11.
Prostate cancer

Background

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 (EBRT) is only one of several options, which 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.[1] A systematic review of 14 randomised phase III clinical trials showed benefit which increases as the risk factors of stage, PSA and Gleason score increase.[2] The National Institute for Health and Care Excellence (NICE) guidelines recommend six months of ADT for intermediate-risk patients, which may be extended for up to three years in high-risk localised prostate cancer.[3]

There are now five randomised dose escalation studies which have demonstrated superior biochemical relapse-free survival (bRFS) with doses from 74–80 Gray (Gy) compared to lower doses. As yet, however, this has not translated into an overall survival advantage.[4–8]

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.[9,10] Hypofractionation, using fraction sizes >2 Gy per day, may therefore be radiobiologically advantageous.

Conventional fractionation (doses-per-fraction in the range 1.8–2 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 versus 74 Gy , 68 Gy versus 78 Gy, 70 Gy versus 78 Gy, 70.2 Gy versus 79.2 Gy) as well as meta-analysis.[4–8,11] Unfortunately, this has not translated into improved overall survival as yet.

There is evidence (Grade B) that doses beyond 80 Gy can now be delivered safely with image-guided intensity-modulated radiotherapy (IMRT).[1] There are no reported randomised 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 86.4 Gy in fraction sizes of 1.8 Gy was 3%, with <1% developing late grade III gastrointestinal toxicity.[12] Analysis of outcomes from this series showed that the ten-year failure free survival (bNED) was significantly improved by dose escalation: 84% (>75.6 Gy) versus 70% for low-risk disease (p=0.04), 76% (>81 Gy) versus 57% for intermediate-risk disease (p=0.0001) and 55% (>81 Gy) versus 41% for high-risk patients (p=0.0001).[13] In a multivariate analysis including the use of six-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 hypofractionation (52.5–55 Gy 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 a lower four-year bNED rate with hypofractionation.[14,15]

The Christie Hospital has reported their experience using 50 Gy in 16 fractions with a conformal technique. The overall bNED rates at five years were 82% for low grade; 56% for intermediate and 39% for high risk. These outcomes are comparable to those achieved using more protracted regimens (Level 2b) with toxicity greater than or equal to Radiation Therapy Oncology Group (RTOG) grade 2 in 5% for bladder and 9% for gastrointestinal (GI).[1,16]

Nearly 8,000 patients have been randomised into completed and ongoing trials of hypofractionation; including the Conventional or Hypofractionated High Dose Intensity Modulated Radiotherapy for Prostate Cancer (CHHiP) trial, the Hypofractionated versus Conventionally Fractionated Radiotherapy for Patients with Localised Prostate Cancer (HYPRO) trial, the Scandinavian-led Phase III Study of HYPOfractionated Radiotherapy of Intermediate Risk Localised Prostate Cancer (HYPO) study, the Canadian PROFIT study and the North American RTOG 0415 study.[4,17–21] Toxicity of moderate hypofractionation at two-year 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.[4] There is a suggestion that equivalent disease-free survival (DFS) can be obtained at the expense of increased genitourinary (GU) or GI toxicity although overall toxicity remains acceptable.[17,22,23]

Results, in terms of disease control, from three of the hypofractionation trials have now been presented in abstract form. The CHHiP trial showed non-inferiority between 60 Gy in 20 fractions and 74 Gy in 37 fractions; the HYPRO study showed non-inferiority between 78 Gy in 39 fractions and 64.6 Gy in 19 fractions; PROFIT showed non-inferiority between 78 Gy in 39 fractions and 60 Gy in 20 fractions and the RTOG 0415 study showed non-inferiority between 73.8 Gy in 41 fractions and 70 Gy in 28 fractions.[24,25]

High-dose-rate (HDR) brachytherapy is an alternative means of delivering hypofractionated radiation as a boost to achieve dose escalation after 45–46 Gy in 1.8–2 Gy daily fractions or 37.5 Gy in 15 fractions.[26–28] The ASCENDE-RT trial shows that low dose rate (LDR) brachytherapy as a boost after 46 Gy in 23 fractions is superior to external-beam 76 Gy in 38 fractions.[28]

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 Prostate Advances in Comparative Evidence (PACE) trial is randomising between standard of care (surgery or image-guided intensity-modulated radiotherapy [IG-IMRT]), and stereotactic radiotherapy (36.25 Gy in five fractions); HYPO compares 78 Gy in 39 fractions versus 42.7 Gy in seven fractions and has recruited 1,000 patients in Scandinavia with a target recruitment of 1,920 patients.[18,269]

Postoperative radiotherapy

There is evidence (Grade A) from three randomised trials, that adjuvant postoperative radiotherapy using 60–64 Gy and 2 Gy per fraction improves recurrence rates in postoperative patients considered to be at high risk of recurrence.[1,30–29] The optimal timing of postoperative 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 postoperative setting are the two primary questions being addressed in the ongoing Medical Research Council (MRC) Radiotherapy and Androgen Deprivation in Combination After Local Surgery (RADICALS) trial, using either 66 Gy in 33 fractions or 52.5 Gy in 20 fractions.[33]

Radiotherapy technique

Dose escalation increases the side-effects of treatment. This can be mitigated by using IMRT or arc techniques (volumetric modulated arc therapy [VMAT] or Rapidarc®) to minimise dose to the organs at risk. The role of lymph node irradiation remains uncertain.[34,35] 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.[36,37]

Recommendations

Radical radiotherapy to the prostate should be delivered using IMRT or arc (VMAT or Rapidarc) techniques with IGRT verifation. Acceptable regimens include:

74–78 Gy to the prostate in 37–39 fractions over 7.5 weeks (Grade A)
60 Gy in 20 fractions over 4 weeks (Grade A)

Or using a brachytherapy boost:

37.5 GY in 15 fractions over 3 weeks followed by 15 Gy HDR brachytherapy boost (Grade B)

46 Gy in 23 fractions over 4.5 weeks followed by 115 Gy LDR brachytherapy boost (Grade B)

Nodal irradiation:

55–60 Gy in 37 fractions over 7.5 weeks or equivalent (Grade D)

Postoperatively:

66 Gy in 33 fractions over 6.5 weeks or
52.5 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.[1]

Palliative radiotherapy

Palliative radiotherapy may be indicated in the event of troublesome haemorrhage, outflow obstruction or pressure symptoms. There is no evidence to guide fractionation.

Recommendations

For palliation standard schedules are used as follows:

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.[1]

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