Radical Radiotherapy for High-Risk Prostate Cancer in Older Men

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ABSTRACT

Historical data for older men with high-risk nonmetastatic prostate cancer treated with radiotherapy alone have demonstrated a 10-year prostate-cancer-specific mortality of around 30%. The development of dose escalation, using techniques such as intensity-modulated radiotherapy, has enabled more targeted delivery of treatment with improved efficacy and a reduction in the risk of toxicity compared with conventional radiotherapy. The combination of radiotherapy and androgen-deprivation therapy (ADT) has been shown to improve overall survival compared with radiotherapy or ADT alone without a significant increase in toxicity in patients with minimal comorbidities. There is evidence that patient age has only a marginal effect on genitouri-

nary and gastrointestinal toxicities following radiotherapy. Further research has shown that although age does have an effect on the likelihood of sexual dysfunction after radiation therapy, there is no significant difference in the proportion of men aged ≥ 75 years who feel that sexual dysfunction is a moderate or serious problem before or 24 months after diagnosis. Radical radiotherapy is effective and well tolerated in senior men with high-risk prostate cancer and should be offered in combination with long-term ADT to patients with minimal comorbidities. In case of significant comorbid conditions, shorter durations of ADT may be considered. *The Oncologist* 2012;17(suppl 1):9–15

INTRODUCTION

There is increasing evidence that when men aged ≥ 70 years are diagnosed with localized prostate cancer, they have a greater incidence of high-risk disease than their younger counterparts [1–3]. High-risk organ-confined prostate cancer can be defined as disease with any of the following features in the absence of lymph node or distant metastases: Gleason grade ≥ 8 , prostate-specific antigen (PSA) ≥ 20 ng/mL, or locally advanced disease (T3a: tumor extends through the capsule; T3b: tumor invades the seminal vesicles; T4: tumor invades adjacent structures). All men with this category of disease have a high risk of both local and distant disease progression and cancer-related death [4, 5].

Albertsen et al. analyzed a retrospective cohort of 767 men treated conservatively for localized prostate cancer [4]. The results demonstrated that men aged ≥ 70 years with high grade (Gleason 8–10) prostate cancer had nearly a 50% probability of dying from their disease within 10 years of diagnosis. In the postprostatectomy setting, Epstein et al. demonstrated that the pathological stage of disease is also an important prognostic factor [5]. Ten-year progression-free survival was significantly decreased in men with focal (67.7%) or established (58.4%) capsular penetration, compared with localized T1/T2 disease (84.7%). Of the men with seminal vesicle invasion, only 27% were progression free at 10 years, and all men with lymph node metastases had progressed [6].

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However, despite a high probability of dying of their disease, a significant number of men aged ≥ 70 years with high-risk localized prostate cancer do not receive curative therapy in either the U.S. [7] or Europe [8]. This is attributed to the wrong belief that older men diagnosed with prostate cancer are more likely to die of another cause than of their disease. Such a statement may be valid for older men with low-risk prostate cancer [4], but does not apply to a 70-year-old “fit” man with high-risk disease who has at least 18 additional years to live [9]. Although it is not possible for a physician to predict the exact life expectancy of a given patient, it can be estimated by an adequate evaluation of health status, as described in the last article of this supplement, “A Comment on the International Society of Geriatric Oncology Guidelines: Evidence-Based Advice for the Clinical Setting” [10–12].

Treatment decisions, whether with curative intent (e.g., radiotherapy with androgen-deprivation therapy [ADT], initial radical surgery with appropriate adjuvant therapy), or not curative (ADT alone, watchful waiting), should be based on the aggressiveness of the disease and associated comorbidities, as well as the preferences of the individual. The efficacy and toxicity of treatment options should be balanced with these factors in mind. Hence, using a Markov model, Alibhai et al. observed that curative therapy results in significantly improved life expectancy and quality-adjusted life expectancy for older men with few comorbidities and moderately or poorly differentiated localized prostate cancer; the authors thus concluded that age should not be a barrier to treatment in this group [13]. Conversely, for men with well-differentiated tumors and few comorbidities, curative therapy prolonged life expectancy but did not improve quality-adjusted life expectancy.

The first part of this article will describe radical therapy options for high-risk prostate cancer with a special focus on senior adults when available. Transperineal interstitial brachytherapy will not be discussed because this treatment modality is restricted to patients with low-risk localized prostate cancer (cT1–T2a, Gleason < 7 , PSA ≤ 10 ng/mL) [14] or as a boost for intermediate risk disease [15]. The second part will be dedicated to the safety aspects of radical radiotherapy and the impact of age and comorbidities.

RADICAL RADIOTHERAPY FOR HIGH-RISK PROSTATE CANCER

A decade ago, in a retrospective analysis of 7,316 men with localized prostate cancer, men aged ≥ 70 years with high-risk prostate cancer treated with radiotherapy alone were reported to have an overall mortality at 10 years of 60%, of which 30% was prostate-cancer-specific [16]. Since then, there have been rapid advances in radiotherapy technology that allow higher and more effective doses of radiotherapy to be delivered without attendant increases in toxicity. These techniques include intensity-modulated radiotherapy (IMRT) and image-guided radiotherapy (IGRT). IMRT tightly restricts the high-dose radiotherapy region to the target volume by modifying both the shape and intensity of radiotherapy beams during treatment, thus minimizing the delivery of a clinically significant dose to surrounding normal tissue. IGRT allows visualization of the

target prior to each treatment delivery, which reduces the chance of a geographical miss and allows the use of smaller additional treatment margins around the prostate to account for minor changes in anatomy between treatments.

Dose Escalation

The importance of dose escalation for improved control of high-risk prostate cancer has been demonstrated by several clinical trials. A Dutch randomized dose-escalation study of 664 men with T1b to T4 prostate cancer demonstrated a significant benefit in freedom from treatment failure (clinical or biochemical) with higher-dose radiation (5-year freedom-from-failure [FFF] rate of 64% with 78 Gy vs. 65% with 68 Gy) [17]. The effect was most marked in those with high-risk disease.

In 2008, Kuban et al. reported the long-term results of a dose-escalation study with a median follow-up of 8.7 years [18]. Patients (median age, 69 years) with stage T1b to T3 disease were randomized to receive 70 Gy or 78 Gy external beam radiotherapy (EBRT). The analysis showed that the overall FFF rate for patients with high-risk disease was again superior in the higher dose arm (63% vs. 26%; $p = .004$). The largest benefit was seen in patients with initial PSA > 10 ng/mL, where the FFF rate for 78 Gy was 78% compared with 39% for 70 Gy.

A meta-analysis of pooled data from seven randomized controlled trials comparing high-dose radiotherapy and conventional-dose radiotherapy for prostate cancer showed a significant reduction in the incidence of biochemical failure in patients treated with high-dose radiotherapy ($p < .0001$) across all risk groups, but with no impact on overall mortality rates or prostate-cancer-specific mortality [19]. Finally, a retrospective analysis of 2,551 patients with T1 to T3 prostate cancer and a median follow-up time of 8 years showed that, in high-risk disease, radiotherapy doses ≥ 81 Gy were associated with improved biochemical relapse-free survival compared to lower doses (55% vs. 41%) [20]. A majority (74%) of study participants were aged 65 years or over.

Despite the potential for improved disease control with dose-escalated EBRT, this treatment in isolation is insufficient to address the risk of systemic relapse in patients with high-risk disease [21]. Indeed, in the Zelefsky et al. retrospective analysis, the use of ADT for patients with high-risk disease further improved biochemical progression-free survival and reduced the appearance of distant metastases [20].

Radiotherapy Plus Long-Term ADT

Several studies have shown that the combination of radiotherapy plus adjuvant ADT significantly improves overall survival of patients with high-risk prostate cancer compared with radiotherapy alone [22–24]. Five studies have focussed on long-term ADT.

Radiation Therapy Oncology Group (RTOG) 85-31 assessed the effectiveness of adjuvant ADT in unfavorable prognosis prostate cancer (stage T3 or with regional lymphatic involvement) in 977 men. Patients were randomized to receive radiotherapy plus indefinite adjuvant ADT or radiotherapy alone followed by observation and use of ADT at relapse [22]. At 10 years, the absolute survival rate was significantly higher for the adjuvant arm than for the control arm (49% vs. 39%,

respectively; $p = .002$); the 10-year local failure rate was 23% for the adjuvant arm and 38% for radiotherapy alone ($p < .0001$). The improvement in survival was preferentially seen in patients with Gleason score 7–10 disease and was present in a subset analysis both for patients aged <70 years and those aged ≥ 70 years. Later analyses found that patients benefited from receiving at least 5 years of ADT as opposed to shorter durations [25].

The RTOG 92-02 study investigated the duration of ADT. It was conducted in patients with T2c to T4 prostate cancer with no pelvic lymph node involvement and PSA <150 ng/mL [23]. The median age of patients in this study was 70 years. All patients received ADT for 4 months before and during radiotherapy and were randomized to then receive no further ADT or 24 months of ADT. At 10 years, the group receiving long-term ADT showed significant improvements over the short-term ADT group for disease-free survival, disease-specific survival, local progression, distant metastasis and biochemical failure, and a nonsignificant improvement in overall survival. Subgroup analysis of patients with Gleason score 8–10 disease showed a difference in all endpoints, including overall survival rates (31.9% vs. 45.1% for short-term and long-term ADT, respectively; $p = .0061$).

European Organization for Research and Treatment of Cancer (EORTC) 22863 reported the 10-year results for treating high-risk prostate cancer in patients with a median age of 70 years, using radical radiotherapy with or without 3 years of concomitant and adjuvant ADT. The study demonstrated clinical disease-free survival rates of 47.7% versus 22.7% in favor of the combination therapy [24]. The 10-year overall survival rates were 58.1% in the combination group and 39.8% with just radiotherapy. The 10-year prostate-cancer-specific mortality rates were 30.4% and 10.3%, respectively.

The addition of radiotherapy to indefinite ADT has also been assessed in high-risk prostate cancer. Ten-year data for the Scandinavian Prostate Cancer Group Study 7/Swedish Association for Urological Oncology 3 (SPCG-7/SFUO-3) trial showed that the combination treatment significantly reduced overall mortality (29.6% vs. 39.4%) and disease-specific mortality rates (11.9% vs. 23.9%) in patients compared with ADT alone (median age, 66 years) [26]. The Medical Research Council (MRC) PR07 study addressed a similar question in the U.K. population, comparing ADT with ADT plus radiotherapy in 1,205 men with a median age of 70 years. This study again demonstrated a survival benefit for combination treatment, with 7-year overall survival rates of 74% with hormone radiotherapy and 66% with ADT alone [27]. As a result of these findings, the combination of external irradiation with long-term (3-year) ADT is currently recommended for patients with intermediate- and high-risk prostate cancer.

Short-Term and Long-Term ADT

Although several phase III clinical trials have shown that long-term ADT can improve overall survival when added to radiotherapy, long-term ADT is associated with adverse events. These include an increased risk of fracture due to osteoporosis [28], development of diabetes and impaired glucose tolerance

[29, 30], thromboembolic events [31], and all-cause mortality, which has been seen in high-risk men with comorbidities such as chronic heart failure and history of myocardial infarction or stroke [32–35]. Men aged ≥ 70 years often have a lower level of circulating androgen and a higher prevalence of cardiovascular risk factors than younger men [36]. Therefore, there is concern that side effects associated with prolonged ADT may counteract the prostate-cancer-specific benefits. However, the risk of cardiovascular mortality has been assessed in the RTOG 85-31, RTOG 92-02, and EORTC 22863 studies of hormone radiotherapy. All studies failed to demonstrate an increase in cardiovascular mortality associated with ADT, with RTOG 85-31 even assessing risk in the subgroup of men ≥ 70 years [24, 37, 38].

However, data also exists on the efficacy of shorter courses of ADT. The Trans-Tasman Radiation Oncology Group (TROG) 96.01 study reported 10-year results of 3-month and 6-month short-term neoadjuvant ADT (NADT) in combination with radiotherapy in a patient population of 818 men with locally advanced prostate cancer and a median age of 68 years. Compared with radiotherapy alone, 3 months of NADT decreased the cumulative incidence of PSA progression and local progression and improved event-free survival [39]. With 6 months of NADT, these endpoints were further improved. An additional improvement in distant progression, prostate-cancer-specific mortality (including the subgroup ≥ 70 years), and all-cause mortality was seen compared with radiotherapy alone. These data show that 6 months of NADT can be an alternative treatment option, particularly in men with pre-existing metabolic comorbidities that could be exacerbated with a longer period of ADT.

However, these findings need to be interpreted in the context of the EORTC 22961 study comparing 6 months of ADT with 3 years of ADT in men with locally advanced prostate cancer (median age, 69 years) [40]. All patients initially received 6 months of ADT and were subsequently randomized to no additional ADT or a further 2.5 years of ADT. Five-year overall survival rates were improved with long-term adjuvant ADT (85% vs. 81% with no additional therapy), demonstrating a survival benefit of radiotherapy plus long-term ADT over radiotherapy plus 6 months of ADT.

The duration of ADT and the age of the patient are important determinants of the time taken for serum testosterone levels to recover to above castrate levels following ADT [41]. A study in 15 patients who received ADT for at least 48 months but had not received the therapy for at least 18 months showed that 78% of patients over 70 years of age retained castrate levels of testosterone after a mean follow-up period of 31 months, compared with 17% of patients aged 70 years or under [42]. It is therefore possible that in the senior adult population, a shorter duration of ADT is sufficient to achieve testosterone suppression for a prolonged period of time, while long-term ADT actually results in castrate levels of androgen for far longer periods than intended.

The addition of hormone therapy to radiotherapy may cause an increase in side effects; however, this risk should not

be viewed as a reason to withhold a therapy that could potentially increase overall survival but instead as a reason to carefully counsel and monitor the patient. Studies have also shown significant survival advantages for radiotherapy in combination with ADT compared with ADT alone [26, 27]. The combination of radiotherapy and ADT is now considered standard of care for high-risk prostate cancer.

The risks of metabolic syndrome and its consequences should not prevent treatment for those men likely to benefit from therapy, but it is important that all men treated with ADT are aware of the cardiovascular risks and that they receive appropriate diet and exercise advice to minimize central weight gain. Regular monitoring of weight, waist circumference, body mass index, lipid profile, and fasting blood glucose should be carried out, with early referral for treatment if any abnormalities are detected.

SIDE-EFFECT REDUCTION

Improvements have been made to reduce the side effects associated with radiotherapy. A study in 843 men with localized prostate cancer assessed the ability of conformal radiotherapy (CFRT) to deliver higher doses of radiation than standard-dose conventional radical EBRT [43]. Patients were randomized to receive standard-dose CFRT or escalated-dose CFRT, both administered with NADT. Relative to the standard dose, for the escalated group the hazard ratio (HR) for biochemical progression-free survival was 0.67 (95% confidence interval [CI]: 0.53–0.85; $p = .0007$), and the HR for clinical progression-free survival was 0.69 (CI: 0.47–1.02; $p = .064$). Late bowel toxicity was reported within 5 years of starting treatment by 33% of the escalated and 24% of the standard group. These data demonstrated that escalated-dose CFRT with ADT improves treatment outcomes but is associated with an increased incidence of long-term adverse events.

There are no reported randomized trials assessing the role of IMRT in prostate cancer treatment, but there is a wealth of data from radiotherapy planning studies and retrospective reviews [44, 45]. For patients receiving potentially curative treatment, the late toxicity effects and treatment-related quality-of-life issues are important to consider. Studies of radiotherapy dose escalation for prostate cancer have shown that it improves treatment-related outcomes, but at the expense of late toxicity (especially rectal toxicity) [46]. Inverse-planned IMRT has been shown to reduce the dose delivered to the rectum and penile bulb (prostate and seminal vesicle radiotherapy), and also the bowel and bladder (pelvic radiotherapy) [47]. Retrospective comparisons of IMRT with three-dimensional conformal radiotherapy are complicated by the fact that IMRT tends to be used to treat larger volumes with higher doses. However, data exists to suggest that IMRT can achieve reduced gastrointestinal (GI) toxicity, at least equivalent genitourinary (GU) toxicity, and effects on sexual function may also be improved [48, 49].

It is known that prostate motion during radiotherapy, which occurs largely as a result of changes in the degree of rec-

tal distension, impacts tumor control [50]. This motion is usually accounted for by adding an additional margin to the prostate when planning the radiotherapy; the resulting larger volume receives the prescribed dose. To fully realize the potential toxicity-sparing benefits of IMRT, it is important to minimize this additional margin as much as it is clinically safe to do so. The ability to image the prostate before each treatment (cone-beam CT or using fiducial markers) would allow this margin to be reduced as the patient can be moved to ensure the prostate is in the treatment field before each fraction.

Hypofractionated radiotherapy schedules have been designed to exploit the fact that prostate cancer may have a higher sensitivity to radiotherapy dose fractionation than nearby tissues (rectum, bladder, urethra) [51]. The current advised schedule for prostate cancer radiotherapy in the U.K. involves 37 daily fractions of 2 Gy (Monday to Friday) to a total of 74 Gy [51]. It can be challenging for some older men to attend so many visits, and delivering a higher dose in a reduced number of fractions (19 or 20) may be more convenient for this age group, especially if the efficacy and late toxicity are unaltered. Retrospective analyses of two large patient databases support this concept [52, 53]. A large randomized trial (the Conventional or Hypofractionated High-dose Intensity Modulated Radiotherapy in Prostate Cancer [CHHiP] trial) comparing conventional versus hypofractionated high-dose IMRT in patients with localized prostate cancer (median age, 68 years) is currently in progress in the U.K. [51].

The multicenter CHHiP study randomized men with localized prostate cancer to receive conventional or hypofractionated high-dose intensity-modulated radiotherapy, with 3–6 months of ADT [51]. Patients in the conventional radiotherapy group received 2-Gy treatments to a total of 74 Gy, and the two hypofractionated groups received 3-Gy treatments to a total of 57 Gy or 60 Gy. Preliminary safety results suggest that the hypofractionated therapy is as equally well tolerated as conventionally fractionated radiotherapy. With a median follow-up of 50.5 months, 4.3% of the 74-Gy conventional-dose group had bowel toxicity of grade 2 or worse on the RTOG scale, as did 3.6% of the 60-Gy group and 1.4% of the 57-Gy group. Grade ≥ 2 bladder toxicities were reported by 2.2% of the 74-Gy group, 2.2% of the 60-Gy group, and none of the 57-Gy group. A longer follow-up is needed to confirm these results because the RTOG 94–06 study of conformal radiotherapy dose-escalation identified, over a median of 6.1 years, an increase in late toxicity of grade 2 or higher associated with the small increase in fraction size from 1.8 Gy to 2.0 Gy [54].

Impact of Comorbidity

Comorbidity is a strong predictor of mortality (not prostate-cancer-specific) among men with unfavorable-risk prostate cancer. A randomized controlled trial assessing ADT plus radiotherapy or radiotherapy alone in patients with a median age of 72.5 years with prostate cancer also investigated the interaction between the level of comorbidity and all-cause

Figure 1. Overall survival in men with no/minimal or moderate/severe comorbidity [55].

Abbreviations: ADT, androgen-deprivation therapy; EBRT, external beam radiotherapy. Adapted from D'Amico AV, Chen MH, Renshaw AA et al. Androgen suppression and radiation vs radiation alone for prostate cancer: A randomized trial. *JAMA* 2008;299:289–295, with permission.

Figure 2. The effect of patient age on treatment side effects [56, 57].

Abbreviations: GI, gastrointestinal; GU, genitourinary.

mortality in these patients [55]. The majority of patients in each treatment group had Gleason score 7–10 disease (71% of patients in the combination group and 74% of those in the monotherapy group). The data showed an increase in all-cause mortality in the radiotherapy group compared with those receiving ADT plus radiotherapy. However, this increased risk in all-cause mortality was significant only for men in the radiotherapy group who had no or minimal comorbidity. For men with moderate or severe comorbidity, the risk of all-cause mortality was similar across the treatment groups (Fig. 1).

Impact of Patient Age

Advanced patient age can deter physicians from offering curative treatment based on fears that toxicities are likely to be worse in elderly patients [56]. However, although age may be a surrogate marker for comorbidities, by itself it may have only a marginal effect on the toxicities of radical therapies.

The impact of age on GU and GI toxicities following radiotherapy was assessed in a single-institution analysis [56]. The data showed that although there was a marginal effect, advancing age did not significantly increase the rates of either GU or GI toxicity (Fig. 2). 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 [57].

Although the proportion of men reporting erectile dysfunction following radiotherapy did increase with age, 55.5% of men aged ≥ 75 years had already experienced problems with sexual function prior to prostate cancer diagnosis (compared with 71.6% at 24 months after diagnosis). Furthermore, the impact of therapy on the perception of problems with sexual function was much less pronounced among this group, with 34.8% of men saying that sexual function was a “moderate” to “big” problem before diagnosis versus 37.4% at 24 months later [57].

When considering the impact on quality of life, the long-term side effects of radiotherapy may be preferable to the effects of indefinite hormone therapy for progressive disease, the risk of general anesthetic for surgical intervention, or the risk (and symptoms) of disease progression if the cancer is left untreated. Elderly men with prostate cancer should be assessed for suitability to receive curative treatment, and radiotherapy in combination with ADT should be offered if it is considered appropriate. Importantly, chronological age should not be used as an independent factor in treatment decision making for curative therapy.

CONCLUSION

Radiotherapy in combination with ADT is an effective treatment in senior men with high-risk prostate cancer [22–24]. The side effects associated with radical radiotherapy can be reduced with the use of more focused methods of radiotherapy delivery, such as IMRT and IGRT, which can be targeted to minimize radiation exposure to other organs [51]. Radiotherapy in combination with ADT should be considered as a treatment of curative intent for appropriate senior men with high-risk prostate cancer and minimal comorbidities. In other patients, depending on health status, shorter durations of ADT may be discussed.

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