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Overview

Biological Dose Escalation and Hypofractionation: What is There to be Gained and How Will it Best be Done?

A.C. Tree *‡, E.J. Alexander †‡, N.J. Van As *, D.P. Dearnaley †, V. Khoo *†

* Royal Marsden NHS Foundation Trust, London, UK
† Institute of Cancer Research, Sutton, Surrey, UK

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Abstract

The evidence supporting dose escalation for localised prostate cancer is widely accepted, but in tandem with improvements in biochemical control, dose escalation increases side-effects. In a scenario where most patients achieve control of their cancer, quality of life concerns predominate. Here we examine the biological ways in which an effective dose can be escalated without an unacceptable increase in toxicity. Possible avenues include exploiting the unusual radiobiology of prostate cancer by hypofractionation, the use of image guidance, adaptive planning and prostate motion management. We await with anticipation the results of large randomised trials of hypofractionation, moderate and profound, to establish whether we can further improve the balance between cure and quality of life.

Key words: Biological; dose escalation; hypofractionation; image-guided radiotherapy; prostate cancer; stereotactic body radiotherapy

Statement of Search Strategies Used and Sources of Information

The search engines of the PubMed, Cochrane and MeSH databases were utilised, as well as the proceedings from the major radiation oncology conferences for the key words outlined in the manuscript. In addition, relevant references listed from identified articles were also cross-reference and assessed for inclusion suitability.

Introduction

Radiation is an effective treatment for localised prostate cancer, curing most patients treated. High-risk patients (prostate-specific antigen [PSA] > 20, T3a, Gleason 8–10) continue to have a significant risk of relapse and further strategies need to be targeted at such patients. Dose escalation should increase local disease control and improve the long-term efficacy of treatment [1]. The postulated low alpha/beta ratio of prostatic adenocarcinoma leads to the hypothesis that radiobiological methods may be used to biologically escalate doses while maintaining current levels of toxicity. This could be achieved with hypofractionation, increasing the convenience to patients and to radiotherapy departments. In prostate radiotherapy, where local control rates are already high and overall survival benefits are yet to be realised, the quality of life after treatment is an equally important consideration. This overview sets out to explore the evidence for dose escalation in prostate cancer and whether we can harness recent developments in technology and the knowledge of radiobiology to improve the therapeutic ratio.

Biological Dose Escalation: What Is There To Be Gained?

Conventional Dose Escalation

Dose escalation has been shown in several well-conducted randomised trials to improve biochemical PSA (bPSA) control at 5 years [2–6]. This is maintained at 8–10 years after treatment [7–9]. The major studies of dose

Author for correspondence: V. Khoo, Royal Marsden NHS Foundation Trust, Fulham Road, London SW3 6JJ, UK. Tel: +44-207-808-2788.
E-mail address: vincent.khoo@rmh.nhs.uk (V. Khoo).
‡ Dr Tree and Dr Alexander contributed equally to this manuscript.

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escalation have not, so far, shown a survival benefit [2,7,8]. There are, however, data that hint towards a survival advantage. The Institute of Cancer Research/Royal Marsden Hospital pilot study, which preceded the larger multicentred RT01 study, has completed 14 years of follow-up [10]. This small randomised study has the longest follow-up of any dose-escalated trial to date. No results reached statistical significance, but they do show a trend towards an overall survival benefit in the dose-escalated group, treated with 74 Gy in 37 fractions (hazard ratio 0.81; 95% confidence interval 0.47–1.40). The lack of survival benefit with dose escalation contrasts with studies assessing the role of adjuvant androgen deprivation therapy (ADT) in clinically localised disease. Here, there is strong evidence of both biochemical and overall survival benefit from randomised trials and meta-analyses, albeit at conventional radiation doses of 60–70 Gy [11–16]. Good evidence of maintaining that survival benefit in the dose-escalated era is lacking. Data have recently been published regarding the use of short-term ADT in patients undergoing radiation at doses of 81 Gy or more [17]. ADT remained an independent predictor for prostate cancer-specific mortality and further factors found to be associated with prostate cancer-specific mortality were primary Gleason grade 4 and $\geq$50% of biopsy cores positive.

Who benefits from dose escalation? Although not all randomised trials individually show a benefit for low-risk prostate cancer patients [18,19], there is evidence that the dose effect occurs across all patients in randomised groups regardless of risk classification [20,21]. Analysis from the MD Anderson randomised trial also suggests that patients with an initial PSA $>$ 10 ng/ml derive significant benefit from the increased dose in terms of the prevention of biochemical, nodal and distant failure [19]. In addition, a small cohort study has raised the hypothesis that dose escalation above 80 Gy may improve survival in high-risk patients, specifically with Gleason 8–10 prostate cancer [22].

Where is the plateau of the dose–response curve? The dose relationship would seem to be essentially linear between 64 and 80 Gy and it has been hypothesised that to achieve 100% local control, doses of between 86.5 and 95.5 Gy would be needed, depending on risk category [20]. However, the lack of series delivering such high doses means that the theoretical benefit of these doses can only be modelled. Data from previous analyses of three-dimensional conformal dose escalation suggest benefits in biochemical control of up to 2.2% for every 1 Gy increase in dose level [20,23], although these figures are probably an overestimation [21]. Meta-analyses cannot control for the parallel improvements in technology and stage migration that occur over time. Additionally, there is a significant contribution of data from non-randomised trials that are subject to selection bias and shorter follow-up in the dose-escalated cohorts. An alternative method, which may be a more robust estimation of the dose–response curve, is to pool the measured gradients of the individual trial dose–response curves (γ50) and so model the overall dose–response as proposed by Diez *et al.* [21]. Such modelling shows a significant discrepancy between the randomised and non-randomised data estimates of the steepness of the curve with γ50 of 0.56 for randomised low-risk patients versus 1.78 for non-randomised low-risk patients. Overall Diez *et al.* [21] estimated a γ50 of 0.84 (95% confidence interval 0.54–1.15). Consequently, perhaps a more reasonable estimate of the improvement in biochemical control would be in the order of 1% per Gy.

Although outcomes after conventional radiotherapy are generally good for low- and intermediate-risk patients, the results for high-risk patients remain less satisfactory with biochemical relapse-free survival (bRFS) of 60–75% [24,25]. Further dose escalation with conformal techniques is limited, as randomised data show about a 50% increase in late bowel toxicity with dose-escalated radiotherapy [2,3,20]. As most patients have prolonged survival after radiation treatment for prostate cancer, survivorship issues are becoming increasingly important. Dose escalation should only be pursued in the context of acceptable toxicity to patients. Other strategies of dose escalation should be explored in order to improve the therapeutic ratio of treatment above that of three-dimensional conformal dose-escalated radiotherapy. Such strategies may include focal dose boosts of radiation at conventional doses (1.8–2 Gy per fraction) or biological dose escalation using hypofractionation with doses above 2 Gy, either with moderate hypofractionation (2–3.5 Gy per fraction) or profound hypofractionation ($>$3.5 Gy per fraction).

The Alpha/Beta Ratio for Prostate Cancer and Rationale for Therapeutic Hypofractionation

Prostate cancer generally has radiobiological features that are atypical compared with most cancers. Prostate cancer cells have long potential doubling times [26–28], low labelling indices [26,29] and late tumour repopulation [27]. There is a known association between levels of proliferation and sensitivity to fraction size [30,31], which suggests that tissues with low levels of cycling cells are more sensitive to hypofractionation [32]. There is now growing consensus that the alpha/beta ratio for prostate cancer cells is low, less than 3–4 Gy [33–36] and there are many data that support a very low alpha/beta in the order of 1–1.5 Gy [32,37–40] (Table 1). If the alpha/beta of prostate cancer is lower than the surrounding late reacting tissues, e.g. rectum (alpha/beta of 3–6 Gy) [36,47–49], there could be biological advantages to hypofractionation. Biological dose escalation could be achieved with a lower total prescribed dose, in which case, an improvement in the therapeutic ratio may be anticipated with increased tumour control and decreased late toxicity. The effect on acute toxicity would depend on the total dose and the overall treatment time. If there is no acceleration of treatment, acute reactions would decrease as early responding tissues have a high alpha/beta ratio and therefore are less sensitive to a change in fraction size.

Brenner and Hall [38] first hypothesised that the alpha/beta ratio was 1.5 Gy in their pioneering analysis of data from low dose rate (LDR) brachytherapy and external beam