Fractionation Choice for Elective Lymph Node Radiotherapy in Prostate Cancer: Slightly More to CHIRP About

In any discussion of elective pelvic lymph node (PLN) radiotherapy in the management of high-risk localised prostate cancer, we must start by examining evidence for its use. Firstly, we can acknowledge that radiotherapy to the prostate must be given to patients with high-risk, localised disease. The PR07 study showed an impressive 0.77 hazard ratio for death (7-yr follow-up), through the addition of prostate external beam radiotherapy (EBRT) to androgen deprivation therapy (ADT) alone in high-risk localised disease.[1] In this trial 72% also had pelvic lymph node (PLN) irradiation, raising the question of whether prostate only radiotherapy (PORT) is sufficient or if prostate and pelvic lymph node radiotherapy (PPLNRT) is needed.

Discerning a benefit to PLN irradiation through randomised comparison of PORT versus PPLNRT has proven difficult. Despite its large size (n=1322), RTOG 94-13 did not show a benefit to PPLNRT (giving 50.4 Gy in 28 fractions (Fr) to PLN).[2] Similarly, the GETUG-01 trial (n=446), also randomising between PORT vs PPLNRT (46 Gy in 23 Fr to PLN), did not show a benefit to PLN irradiation in the 'high risk' subgroup (in NCCN terms, an intermediate to high risk group).[3] Interestingly, a recent smaller randomised trial, POP-RT (n=224), has shown a disease-free-survival benefit when randomising those with PLN risk >20% to PORT vs PPLNRT (50 Gy in 25 Fr to PLN).[4] While more modern radiotherapy techniques, such as intensity modulated radiotherapy (IMRT), may have contributed, the use of prostate specific membrane antigen (PSMA) PET in staging 80% of patients likely refined the patient group, avoiding patients with occult metastatic disease that would have entered the older trials. Assuming that other modern randomised trials examining PPLNRT confirm this disease benefit (e.g. PIVOTALboost (ISRCTN80146950), PEACE-2 (NCT01952223), RTOG-0924 (NCT01368588)), then elective nodal radiotherapy in high risk localised prostate cancer will likely become a well-accepted standard-of-care.

Given the direction towards more utilisation of elective nodal radiotherapy, the toxicity of such treatment becomes a key concern. Limiting our consideration to modern IMRT treatment, the phase II PIVOTAL trial (n=124) randomised high-risk localised PCa patients to PORT vs PPLNRT IMRT (60 Gy in 37 Fr to pelvis), examining clinician and patient reported outcomes.[5] Acute bowel toxicity was higher with PLN RT, but settled by week 18; while late toxicity was similar. Further data comes from the SPPORT trial, which although in the salvage setting, showed increased acute gastrointestinal (GI) toxicity, but no differences in late bowel or bladder toxicity with the addition of PLN radiotherapy (45 Gy in 25 Fr to PLN, 87% IMRT).[6] Interestingly, bone marrow toxicity (both acute and late) was worse with nodal radiotherapy in SPPORT, an endpoint not reported in the PIVOTAL trial, nor POP-RT. With conventionally fractionated radiotherapy to the pelvis appearing to produce generally acceptable toxicity, we can then consider hypofractionated radiotherapy. Moderate hypofractionation for prostate only treatments is now standard-of-care following the CHHiP[7], RTOG-0415[8] and PROFIT[9] trials. In the ultrahypofractionation setting, the HYPO-RT-PC trial has provided randomised phase III efficacy and safety evidence for prostate-only irradiation in as few as seven fractions.[10] Such abbreviated regimens are more convenient for patients and more cost-effective for health systems, so hypofractionated radiotherapy incorporating PLN radiotherapy would therefore hold similar appeal if it was safe.

In this issue, Yang *et al* report quality of life outcomes from CHIRP: a single-institution randomised phase II study, recruiting 111 high-risk localised prostate cancer patients.[11] Patients were

randomised to conventional 78 Gy in 39 fractions (46 Gy in 23 fractions PLN dose) vs hypofractionated 68 Gy in 25 Fr (45 Gy in 25 Fr pelvic dose). Abbreviation of the investigational regimen was achieved through use of simultaneous integrated boost, rather than the conventional 2-phase treatment. Modern radiotherapy methods were utilised in both arms: IMRT and daily image guidance. 18 months of ADT was standard.

We should highlight similarities in the investigational arm to the POP-RT study, having the same prostate dose and fractions, although the PLN dose is lower (45 Gy vs 50 Gy, both in 25 fractions). On publication, despite the successful efficacy outcomes of POP-RT, some practitioners may have felt reticent in adopting the investigational regimen, the hypofractionated prostate dose being different to the current PPLNRT trials (e.g. RTOG 09-24: 79.2 Gy / 44 Fr to prostate, 45 Gy / 25 Fr to PLN). Additionally, although GI side effects were similar, POP-RT showed a higher rate of genitourinary (GU) G2+ cumulative late toxicity with PPLNRT (20.0% v 8.9%, p=0.02). Comparative toxicity data between a POP-RT style regimen and a wholly conventionally fractionated regimen is therefore desirable, a gap which Yang *et al* have filled with the CHIRP trial. They have previously reported clinician reported outcomes, which were statistically similar between the arms at 38 months follow-up.[12] Given the POP-RT outcomes, it is worth noting that there was a non-statistically significant increase in late GU toxicity in the hypofractionated arm of CHIRP (16% vs 10%, p=0.554), with the trial size likely to be underpowered to detect differences of this magnitude.

The quality-of-life data reported by Yang *et al* in this issue is therefore an interesting complement to the existing data. The urinary data is of particular interest given the higher PPLNRT urinary toxicity in POP-RT. The authors report no statistically significant differences in the rates of overall EPIC urinary bother, with visual inspection of Figure 2A showing rates of moderate-big urinary problems are not consistently worse for either arm. Sexual function was similar between the two arms.

For GI data, the bowel bother change at 12 months was significantly worse in the hypofractionated arm, although the difference had largely abated at 2 years. Given the similar doses to the pelvis in each arm of the CHIRP trial, might it be driven by differences in the equivalent dose in 2 Gy per fraction (EQD2) for the prostate? This is probably unlikely: assuming a rectal α/β ratio of 3 Gy [13], 68 Gy in 25 Fr has an EQD2 of 77.8Gy_{EQD2}, almost identical to the CHIRP control arm. Given the size of the study and the number of scales and timepoints examined, no firm conclusions can be drawn but the data suggests low levels of significant toxicity with hypofractionation.

On the subject of hypofractionation to the pelvis, it is worth noting that PPLNRT can be delivered with truly hypofractionated PLN doses (i.e. >2 Gy per fraction to the pelvis). A phase I/II dose-escalation trial of PLN RT (n=447) examined two hypofractionated regimens (47 Gy in 20 Fr over 4 or 5 weeks) in addition to three conventional regimens (50, 55 & 60 Gy in 35-37 fractions).[14] Both acute and late GI side effects were worse than other cohorts for the shorter hypofractionated arm (PLN dose 47 Gy in 20 Fr over 4 weeks). The ongoing PIVOTAL-BOOST study (n=1952) is delivering hypofractionated PLN radiotherapy (47 Gy in 20 Fr) as standard, so trial reporting will provide substantial toxicity data for moderately hypofractionated PLN treatment. Phase II randomised data examining ultrahypofractionated PPLNRT should come from the HOPE trial (NCT04197141), which is allocating patients to PLN radiotherapy in 45 Gy / 25 Fr vs 25 Gy / 5 Fr, with late bowel toxicity as the primary outcome measure[15] and the forthcoming PACE-NODES trial.

To summarise, Yang *et al* have presented new quality of life data from CHIRP, a randomised trial of conventionally vs hypofractionated PPLNRT. Although a small study, the small differences seen are

largely abated by the two-year mark. CHIRP's hypofractionated arm bears strong similarity to the POP-RT PPLNRT arm, which showed a survival benefit over PORT in selected high risk localised prostate cancer. For those considering adopting the POP-RT regimen, but concerned over potential increased toxicity with the 25 fraction regimen, the CHIRP trial may help to assuage some of those fears. The elective PPLNRT research space has major ongoing phase III trials (RTOG 09-24, PEACE-2 and PIVOTAL-BOOST) so optimal practice for men with localised prostate cancer is unlikely to be resolved until these trials have reported.

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