

Improved survival with the addition of radiotherapy to androgen deprivation: questions answered and a review of current controversies in radiotherapy for non-metastatic prostate cancer

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Abstract: The contemporary standard of care for locally advanced high-risk prostate cancer includes a combination of dose-escalated radiotherapy (RT) plus androgen-deprivation therapy (ADT). However, 20 years ago, at the inception of the National Cancer Institute of Canada (NCIC) led study (NCIC Clinical Trials Group PR.3/Medical Research Council PR07/Intergroup T94-0110), the survival impact of prostate RT for high-risk disease was uncertain. Recently, Mason, Warde and colleagues presented the final results of this NCIC/MRC study (PMID: 25691677) randomizing 1,205 high-risk prostate cancer patients to ADT + RT *vs.* ADT alone. These updated results confirm substantial improvements with the addition of RT to ADT for the endpoints of overall survival (OS), disease-free survival (DFS), and biochemical recurrence. Close examination of subtleties of this trial's design highlight some of the most salient controversies in the field of prostate RT, including the risk-stratified roles of ADT, optimal ADT duration, and RT field design in the dose-escalated and intensity-modulated radiotherapy (IMRT) era.

Keywords: Androgen-deprivation therapy (ADT); dose-escalated radiotherapy; radiotherapy (RT); whole-pelvic radiotherapy (WPRT)

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A recent report by Mason *et al.* (1) presented the updated results of the National Cancer Institute of Canada (NCIC) Clinical Trials Group PR.3/Medical Research Council PR07/Intergroup T94-0110 (PMID 25691677) randomized trial comparing androgen-deprivation therapy (ADT) plus radiotherapy (RT) *vs.* ADT alone for locally-advanced non-metastatic prostate cancer. The NCIC/MRC trial evaluated 1,205 patients with high-risk prostate cancer, including patients with T3-4 N0/Nx M0 disease or T1-2 with a PSA >40 ng/mL or prostate-specific antigen (PSA) 20-40 ng/mL and Gleason score (GS) 8-10. Patients were randomized to lifelong ADT alone *vs.* ADT + RT with a primary endpoint of overall survival (OS). Patients randomized to the RT arm received a total dose to the prostate of 65-69 Gy delivered with a four-field box technique. Whole pelvic RT (WPRT) to 45 Gy was delivered in 72% of RT patients, while 28%

received prostate RT alone at the discretion of the treating physician. Nodal staging by imaging and/or surgery was not required. ADT included either intended lifelong treatment with luteinizing hormone-releasing hormone (LHRH) agonists (92%) or orchiectomy (8%). Quality of life forms were used to assess toxicity. Biochemical relapse was defined as a PSA >10 ng/mL (later refined to reflect the *Phoenix definition* of PSA nadir plus 2 ng/mL) (2). The study was opened in 1995 and accrued patients until 2005; two interim analyses were performed prior to closing. After 320 deaths at the second interim analysis, the study had met stopping criteria by the data safety monitoring committee and was closed.

In the initial analysis presented by Warde *et al.* in 2011 (3), the addition of RT to ADT resulted in a significant improvement in OS (HR =0.77; P=0.03); 7-year OS for

ADT + RT *vs.* ADT alone was 74% and 66% respectively. RT also reduced the risk of death from prostate cancer by approximately 50% (HR =0.54; P<0.001). Higher rates of short-term genitourinary and gastrointestinal toxicities in the ADT + RT cohort were observed; however, long-term toxicities were comparable in both groups. In the updated results presented by Mason *et al.* (1), with nearly 8 years of follow up, the benefits of RT remained for both OS (HR =0.70; P<0.001) and disease-free survival (DFS) (HR =0.46; P<0.001), with further improvement in the hazard ratios in the updated analysis. The 10-year biochemical progression-free rates using the Phoenix definition were 63% with ADT + RT *vs.* 27% with ADT alone. Additional toxicities including sexual function and cardiovascular were reported in the update and demonstrated no significant difference between the two groups. In conjunction with this publication, Brundage *et al.* (4) published quality of life outcomes from the trial, showing no significant difference in patient reported outcomes at 3 years.

Parallel results to the NCIC/MRC study were reported in a similar multicenter Scandinavian trial, the SPCG-7/SFUO-3 (5), which had several distinguishing features from the NCIC/MRC study design. The Scandinavian trial including patients with slightly lower risk features (T1b-T2, grade 2-3, or T3 with any grade, and a PSA \leq 70 ng/mL), prostate-only radiation to 70 Gy (without pelvic lymph node RT), mandatory surgical nodal staging of the obturator fossa for patients with PSAs \geq 11 ng/mL, and ADT consisting of 3 months of LHRH agonist followed by lifelong androgen receptor blockage with flutamide. The final results of the Scandinavian trial demonstrated similar improvements with RT to the NCIC/MRC trial in terms of OS (HR =0.52; P=0.004) and DFS (HR =0.44; P<0.001). The 10-year biochemical progression-free rates were 75% *vs.* 26% for the ADT + RT and ADT cohorts, respectively. The results from this study were published alongside the patient-reported quality of life, also demonstrating higher short-term toxicities in the ADT + RT cohort but again no significant difference in long-term quality of life outcomes (6).

Historical context is useful to consider when evaluating the designs of these landmark trials. Although, at the time of trial initiation the best outcomes for men with locally-advanced non-metastatic cancer had been observed with combination therapy, many clinicians wondered if the favorable survival outcomes were, in fact, driven by ADT alone. Ultimately, the NCIC/MRC and Scandinavian trials would each demonstrate a 50% reduction in prostate cancer specific-mortality with the addition of RT to ADT and laid

this fundamental question to rest. However, over the past 20 years a battery of more granular questions regarding the optimal combined-modality RT strategy for prostate cancer have emerged. Since the initiation of these trials, intensity-modulated radiotherapy (IMRT) has supplanted the 3D techniques used in these studies and dose-escalated RT (e.g., total doses of 76-82 Gy in conventional fractionation) has become the standard of care in the wake of multiple randomized trials demonstrating improvements in progression-free survival (PFS) with dose-escalation over lower doses of approximately 70 Gy or less (7-12). Moreover, the lifelong ADT used in the NCIC/MRC trial has been replaced by contemporary recommendations of 2-3 years for patients with high-risk disease, with numerous reported and ongoing studies aiming to refine the ADT recommendations with improved risk stratifications. Here, we address a number of the contemporary controversies in RT for non-metastatic prostate cancer in the context of the final results of the NCIC/MRC randomized trial.

Is it reasonable to omit ADT in the setting of dose-escalated radiotherapy for patients with intermediate-risk prostate cancer?

This is an area of considerable debate and the topic of an ongoing North American cooperative randomized trial [Radiation Therapy Oncology Group (RTOG) 0815] for patients with intermediate-risk prostate cancer (clinical stage T2b or T2c, GS of 7, or PSA of 10-20 ng/mL). Interestingly, it is also the inverse question to that of NCIC/MRC trial and a return to a question which has been addressed numerous times in favor of ADT for patients with high-risk disease, albeit in the setting of lower doses radiation between 60-70 Gy (citations). Among patients with intermediate-risk disease, several studies predating dose-escalated RT have also reported improved OS with the addition of short-term ADT to RT (13,14). The RTOG 9408 trial included mostly low- and intermediate-risk patients all receiving conventional RT, 66.6 Gy, with or without 4 months of ADT. In that study, ADT resulted in an OS improvement of 5% at 10 years, largely driven by the intermediate-risk cohort (13). Similarly D'Amico *et al.* reported a randomized trial including predominately intermediate-risk patients, randomized to conventional RT (70 Gy) with or without 6 months ADT (14). After a median follow up of 8 years, the addition of ADT yielded an absolute OS benefit of 10% (P=0.04). It is debated whether the benefits of ADT for men with intermediate-risk

disease may simply be a compensation for the suboptimal doses delivered in these older studies or, alternatively, if the benefits observed with ADT were related to independent and synergistic benefits when combined with RT irrespective of radiation dose. Certainly, the appeal of eliminating the need for ADT in the treatment regimen for men with intermediate-risk prostate cancer is related to its typical side effect profile: erectile dysfunction, fatigue, weight gain, osteoporosis, insulin resistance, and risk of cardiovascular disease (15,16).

Several more recent studies have evaluated the role of ADT for intermediate-risk patients in the setting of dose-escalated RT. The Groupe d'Etude des Tumeurs Uro-Genitales 14 (GETUG 14) presented preliminary results on a prospective randomized trial including 377 patients receiving dose-escalation (80 Gy) randomized to RT alone or RT and 4 months of ADT (17). Median follow up was 27 months and the trial was closed prematurely due to slow accrual; results showed a trend for improved biochemical and local control in the ADT arm ($P=0.09$). A recent phase III trial of short-term ADT for intermediate risk patients was presented at the American Society of Clinical Oncology (ASCO) 2015 conference (18). The study, consisted of 600 patients, randomized one of three arms. Including 6 months of ADT with 70 Gy (arm 1), 6 months of ADT with 76 Gy (arm 2), or 76 Gy RT alone (arm 3). At a median follow up of 6.5 years, there was a significant DFS benefit with the addition of ADT to 76 Gy of RT; although, this did not translate to significant OS benefit. Zumsteg *et al.* retrospectively reviewed 710 intermediate risk prostate patients treated with high-dose RT (≥ 81 Gy), demonstrating a significant PSA relapse-free survival difference, favoring those who received ADT, especially in patients with a GS 4+3 or percent positive cores $\geq 50\%$ (19). In contrast, other retrospective studies have observed no benefit with the addition of ADT to dose-escalated RT for intermediate-risk patients (20,21). Valicenti *et al.* analyzed 883 patients enrolled on RTOG 9406, a phase I/II dose escalation (mean dose of 78.4 Gy), who either did or did not receive short-term ADT at the discretion of the treating physician (20). At a median follow up of 7 years for the intermediate-risk group, there was no significant benefit from ADT in terms of biochemical failure or DFS; only the high-risk population approached significance. Given the conflicting results between studies, differences in RT doses across eras, and the potential role of selection bias in retrospective analyses, the role of ADT for intermediate-risk patients remains unclear. The accruing RTOG 0815,

which randomizes intermediate-risk patients to 6 months of ADT with dose-escalated RT *vs.* dose-escalated RT alone, is designed specifically to address this question. In the meantime, the NCCN (22) and ESMO (23) guidelines continue to recommend "consideration" of 4-6 months of ADT for patients with intermediate-risk prostate cancer.

What is the optimal duration of ADT for patients with high-risk prostate cancer in the dose-escalation era?

The NCIC/MRC study included intended lifelong ADT. However, since the initiation of that trial, multiple studies for patients with high-risk prostate cancer have addressed the optimal duration of ADT (*Table 1*) (24-34). The European Organization for Research and Treatment of Cancer (EORTC) 22961 study compared 6 *vs.* 36 months of ADT in patients treated to 70 Gy and found an improvement in 5-year OS with long-term ADT (31), defining 36 months as a *de facto* standard duration for high-risk prostate cancer. Given long-term toxicities from extended ADT use, more recent studies have attempted to reduce the duration of ADT. Abstract results from a phase III non-inferiority Canadian study comparing 18 *vs.* 36 months of ADT for high-risk disease treated to 70 Gy found no difference in OS, DFS, or rates of biochemical, regional or distant failure at 10 years (33). In the dose-escalation era, the Duration of Androgen-Deprivation Therapy (DART) 01/05 study compared 4 *vs.* 28 months of ADT delivered with 76-82 Gy and reported improved 5-year outcomes with longer ADT duration for OS, biochemical DFS and metastasis-free survival at a median follow up of 63 months (34). While provocative, the DART trial had some limitations including higher rates of unknown death in the short-term ADT arm, suggesting the presence of competing risks. In the United States, the ongoing phase III randomized RTOG 0924 trial evaluating the benefit of whole-pelvic RT (WPRT) may also indirectly address the duration of ADT for high-risk, with the inclusion of ADT courses of 6 *vs.* 32 months chosen at the discretion of the physician (35).

Should the pelvic lymph nodes be treated in addition to the prostate for patients with high-risk prostate cancer?

A subgroup analysis of the NCIC/MRC trial addressed the role of WPRT compared to prostate-only (PO-RT), used at the physician's discretion in 72% and 28% of patients in the RT cohort, respectively. In this post hoc

Table 1 Randomized trials comparing duration of androgen deprivation therapy of high-risk prostate cancer

Study	Patients (N)	Median follow up (years)	Duration of ADT	Outcomes
RTOG 85-31 (24)	977	7.6	0 vs. indefinitely; RT 65-70 Gy	10-yr CSS 78% vs. 84% (P=0.0052); 10-yr OS 39% vs. 49% (P=0.002)
RTOG 86-10 (25)	456	8.7	0 vs. 4 months; RT 65-70 Gy	10-yr CSS 64% vs. 77% (P=0.01); 10-yr OS 34% vs. 43% (P=0.12)
EORTC 22863 (26)	415	9.1	0 vs. 3 months; RT 70 Gy	10-yr CSS 69% vs. 89% (P=0.001); 10-yr OS 40% vs. 58% (P=0.0004)
Quebec L-100 (27)	161	5.0	0 vs. 3 vs. 10 months; RT 64 Gy	7-yr BRFS 42% vs. 66% vs. 69% (P=0.003)
Quebec L-200 (27)	325	3.7	5 vs. 10 months; RT 64 Gy	4-yr BRFS 70% vs. 70% (P=0.55)
RTOG 92-02 (28)	1,554	11.3	4 vs. 28 months; RT 65-70 Gy	10-yr CSS 84% vs. 89% (P=0.004); 10-yr OS 52% vs. 54% (P=0.36); 10-yr OS 32% vs. 45% for GS 8-10 (P=0.006)
CUOG (29)	378	6.6	3 vs. 8 months; RT 66 Gy	7-yr CSS 94% vs. 93% (P=0.24); 7-yr CSS 42% vs. 71% for high-risk (P=0.01); 7-yr OS 81% vs. 79% (P=0.7)
TROG 96.01 (30)	818	10.6	0 vs. 3 vs. 6 months; RT 66 Gy	10-yr CSS 78% vs. 81% vs. 89% (P=0.0002); 10-yr OS 58% vs. 63% vs. 71% (P=0.0005)
EORTC 22961 (31)	970	6.4	6 vs. 36 months; RT 70 Gy	5-yr CSS 95% vs. 97% (P=0.004); 5-yr OS 81% vs. 85% (P=0.65 for non-inferiority)
ICORG 97-01 (32)	276	8.5	4 vs. 8 months; RT 70 Gy	7-yr CSS 93% vs. 90% (P=NS); 7-yr OS 85% vs. 77% (P=NS)
PCS IV Quebec (33)	630	6.4	18 vs. 36 months; RT 70 Gy	10-yr CSS 87.2% vs. 87.2% (P=0.838); 10-yr OS 63.2% vs. 63.6% (P=0.429)
DART 01/05 (34)	355	5.3	4 vs. 28 months; RT 76-82 Gy	5-yr BRFS 81% vs. 90% (P=0.01); 5-yr OS 86% vs. 95% (P=0.009)

ADT, androgen-deprivation therapy; RTOG, Radiation Therapy Oncology Group; yr, year; RT, radiotherapy; CSS, cancer-specific survival; OS, overall survival; EORTC, European Organization for Research and Treatment of Cancer; BRFS, biochemical relapse-free survival; CUOG, Canadian Urologic Oncology Group; TROG, Trans-Tasman Radiation Oncology Group; ICORG, Irish Clinical Oncology Research Group; NS, non-significant; DART, duration of androgen-deprivation therapy.

analysis, no significant differences in OS were reported, although the authors commented that a trend was observed toward improved survival with WPRT over PO-RT (HR =0.70; 95% CI, 0.45-1.09; P=0.12). In their discussion, however, the authors rightly point out the importance of selection bias, low patient numbers, and lack of nodal staging as potential contributing factors. Notably, the Scandinavian trial also demonstrated similar improvements in all oncologic endpoints to the NCIC/MRC study without the use of WPRT.

The role of WPRT for high-risk prostate cancer continues to be an area of controversy in the field of radiation oncology. To date, three randomized studies have failed to demonstrate a benefit with the addition of WPRT

in node-negative prostate cancer (Table 2). The RTOG 7706 trial reported results of 445 prostate cancer patients in the pre-PSA era, which presented with clinical T1c-2c, and were randomized to WPRT vs. PO-RT; at 12-year median follow-up, no survival difference was detected (36). This was followed by RTOG 9413, which examined the role of WPRT in patients with $\geq 15\%$ risk of lymph node involvement based on the Roach formula (37,38,42). The study included four arms: (I) WPRT with neoadjuvant and concurrent ADT (NCHT); (II) WPRT with adjuvant ADT (AHT); (III) PO-RT with NCHT; and (IV) PO-RT with AHT. Initial results demonstrated a significant improvement in 4-year PFS, favoring WPRT (54% vs. 47%; P=0.022); WPRT with NCHT had the highest 4-year PFS (60%).

Table 2 Randomized trials comparing whole pelvis *vs.* prostate only radiotherapy for high-risk prostate cancer

Study	Patients (N)	Median follow up (years)	Treatment arms	Outcomes (WPRT <i>vs.</i> PORT)
RTOG 77-06 (36)	445	7.0	Prostate (65 Gy) ± pelvis (45 Gy) (± estrogen or orchiectomy)	5-yr PFS 83% <i>vs.</i> 84%; 5-yr OS 80% <i>vs.</i> 78%; 5-yr OS w/LC [†] : 90% <i>vs.</i> 88%
RTOG 94-13 (37,38)	1,292	6.6	Prostate (70.4 Gy) ± pelvis (50.4 Gy); 4 months ADT given NHT or AHT (2×2 factorial design)	PFS 62% (WP + NHT) <i>vs.</i> 66% (PO + NHT) <i>vs.</i> 69% (WP + AHT) <i>vs.</i> 62% (PO + AHT) (P=NS)
GETUG-01 (39)	444	3.5	Prostate (66-70 Gy) ± pelvis (46 Gy); 4-8 months ADT for high-risk	High-risk 5-yr PFS 66% <i>vs.</i> 65% (P=NS)
RTOG 09-24 (35)	2,580 (target accrual)	–	Prostate (79.2 Gy or 45 Gy + brachy) ± pelvis (45 Gy); 6 or 32 months ADT	Ongoing
PEACE2 (40)	1,048 (target accrual)	–	Prostate (74-78 Gy) ± pelvis (46-50 Gy); 36 months ADT ± cabazitaxel	Ongoing
PIVOTAL (41)	–	–	Prostate (74 Gy) ± pelvis (60 Gy); 6-9 months ADT	Ongoing

[†], progression or measurable disease. WPRT, whole pelvis radiotherapy; PORT, prostate only radiotherapy; RTOG, Radiation Therapy Oncology Group; PFS, progression-free survival; OS, overall survival; yr, year; LC, local control; ADT, androgen-deprivation therapy; NHT, neoadjuvant hormone therapy; AHT, adjuvant hormone therapy; NS, non-significant; GETUG, Groupe d'Etude des Tumeurs Uro-Genitales; Brachy, brachytherapy.

However, when Lawton *et al.* (38) published the updated results of RTOG 9413 after a median follow up of 6.6 years, no statistically significant differences were found in PFS or OS between NHT *vs.* AHT and WPRT *vs.* PO-RT, rendering the RTOG 9413 a negative study with mature follow up. Lastly, Groupe d'Etude des Tumeurs Uro-Genitales 01 (GETUG 01), which included all localized, node-negative prostate cancer patients (irrespective of risk category) also demonstrated no difference in PFS between WPRT and PO-RT (39). These results have also been redemonstrated in non-randomized analyses of more modern treatment cohorts. The GETUG 12 randomized phase III study evaluating the role of ADT plus docetaxel and estramustine for high-risk prostate cancer patients performed an unplanned secondary analysis to evaluate the role of elective nodal RT for high-risk, clinically node-negative prostate cancer and found no benefit with WPRT. A recent review of the National Cancer Data Base (NCDB) performed at our institution confirmed the above findings, again demonstrating no OS differences with WPRT for high-risk, node-negative prostate cancer, even in the present dose-escalation era (43). Nevertheless, the topic of WPRT for high risk clinically node negative patients will be debated until the results of RTOG 0924 (35), the European

PEACE2 study (40), and the United Kingdom PIVOTAL trial (41) mature and, perhaps, irrespective of their results.

Conclusions

At the design of the NCIC/MRC study the survival impact of RT for locally-advanced prostate cancer was debated within the urologic oncology community. The updated study results presented by Mason *et al.* provides closure to this topic and confirms that local control of high-risk prostate cancer categorically improves survival at long term follow up. Close examination of subtleties of this trial's design and era of treatment also highlight some of the most salient controversies in the contemporary era of IMRT and dose-escalated RT, including the risk-stratified roles of ADT, optimal ADT duration, and RT field design.

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Footnote

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