Radical radiotherapy for high risk prostate cancer in older men

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Male life expectancy continues to increase worldwide, driven in developed countries by a reduction in mortality in individuals aged over 65. In the US it is anticipated that the incidence of prostate cancer will rise by 55% between 2010 and 2030, predominantly in older men (>65) for whom a 75% rise has been estimated.1 Determining the most appropriate evidence-based management strategy in this cohort is therefore a significant healthcare issue.

Based on US social security data, the median life expectancy for a man aged 70 years is 12.4 years. However, 25% of men aged 70 years will live at least 18 years and another 25% less than 6.7 years. Similarly for an 80-year-old man, the median life expectancy is 6.7 years.2 Although accurate prediction of an individual’s life expectancy is not possible, it may be estimated based on the number and severity of any comorbidities, and their functional status.

A risk/benefit analysis is recommended when making treatment decisions in elderly men. Factors to be considered include the risk of dying from prostate cancer, the predicted life expectancy and risk of dying from co-morbidities, the efficacy of the treatment being considered and its potential side effects. Patient involvement in decision making is essential as their own experiences and perceptions will allow appropriate weighting of the factors being considered, especially when considering active surveillance and watchful waiting strategies, where patient anxiety is a significant issue.

A SEER-Medicare database study was performed in the US to determine the natural history of organ-confined prostate cancer in men aged ≥70, diagnosed between 1992 and 2002 managed conservatively.3 In low to intermediate risk disease, the 10-year prostate cancer specific death rate was 5-15% with the risk of non-prostate cancer related death increasing with age and approaching 70% for men aged ≥80. However, in high risk organ-confined disease, the 10-year cancer-specific death rate approached 30%, indicating that a significant proportion die from prostate cancer rather than with prostate cancer. It is also a common misconception that prostate cancer is less aggressive in older patients. A retrospective analysis of radical prostatectomy histology samples in North Carolina revealed that men ≥70 had higher risk prostate cancer than their younger counterparts with respect to T stage, Gleason score and tumour volume.4 Despite this data, men aged 70 and above are far less likely to receive radical treatment than younger men. In fact they have a greater chance of being treated radically if they have low risk rather than high risk disease.5

A SEER-Medicare database analysis from the 1990s studied men aged 68-77 who had been diagnosed with low to intermediate risk prostate cancer. Radical treatment (surgery, external beam radiotherapy or brachytherapy) was associated with a survival advantage (HR 0.70-0.74) when compared to conservative management, although the benefit decreased with age.6 In high risk prostate cancer, two recent landmark trials have reported a survival advantage with the addition of radical radiotherapy to lifelong androgen deprivation therapy (ADT). The Scandinavian Prostate Cancer Group – 7 (SPCG-7) reported a 10% increase in overall survival (OS) at 10 years. Participants had a median age of 66 years and, on subset analysis, the survival benefit favoured patients aged over 67. The PRO7 trial addressed a similar question, again demonstrating a survival benefit (at seven years) in a population with a median age of 70 years.7 As a result of these studies, radical radiotherapy in combination with ADT of varying durations is now standard practice for high risk localised prostate cancer in the UK.

Aside from treating micrometastatic disease, ADT augments local control, and in the neoadjuvant setting reduces prostate size, resulting in a smaller target volume to irradiate.8 The duration of ADT remains open to debate. In high risk disease, short course (six months) ADT in combination with radical radiotherapy has been shown to confer a 13% OS benefit at eight years (median age of patients 72.5 years). However, in men with moderate to severe comorbidities there was no additional benefit.9 Several studies have addressed the role of long course (at least 2.5 years) ADT in combination with radical radiotherapy for the treatment of high risk prostate cancer (including locally advanced disease).10,11 All show a survival advantage for the combination therapy, although in some cases the age demographics of the study population are either not mentioned or the study was restricted to men aged <80 years. However, where reported, the survival benefit persisted in patients >70 years. It should be noted that all these studies delivered radiotherapy doses that would be viewed inadequate in today’s clinical practice.

Modern radiotherapy planning and delivery techniques have enabled us to escalate the treatment dose with only a small increase in the associated rectal toxicity. A recently updated meta-analysis of dose escalation for patients receiving conformal radiotherapy has demonstrated a significant increase in prostate cancer-specific survival, although this has yet to translate into an OS advantage.12 A study conducted at the MD Anderson, where patients were re-biopsied 2.5 years post-completion of radical radiotherapy, has demonstrated that the positive biopsy rate decreases as the radiotherapy dose is escalated.13 It also demonstrated that the addition of ADT also reduces the positive re-biopsy rate, although the impact of ADT is reduced as radiotherapy dose is escalated.14 This is of particular interest in an elderly population who may already have co-morbidities potentially exacerbated by ADT such as reduced bone mineral density, insulin resistance, erectile dysfunction and features of the metabolic syndrome.

Advanced patient age may deter clinical oncologists from offering curative external beam radiotherapy (EBRT) based on fears that toxicities are likely to be worse. However, while age may be a surrogate marker for additional comorbidities, age alone may only have a marginal effect on the toxicity of radical therapies. A single institution analysis found that
age did not have a significant impact on the rate of genitourinary (GU) and gastrointestinal (GI) toxicity following EBRT. A separate population-based study reported that, although age was associated with a higher risk of sexual dysfunction, patient satisfaction with the choice of treatment was high, with approximately 90% of the men saying they would ‘probably’ or ‘definitely’ make the same decision again.

Most of the landmark trials that have influenced radiotherapy practice used non-image guided conformal radiotherapy planning and delivery techniques. However, in the past 10 years there have been rapid advances in radiotherapy technology that allow higher and more effective doses of radiotherapy to be delivered with minimal attendant increases in toxicity. Intensity modulated radiotherapy (IMRT) tightly conforms the high dose radiotherapy volume to the target by modifying both the shape and fluence of the radiation field in real-time during treatment delivery. There are no reported randomised trials assessing the role of IMRT in prostate cancer treatment, but there is a wealth of data from radiotherapy planning studies and retrospective reviews.

For patients receiving potentially curative treatment, late toxicity and treatment-related quality of life issues are important considerations. Compared to conformal radiotherapy, inverse planned IMRT has been shown in planning studies to reduce the radiation dose delivered to the rectum, penile bulb, bowel and bladder (depending on the target volume). Retrospective clinical comparisons of the two treatment techniques are complicated by the fact that IMRT has tended to be used to treat larger volumes with higher doses. However, data suggests that IMRT can achieve reduced GI toxicity, and potentially reduced sexual dysfunction. Image guided radiotherapy (IGRT) allows visualisation of the target prior to, and in between and during treatments.

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IGRT reduces the chance of a geographical miss, and allows the use of smaller additional treatment margins around the prostate to account for these minor changes in anatomy between and during treatments.

Finally, advances in radiobiological modelling have allowed the development of radiotherapy schedules to test the hypothesis that prostate cancer has a lower alpha-beta ratio than surrounding normal tissue (rectum, bladder, urethra). If proven, this would permit the delivery of hypofractionated schedules in prostate cancer without compromising tumour control and side effects. Preliminary results from the multicentre CHHiP study suggest that, with respect to assessments of acute and initial late toxicity, the different fractionation schedules are equivalent.

In conclusion, radical radiotherapy in combination with ADT should be considered for men of all ages presenting with intermediate and high risk localised prostate cancer after careful assessment of disease risk and co-morbid factors. The long-term side effects of radiotherapy need to be balanced with the effects of progression of untreated disease and the impact of long-term ADT in elderly patients who have an increased incidence of metabolic syndrome and reduced bone density. New developments such as IMRT and IGRT have the potential to reduce toxicity, and hypofractionation, if shown to have equivalent efficacy and toxicity to conventional fractionation schedules, would be a more convenient schedule for older patients.

References