy for England 2015-2020*. 2015.
28. NHS England, *Achieving World-Class Cancer Outcomes: Taking the Strategy Forward*. 2016.
29. NHS England, *Next Steps on the Five Year Forward View*. 2017.
30. NHS England. *Modernising radiotherapy services in England*. 2019 07/10/2019]; Available from: https://www.engage.england.nhs.uk/consultation/radiotherapy-service-specification-consultation/.
31. NHS England, *NHS England's response to the radiotherapy consultation report*. 2019.
32. Department of Health, *Radiotherapy Services in England 2012*. 2012.
33. Morris, E.J.A., P.J. Finan, K. Spencer, et al., *Wide Variation in the Use of Radiotherapy in the Management of Surgically Treated Rectal Cancer Across the English National Health Service.* Clinical oncology (Royal College of Radiologists (Great Britain)), 2016. **28**(8): p. 522-531.
34. *National guidance for IMRT in anal cancer* Version 3.0, 18/04/2016.
35. Gilbert, A., K. Drinkwater, L. McParland, et al., *UK national cohort of anal cancer treated with intensity-modulated radiotherapy: One-year oncological and patient-reported outcomes.* Eur J Cancer, 2020. **128**: p. 7-16.
36. Jones, C.M., R. Adams, A. Downing, et al., *Toxicity, Tolerability, and Compliance of Concurrent Capecitabine or 5-Fluorouracil in Radical Management of Anal Cancer With Single-dose Mitomycin-C and Intensity Modulated Radiation Therapy: Evaluation of a National Cohort.* Int J Radiat Oncol Biol Phys, 2018. **101**(5): p. 1202-1211.
37. Shakir, R., R. Adams, R. Cooper, et al., *Patterns and Predictors of Relapse Following Radical Chemoradiation Therapy Delivered Using Intensity Modulated Radiation Therapy With a Simultaneous Integrated Boost in Anal Squamous Cell Carcinoma.* Int J Radiat Oncol Biol Phys, 2020. **106**(2): p. 329-339.
38. Muirhead, R., K. Drinkwater, S.M. O'Cathail, et al., *Initial Results from the Royal College of Radiologists' UK National Audit of Anal Cancer Radiotherapy 2015.* Clinical oncology (Royal College of Radiologists (Great Britain)), 2017. **29**(3): p. 188-197.

39. Delhorme, J.-B., D. Antoni, K.S. Mak, et al., *Treatment that follows guidelines closely dramatically improves overall survival of patients with anal canal and margin cancers.* Critical Reviews in Oncology/Hematology, 2016. **101**: p. 131-138.
40. Gwynne, S., E. Spezi, D. Sebag-Montefiore, et al., *Improving radiotherapy quality assurance in clinical trials: assessment of target volume delineation of the pre-accrual benchmark case.* The British journal of radiology, 2013. **86**(1024): p. 20120398-20120398.
41. Hanna, T.P., J. Shafiq, G.P. Delaney, et al., *The population benefit of evidence-based radiotherapy: 5-Year local control and overall survival benefits.* Radiotherapy and Oncology, 2018. **126**(2): p. 191-197.
42. Joye, I., M. Lambrecht, D. Jegou, et al., *Does a central review platform improve the quality of radiotherapy for rectal cancer? Results of a national quality assurance project.* Radiotherapy and Oncology, 2014. **111**(3): p. 400-405.
43. Ohri, N., X. Shen, A.P. Dicker, et al., *Radiotherapy protocol deviations and clinical outcomes: a meta-analysis of cooperative group clinical trials.* J Natl Cancer Inst, 2013. **105**(6): p. 387-93.
44. The Royal College of Radiologists. *Radiotherapy target volume definition and peer review – RCR guidance*. 2017 09/07/2019]; Available from: https://www.rcr.ac.uk/publication/radiotherapy-target-volume-definition-and-peer-review.
45. Weber, D.C., M. Tomsej, C. Melidis, et al., *QA makes a clinical trial stronger: evidence-based medicine in radiation therapy.* Radiother Oncol, 2012. **105**(1): p. 4-8.
46. O'Cathail, S.M., R. Muirhead, D. Sebag-Montefiore, et al., *PH-0161 Elective clinical target volumes for rectal IMRT delivery- moving towards a UK wide consensus*, in *ESTRO 39*. 2020: Vienna, Austria.
47. *ARISTOTLE: A phase III trial comparing standard versus novel CRT as pre-operative treatment for MRI defined locally advanced rectal cancer*. Protocol version 5.0, 31/07/2015.
48. Appelt, A.L., M. Beasley, M. Teo, et al. *PO-1638 Treatment delivery uncertainties in rectal cancer radiotherapy – evidence-based margin estimates*. In: *ESTRO 39*, 2020, Vienna, Austria.