The management of high-risk, locally advanced, prostate cancer radiation therapy

Swetha Sridharan, BSc, MBBS, FRANZCR; Padraig Warde, MB, MRCPI, FRCPC

Department of Radiation Oncology, University of Toronto and the Radiation Medicine Program, Princess Margaret Cancer Centre, Toronto, ON

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Prostate cancer is a common malignancy with 913 000 new cases and 215 000 deaths worldwide in 2008.[1] Risk stratification systems are widely used to assist with patient counselling and guide treatment selection risk, as well to ensure prognostic uniformity in clinical trials and in the evaluation of treatment outcomes. Based on work by D'Amico and colleagues, the Genitourinary Radiation Oncologists of Canada (GUROC) developed a classification system for patients with localized/locally advanced disease based on T category, prostate-specific antigen (PSA) level at diagnosis and Gleason score.[2,3] High-risk disease is defined as the presence of any of these factors: cT3 or cT4 category, PSA >20 ng/mL or Gleason score ≥8. Patients studied in clinical trials of "high-risk prostate cancer" represent a very heterogeneous group; this group includes patients with clinically organ-confined disease (cT1/T2) with high Gleason score, and/or PSA and also those with locally advanced disease.

In the landmark EORTC (European Organisation for Research and Treatment of Cancer) 22863 trial, overall survival (OS) and local control were considerably improved with the use of 3 years of adjuvant androgen deprivation therapy (ADT) when given with external beam radiotherapy (EBRT) in patients with high-risk locally advanced disease (90% had cT3/T4).[4] With a median follow-up of 9.1 years, the survival advantage for combination treatment was substantial with a 10-year OS of 58% in the combined treatment group compared with 40% in the radiotherapy (RT)-only group. However, despite the fact that combined modality treatment was superior to RT alone, the value of local treatment with RT remained under question as it was felt that the benefit seen may have been due to the early introduction of ADT. This has now been explored in three randomized trials (Table 1).[5-7] The National Cancer Institute of Canada (NCIC) PR3/ Canadian Urologic Oncology Group (CUOG)/Medical Research Council (MRC) UK PR07 study randomized 1205 patients with high-risk, locally advanced disease to treatment with combined modality therapy (RT and lifelong ADT) or treatment with ADT alone.[5] With a median follow-up of 6 years, combined modality treatment resulted in a 23% reduction in overall mortality and a 46% reduction in disease-specific mortality (Fig. 1). There was a 70% reduction in disease progression with the addition of RT, and local disease progression as a first manifestation of overall progression was reduced from 39% to 15%. The side effects of RT were of modest clinical magnitude and serious long-term genitourinary or gastrointestinal toxicity was uncommon. Patient-reported outcomes also showed that the negative impact of RT on bowel function was of modest clinical magnitude, with recovery scores matching those of patients without RT by 36 months.[8]

Similar data have been reported by Widmark and colleagues in the SPCG-7 study; 875 patients with prostate cancer were randomized to endocrine therapy alone or endocrine therapy and EBRT.[6] With a median follow-up of 7.6 years, the cumulative incidence at 10 years for prostate-cancer-specific mortality was 23.9% in the endocrine alone group and 11.9% in the endocrine plus RT group. At 10 years, the cumulative incidence for overall mortality was 39.4% in the endocrine alone group and 29.6% in the endocrine plus RT group for a relative risk of death of 0.6. Urinary, rectal and sexual problems were slightly more frequent in the endocrine plus RT group. About 80% of patients in this study had locally advanced disease. Although this trial, like the NCIC PR3/MRC-UK PR07 study, addressed the issue of impact of RT on survival, there were some differences between the studies. Patients in the SPCG-7 trial had a favourable prognosis. The maximum allowable PSA for trial entry was 70 ng/ml and patients with PSA >11 ng/mL were surgically staged and those with positive pelvic nodes on histological examination were excluded from the study. There were also some differences in the treatment between

Table 1. Randomized trials assessing benefit of local radiotherapy in combination with androgen deprivation therapy

Study	No. patients	Median follow-up	PFS: ADT vs. ADT+RT	DSS: ADT vs. ADT+RT	OS: ADT vs. ADT+RT
Warde et al.[13]	1205	6 years	HR 0.3, 95% CI 0.23-0.39 $p = 0.001$	HR 0.54 CI 0.27-0.78 $p = 0.0001$	HR 0.77, 95% CI 0.61-0.98 $p = 0.03$
Widmark et al.[14]	875	7.6 years	26% vs. 75% $p = 0.0001$	76% vs. 88% $p < 0.0001$	61% vs. 70%
Mottet et al.[15]	264	5.6 years	9% vs. 61% $p < 0.0001$	86% vs. 93% $p = 0.0586$	71.5% vs. 71.4%*

PFS: progression-free survival; DSS: disease-specific survival; OS: overall survival; ADT: androgen deprivation therapy; RT: radiotherapy; HR: hazard ratio; CI: confidence interval. *Median OS not reached in either arm.

the two trials. In the SPCG-7 study, total androgen blockade was administered for the first 3 months followed by anti-androgen therapy until progression or death; in the NCIC PR3/MRC-UK PR07 study, hormonal therapy was ADT with lifelong luteinizing hormone releasing hormone analogue or bilateral orchiectomy.

Mottet and colleagues recently reported the results of a randomized phase III trial in which 264 patients, all with locally advanced disease, were randomized to ADT alone for 3 years or ADT and EBRT.[7] With a median follow-up of 67 months, there was a marked improvement in loco-regional control with the use of combined modality therapy (90.2% vs. 70.8% with ADT alone). There was also a marked improvement in progression-free survival with the addition of EBRT (60.9% vs. 8.5% with ADT alone). However, likely due to the small sample size, no improvement in OS has been seen to date.

The dose of RT used in these trials (65-70 Gy) represented the standard of care in the 1990s when these trials were started. Over the past 15 years, the development of new RT techniques has allowed for a considerable increase in RT dose with acceptable morbidity in patients with localized prostate cancer. Multiple clinical trials have shown an improvement in local control and improved freedom from relapse with higher doses of radiation.[9-11] It is therefore likely that the improvement in survival seen with the addition of RT to ADT in these studies would be even more impressive with the use of modern RT dose fractionation schemes. In a single institution cohort study, Zelefsky and colleagues demonstrated that local control, as assessed by post-treatment biopsies, is improved with RT dose-escalation.[12] Local tumour control was associated with a decrease in distant metastases and prostate cancer mortality – again, this emphasizes the importance of achieving optimal local control in these patients.

While dose escalation techniques with megavoltage EBRT have evolved greatly in recent years, rectal dose constraints limit the total dose of EBRT that can be administered. This makes dose escalation using brachytherapy an attractive option. A randomized trial by Sathya and colleagues compared the efficacy of an iridium implant plus EBRT versus EBRT alone in patients with T2/T3 disease.[13] The 104 patients (40% cT3) were randomized into 2 groups: (1) 51 received iridium implant of 35 Gy delivered to the prostate over 48 hours plus 40 Gy EBRT delivered at 2 Gy/fraction over 4 weeks and (2) 54 patients were randomized to EBRT alone of 66 Gy in 33 fractions. After a median follow-up of 8.2 years, the rates of biochemical failure were 29% in the implant and EBRT group versus 61% in the EBRT alone group. Local control was also better in the combined treatment group (51% vs. 24%). However, the dose of EBRT used in this study was low by modern day standards. While dose escalation using brachytherapy in locally advanced disease may well be effective, there is insufficient data available at

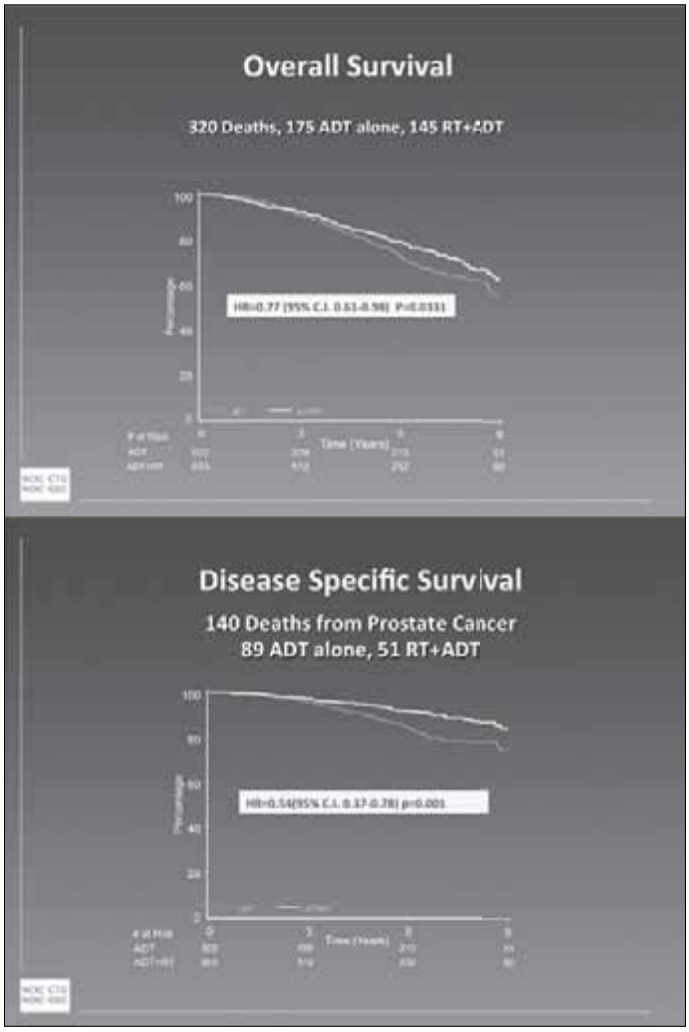

Fig. 1. Kaplan-Meier Curves for overall and disease-specific survival by treatment arm – PR3 study. Reproduced with permission from *The Lancet*.[5]

present to recommend this approach outside of a clinical research setting.

The heterogeneous nature of patients with high-risk locally advanced disease makes definitive statements regarding optimal management of this group of patients very difficult to make. Patients with localized disease with a high Gleason score and/or moderately elevated PSA may benefit from local treatment approaches other than RT. However, there is now mature level 1 evidence from multiple randomized trials that improved local control using EBRT in addition to ADT in patients with locally advanced prostate cancer improves overall and disease-specific survival. No such data exist for any other local treatment modality, such as surgery, and therefore in this era of evidence-based medicine EBRT combined with ADT remains the treatment of choice in this group of patients.

Competing interests: None declared.

This paper has been peer-reviewed.

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Correspondence: Dr. Padraig Warde, Department of Radiation Oncology, Princess Margaret Cancer Centre, 610 University Ave., Toronto, ON M5G 2M9; fax: 416-946-4568; padraig.warde@rmp.uhn.on.ca