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REVIEW ARTICLE

The importance of local control in high-risk locally advanced prostate cancer

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ABSTRACT

Prostate cancer is a common malignancy worldwide, and in Canada, it is the most frequently diagnosed cancer in men. The stratification of prostate cancer into risk categories has allowed for improved counselling of patients and provides guidance for treatment selection. However, the exact definition of high-risk prostate cancer remains controversial, and that lack of consensus remains a barrier to assessing available data from various institutions and from clinical trials. The proportion of patients with locally advanced high-risk disease has fallen in the last 20 years largely because of screening for prostate-specific antigen, but management in this population continues to be an important clinical problem. A factor that has emerged in recent years is the importance of local disease control, with data from multiple randomized trials suggesting that local therapy improves progression-free survival, disease-free survival, and overall survival. Further research in this population is necessary to improve outcomes.

KEY WORDS

Prostate cancer, radiotherapy, locally advanced, local control

1. INTRODUCTION

Prostate cancer is a common malignancy, with 913,000 new cases and 215,000 deaths estimated worldwide in 2008[1]. In the United States, prostate cancer is the most frequently diagnosed cancer in men, and it is second only to lung cancer as a cause of cancer death[2].

Risk stratification systems are widely used to assist with patient counselling, to guide treatment selection risk, and to ensure prognostic uniformity in clinical trials and in the evaluation of treatment outcomes. Based on work by D'Amico *et al.,* the Genitourinary Radiation Oncologists of Canada developed a classification system[3,4] based on T category, prostate-specific antigen (PSA) level at diagnosis, and Gleason score for patients with localized or locally advanced disease. In that system, high-risk disease is defined as the presence of any of cT3 or cT4 category, PSA greater than 20 ng/mL, or Gleason score 8 or higher. That model has been demonstrated to be internally consistent and to accurately predict prostate cancer–specific mortality in patients treated with surgery or radiation therapy (RT)[5,6]. However, the exact definition of high-risk prostate cancer at diagnosis remains controversial, and that lack of consensus constitutes a barrier to comparisons of clinical outcomes in various institutional series and of the results of clinical trials (Table I). As a result, the patients studied in clinical trials of high-risk prostate cancer constitute a very heterogeneous group, including those having clinically organ-confined disease (cT1/T2), with a Gleason score of 8–10 or a PSA level exceeding 20 ng/mL (or both), and those having locally advanced disease (cT3/T4).

The proportion of patients presenting with locally advanced disease at diagnosis has declined since the early 1990s, largely as a result of widespread PSA screening. However, this presentation remains a common clinical problem, and management remains controversial[10]. The term "high-risk locally advanced disease" has also been applied in the post-surgery setting to patients with pathologic T category T3 or T4. In the present article, we discuss the importance of achieving local disease control only in patients presenting with locally advanced disease (cT3/T4) at diagnosis and in those with pT3/T4 tumours after radical prostatectomy (RP).

2. PRESENTATION WITH CLINICALLY LOCALLY ADVANCED DISEASE

2.1 Primary Treatment with RT

External-beam RP (EBRT), even with dose escalation, used as monotherapy for patients with locally advanced disease has been shown not to be effective in locally

TABLE I Definitions of high-risk prostate cancer

Source	*Definition*
Genitourinary Radiation Oncologists of Canada[4]	Clinical stage ≥ T3a OR Gleason score 8–10 OR PSA ≥ 20 ng/mL
D'Amico *et al.,* 1998[3]	Clinical stage ≥ T2c OR Gleason score 8–10 OR PSA ≥ 20 ng/mL
Radiation Therapy Oncology Group[7]	Clinical stage ≥ T2c OR Gleason score 8–10 AND PSA < 100 ng/mL OR Any clinical stage AND Gleason score 8–10 AND PSA 20–100 ng/mL
National Comprehensive Cancer Network[8]	Clinical stage ≥ T3 OR Gleason score 8–10 OR PSA > 20 ng/mL OR Any two of • Clinical stage T2b/c • Gleason score 7 • PSA 10–20 ng/mL
European Association of Urology[9]	Clinical stage ≥ T3 OR Gleason score 8–10 OR PSA ≥ 20 ng/mL

PSA = prostate-specific antigen.

advanced prostate cancer, and combined-modality treatment with androgen deprivation therapy (ADT) is now the accepted treatment approach in this setting[11].

In the landmark 22863 trial by the European Organisation for Research and Treatment of Cancer, overall survival and local control were considerably improved with the use of 3 years of adjuvant ADT. An update of that trial with a median follow-up of 9.1 years confirmed the survival advantage for combination treatment, showing a 10-year overall survival of 58% in the combined-treatment group compared with 40% in the RT-only group. The proportion of patients with locally advanced disease in that trial was in the order of 90% in both arms[12].

Three large randomized trials have now demonstrated the importance of local treatment and local control of tumour in improving outcomes in patients with locally advanced disease (Table II). The NCIC PR.3–U.K. Medical Research Council (MRC) PR07 study randomized 1205 patients with high-risk locally advanced disease to treatment with combined-modality therapy (RT and life-long ADT) or to treatment with ADT alone[14]. In excess of 85% of the patients had cT3/T4 disease. With a median follow-up of 6 years, combined-modality treatment resulted in a 23% reduction in overall mortality (Figure 1) and a 46% reduction in disease-specific mortality. A 70% reduction in disease progression was observed with the addition of RT, and local disease progression as a first manifestation of overall progression was reduced to 15% from 39%. The side effects of RT were of modest clinical magnitude, and serious long-term genitourinary or gastrointestinal toxicities from RT were uncommon. Patient-reported outcomes also showed that the negative impact of RT on bowel function was of modest clinical magnitude, with recovery by 36 months of scores tending to match those in patients not receiving RT.

Similar data were reported by Widmark *et al.* in the Scandinavian Prostate Cancer Group Study 7 (SPCG-7), in which 875 patients with prostate cancer were randomized to endocrine therapy alone or to endocrine therapy and EBRT[13]. With a median follow-up of 7.6 years, the cumulative incidence of prostate-cancer-specific mortality at 10 years was 23.9% in the endocrine-alone group and 11.9% in the endocrine plus RT group, for a relative risk of 0.44. 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 0.6. Urinary, rectal, and sexual problems were slightly more frequent in the endocrine plus RT group. Approximately 80% of patients in the study had locally advanced disease. Although this trial—like the NCIC PR.3–MRC PR07 study—addressed the issue of the effect of RT on survival, some differences between the studies were evident, with patients in the SPCG-7 trial having a favourable prognosis. The maximum allowable PSA for trial entry was 70 ng/mL. Patients with a PSA exceeding 11 ng/mL were surgically staged, and those with positive pelvic nodes on histologic examination were excluded from the study. There were also some differences in treatment between the trials. In the SPCG-7 study, total androgen blockade was administered for the first 3 months, and then antiandrogen therapy was given until progression or death. In the NCIC PR.3–MRC PR07 study, hormonal therapy was ADT, with lifelong luteinizing-hormone releasing-hormone analogue treatment or bilateral orchiectomy.

Mottet *et al.* 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 to ADT and EBRT[15]. With a median

TABLE II Randomized trials assessing the benefit of local radiotherapy (RT) in combination with androgen deprivation therapy (ADT)

Reference	*Patients* (n)	*Median follow up (years)*	*PFS* ADT vs. ADT+RT	*DSS* ADT vs. ADT+RT	*OS* ADT vs. ADT+RT
Widmark *et al.,* 2009[13]	875	7.6	26% vs. 75% p=0.0001	76% vs. 88% p<0.0001	61% vs. 70%
Warde *et al.,* 2011[14]	1205	6	HR: 0.3 95% CI: 0.23 to 0.39 p=0.001	HR: 0.54 95% CI: 0.27 to 0.78 p=0.0001	HR: 0.77 95% CI: 0.61 to 0.98 p=0.03
Mottet *et al.,* 2012[15]	264	5.6	9% vs. 61% p<0.0001	86% vs. 93% p=0.0586	71.5% vs. 71.4%[a]

[a] Median overall survival not reached in either arm.

PFS = progression-free survival; DSS = disease-specific survival; OS = overall survival; HR = hazard ratio; CI = confidence interval.

follow-up of 67 months, marked improvement in locoregional control was observed with the use of combined-modality therapy (90.2% vs. 70.8% with ADT alone). There was also marked improvement in progression-free survival with the addition of EBRT (60.9% vs. 8.5% with ADT alone). However, likely because of the small sample size, no improvement in overall survival has been seen to date.

The dose of RT used in those trials, 65–70 Gy, represented the standard of care in the 1990s when the trials were started. Since the late 1990s, the development of new RT techniques has allowed for a considerable increase in the 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[16–18]. It is therefore possible that the improvement in survival seen with the addition of RT to ADT in the foregoing studies could be greater with the use of modern RT dose–fractionation schemes. Zelefsky *et al.,* in a single-institution cohort study, demonstrated that local control, as assessed by post-treatment biopsies, is improved with the use of RT dose escalation[19]. Local tumour control was associated with a decrease in distant metastases and prostate cancer mortality—again emphasizing the importance of achieving optimal local control in these patients. In a number of recent studies, local recurrence of prostate cancer after EBRT has also been shown to occur predominantly at the site of the primary tumour before treatment, suggesting that supplementary focal therapy to the dominant primary tumour might also improve outcomes[20,21].

Although dose-escalation techniques with megavoltage EBRT have evolved greatly in recent years, rectal dose constraints limit the total dose of RT that can be given using this strategy. That problem makes brachytherapy—usually in combination with EBRT as a form of dose escalation—an attractive option.

For 1342 men with high-risk prostate cancer, D'Amico *et al.* reported the risk of prostate cancer–related mortality after brachytherapy alone or in combination with ADT, EBRT, or both[22]. Men who received brachytherapy and both ADT and EBRT were significantly more likely to have multiple high-risk factors, and yet a significant reduction in prostate cancer mortality was observed in that cohort [hazard ratio (HR): 0.32; 95% confidence interval (CI): 0.14 to 0.73; p = 0.0006]. However, the proportion of patients with cT3/T4 disease in the trial was only 12%. A retrospective analysis from a Swedish group (Aström *et al.*[23]) of 214 consecutive patients treated with EBRT (50 Gy in 25 fractions) and high-dose-rate brachytherapy (two 10-Gy fractions) reported their results after a median follow-up of 48 months. In the high-risk group of 47 patients (32 with cT3/T4 disease), the 5-year biochemical no evidence of disease rate was 61%. A randomized trial by Sathya *et al.*[24] compared the efficacy of an iridium implant plus EBRT with EBRT alone in patients with T2/T3 disease. Of the 104 patients randomized (40% with cT3 disease), 51 received an iridium implant of 35 Gy delivered to the prostate over 48 hours, plus 40 Gy EBRT delivered at 2 Gy per fraction over 4 weeks, and 54 received EBRT alone (66 Gy in 33 fractions). At a median follow up of 8.2 years, the rates of biochemical failure were 29% in the implant plus EBRT group and 61% in the EBRT-alone group. Local control was also better in the combined-treatment group (51% vs. 24%).

Although dose escalation using brachytherapy in locally advanced disease is a reasonable strategy, the data are currently insufficient to recommend that approach outside of a clinical research setting.

2.2 Primary Treatment with Surgery

In the past, RP was not considered an acceptable treatment approach in patients with locally advanced disease. However, because of improvements in surgical techniques, RP is now increasingly being used in selected patients with cT3a disease. Table III lists the results of series investigating the primary use of surgery in this setting. Stephenson *et al.*[28] reported the results of 6398 patients with prostate cancer treated with RP at the Memorial Sloan–Kettering

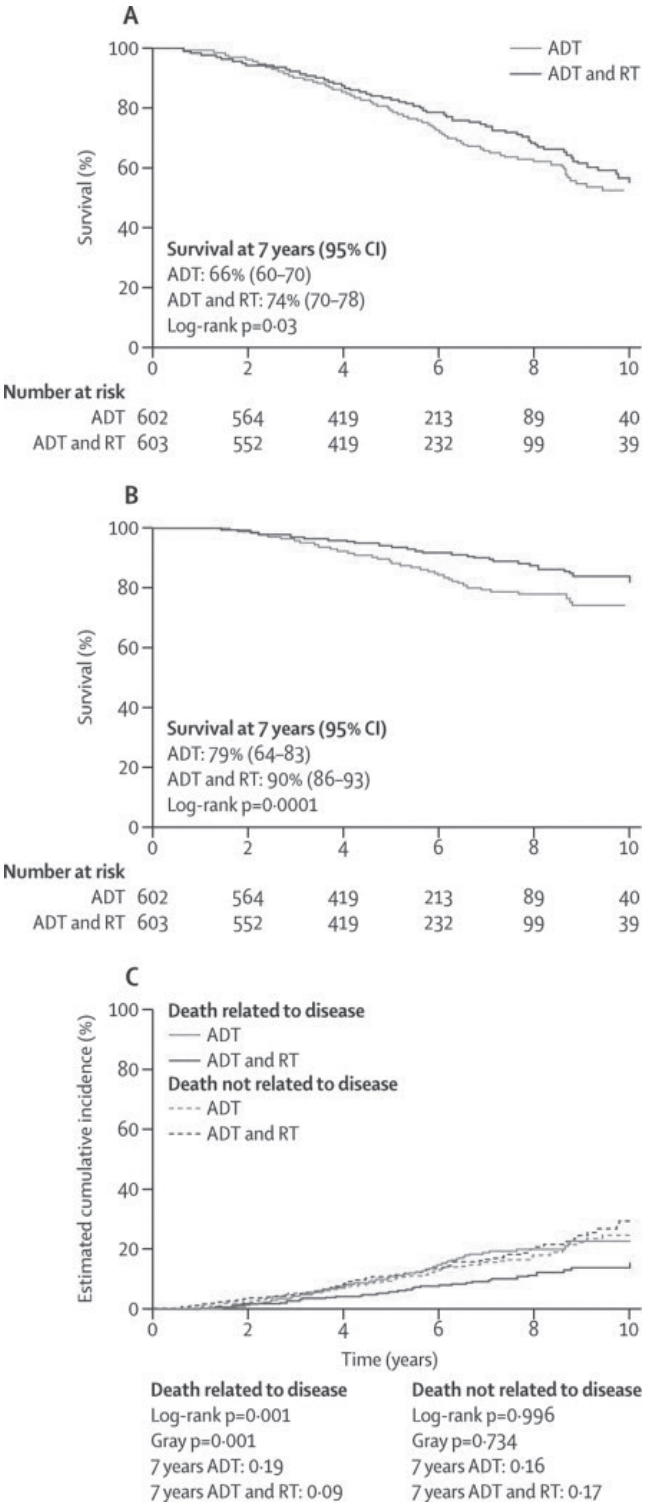

FIGURE 1 Overall and disease-specific survival at 7 years in the PR.3 study. (A) Kaplan–Meier curve for overall survival by treatment group. (B) Kaplan–Meier curve for disease-specific survival by treatment group. (C) Cumulative incidence of disease-specific survival. ADT = androgen-deprivation therapy; RT = radiotherapy; CI = confidence interval. Reproduced, with permission, from The Lancet.

Cancer Center and Baylor College of Medicine. Of that group, only 4% (n = 254) had cT3/T4 disease. The 15-year prostate cancer–specific mortality was 38% for those patients.

The guidelines from the European and American associations of urology for the management of locally advanced disease suggest that an extended lymph node dissection be performed at the time of RP. Whether that procedure is just for staging or has any therapeutic value is controversial, and that question is currently being addressed in a randomized trial in Germany. Furthermore, patients with advanced disease undergoing RP would need to be advised that they have a risk of possible further adjuvant therapy in the form of RT with or without hormonal therapy. The possible value of local therapy in the form of prostatectomy, even in lymph-node-positive patients, was addressed by Engel *et al.*[30], who used the Munich cancer registry to compare outcomes for patients with positive lymph nodes in whom RP was completed and for those in whom prostatectomy was abandoned. Among 1413 patients, prostatectomy was aborted in 456 with lymph-node-positive disease; in the remaining 957 patients, the prostatectomy was completed. At 28% versus 64%, 10-year survival was inferior for patients who did not undergo RP. Those results show a survival benefit for local treatment even in lymph-node-positive disease and therefore suggest that local control may result in improved outcomes overall. However, given the inherent bias in the study (the greater potential for prostatectomy abandonment in patients having unresectable and therefore more advanced disease), the results must be viewed with caution.

The use of adjuvant ADT has not been shown to improve outcomes, except in the case of a small randomized trial by Messing *et al.*[31], in which 98 patients with node-positive disease were randomized to receive observation or adjuvant hormonal therapy. However, the relevance of that study in contemporary practice is unclear, because the trial was started in the pre-PSA era and ADT was therefore given only at clinical progression.

Because of the highly selected nature of patients whose primary management was surgery, it is not possible to comment on the efficacy of that approach. Certainly, when used in selected patients and combined with adjuvant RT, surgery does achieve good local control. However, whether the additional morbidity associated with the use of combined treatment improves overall outcome is unknown at this time.

3. PRESENTATION WITH LOCALLY ADVANCED DISEASE AFTER RP

3.1 Role of Adjuvant RT

About 20% of patients who undergo RP for localized disease experience a biochemical relapse. Three randomized controlled trials have all showed a

TABLE III Outcomes for high-risk prostate cancer treated with prostatectomy

Reference	*Patients (n)*	*Median follow-up*	*10-Year survival (%)*		
			Biochemical recurrence–free	*Prostate cancer–specific*	*Overall*
Ward *et al.,* 2005[25]	841[a]	10.3 years	43	90	76
Yossepowitch *et al.,* 2007[26]	957[b]	46 months	59		
Zwergel *et al.,* 2007[27]	275	42 months	25[c]	83	70
Stephenson *et al.,* 2009[28]	1962	48 months		92	
Spahn *et al.,* 2010[29]	712	77 months	52	90	74

[a] Results for patients with cT3 disease.
[b] Results for cohort of patients using definition of high risk from D'Amico *et al.,* 1998[3].
[c] With deferred hormonal therapy.

benefit for adjuvant RT in men with pathologically advanced cancer (pT3 disease with extracapsular extension, positive surgical margins, or seminal vesicle invasion).

The Southwest Oncology Group 8794 study randomized 425 men with pT3 disease to adjuvant radiotherapy (60–64 Gy) or to observation[32]. Of the 211 men randomized to observation, 70 received salvage RT. With a median follow-up of more than 12 years, adjuvant RT was associated with significant improvements in metastasis-free survival (HR: 0.71; $p = 0.016$) and overall survival (HR: 0.7; $p = 0.023$).

Similarly, the European Organisation for Research and Treatment of Cancer 22911 trial randomized 1005 patients with pT3 disease to immediate postoperative RT of 60 Gy or to a wait-and-see policy[33]. With a median follow-up of 5 years, adjuvant RT was associated with an improvement in biochemical progression-free survival (74% vs. 52.6%, $p < 0.0001$). Updated results for that trial revealed that, after a median follow-up of 10.6 years, the 10-year biochemical progression-free survival was 60% in the RT arm compared with 40% in the observation arm. A reduction in locoregional failure to 7.3% from 16.6% with RT was also reported ($p < 0.0001$). Longer follow-up is necessary to determine whether those benefits will translate into an overall survival benefit.

The ARO 96-02 study randomized 388 patients with pT3 disease to observation or to immediate postoperative RT[34]. By protocol design, 78 patients with persistently elevated PSA after prostatectomy were excluded from the intention-to-treat analysis. Results were reported for 307 patients (159 in the observation arm, 148 in the adjuvant RT arm). Results favoured RT, with a 5-year progression-free survival of 54% in patients receiving adjuvant RT compared with 72% in patients in the observation arm ($p = 0.0002$).

All three trials provide strong evidence to support the importance of achieving local control of disease in patients with locally advanced disease after surgery. Whether there is a benefit of adjuvant compared with early salvage RT in the era of ultrasensitive PSA testing is currently being tested in a large multicentre clinical trial—RADICALS[35].

4. DISCUSSION AND SUMMARY

The importance of achieving local control in patients presenting with locally advanced prostate cancer is not surprising. Similar data are available for other cancers. Data for adjuvant RT to the breast in women who have had breast-conserving surgery and for post-mastectomy RT showed that the addition of RT led to an improvement in locoregional control and overall survival[36,37]. However, this comparison has been somewhat confusing in prostate cancer because of the competing risks for mortality in this group of patients (attributable to age at presentation) and also because of the difficulty in ascertaining local control. The mature level 1 evidence from multiple randomized trials that is now available shows that improved local control in this setting improves overall and disease-specific survival. The final analysis of the NCIC PR.3–MRC PR07 study confirms the substantial benefit for the use of local treatment in the management of these patients. Data showing the benefit of local therapy (adjuvant RT after surgery in high-risk postoperative patients) also points to the importance of achieving local control of disease. The role of focal RT in this setting—either with high-dose-rate or interstitial brachytherapy—needs to be explored, as does the role of surgery, possibly with the use of preoperative EBRT (as routinely used in locally advanced rectal cancer). Only by accruing patients to prospective randomized trials will all of these issues be addressed.

5. CONFLICT OF INTEREST DISCLOSURES

The authors have no financial conflicts of interest to disclose.

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