4.11 Prostate cancer

Introduction

Early prostate cancer is being diagnosed more frequently because of prostate specific antigen (PSA) screening. This change in natural history poses new management opportunities, and external-beam radiotherapy is only one of several options. These include: active surveillance and monitoring, radical surgery, and brachytherapy.

Hormonal therapy and radiation dose

There is Grade A evidence in favour of neoadjuvant or adjuvant androgen deprivation therapy (ADT) for patients with intermediate or high-risk (PSA > 10 or Gleason score > 7 or T2C-T3) prostate cancer treated with radical radiotherapy although with the likelihood of significant toxicity reducing quality of life. A systematic review of fourteen randomised phase III clinical trials (level 1++) showing benefit which increases as the risk factors of stage, PSA and Gleason score increase. NICE guidelines recommend 6 months of ADT for intermediate risk patients which may be extended for up to three years in high risk localised prostate cancer.

There are now five randomised dose escalation studies which have demonstrated superior biochemical relapse free survival with doses from 74-80Gy compared to lower doses. As yet however this has not translated into an overall survival advantage.

Radiotherapy technique

Dose escalation increases the side effects of treatment. This can be mitigated by using IMRT or arc techniques (VMAT or Rapidarc) to minimise dose to the organs at risk. The role of lymph node irradiation remains uncertain. It is possible to identify patients who have a significant risk of lymph node involvement but the results of randomised trials to address the value of elective nodal irradiation are equivocal. It may be considered for high risk patients recognising that the larger volume is associated with higher toxicity.

IMRT or arc techniques (VMAT or Rapidarc) with appropriate IGRT are the standard of care when delivering high dose radiation to the prostate. Fiducial markers or cone beam images should be used for verification to minimise interfraction variation.

Fractionation

A full discussion of the radiobiology of prostate cancer is outside of the remit of this guideline. There is consistent evidence from large retrospective series to support the hypothesis that prostate cancer has a low α/β ratio. Hypofractionation, using fraction sizes >2Gy per day therefore, may be radiobiologically advantageous.

Conventional fractionation (doses-per-fraction in the range 1.8 Gy–2 Gy)

The results of conventional fractionation have been comprehensively reviewed and reported. Dose escalation has been shown to improve bRFS in randomised controlled trials (RCT) (64 Gy vs 74 Gy, 68Gy vs 78Gy, 70Gy vs 78Gy, 70.2 Gy vs 79.2Gy) as well as meta-analysis. Unfortunately, this has not translated into improved overall survival as yet.
There is level 2++ evidence that doses beyond 80Gy can now be delivered safely with image guided IMRT. There are no reported randomized trials of higher levels of dose escalation, but results from the Memorial Sloan Kettering Cancer Center have shown that the late grade II gastrointestinal toxicity rates of patients treated to 86.4Gy in fraction sizes of 1.8Gy was 3% with <1% developing late grade III gastrointestinal toxicity. Analysis of outcome from this series showed that the 10-year bNED was significantly improved by dose escalation: 84% (> 75.6 Gy) vs 70% for low-risk disease (p = 0.04), 76% (> 81 Gy) vs. 57% for intermediate risk disease (p = 0.0001) and 55% (> 81 Gy) vs. 41% for high-risk patients (p = 0.0001). In a multivariate analysis including the use of 6-months ADT, a dose > 81 Gy (p = 0.027) and ADT (p = 0.052) were found to be predictive factors for distant metastasis-free survival, but not overall survival.

Hypofractionation (doses of 2.5 Gy per fraction and above)

Two historical randomised trials which compared hypo-fractionation (52.5-55Gy in 20 fractions) with control arms of 60-66 Gy in 33 fractions in 6.5 weeks, doses that, by current standards, are low. The results show a trend towards lower 4-year bNED rate with hypo-fractionation. The Christie Hospital has reported their experience using 50 Gy in 16 fractions with a conformal technique. The overall bNED rates at 5 years were 82% for low grade; 56% for intermediate and 39% for high risk, comparable to those achieved using more protracted regimens (level 2+) with toxicity ≥ RTOG grade 2 in 5% for bladder and 9% for GI.

Nearly 8000 patients have been randomised into completed and ongoing trials of hypofractionation, including the CHHIP trial, the HYPRO trial, the Scandinavian-led HYPO study and the North American RTOG 0415 study. Toxicity of moderate hypofractionation to 2 years follow up (based on physician reported outcomes) was as low as with conventional fractionation in the CHHIP study, which compared 74 Gy in 37 fractions to 60 Gy in 20 fractions and 57 Gy in 19 fractions. There is a suggestion that equivalent DFS can be obtained at the expense of increased GU or GI toxicity, although overall, toxicity remains acceptable.

High dose rate (HDR) brachytherapy is an alternative means of delivering hypofractionated radiation as a boost to achieve dose escalation after 45-46Gy in 1.8-2Gy daily fractions.

Profound hypofractionation (defined as 6 Gy per fraction or more) has been shown to be feasible and safe in cohort studies, with high levels of disease control in low risk patients. The PACE trial is randomising between standard of care (surgery or IG-IMRT) and stereotactic radiotherapy (36.25 Gy in 5 fractions) and HYPO which compares 78 Gy in 39 fractions vs 42.7 Gy in 7 fractions and has recruited 1000 patients in Scandinavia with a target recruitment of 1920 patients.

Post-operative radiotherapy

There is level 1++ evidence from three randomized trials that adjuvant post-operative radiotherapy, using 60-64 Gy and 2 Gy per fraction, improves recurrence rates in post-operative patients considered to be at high risk of recurrence (Grade A recommendation). The optimal timing of post-operative radiotherapy in this group, whether immediate or at first evidence of PSA recurrence, is not known; this and the benefit of adjuvant ADT in the post-operative setting are the two primary questions being addressed in the ongoing MRC RADICALS trial using either 66Gy in 33 fractions or 52.5Gy in 20 fractions.
Radical radiotherapy to the prostate should be delivered using IMRT or arc (VMAT or Rapidarc) techniques with IGRT verification. Acceptable regimens include:

- 74–78 Gy to the prostate in 37–39 fractions over 7.5–8 weeks (Grade A)
- 57-60 Gy in 19-20 fractions (Grade C)
- 50 Gy in 16 frac
- Nodal irradiation 55-60 in 37 fractions or equivalent
- Postoperatively 66Gy in 33 fractions or 52.5Gy in 20 fractions (Grade C)

References


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9. Lawton, C.A., et al., An update of the phase III trial comparing whole pelvic to prostate only radiotherapy and neoadjuvant to adjuvant total androgen suppression: updated analysis of RTOG


