Editorial

Anal Cancer: Developing an Intensity-modulated Radiotherapy Solution for ACT2 Fractionation

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Anal squamous cell carcinoma affects approximately 1100 patients per year in the UK, with the incidence increasing yearly [1]. The ACT2 trial, delivering radical chemoradiotherapy, determined the UK standard of care; reporting a complete response rates of 90% and a 3 year progression-free survival of 73% [2]. Due to the large parallel-opposed anterior-posterior/posterior-anterior (AP/PA) fields, there was significant associated acute toxicity; grade 3/4 gastrointestinal and haematological toxicity of 16 and 26%, respectively. Acute toxicity results in delays and interruptions; a concern, as there is evidence to suggest overall treatment time is associated with local control [3–5]. Finally, there is a lack of prospective data quantifying the recognised late side-effects on bowel, urinary and sexual function. Late bowel toxicity culminating in colostomy was seen in 2% of patients in the ACT2 trial [6].

Since the completion of ACT2 there have been significant developments in the staging and treatment of anal cancer. There is interest in improving late morbidity by withholding inguinal node irradiation in early disease. This has led to reports addressing the role of sentinel node biopsy and positron emission tomography/computed tomography in staging. Recent trials have individualized radiotherapy dose according to tumour size and nodal status. Finally, there has been widespread implementation of intensity-modulated radiotherapy (IMRT) to reduce acute toxicity and potentially dose-escalate selected patients.

The Radiation Therapy Oncology Group (RTOG) 0529 phase II study, open from December 2006 to March 2008, delivered a prophylactic dose to uninvolved nodal groups with a simultaneous integrated boost to the primary tumour and involved nodes using IMRT; acute dermatological toxicity was the primary end point [7]. The acute toxicity was compared with that seen in previous RTOG studies using radiotherapy techniques used in the late 1990s, and a statistically significant reduction in grade 2 haematological, grade 3 gastrointestinal and grade 3 dermatological toxicities was reported, although not fulfilling the primary end point. Although not a randomised trial, this study adds further weight to the reduction in toxicity observed in published IMRT series [8–14].

Current controversies regarding IMRT implementation include the optimal duration of treatment with chemoradiotherapy. Since 1987, ACT1 and ACT2 studies have maintained a different approach to European and North American dose and fractionations; with a shorter overall treatment time, no gaps in treatment and lower prescribed and delivered doses. Due to the excellent outcomes within ACT2, this strategy should be maintained moving forward. However, to definitively convert the delivered dose in ACT2 into a simultaneous integrated boost technique remains a challenge. Second, defining and maintaining a consistent planning and delivery technique is of vital importance to facilitate robust outcome comparisons. Thinking towards the future, with an ACT3/4 study on the horizon, a consensus IMRT technique will facilitate set-up and entry into future anal cancer trials. A survey of anal cancer techniques currently in use in the UK was undertaken with the Faculty of Clinical Oncology of The Royal College of Radiologists in October/November 2013. This highlighted a great variation in delineation, volumes and doses currently in use in those centres using IMRT, reflecting the lack of
consistency in published series. Finally, the rigorous quality assurance programme in RTOG 0529 highlighted the risks of implementation without adequate guidelines and support; 81% of plans required revisions, with 46% requiring multiple revisions, primarily due to poor delineation. Robust quality assurance will maintain quality of delivery of IMRT and the integrity of future anal cancer trials. A previous editorial published in Clinical Oncology highlighted the need for a UK protocol with robust collection of prospective toxicity and outcome data to maintain quality of planning and delivery [15].

In response to the Editorial, the Anorectal Subgroup of the National Cancer Research Institute (NCRI) Clinical Studies Group met and produced IMRT guidance. A systematic review of the published literature informed decisions regarding immobilisation, delineation, doses and delivery technique. Representatives from a number of large teaching hospitals and all members of the Anorectal Clinical Studies Group, with a wealth of clinical experience and knowledge of the literature, met a number of times to debate different aspects of planning and delivery. Thereafter, the guidance was circulated to a further nine centres for comment, followed by a presentation and further modifications at the annual NCRI cancer conference before reaching a consensus [16].

There are limitations to these guidelines. As with any rare tumour type, randomised controlled evidence in the literature is lacking, and retrospective studies or small single centre studies are often used to direct guidance. These publications must be interpreted with care and all have limitations; for example, varied staging and treatment strategies, varied follow-up, small sample size, retrospective assessment of toxicity. Therefore, recommendations proposed here are limited by current knowledge from a small number of prospective studies and should not be considered definitive; they will evolve as knowledge expands. The guidance is available from the corresponding author or at www.analimrtguidance.co.uk.

The aim of the proposed guidance is to facilitate the adoption and implementation of IMRT in anal cancer treatment. The prospective audit, in collaboration with the Royal College of Radiologists, planned for November 2014 will test if adoption has been successful and document toxicity and outcomes of the novel doses and fractionations in comparison with published data, including ACT2. If outcomes appear favourable, the proposed technique will form the basis of the standard arm for the next national study.

References


