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Original Article

Radiotherapy for Prostate Cancer: is it 'what you do' or 'the way that you do it'? A UK Perspective on Technique and Quality Assurance

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Abstract

Aims: The treatment of prostate cancer has evolved markedly over the last 40 years, including radiotherapy, notably with escalated dose and targeting. However, the optimal treatment for localised disease has not been established in comparative randomised trials. The aim of this article is to describe the history of prostate radiotherapy trials, including their quality assurance processes, and to compare these with the ProtecT trial.
Materials and methods: The UK ProtecT randomised trial compares external beam conformal radiotherapy, surgery and active monitoring for clinically localised prostate cancer and will report on the primary outcome (disease-specific mortality) in 2016 following recruitment between 1999 and 2009. The embedded quality assurance programme consists of on-site machine dosimetry at the nine trial centres, a retrospective review of outlining and adherence to dose constraints based on the trial protocol in 54 participants (randomly selected, around 10% of the total randomised to radiotherapy, $n = 545$). These quality assurance processes and results were compared with prostate radiotherapy trials of a comparable era.
Results: There has been an increasingly sophisticated quality assurance programme in UK prostate radiotherapy trials over the last 15 years, reflecting dose escalation and treatment complexity. In ProtecT, machine dosimetry results were comparable between trial centres and with the UK RT01 trial. The outlining review showed that most deviations were clinically acceptable, although three (1.4%) may have been of clinical significance and were related to outlining of the prostate. Seminal vesicle outlining varied, possibly due to several prostate trials running concurrently with different protocols. Adherence to dose constraints in ProtecT was considered acceptable, with 80% of randomised participants having two or less deviations and planning target volume coverage was excellent.
Conclusion: The ProtecT trial quality assurance results were satisfactory and comparable with trials of its era. Future trials should aim to standardise treatment protocols and quality assurance programmes where possible to reduce complexities for centres involved in multiple trials.

Key words: Prostate cancer; quality assurance; radiotherapy; randomised controlled trials

Introduction

In 2016, the first outcome data from the UK ProtecT trial will be reported. In this landmark UK National Institute for Health Research (NIHR)-funded trial, men with clinically localised prostate cancer were randomised to radical prostatectomy, external beam radiotherapy or active monitoring [1]. Whether or not there are differences in outcomes between these three approaches, there will undoubtedly be an appraisal of the trial's treatment technique in the light of today's technology, the use of dose escalation in 'conventional' 2 Gy fractions and the quality assurance data. This is inevitable, given that the ProtecT trial is unique in comparing three prostate treatment modalities, probably was only

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achievable when it was done and in the UK – and so will never be repeated. There have been several other landmark trials in the UK of radiotherapy for prostate cancer, including the Medical Research Council (MRC) RT01 and PR07 trials, the Cancer Research UK/NIHR Cancer Research Network CHHIP trial and exploratory data from the MRC STAMPEDE trial [2–5]. This article aims to put these radiotherapy trials into their historical context as a backdrop when the first results of the ProtecT trial are unveiled in 2016.

Radiotherapy for Prostate Cancer: Technology Shifts the Goalposts

The first descriptions of radiotherapy for prostate cancer come from the early 1900s, when reports of radium needle insertions were published in the *Journal of the American Medical Association* [6]. The advent of external beam radiotherapy during the course of the century led to more patients being treated, but a paucity of evidence. Notable from the era in the 1970s and early 1980s were the Stanford case series of Bagshaw, which laid the foundations of clinical practice [7]. At that time, conventional radiotherapy planning involved a planning cystogram, and the manual definition of radiotherapy fields based – ultimately – on the physician's opinion. The advent of computed tomography planning in the late 1980s radically changed practice, the initial hope being that radiotherapy fields could be made smaller, because the tumour definition was more accurate, and so more normal tissue would be spared. In fact, the hope was based on a false premise, although the reasoning was correct. Tumour definition was much more precise, but in turn radiotherapy fields often became larger, as it was evident, in retrospect, that geographical miss had been more common than was previously supposed [8].

Using computed tomography planning, it was also possible to accurately define the extent of rectum included in a high dose volume, even though there was no obvious consensus as to how much rectal irradiation was 'acceptable'. The new level of accuracy, coupled with isocentric planning and delivery on linear accelerators rather than on cobalt, also permitted another development – conformal radiotherapy. In its early days, this was achieved by the manufacture of customised lead blocks, which were mounted on a tray placed on the linear accelerator head. It was presumed that this would, by reducing the volume of normal tissue irradiated, also reduce radiotherapy side-effects, and this was proven in a landmark publication of the first randomised trial comparing conformal and conventional radiotherapy for pelvic tumours [9].

Even in the early days of conformal radiotherapy, another goal was envisaged – that of dose escalation, based on the philosophy that, if a rate of 5% of grade 3–4 late toxicity was 'acceptable' and if conformal radiotherapy reduced this rate, it would permit dose escalation, hopefully with improved tumour control, titrated against this 'acceptable' level of toxicity. Several randomised trials of dose escalation for prostate cancer were opened in the 1990s, following pilot studies that suggested that this approach was safe, and these trials have now all reported outcome data [2,10–13]. Although dose escalation is now routine practice, it was not state of the art in external beam radiotherapy for prostate cancer at the time when the UK ProtecT study was designed in the late 1990s. Importantly, although several clinical centres had the capacity for conformal radiotherapy, it was by no means uniformly available across the UK, and even computed tomography planning was not universal at that time.

In the ProtecT trial, patients with clinically organ-confined prostate cancer were to be randomised to radical prostatectomy, radical external beam radiotherapy or active monitoring. The problem for the designers of ProtecT in the late 1990s was how to make the radiotherapy technique as 'future-proof' as possible, against a backdrop of limited or non-existent evidence of long-term efficacy. Too conservative, and in the event of radiotherapy turning out to be less effective, the trial would be criticised for under-treating patients. Too aggressive and it would be criticised for over-treating patients. Another factor in the UK was the increasing use of neoadjuvant hormone therapy in combination with radiotherapy and whether this was also to be included in the ProtecT trial, although this was not standard practice in the USA. Other contrasts existed between the UK and the USA in terms of dose escalation; in the USA, the dose per fraction was limited to 1.8 Gy and the total dose was being escalated to 78 or 80 Gy [14], whereas in the UK, the dose per fraction was 2 Gy and the total dose was limited to 74 Gy. The latter technique was used in the MRC's RT01 trial [2], which recruited between 1998 and 2001 and randomised patients to a 'standard' dose of 64 Gy in 32 fractions versus an escalated dose of 74 Gy in 37 fractions.

In the event, the technique chosen for ProtecT was similar to that used for RT01, in that it used (i) neoadjuvant hormone therapy and (ii) dose-escalated radiotherapy to a total of 74 Gy in 37 fractions. There were, however, differences between the two trials; although the treatment was given in two phases, in RT01 the phase II dose was 10 Gy, whereas in ProtecT it was 18 Gy. ProtecT also had organ at risk dose constraints pre-specified, unlike in RT01.

The ProtecT trial recruited patients from late 1999 to early 2009, a period when technical developments in radiotherapy have continued apace. First came the development of portal imaging – another technology that was far from universal in the UK at the ProtecT trial outset. Then, the first reports of intensity-modulated radiotherapy (IMRT) for prostate cancer and subsequently the use of image-guided radiotherapy (IGRT) led to a growing pressure to use these techniques routinely [15,16]. Indeed, the current European Guidelines state that the use of IMRT for prostate cancer radiotherapy should now be standard [17]. Conceptually, the argument for IMRT is compelling, but does that weaken the conclusions from trials that came too early to use it? It could be argued that long-term radiotherapy toxicity in trials such as RT01 and ProtecT might have been lessened through the use of IMRT, but in a comparative setting with other modalities, similar arguments could also be made about the evolution of open to robotic prostatectomy.