4.11 Prostate cancer

Introduction

4.11.1 Early prostate cancer is being diagnosed more frequently because of PSA (Prostate Specific Antigen) 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. Cryotherapy and high intensity focused ultrasound may have roles in the future.

Hormonal therapy and radiation dose

4.11.2 This guidance is concerned with radiotherapy dose-fractionation in the radical treatment of prostate cancer with external beam radiotherapy. The interaction of hormonal therapy and radiation dose is complex and interpretations of the available evidence are divergent.

4.11.3 The role of neoadjuvant or adjuvant androgen deprivation with LHRH (luteinizing hormone-related hormone) analogues depends on the risk group of the patient. For patients with low risk (PSA ≤ 10 and Gleason 2–6 and T1 to T2c) early prostate cancer, there is no proven role for adjuvant hormone therapy.

4.11.4 There is Grade A evidence in favour of neoadjuvant or adjuvant hormone therapy for patients with intermediate or high-risk (PSA > 10 or Gleason score > 7 or T ≥ 3) prostate cancer treated with radical radiotherapy, with seven randomised phase III clinical trials (level 1++) showing benefit. Very few patients in these trials had low risk (PSA ≤ 10 and Gleason 2–6 and T1 to T2c) disease, and no firm recommendations on the use of hormone therapy can be made for this group. Men who have advanced localised disease (T3 and Gleason score ≥ 8) benefit from prolonged hormonal therapy (2 years of androgen suppression) compared to short course androgen therapy alone. For patients in the intermediate risk group, there may be a balance between higher doses of radiotherapy and the use of neoadjuvant hormone therapy. Ongoing studies address this question.

4.11.5 In patients who do receive longer-term hormone therapy, there is no evidence that doses > 70 Gy are beneficial. In addition, prostate volume and prostate target volume are reduced by up to 46% following neoadjuvant therapy with associated sparing of the bladder and rectum.

Radiotherapy technique

4.11.6 Because of the issues outlined above, the fractionation schemes which follow are considered independently of the use of hormonal therapy. Fractionation and technique must be considered together. Some centres use a two-phase (large pelvic volume / small prostate volume) approach: there is no published evidence using fraction sizes other than 1.8–2.0 Gy for this approach. It has been advocated in selected cases considered to have a risk of lymph node metastases > 15% (level 1–). In the following discussion any consideration of fraction sizes > 2.2 Gy applies to PTVs (Planning Target Volumes) of < 1000 ml.

4.11.7 Since technique directly affects the tolerable dose, and since most UK centres now use 3-D conformal radiotherapy, the following comments deal solely with this technique (level 1+). Conformal radiotherapy, using multileaf collimators which allow treatment using an irregular shaped beam, is the optimum mode of delivery. It has been recommended that all centres should provide this form of treatment (Grade A).
Radiobiological modelling

4.11.8 The results and implications of radiobiological modelling of external beam treatment for prostate cancer are controversial. Plausible arguments have been developed for both hypo-fractionation (fraction sizes of ≥ 2.5 Gy) and for hyper-fractionation (fraction sizes of ≤ 1.5 Gy). The advice that follows is based exclusively on clinical studies.

Hyper-fractionation (doses-per-fraction of ≤1.5 Gy)

4.11.9 There are two studies reporting results of hyper-fractionated radiotherapy for prostate cancer. Level 3 evidence supports the following conclusions: in terms of efficacy, there is no advantage in using hyper-fractionation compared to conventional fractionation; there may be some decrease in late genitourinary, but not late gastrointestinal, toxicity.

Conventional fractionation (doses-per-fraction in the range 1.8 Gy–2.2 Gy)

4.11.10 The results of conventional fractionation have been comprehensively reviewed and reported. Unfortunately, this systematic review completely overlooked the use of 20 fraction regimens in the radical treatment of prostate cancer. It does, however, provide a vast amount of information on the reported experience with doses of > 60 Gy given in 1.8–2.0 Gy fractions.

As technology has evolved, doses have increased from 60 to 65 Gy in 30–35 fractions using 2-D planning through 65–78 Gy using 3-D conformal techniques, and up to 80 Gy and beyond using IMRT. Four randomised trials have addressed the question: does dose-escalation improve freedom from failure or biochemical evidence of disease control (bNED)? The MD Anderson trial in 305 patients with T1–3 disease showed a 6% improvement in failure-free survival at 6 years when 78 Gy in 39 fractions was compared to 70 Gy in 35 fractions. For the subgroup of patients with a PSA > 10 ng/ml, a 19% PSA control advantage was seen. The increase in failure-free survival was accompanied by an increase in late rectal complications (level 1+) which may now be avoidable with adjustments to radiotherapy technique (level 4).

The RMH (Royal Marsden Hospital) pilot trial of 126 patients showed a statistically non-significant improvement of 12% in freedom from PSA failure when 74 Gy in 37 fractions was compared to 64 Gy in 32 fractions. Patients treated to a higher dose had a higher rate of late bowel complications (level 1+).

The Dutch trial, which has reported toxicity data only, also found an increased rate of serious late rectal complications in patients treated with 78 Gy when compared to patients treated with 68 Gy (10% versus 2% at 3 years) (level 1+).

The recent trial comparing photon therapy alone (70 Gy) to photons + proton boost (79 Gy equivalent) showed a 19% increase in PSA control with the higher dose, but a doubling of bowel toxicity (level 1+).

Hypo-fractionation (doses of 2.5 Gy per fraction and above)

4.11.11 Despite extensive use of such regimens, both in the UK and abroad, the number of reported series and trials is small. Two randomised trials have compared hypo-fractionation to conventional fractionation in the radical radiotherapy treatment of prostate cancer. The hypo-fractionated regimens were 55 Gy in 20 fractions in 4 weeks and 52.5 Gy in 20 fractions in 4 weeks. Both regimens used control arms of ≤ 66 Gy in 33 fractions in 6.5 weeks, doses that, by current standards, might be considered low (see above). The results show a trend towards lower 4-year bNED rate with hypo-fractionation. The
evidence suggests that, although 20 fraction regimens can be effective and safe, doses of ≤ 55 Gy may be too low. In the UK, the CHHIP randomised controlled trial is comparing 2 Gy (total dose 74 Gy) and 3 Gy (total doses 57 Gy and 60 Gy) and has already recruited 300 patients. Broadly similar trials are planned in Canada and The Netherlands, comparing 78 Gy in 2 Gy fractions and 60 Gy and 63 Gy in 20 and 21 fractions respectively.

The Christie Hospital has used 50 Gy in 16 fractions using a conformal technique. The overall bNED rates at 5 years were 65% (T1); 62% (T2); 38% (T3 and 4), comparable to those achieved using more protracted regimens (level 2+).

Experience, demand and capacity will influence departmental policies for the management of prostate cancer with external beam radiotherapy.

Given inter-departmental variations in definition of PTV, radiotherapy technique (conformal, IMRT), prescribing conventions and use of adjuvant hormone therapy, it is not appropriate to make any universal recommendation concerning dose.

Acceptable regimens include:

- 74–78 Gy to the prostate in 37–39 fractions over 7.5–8 weeks (Grade A)
- 50 Gy in 16 daily fractions over 3.5 weeks to the prostate only (Grade C)
- 20 fraction regimens have been extensively used—the optimal dose is uncertain, but is probably at least 55 Gy (Grade D).

4.11.12 This is a rapidly changing area of clinical practice and further clinical trials should be encouraged and supported.

References


