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Overview

Functional Radiotherapy Targeting using Focused Dose Escalation

R. Alonzi

Mount Vernon Cancer Centre, Northwood, UK

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Abstract

Various quantitative and semi-quantitative imaging biomarkers have been identified that may serve as valid surrogates for the risk of recurrence after radiotherapy. Tumour characteristics, such as hypoxia, vascularity, cellular proliferation and clonogen density, can be geographically mapped using biological imaging techniques. The potential gains in therapeutic ratio from the precision targeting of areas of intrinsic resistance makes focused dose escalation an exciting field of study. This overview will explore the issues surrounding biologically optimised radiotherapy, including its requirements, feasibility, technical considerations and potential applicability.

Key words: Brachytherapy; dose painting; functional imaging; hypoxia; IMRT; radiation dose escalation; targeted radiotherapy

Statement of Search Strategies Used and Sources of Information

Pubmed and Google Scholar were used for searches. Other sources of information include text books and conference proceedings.

Introduction

The failure of radiation therapy to control any particular cancer can be attributed to one of three main causes. Inadequate initial staging resulting in the incorrect belief that the tumour was contained within the proposed radiotherapy field; geographical miss during treatment or intrinsic biological radio-resistance. Major improvements have been made in the first two of these areas. Advanced multimodality diagnostic imaging is commonplace for most tumour sites and has led to greater staging accuracy [1–6]. The introduction of image-guided radiotherapy using on-board imaging technology or fiducial marker tracking has reduced the probability of missing the intended target volume [7–14]. However, our ability to overcome intrinsic resistance is currently lacking. There has been an abundance of research investigating a host of biomarkers that may prove to be valuable targets for either pharmacological radio-sensitisation or focused dose escalation [15–24]. These markers are at various stages of the validation process. Some tumour characteristics, such as hypoxia, vascularity, cellular proliferation or clonogen density, can be mapped geographically using functional imaging techniques or by using systematic biopsies with subsequent immunohistochemistry or molecular characterisation. In spite of this, this information is rarely incorporated into the radiotherapy planning process and most radiotherapy fractions are given using homogeneous dose distributions with conventional fractionation and no radio-sensitisation. The ability to assimilate this functional information into the radiotherapy planning process poses a number of challenges, but the technology to achieve biological conformity is widely available and routinely used in most radiotherapy departments. The potential gains in therapeutic ratio from the precision targeting of areas of intrinsic resistance makes focused dose escalation an exciting field of study. This overview will explore the issues surrounding biologically optimised radiotherapy, including its requirements, feasibility, technical considerations and potential applicability.

R. Alonzi, Mount Vernon Cancer Centre, Northwood HA6 2RN, UK. Tel: +44-1923-844710.
E-mail address: ralonzi@nhs.net

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Rationale for Biologically Optimised Radiotherapy

Focused dose escalation is based on the principle that areas of tumour with relative radio-resistance can be overcome by administering a higher biologically effective radiation dose. This can be achieved either by giving a higher total dose or a higher dose per fraction. There is evidence to support this.

First, we have long been aware that most human tumours exhibit a dose–response relationship [25]. In practise this means that the more dose given to a tumour, the higher the tumour control probability. The sigmoid shape of the dose–response curves for most human tumours (and normal tissues) reflects the variability in clinical radioresponsiveness of individual patients (Figure 1). For any given radiation dose there will be individuals whose tumours possess biological characteristics that make them resistant, and will therefore fail at that dose level. The fact that the probability of tumour control can be improved by increasing the dose indicates that these relatively resistant clonogens can be destroyed simply by using more radiation. This may seem obvious, but it is fundamental to the concept of biological dose optimisation. It is worth mentioning that there are a few tumour types, such as glioblastoma, where no such relationship exists [26,27]. In these situations there is no improvement in tumour control with higher radiation doses and therefore there would be no rationale for dose escalation or basing the planned radiation dose distribution on any particular biological characteristic.

There is evidence for the clinical advantages of dose escalation in a variety of tumour types [28–31]. Prostate cancer is a particularly good example. In a study of 2047 patients, Zelefsky *et al.* [32] reported that in high-risk patients with localised prostate cancer, higher dose levels were associated with improved biochemical outcomes. Five year prostate-specific antigen relapse-free survival outcomes for patients who received 86.4, 81, 75.6 and 70.2 Gy or less were 71, 66, 61 and 40%, respectively. A Cox proportional hazards regression analysis showed that dose level was a significant predictor for prostate-specific antigen relapse-free survival ($P < 0.0001$; hazard ratio 0.758). In addition, the analysis showed that dose, as a continuous variable, was a significant predictor of improved biochemical outcomes ($P = 0.023$; hazard ratio 0.822) and was most apparent between patients who received 86.4 Gy compared with those who received 75.6 Gy ($P = 0.05$). Eade *et al.* [33] reported results from 1530 men with prostate cancer treated with three-dimensional conformal radiotherapy. Of four dose groups analysed (<70, 70–74.9, 75–79.9 and > 80 Gy), there was a 20% improvement at 5 years in biochemical control rates from the lowest to the highest dose levels and a 6% improvement in distant metastases-free survival. The authors concluded that dose levels of 80 Gy or higher may be necessary to achieve optimal tumour control. In the UK, the Medical Research Council RT01 study showed that at a median follow-up of 10 years, dose escalation resulted in a significant improvement in biochemical progression-free survival (43%, 95% confidence interval 38–48) in the control group and 55% (50–61) in the escalated-dose group (hazard ratio 0.69, 95% confidence interval 0.56–0.84; $P = 0.0003$) [34].

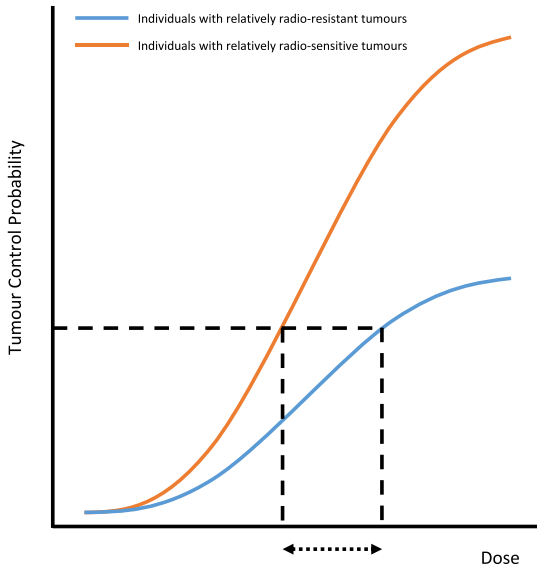

Fig 1. Examples of dose–response curves for individuals with relatively resistant tumours (blue) and for individuals with relatively sensitive tumours (orange). Equivalent tumour control probabilities can be achieved for the two groups of individuals by administering a higher dose to the group with relatively radio-resistant tumours.

Therefore, data from both pre-clinical and clinical studies suggest that higher administered radiation doses can overcome intrinsic radio-resistance. However, dose escalation to the entire tumour volume may not always be possible. Increasing the tumour dose will inevitably increase the dose to the surrounding critical normal tissues, leading to worse acute and late toxicity. Continuing with the above example of prostate cancer, five randomised dose escalation trials consistently showed worse late gastrointestinal toxicity for dose escalated whole gland radiotherapy compared with standard dose radiotherapy to similar treatment volumes [35–42] (Table 1). Without altering the planning technique, improved tumour control from dose intensification will always come at the penalty of worse toxicity. A potential way to avoid this is to use techniques to focus the escalated dose to the high-risk regions.

'Anatomically' focused dose escalation has been practiced for many years in numerous tumour types using two-phase planning techniques, concomitant boosts or brachytherapy in combination with external beam therapy. For example, in the ACT I UKCCCR Anal Cancer Trial (1996), patients were treated with 45 Gy in 20–25 fractions to the pelvis (anus up to the mid-pelvic line to include the inguinal lymph nodes), which was subsequently followed by 15 Gy in six fractions to the perineal field with electrons or photons, or by an iridium-192 implant to 25 Gy at 10 Gy per day [43]. Similar techniques can be cited for cervical cancer [44,45], head and neck cancer [46,47] and prostate cancer [48,49]. In these examples the choice of the volume for the boost was not based on any biological information, but instead it was determined by the area perceived to be at