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Prostate cancer

Background

Prostate cancer is a common malignancy, with 52,300 cases diagnosed annually in the UK.¹ Standard management for low-risk groups is surveillance. External beam radiotherapy (EBRT) is a non-surgical curative treatment modality for patients with localised intermediate, high-risk or locally advanced prostate cancer.^{2–4} Depending on staging, performance status, urinary symptoms and co-morbidities, EBRT, brachytherapy or a combination of both can be used and many patients benefit from the addition of androgen deprivation therapy (ADT) to EBRT.

Androgen deprivation therapy and additional systemic therapies

The relative risk reduction for disease progression and metastatic relapse with the addition of ADT to EBRT applies to all risk groups. For lower-risk groups (low and intermediate risk with favourable features),³ the addition of short-duration ADT (6 months) to radiotherapy (RT) significantly improves metastasis-free survival (MFS) (HR 0.83 [95% CI 0.77–0.89], $p < 0.0001$).^{5,6} ADT started at the time of RT performs better for all disease-related endpoints with no differences in toxicity compared with neoadjuvant scheduling.⁷ Extending neoadjuvant ADT does not improve outcomes compared with shorter neoadjuvant ADT and the same adjuvant treatment.⁵ For patients with intermediate risk with unfavourable features or high-risk patients treated with radical RT, ADT prolongation from 6 to 18–36 months improves all disease-related endpoints including MFS (HR 0.84 [95% CI 0.78–0.91], $p < 0.0001$).^{5,8}

The Radiation Therapy Oncology Group (RTOG) 9413 trial found a significant interaction between RT field size and ADT sequencing. Neoadjuvant and concurrent ADT had a more favourable 10-year progression-free survival (PFS) with prostate and pelvic nodal RT and adjuvant ADT; the reverse was true when prostate-only RT was delivered.⁹ Local dose escalation does not negate the benefits of ADT.^{10,11} In a meta-analysis, the addition of docetaxel to EBRT and long-term ADT for patients with localised high-risk disease improved failure-free survival (FFS) but not other survival endpoints, with a greater risk of any grade and Grade ≥ 3 adverse events (OR 3.19, [95% CI 2.70–3.77]; $p < 0.001$).¹² In patients with non-metastatic, high-risk localised disease, abiraterone + ADT was associated with significantly better OS (HR 0.69, 95% CI 0.50–0.95), MFS (HR 0.63, 95% CI 0.45–0.88) and FFS (HR 0.53, 95% CI 0.41–0.70). There were no significant differences between abiraterone + ADT and abiraterone + enzalutamide + ADT for any of the survival endpoints studied.¹³

In summary, for patients treated with prostate-only RT and 6 months of ADT, radiotherapy should commence shortly after starting ADT; for extended-course ADT (>12 months) and prostate and pelvic nodal RT (PNRT), any neoadjuvant, concurrent and adjuvant sequencing can be used.

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Prostate-only radiotherapy

There are now five randomised radiation dose escalation studies that have demonstrated superior biochemical relapse-free survival with whole-gland doses ranging from (conventionally fractionated) 74 to 80 Gray (Gy)¹⁴. However, this has not translated into an OS benefit.^{10,15} Further whole-gland dose escalation is limited by concerns about excessive toxicities. Focal dose escalation to the dominant intraprostatic nodules (DIL) identified on staging mpMRI and/or prostate-specific membrane antigen positron emission tomography (PSMA PET) scan has been shown to improve biochemical control in a phase III randomised FLAME trial compared with the standard 78 Gy whole-gland RT.¹⁶

Hypofractionation (fraction size of 2.5 Gy and above)

So far, over 8,000 patients have been treated in randomised trials of moderate hypofractionation schedules (fraction size 3.0–3.4 Gy), and findings of these trials suggest that moderate hypofractionation results in similar oncological outcomes in terms of disease-free survival, MFS and OS. There appears to be little to no increase in both acute and late toxicities in a recent Cochrane review.^{17,18} In the UK, the CHHiP fractionation schedule of 60 Gy in 20 fractions is currently the recommended schedule.¹⁹

Stereotactic radiotherapy

Ultra-hypofractionation (stereotactic ablative body radiotherapy [SABR] defined as fraction size of 6 Gy or more) has been shown to be feasible and safe in cohort studies, with high levels of disease control.²⁰ HYPO-RT-PC compared 78 Gy in 39 fractions versus 42.7 Gy in 7 fractions without hormone therapy in 1,200 patients with intermediate-to-high-risk prostate cancer. SABR has a non-inferior biochemical control compared with conventional fractionation. Early side-effects were more pronounced with SABR whereas late toxicities were similar in both treatment groups.^{21,22} The PACE-B trial randomised 874 patients between conventional or stereotactic radiotherapy (36.25 Gy in 5 fractions) without ADT; SABR did not increase either gastrointestinal (GI) or genitourinary (GU) acute toxicities.²³ At 2 years, incidence of G2+ GI toxicities was low with no differences between groups; however, incidence of CTCAE G2+ GU toxicity was higher with SABR (6.4% versus 11.1%, $p=0.02$); the increase in RTOG G2+ GU toxicity was not statistically significant.

Brachytherapy

Prostate brachytherapy allows radiation dose escalation beyond what would be achievable by EBRT. In addition, there are fewer issues with changes in prostate position during treatment delivery.²⁴ Brachytherapy as monotherapy for low-risk and intermediate-risk patients with favourable features can be used as a single implant, most commonly with iodine-125 (I-125) seeds. For low-dose-rate (LDR) I-125 monotherapy the prescription dose to the CTV is 145 Gy.^{25,26} An alternative option is fractionated high-dose-rate (HDR) brachytherapy with a recommended dose of 27 Gy in 2 treatments 1–2 weeks apart; single-fraction HDR schedules are associated with higher biochemical relapse rates.²⁷ For high-risk patients LDR or HDR brachytherapy in combination with ADT and EBRT to the prostate or prostate and pelvic nodes is an effective treatment.^{10,28–30} Brachytherapy boost may be delivered before or after EBRT. Recommended fractionation schedule for LDR boost is 110 Gy and for HDR boost it is 15 Gy. Recommended EBRT schedules are 37 Gy in 15 fractions for prostate-only RT. Most published series for brachytherapy and EBRT combinations have used 46 Gy in 23 fractions for PNRT. For the pelvic nodal dose, please refer to the discussion below.

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In a meta-analysis of three RCTs, there was a significant benefit in 5-year biochemical-progression-free survival in favour of brachytherapy and EBRT combination versus EBRT alone (HR 0.49 [95% CI, 0.37–0.66], $p < 0.01$) with no difference in 5-year OS. Late Grade 3 or worse toxicities were higher in the combination arms for both GU and GI with large confidence intervals: GU (RR 2.19 [95% CI, 0.76–6.30], $p = 0.15$) and GI toxicities (RR 1.85 [95% CI, 1.00–3.41], $p = 0.05$).³¹ Omitting ADT for brachytherapy and EBRT combinations results in an inferior OS.³²

Pelvic nodal radiotherapy

There is no large randomised trial evidence (GETUG-01, RTOG 9413) supporting that PNRT improves oncological outcomes.^{33,34} A recent smaller trial showed improved biochemical control with PNRT.³⁵ However, in this study more than 80% of patients had staging PSMA PET, confirming NO staging, pelvic nodes were treated to L4/5 level and the dose used was 68 Gy (prostate) and 50 Gy (lymph nodes) in 25 fractions. The acute toxicities were similar in both arms, but there was more late bladder toxicity in the PNRT arm.³⁶ Equivalent PNRT biological effective doses are 47 Gy in 20 fractions and 50–60 Gy in 37–39 fractions; the doses are computed for $\alpha/\beta = 1.5$ or 3 without time corrections. Commonly used schedules in the UK (46 Gy in 23 fractions and 44 Gy in 20 fractions) have a lower BED and may not control microscopic nodal disease. Results from the PIVOTALboost and RTOG 0924 trials are awaited to better define the role of PNRT. Patients with positive pelvic lymph nodes at the initial staging scans should be considered for PNRT as part of their management.³⁷ The PEARLS trial is currently recruiting, delivering 44 Gy in 20 fractions to uninvolved nodes with a boost to involved nodes of 51 Gy.³⁸

Postoperative radiotherapy

From three randomised trials (RADICALS-RT, GETUG-17, RAVES) and a meta-analysis, there is no evidence that event-free survival improves with adjuvant radiotherapy compared with early salvage radiotherapy (HR 0.95, 95% CI 0.75–1.21; $p = 0.70$), with only 1 percentage point change in 5-year event-free survival (89% versus 88%).^{39–42} The use of hormone therapy in combination with salvage postoperative radiotherapy has been tested in three randomised controlled trials. RTOG 9601 showed a survival benefit with 24 months of bicalutamide.⁴³ GETUG-16 showed a PFS but not an OS benefit; the 12-year OS was 86% for radiation therapy plus goserelin versus 85% for radiation therapy alone.⁴⁴ In the SPORRT trial, 1,716 patients were randomised to prostate bed RT, prostate bed RT plus 6 months ADT or PNRT plus 6 months ADT. At a median follow-up of 8.2 years, the 5-year FFS rates were 70.9% (95% CI 67.0–74.9) in group 1, 81.3% (78.0–84.6) in group 2 and 87.4% (84.7–90.2) in group 3.⁴⁵ There is currently no evidence supporting dose escalation in postoperative settings that would improve outcomes. Recommended schedules are either 66 Gy (46–50 Gy for nodes) in 33 fractions or 52.5–55 Gy (44 Gy for nodes) in 20 fractions.³⁷

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Recommendations

Prostate-only RT:

- 60 Gy in 20 fractions over 4 weeks (Grade A)

In addition to a brachytherapy boost:

- 37.5 Gy in 15 fractions (prostate only) over 3 weeks before or after 15 Gy HDR brachytherapy boost (Grade A)
- 46 Gy in 23 fractions (prostate and pelvic nodes) over 4.5 weeks followed by 15 Gy HDR or 115 Gy LDR brachytherapy boost (Grade A)

Stereotactic radiotherapy (SBRT):

- 36.25 Gy in 5 fractions (Grade A)

Pelvic nodal RT:

- 50 Gy in 25 fractions over 5 weeks or equivalent (Grade A)
- 46 Gy in 23 fractions over 4.5 weeks (Grade A)
- 44–47 Gy in 20 fractions over 4 weeks (Grade D)

Postoperative RT:

- 66 Gy in 33 fractions over 6.5 weeks or
- 52.5–55 Gy in 20 fractions over 4 weeks (Grade C)

The types of evidence and the grading of recommendations used within this review are based on those proposed by the Oxford Centre for Evidence-Based Medicine.⁴⁶

Palliative radiotherapy

For patients with high-risk localised disease, who are not fit or unsuitable for daily treatment and unsuitable for a watch and wait policy, hypofractionated radiotherapy may be used similar to the schedule tested in the STAMPEDE trial.⁴⁷ Prostate radiotherapy should be considered for patients with metastatic hormone-sensitive prostate cancer with a low metastatic burden (defined as per the CHAARTED trial), which showed an improvement in PFS and OS.⁴⁸ In the castration-resistant group, useful and long-term disease control is possible and symptom relief for troublesome haemorrhage, pain, outflow obstruction or pressure symptoms can be achieved with palliative RT. There are only cohort studies as supporting evidence that patients with a reasonable life expectancy benefit from radiotherapy in this setting.^{8,49–52}

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Recommendations

Recommended palliative RT schedules

High-risk localised disease, unsuitable for longer-course fractionation and hormone-sensitive disease with low metastatic burden:

- 55–60 Gy in 20 fractions over 4 weeks (Grade A)
- 30–36 Gy in 6 fractions over 6 weeks (Grade A)

Castration-resistant disease with local progression and/or symptoms:

- 21 Gy in 3 fractions, alternate days over 1 week (Grade D)
- 20 Gy in 5 fractions over 1 week (Grade D)
- 30 Gy in 10 fractions over 2 weeks (Grade D)
- 8–10 Gy single dose (Grade D)

The types of evidence and the grading of recommendations used within this review are based on those proposed by the Oxford Centre for Evidence-Based Medicine.⁴⁶

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