Condensed Evidence Review for the Prostate Cancer Decision Tree

Although surgery, external beam radiotherapy (EBRT), brachytherapy and active surveillance (AS) remain the mainstay of radical treatment options for localised prostate cancer, the proportion of men undergoing AS for 'low-risk' lesions has increased significantly in recent years. The ProtecT study supports the parity of AS with other treatment options for this patient group, showing that cancer-related and overall survival was not significantly different among patients (mostly with low-grade disease) treated with surgery, EBRT or AS (Hamdy et al. 2016). This has led to a significant change in practice, with data from the National Prostate Cancer Audit suggesting that only 5% of men presenting with low risk disease receive interventional treatment up front (National Prostate Cancer Audit 2020). The 10% figure we have used allows for any under-reporting of men with such low-risk disease.
We have based our estimate of the proportions of men moving from AS to other radical therapies on data from the ProtecT study. This may differ from modern AS protocols, which include MRI surveillance, but long-term data on disease progression in patients followed up in this way is not yet available.

The most significant change in dose-fractionation of radiotherapy for localised prostate cancer has been the adoption of hypofractionated external beam radiotherapy (EBRT), using a schedule of 60Gy/20#/4 weeks. This follows largely from the CHHiP trial, which compared conventional (74Gy/37#) and hypofractionated treatments in 3216 men with low-high risk localised disease (Dearnaley et al. 2016). The 5-year outcomes of the study showed non-inferiority between the conventional and 60Gy/20# schedules, using incidence of biochemical or clinical failure as the primary outcome. Similar conclusions were also from the PROFIT, RTOG O415 and HYPRO trials (Catton et al. 2017; Lee et al. 2016; Incrocci et al. 2016). All of these trials showed an increase in genitourinary and/or gastrointestinal toxicity with hypofractionated treatment, but this was usually of RTOG Grade 1-2 severity, and thus considered acceptable. 60Gy/20# is now by far the most commonly used schedule, although 74Gy/37# remains in use in the RCR guidelines, our new decision tree, and clinical practice (Royal College of Radiologists 2019). Another less commonly-used schedule is 36Gy/6#/6 weeks (for some frail men with higher risk disease who could not have 20 daily fractions of radiotherapy). This has also been added to our decision tree.

There is increasing interest 'ultrahypofractionated' schedules, using >5Gy per fraction, which can be delivered safely using stereotactic ablative radiotherapy (SABR). In the PACE-B trial, a SABR regimen of 36.25Gy/5# was found not to be associated with significantly worse toxicity than conventional/moderately hypofractionated schedules in low-intermediate risk cancer (Brand et al. 2019). Oncological outcomes of this trial are awaited, but are expected to show non-inferiority of the SABR regimen. Indeed, some centres implemented this schedule to reduce patients' hospital visits during the Covid-19 pandemic. Meanwhile, the HYPO trial, which compared 58Gy/39# and 42.7Gy/7# schedules in mostly intermediate-risk disease, found no significant difference in failure-free or overall survival after 5 years (Widmark et al. 2019). This adds to the evidence base in favour of ultrahypofractionated radiotherapy. However, this study did not allow androgen deprivation therapy prior to treatment, and the majority of treatment schedules were delivered using technology that

would now be considered outdated. The study is therefore not entirely applicable to current UK practice, and so this 7# schedule is not included in our decision tree.

The PACE-B schedule is likely to become far more commonplace following publication of the trial's oncological efficacy results. Furthermore, the ongoing PACE-C trial is investigating a SABR regimen in men with unfavourable intermediate risk and some high-risk cancers. If this trial also shows non-inferiority, 5# SABR could become the most commonly used EBRT schedule for localised and locally advanced prostate cancer. Clearly this would significantly reduce the radiotherapy fraction demand for this tumour site. We have modelled this scenario, estimating that close to 100% of patients with low and intermediate-risk disease would receive 5# SABR, as would 50% of patients with high-risk disease (with the others requiring 20# treatment to incorporate pelvic nodes or for otherwise complicated treatment plans).

In the recent RADICALS-RT trial, adjuvant radiotherapy after prostatectomy in men with high-risk disease and/or an R1 resection gave no progression-free survival benefit compared to salvage radiotherapy upon evidence of biochemical progression. However, adjuvant radiotherapy was associated with increased genitourinary toxicity (Parker et al. 2020). This provides convincing evidence for delaying all radiotherapy after prostatectomy until there is biochemical evidence of progression, as is now recommended in the RCR guidelines (Royal College of Radiologists 2019) and our decision tree. This salvage radiotherapy may be extended to cover the whole pelvis, depending on the awaited outcomes of the SPPORT trial (US National Library of Medicine 2017).

Meanwhile, a subgroup analysis of the STAMPEDE trial showed a significant overall survival benefit in patients presenting with low-burden oligometastatic disease (<4 bone metastases or more if confined to the axial skeleton, and no visceral metastases) with combined prostate irradiation and hormone therapy, compared to androgen deprivation therapy (ADT) alone (Parker et al. 2018). This is already starting to translate to the clinical arena, but further investigation is required to decide whether irradiation of the primary tumour is beneficial with novel ADT drugs. Our updated decision tree includes both 55Gy/20# and 36Gy/6# options in this setting, as these were used in STAMPEDE and are both employed in clinical practice (with a roughly 50:50 split).

The recent commissioning of SABR directed to 3 or fewer metachronous, extracranial oligometastases from any primary may also affect radiotherapy fraction demand. Two Phase II clinical trials have specifically investigated SABR in this setting in prostate cancer. The STOMP trial (Ost et al. 2018) randomised 62 men with oligometastatic prostate cancer (i.e. 3 or fewer metastases) to receive either surveillance or metastasis-directed therapy (MDT- this could include surgery or SABR). After 3 months, median ADT-free survival was 13 months in the group under surveillance, vs. 21 months in the group receiving MDT. Meanwhile, the ORIOLE trial (Radwan et al. 2017) involved a similar analysis of 54 men with prostate cancer and 1-3 metastases, and showed progression after 6 months in 61% vs. 19% of the men receiving SABR-MDT or surveillance respectively.
A further trial which has influenced this NHS England commissioning decision is the SABR-COMET trial (Palma et al. 2019), which compared standard of care to the addition of SABR-MDT is 99 patients with any primary malignancy and up to 5 metastases. With a median

follow-up of just over 2 years, there was a 6-month difference in progression-free survival between the two groups.

Although all of these trials suggest that SABR warrants further investigation in the setting of metachronous oligometastases, Phase III RCT evidence with larger sample sizes and longer follow-up is lacking. Hence, uptake into clinical practice has been hitherto mixed, and so this is not yet having a large impact on radiotherapy demand for prostate cancer.

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