Six Irish radiation oncology departments to participate in study to reduce side effects for patients undergoing radiotherapy (RT) treatment for rectal cancer.

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TRI LARC is a randomised Phase II Study of Pre-operative 3 -D Conformal Radiotherapy (3-DCRT) versus Intensity Modulated Radiotherapy (IMRT) for Locally Advanced Rectal Cancer. It is sponsored by Cancer Trials Ireland and will involve 268 patients across 6 Irish radiation oncology departments. The study aims to reduce side effects, and hence improve quality of life for patients undergoing radiotherapy (RT) treatment for rectal cancer. The trial is already open in the St Luke's Radiation Oncology Network centres in Beaumont Hospital, St James's Hospital and St Luke's Hospital, Dublin, with over 60 patients enrolled.

Colorectal cancer accounts for 11% of cancers in women and 14% in men in Ireland and is the third leading cause of cancer death in women and the second in men (Source: NCRI).

Pre-operative RT or chemoradiotherapy (CRT) is internationally accepted as standard practice in the management of locally advanced rectal cancer (i.e. cT3N0-2, cT4N0-2, cT(any)N1-2). Multiple randomised trials have proven pre-operative CRT and RT, compared to surgery alone, reduces local recurrence (even prior to optimal surgery) and may improve survival for T3 circumferential resection margin (CRM) negative patients. Pre-operative treatment is theoretically superior to post-operative treatment due to well oxygenated pre-operative tissue, better treatment compliance, and the potential for tumour downsizing/ downstaging, and increasing CRM clearance rates.

The therapeutic aim in the delivery of RT is optimal radiation dose delivery to the planning target volume (PTV), while minimising radiation dose to surrounding normal structures. Three-dimensional conformal radiotherapy (3-DCRT) is the current RT technique of choice in Ireland for the treatment of rectal cancer. Using this technique, the Gross Tumour Volume, Clinical Target Volume and PTV are contoured on a CT dataset. A 3 or 4 field beam arrangement is typically used to target the pelvis in order to treat those areas at risk of recurrence: the rectum, the mesorectum and the draining pelvic lymph nodes. However, when using such a technique relatively large volumes of normal tissues such as bowel and bladder are needlessly irradiated. Rates of 27% acute grade III and IV toxicity (12% acute diarrhoea, 11% dermatologic effects), and 14% grade III and IV late toxicity (9% chronic diarrhoea and/or small bowel obstruction, 2% re-operation rate for small bowel obstruction, 4% anastomotic strictures, 2% bladder) have been reported (Sauer et al., 2004).

Intensity Modulated Radiation Therapy (IMRT) is a newer but established RT technique which subdivides radiation beams into smaller beamlets, and varies the individual intensities of these beamlets, in order to achieve highly conformal dose distributions (see Figure). The advantages of this technique

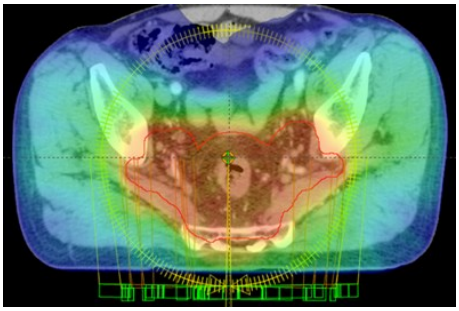

Figure: Volumetric Modulated Arc Therapy plan for patient with rectal cancer.

are improved target volume conformity, particularly for complex volumes (especially concave, such as pelvic volumes for rectal cancer), with improved sparing of organs at risk (OARs).

Disadvantages of IMRT are the more complex and time-consuming planning and quality assurance processes and a larger number of monitor units (MU) compared with conventional RT leading to an increase in the amount of low dose radiation, though this depends on the specific IMRT technique.

There are no randomised studies comparing 3-DCRT pelvic irradiation with IMRT in pre-operative patients who have had surgery for rectal cancer. However, there are several small studies that report considerable sparing of normal tissues using IMRT and when compared retrospectively with conventionally treated patients demonstrate marked reductions in acute gastrointestinal (GI) and genitourinary (GU) toxicity.

It is clear from the available data that IMRT spares small bowel and bladder compared to 3-DCRT with acceptable PTV coverage in planning studies; and that IMRT has been introduced into clinical practice in many centres and is feasible and appears to clinically reduce GI and GU toxicity. The aim of the TRI LARC study is to determine in the context of a randomised clinical trial whether delivering pre-operative CRT to the pelvis using IMRT (as opposed to 3-DCRT) will reduce acute and late toxicity, while maintaining local control and survival.

There are also two exciting translational components to this trial, led by the Royal College of Surgeons in Ireland (RCSI) / Beaumont Hospital and the National Institute for Cellular Biotechnology / Dublin City University respectively. RCSI / Beaumont Hospital are investigating somatic mutations and their proteomic and transcriptomic effects and associations and are aiming to validate known and identify new gene mutations in blood (circulating DNA (ctDNA) and circulating tumour cells (CTCs)) and tissue. They are also exploring the effect of RT on these mutations and the mismatch repair system, and investigating the utility of an RNA degradation assay in on-treatment biopsies as a pharmacodynamic biomarker of responsiveness of chemoradiotherapy. The team at NICB / DCU are working to identify blood biomarkers as indicators for responders/non-responders to treatment and to develop a panel of predictive/prognostic biomarkers.

Acknowledgement: Saint Luke's Institute of Cancer Research for its support of the translational sub-studies.