Editorial

Radiotherapy versus Prostatectomy: a Question of Survival or Survivorship? Addressing Ongoing Questions and Controversies in the Management of Localised Prostate Cancer in the UK

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Received 12 April 2016; accepted 27 April 2016

The landscape of prostate cancer is evolving. Although the introduction of prostate-specific antigen (PSA) testing into clinical practice some 30 years ago has seen a greater detection of organ-confined disease due to stage migration, as yet this has not resulted in any significant reduction in mortality [1]. In addition, although a third of cases are diagnosed in men above the age of 75 years, only a minority actually undergo curative treatment, leaving a significant proportion of men to have to live with their prostate cancer. With an increasing demand for preserving quality of life and functional outcome, there is thus an impetus to define organ-confined disease more clearly and select patients for treatment who are at risk of metastatic spread while avoiding over-treating those with indolent cancer.

The management of localised prostate cancer continues to polarise opinion between surgery and radiotherapy. This is largely because there has never been a prospective randomised trial directly comparing them to inform decision making. Attempts at retrospective comparisons/meta-analysis have yielded conflicting results, mainly due to inherent bias when comparing two fundamentally different approaches to treatment [2]. These include a failure to include androgen deprivation therapy with radiotherapy, using surrogate end points rather than overall and cancer-specific survival, and the obvious discrepancy between definitive pathology obtained at prostatectomy versus the limited histology that guides radiotherapy treatment. In addition, many retrospective studies were started in the pre-PSA era. These issues are discussed in more detail in the accompanying editorial by Dr Roach [3], but it would seem that any survival gains between either modality are small and not clinically meaningful. Thus, the more important factors driving the treatment decision are probably related to the morbidity of treatment and the impact on quality of life for the individual.

For those with low-risk organ-confined disease, there is now general acceptance that Gleason Score 6 tumours behave in an indolent manner. Historically, we may have been over-treating this group of patients who are more likely to die of non-prostate-related causes [4]. The PIVOT study trial, which randomised over 730 patients with localised disease to prostatectomy versus observation, found no difference in overall survival or cause-specific mortality after a median follow-up of 10 years [5]. The Royal Marsden experience of active surveillance suggests that 78% of patients do not experience histological progression at 5 years and are thus spared side-effects from having radical treatment [6]. Nevertheless, there still remain unanswered questions about surveillance – in particular, the duration of follow-up and intervention thresholds. It is important to remember that patients may be precluded from receiving certain treatments the longer they remain on surveillance. For example, in the UK there is a trend to offer patients over the age of 70 years radiotherapy rather than surgery [7]. This may not just reflect cumulating medical co-morbidity and the increased risks of anaesthetic, but also the greater risk of urinary incontinence with surgery in the elderly [8].

The intermediate-risk group (T2b-c/GS7or PSA 10–20), as defined by D’Amico et al. [9], presents a greater challenge, for although there is a clear therapeutic advantage in favour of treatment, the variety of surgical and radiotherapy treatment options now available can be bewildering for patients and clinicians alike. Data from retrospective studies are inherently difficult to interpret due to patient heterogeneity and selection bias, with radiotherapy reserved for older, less fit patients. Irrespective of this, the survival rates are respectable, with the most reliable studies suggesting that the differences in 10 year cancer-specific survival between surgery and radiotherapy are small [10].
The results from the PROTEC-T trial, which randomised over 225,000 men with localised disease to active monitoring, radical radiotherapy and prostatectomy, are eagerly awaited. However, the results may not be wholly applicable to the intermediate-risk group, given that most of those enrolled were low-risk whose outcomes are likely to be favourable irrespective of treatment received. The PACE trial, which randomises patients between conventional or stereotactic radiotherapy versus laparoscopic prostatectomy, is now recruiting and will be key to understanding the effect of such contemporary treatments.

With regards to external beam radiotherapy, we now have mature data from randomised trials conducted at treatment centres in the UK to help standardise treatment. The RT01 trial has helped to determine a benchmark dose of at least 74 Gy using three-dimensional conformal radiotherapy. Subsequently dose escalation with hypo-fractionated regimens that exploit the low alpha/beta ratio of prostate cancer, using intensity-modulated radiotherapy with image guidance are now feasible. The CHHiP trial reported non-inferiority outcomes using 60 Gy/20 fractions, is now set to become the new standard for UK practice.

Both of these trials used short-course androgen deprivation to allow for tumour cytoreduction and to exploit the synergistic effect with radiotherapy. Although the outcome figures for RT01 are comparable with most reported surgical series, the quest for improved cancer survival from both dose escalation and hypo-fractionation comes at the expense of increased toxicity, notably bowel and bladder acute and late effects.

In addition we must not forget the risk of radiation-induced secondary cancers, notably rectal and lethal bladder cancer, due to local radiation scatter. This is generally a late occurrence, with a reported 1 in 70 chance of development 10 years after treatment and may swing the decision for younger patients in favour of surgery. Emerging radiotherapy techniques using volumetric modulated arc therapy or brachytherapy (high dose rate/low dose rate) are associated with less radiation scatter and have the potential to reduce secondary cancer risk.

It is the high-risk group that presents the greatest therapeutic challenge. The heterogeneity of patients included in this cohort include those with a high Gleason Score 8–10/PSA > 20 and organ-confined disease, locally advanced node negative (T3, T4/N0) and node positive disease, which makes interpretation from studies difficult. As such, although retrospective studies between surgery and radiotherapy show in favour of surgery, most have focussed on node-negative disease, excluded the use of androgen deprivation therapy and are confounded by the use of salvage radiotherapy.

Although androgen deprivation forms the mainstay of treatment for node-positive disease irrespective of primary radical therapy, there is compelling evidence from prospective studies to suggest a survival advantage for the addition of radiotherapy in node-negative disease. For example, a European Organization for the Research and Treatment of Cancer (EORTC) study showed a survival advantage for a combination of 3 years of hormones with prostate and pelvic radiotherapy treatment for locally advanced high-risk, node-negative disease. Likewise, a survival advantage was also seen in the PR07 trial, although the use of extending the radiation field to include the pelvis was optional and androgen deprivation was lifelong. Although pelvic radiotherapy improves local control, with no effect on overall survival as yet, it comes at the expense of increasing gastrointestinal toxicity. This, however, could be mitigated with the use of highly conformal techniques such as intensity-modulated radiotherapy to spare the bowel. The PIVOTAL study looking at prostate alone versus prostate plus pelvic radiotherapy in locally advanced disease will help to answer this question.

In addition to the ongoing debate about the optimal radiotherapy volume, there still remain questions about the optimal duration of androgen deprivation given its toxicity profile. Hormonal treatment is associated with the development of a metabolic syndrome leading to an increased risk of diabetes, hypertension and coronary artery disease. This is an addition to the risk of osteoporosis as a result of castrate levels of testosterone. In particular, the increased risks of cardiovascular mortality may tip the balance in favour of a shorter course of androgen deprivation, especially in those patients who already have pre-existing ischaemic heart disease.

Although androgen deprivation and radiotherapy forms the standard of care in the UK and Europe, the role of surgery as an initial step in the management of carefully selected high-risk patients should not be completely dismissed. In particular for those who are locally symptomatic with a decision for adjuvant or salvage treatment based on adverse features from the full pathological specimen. This is an attractive option with the potential to avoid overtreatment and indeed may be curative in some instances. However, it is important to bear in mind that salvage radiotherapy may not only potentiate any incontinence and erectile dysfunction due to surgery, but is also associated with radiotherapy-specific bowel and bladder toxicity, arising from the uncertainties in treating a potential space that is now filled by the bladder and rectum. It is hoped that the RADICALS trial will inform us as to whether a truly multi-modality approach is feasible in such patients.

Although the debate about surgery and radiotherapy for localised prostate cancer will probably continue, the end point for judging success will probably evolve, with emphasis more on survivorship rather than just survival. For high-risk disease, a willingness to adopt a multi-modality approach may be beneficial and actually avoid overtreatment in carefully selected patients. Selecting primary therapy using algorithms that take individual factors into account, such as life expectancy, co-morbidity and risk of requiring salvage therapy, may aid this decision making.

A greater understanding of tumour biology and genetics may also help to predict and thus stratify treatment outcomes in the future. The UK RAPPER study is seeking to determine whether DNA polymorphisms can predict for radiation toxicity and there is now evidence to suggest those with BRCA2 mutations may be better suited for...
radiotherapy [28]. This will surely transform the surgery/radiotherapy debate from a generalised discussion based on data from selected patient cohorts, to a more personalised decision based on patient-specific factors in order to optimise both survival and survivorship.

References


