Editorial

Radiation therapy to the primary tumor in locally advanced prostate cancer is not "closing the barn door after the horse has bolted"

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The National Cancer Institute of Canada (NCIC) Clinical Trials Group PR.3/Medical Research Council PR07/Intergroup T94-0110 (1) was a randomized controlled trial (RCT) of radiation therapy (RT) and androgen deprivation therapy (ADT) *vs*. ADT alone, for men with locally advanced prostate cancer. The authors defined locally advanced as: (I) T3-4, N0/X, M0; or (II) T1-2 with prostate specific antigen (PSA) > 40 ng/mL; or (III) PSA 20-40 ng/mL and Gleason 8-10. Men were randomized to lifelong ADT *vs*. ADT + RT, 65-69 Gy in 1.8 Gy fractions, using 3D conformal RT, to the prostate and pelvis or prostate alone. Of the 1,205 patients treated between 1995 and 2005, 602 received ADT alone and 603 received ADT + RT. Overall survival (OS) was significantly improved in the patients allocated to ADT + RT [hazard ratio (HR) =0.70; 95% CI, 0.57-0.85; P<0.001]. Prostate cancer specific mortality (CSM) was improved in the patients allocated to ADT + RT (HR =0.46; 95% CI, 0.34-0.61; P<0.001). Although patients on ADT + RT arm reported a higher rate of gastrointestinal (GI) toxicity, only 2 of 589 patients had grade 3 or greater diarrhea at 24 months after RT.

The authors of this study should be congratulated for their work. In the early 1990s, the addition of RT to ADT in locally advanced prostate cancer was questioned, and a RCT by the Medical Research Council revealed no benefit with the addition of local therapy (2). Among various cancers (e.g., prostate, breast), treatment of a primary tumor for local control (LC), when there is suspicion of metastatic disease, was compared to "closing the barn door after the horse had bolted" (3). Critics of local therapy in the locally advanced setting emphasized the toxicity of RT: if patients were already being treated systemically with ADT, why subject them to additional toxicity of local therapy?

Strikingly, the INT T94-0110 (1,4) trial reveals a clear benefit for "closing the barn door" with local therapy, as adding RT to ADT improved OS, CSM, and freedom from biochemical failure (FFBF) compared to ADT alone [Figures 2-4, respectively (1)]. The trial underscores the importance of adding RT to ADT in high-risk, locally advanced (and possibly metastatic) prostate cancer patients. Notably, this is not the only RCT suggesting the benefit of multimodal therapy to achieve LC in locally advanced or metastatic prostate cancer (*Table 1*) (9). For locally advanced patients, a similar RCT from Sweden also revealed a CSM benefit for RT + ADT over ADT alone (5). Second, the French RCT (6) revealed a benefit for progression free survival, but not other outcomes. The CSM benefit was not realized in the French RCT likely due to a short median follow-up of 67 months.

Currently, the literature is more robust for RT rather than radical prostatectomy (RP) in the locally advanced or M1 settings. Retrospective analyses of prospective trials evaluating RP in the M1 setting have revealed mixed results. For example, the Southwestern Oncology Group (SWOG) 8894 revealed a survival benefit with RP (7). The Cancer and Leukemia Group B (CALGB) did not reveal improved CSM with ADT + RP *vs*. RP alone (8). Similarly, a recent review article of LC in M1 patients highlighted preclinical rationale and limited high-level prospective evidence (10). It is unclear why all analyses do not reveal a benefit for LC. Significant selection bias is inherent among these unplanned subset analyses. Moreover, perhaps the benefit of LC is greatest when the extraprostatic burden of disease is the lowest (7). In support of this concept, a feasibility

Table 1 Benefit of local control in prostate cancer RCTs

Author (reference)	Trial or registry	Study type	Years accrued [published]	Prostate cancer stage	n	Treatment	CSM	Absolute reduction CSM; P value	HR or RR of survival; 95% CI; P value	Conclusion(s)
Widmark (5)	SPCG-7	Phase III RCT	1996-2002 [2009]	Locally advanced, T3N0M0	439	ADT + RT	CSM: 29.6% at 10 years	12%; P<0.0001	RR =0.44; CI: 0.30-0.66; P<0.0001	Addition of local RT to ADT halved 10-year CSM
					875	ADT alone	CSM: 39.4% at 10 years			
Mottet (6)	French	Phase III RCT	2000-2003 [2012]	Locally advanced, mostly T3-4N0M0	133	ADT + RT	NR	NR	NA	Improved PFS (61% *vs*. 8% at 5 years) with RT + ADT *vs*. ADT alone; median OS times not reached
					130	ADT alone	NR			
Warde (4), Mason: current work (1)	NCIC PR.3/UK PR07	Phase III RCT	1995-2005 [2011, 2015]	Locally advanced, mostly T3-4N0M0	603	ADT + RT	CSM: 9% at 10 years	9%; P=0.001	HR =0.54; CI: 0.27-0.78; P=0.0001	The addition of RT to ADT improved OS and CSM
					602	ADT alone	CSM: 19% at 10 years			
Thompson (7)	SWOG 8894	Retrospective analysis of Phase III RCT	1989-1994 [2002]	M1	148	Orchiectomy ± ADT + RP	NR	NR	NA	RP had associated with improved OS; patients who received previous RT had improved OS
					1,138	Orchiectomy ± ADT, no RP	NR			
Halabi (8)	CALGB	Retrospective analysis of 9 Phase II-III RCTs	1991-2005 [2009]	M1, progressing on ADT	310	ADT + RP	CSM: 3% at 5 years	0%; P=NS	HR =1.08; CI: 0.93-1.26; P=0.329	Men with mCRPC did not have improved CSM following RP
					928	ADT, no RP	CSM: 4% at 5 years			

ADT, androgen deprivation therapy; CALGB, Cancer and Leukemia Group B; CI, 95% confidence interval; CSM, cancer specific mortality; HR, hazard ratio; m: months; LC, local control; LN, lymph node; LR, local recurrence; MST, median survival time; NCIC, National Cancer Institute of Canada; NR, not reported; NS, not significant; OS, overall survival; RCT, randomized controlled trial; RP, radical prostatectomy; RR, relative risk; RT, radiation therapy; SPCG, Scandinavian Prostate Cancer Group Study; SWOG, South Western Oncology Group.

study exploring the potential benefit of cytoreductive RP for a men receiving ADT with oligometastatic prostate cancer demonstrated a significant improvements in PFS and CSM compared to treatment with ADT only in a carefully selected population (11).

The INT T94-0110 RCT (1) may be subject to the Will Rogers phenomenon. Most of these patients were staged M0; however, many had T3/4 disease (87%) or PSA >20 (63%) and were at high risk for subclinical metastasis. Currently, most clinicians would order computerized tomography and bone scan for these patients to rule out N1/M1 disease. We agree with the authors (1) in that their patient population represents a higher risk group than that of the Swedish group (5). The Swedish group patients had pathologic confirmation of N0 status if the PSA was >11 ng/mL (2% of the Intergroup T94-0110); 20% of patients had T1-2 disease (10% in Intergroup T94-0110); 60% of patients had a PSA of less than 20 ng/mL (37% of Intergroup T94-0110); and the maximum allowed PSA level was 70 ng/mL (unlimited in Intergroup T94-0110). Thus, in the context of the contemporary era, the INT T94-0110 RCT results can be extrapolated to imply that certain N1/M1 patients may similarly benefit from RT + ADT over ADT alone.

The INT T94-0110 RCT has certain limitations, mainly due to the era in which it was conducted. During the 1990s, dose escalation with conventional fractionation (CFRT, i.e., 1.8-2 Gy fractions, from 64 Gy to ~80 Gy) was being explored in multiple RCTs (12-18). The radiation dose that was used is now known to be inferior to the current standard of escalation to doses exceeding 74 Gy and commonly to ~80 Gy. It is possible that further dose escalation would be advantageous; as multiple RCTs and subsequent meta-analyses revealed a BF benefit of radiation dose escalation (19-21).

Additionally, the INT T94-0110 study (1) used CFRT with 3D conformal RT and elective pelvic lymph node RT. The use of intensity modulated RT is associated with fewer toxicities than 3D-CRT (12). Moreover, the benefit of pelvic lymph node RT remains unclear and is currently under investigation in Radiation Therapy Oncology Group 0924.

Next, the INT T94-0110 study does not report patient race or demographics. Studies reveal that Asian subgroups have better CSM than non-Hispanic white patients (22), that African Americans harbor a biomarker signature that portends a poor prognosis (23). With respect to toxicities and quality of life, certain subpopulations (particularly minorities) are susceptible to increased toxicity (24), and the INT T94-0110 arms may have not been balanced with respect to these subpopulations.

FFBF was one of the few endpoints to track disease progression. There is unfortunately no use of follow-up imaging to report location of failure (local *vs.* distant), and to track the extent of intra- *vs.* extra-prostatic disease. As of 2015, newer imaging modalities (including NaF positron emission tomography and multiparametric magnetic resonance imaging) would be able to quantify intraprostatic *vs.* extraprostatic disease recurrence and guide clinicians in recommending further focal or systemic therapy (25). The combination of advanced imaging and increasingly effective therapies for disease progression is likely to improve oncologic outcomes and confound the independent benefits of local and systemic therapies.

Finally, the use of life-long ADT is questioned in the contemporary era. Studies published since the 2000s have suggested that ADT worsens cardiovascular risk factors (obesity, type 2 diabetes mellitus, and dyslipidemia). These risk factors may lead to increased risk of cardiac mortality, which would decrease the OS benefit of both arms of INT T94-0110 (26,27).

While INT T94-0110 provides additional supporting evidence for local therapy for men with locally advanced and high-risk prostate cancers, a very intriguing aspect of this study is the predominance of high-risk features among the study population and the likelihood that current staging technologies would identify metastatic disease in large proportion of the study population. To further clarify the role of local therapy in patients presenting with metastatic disease, a prospective, multi-institutional, randomized, phase II trial of best systemic therapy *vs.* best systemic therapy plus definitive treatment (RT or RP) of the primary tumor in M1 prostate cancer is currently recruiting patients (NCT01751438). Best systemic therapy includes ADT, secondary hormonal therapies, chemotherapy, tyrosine kinase inhibitors, and/or immunotherapy. RP may use a variety of surgical approaches (e.g., robotic assisted, radical retropubic prostatectomy, radical cystoprostatectomy, total pelvic exenteration); RT may use IMRT, 3D-CRT, or proton therapy. A maximum of 120 patients will be randomized with 1:1 ratio between the arms. Progression will be defined by PSA response or change in lesion size on imaging. If RP and RT have similar efficacy, PFS should be improved with either treatment, and there should not be a CSM difference between the two arms; OS may depend on other factors, including patient comorbidities.

In conclusion, the INT T94-0110 study (1) demonstrates a substantive benefit of LC with RT in locally advanced

prostate cancer patients, and provides the suggestion of potential benefit in those with micrometastatic or limited metastatic disease. Although this is not the only study to suggest a benefit of LC, it is one of the few studies that is prospective and randomized. Compared to contemporary techniques, INT T94-0110 did not employ an "adequate" dose of RT (i.e. ≥74 Gy), it used older RT techniques, it did not differentiate local *vs*. distant recurrence, and it did not contain patient-specific data (e.g., genetics, demographics or comorbidities). These differences may all be key factors in identifying the subset of patients where LC is most important.

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Footnote

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