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A phase I pilot study of pre-operative radiotherapy for prostate cancer:

Long-term toxicity and oncologic outcomes

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Short Running Title: Pre-operative radiotherapy in prostate cancer

Abstract:

Background:

Neoadjuvant radiotherapy (RT) improves disease control in various cancers, and has become an established oncologic treatment strategy. During 2001-2004, we conducted a phase I pilot study assessing the role of short-course pre-operative RT (PreORT) for men with unfavourable intermediate- and high-risk localized prostate cancer. Herein, we present long-term follow-up toxicity and oncologic outcomes.

Materials and Methods:

Eligible patients had histologically proven prostate cancer, cT1-T2N0M0 disease, PSA >15-35 ng/ml regardless of Gleason score, or PSA 10-15 ng/ml with Gleason score ≥ 7 . Patients received 25 Gy in five consecutive daily fractions (5 Gy per fraction) to the prostate-only, followed by radical prostatectomy within 14 days after RT completion. Primary outcomes were intra-operative morbidity, and late genitourinary (GU) and gastrointestinal (GI) toxicities.

Results:

In total, 15 patients were enrolled; 14 patients completed PreORT followed by radical prostatectomy, which also included bilateral lymph node dissections in 13 cases. Median follow-up was 12.2 years (range 6.7-16.3 years). Late GU toxicity was common, with 2 patients (13.3%) experiencing G2 toxicity, and 6 patients (40%) G3 toxicity. There were no patients with G4-5 late GU toxicity. Late GI toxicity was infrequent, with only 1 patient (6.7%) experiencing transient G2 proctitis. At last follow-up, 8 (53.3%) and 6 (40%) patients experienced biochemical and metastatic disease recurrence, respectively.

Conclusion:

The use of PreORT in men with high-risk prostate cancer is associated with unexpected high-rates of late GU toxicity. Future studies examining the role of RT pre-radical prostatectomy must cautiously select RT technique and dose schedule. Importantly, long-term follow-up data is essential to fully determine the therapeutic index of PreORT in the management of localized disease.

Background:

Approximately one third of men who undergo radical prostatectomy (RadP) for localized prostate cancer (PCa) will experience biochemical relapse and require post-operative radiotherapy (PORT)¹. Nonetheless, despite high-level evidence showing improved disease-free²⁻⁴ and overall survival⁵ with adjuvant PORT, it remains underutilized⁶. Therefore, novel radiotherapy (RT) approaches seem warranted to maximize PCa cure rates.

The conventional model of improving local control with PORT has been challenged in other malignancies such as locally advanced rectal cancer⁷ and sarcoma⁸, migrating the use of RT to the pre-operative setting. In PCa specifically, there are a number of theoretical advantages to pre-operative RT (PreORT). Firstly, the potential to down-stage and/or sterilize extra-prostatic clonogenic cells, decreasing the likelihood of residual viable cancer cells after surgery^{9,10}. Secondly, in the pre-operative setting, there is a decreased proportion of radioresistant hypoxic cells, as the prostatic blood supply has not undergone surgical perturbation¹⁰. Lastly, PreORT may be delivered to a significantly smaller volume compared to PORT leading to potential decrease in RT-related toxicity^{9,10}.

Given these theoretical advantages and favourable experiences in other malignancies, a phase I study to assess feasibility, safety and efficacy of PreORT followed by RadP was conducted in men with localized PCa harbouring high risk of extra prostatic extension. Initial results after a median follow up 45 months were previously reported⁹. Herein, we report long-term toxicity and oncologic outcomes.

Materials and Methods:*Patient eligibility:*

This prospective study was approved (XXX REB) and registered (clinicaltrials.gov XXX). Eligibility criteria included patients with cT1-T2N0M0 PCa (UICC TNM classification system, 7th edition), with PSA >15-35 ng/ml regardless of Gleason score, or PSA 10-15 ng/ml with Gleason score ≥ 7 . All patients underwent staging investigations including pelvic computed tomography (CT) and bone scan, within 4 months of enrollment.

Radiation therapy:

Patients received a course of hypo-fractionated PreORT consisting of 25 Gy in 5 consecutive daily fractions to the prostate only¹¹⁻¹⁴. Planning parameters were previously described⁹. Daily image-guidance was employed based on orthogonal imaging registration to 3 intraprostatic fiducials.

Surgery:

All patients were planned to undergo non-nerve sparing retropubic RadP and bilateral pelvic lymphadenectomy by experienced urologic oncologists within 14 days of PreORT completion.

Follow-up:

Assessment and grading method for acute, intra- and post-operative toxicity have been previously described⁹. Patients were followed after surgery with PSA and clinical assessment at 1 and 6 months post-RadP, and every 6 months thereafter or sooner if clinically warranted. Long-term toxicity was assessed and documented at each visit, and subsequently scored as per Common Terminology Criteria for Adverse Events (CTCAE) v4.0. Biochemical failure was determined based on two consecutive post-operative PSA values greater than 0.2 ng/ml.

Results:

Patient characteristics:

The pre- and post-operative patient characteristics are summarized in Table 1⁹. Of the 15 patients enrolled in the study, all underwent planned PreORT [14 with 6-field conformal RT and 1 with intensity modulated RT (IMRT)] and were taken to the operating room at a median of 6 days (range 3-12 days) following PreORT. In total, 14 patients completed the RadP procedure, while 13 had bilateral lymphadenectomies⁹.

Baseline clinicopathologic indices are included in Table 1. In brief, post-operatively, 5 patients had detectable PSA values (range 0.08-0.28 ng/mL), all had Gleason score 7 disease, 9 had pT3 disease, 7 had positive surgical margins, and 3 had pN1 disease. Acute RT, intra- and post-operative toxicities have been previously reported⁹. In summary, no G3+ acute toxicities were observed during PreORT; a total of 4 patients required transfusion of 1-2 units of packed red blood cells during the intra- or post-operative periods.

Long-term outcomes:

Median follow-up was 12.2 years (range 2.0-16.3 years).

Late genitourinary (GU) toxicity occurred in 12 patients (Table 2 and Figure 1A-B): 3 patients had G0, 4 had G1, 2 had G2, and 6 had G3 toxicity. Eleven of the 12 patients with late GU toxicity developed their toxicity within 2 years of starting PreORT; with one patient developing G1 toxicity 3.6 years after treatment. Nevertheless, a significant proportion of G2-3 toxicity events (5 out of 8) resolved during the first 10 years following treatment (Figure 1A-B).

A single patient had late G2 gastrointestinal (GI) toxicity (proctitis) three months following completion of RT, which resolved completely within 1 week of a single dose of intra-rectal corticosteroids. No patients experienced G3+ late GI toxicity (Figure 1C-D).

In total, 8 patients developed biochemical relapse (BCR) (Table 3 and Figure 2A). Of these, 7 received salvage ADT at a median of 57.5 months (range 0-130 months) following treatment, and 2 received second-generation hormonal agents. Six patients developed metastatic disease (Figure 2B), which was nodal, bony or mixed in 2, 1 and 3 cases respectively. All these 6 patients developed castrate-resistant disease. Four death events were recorded, 2 attributable to PCa.

Discussion:

Although PreORT is increasingly used in oncology, our long-term results demonstrate that short-course PreORT for localized PCa should be considered cautiously. The observed crude rate of G3 GU late toxicities is unexpectedly high (6 out of 14 [42.8%] patients), particularly when contrasted to those observed in the PORT setting. For example, the SWOG-8794/PR-2 trial reported rates of urethral stricture and total urinary incontinence of 17.8% and 6.5%, respectively¹⁵. Similarly, the EORTC-22911 trial reported 10-year cumulative incidence of G2+ GU toxicity of 21.3%². Therefore, the use of PreORT for PCa should remain investigational, and future studies must aim to determine the optimal dose schedule and delivery techniques.

Rapidly evolving technologies, such as stereotactic body RT (SBRT), are enabling increasingly precise planning and delivery of RT, and may boost the interest for PreORT in PCa. Presently, there is an ongoing single-arm single-institution prospective trial (NCT02946008), aiming to determine the safety and maximum tolerated dose of pre-operative SBRT for high-risk PCa. In addition, advances in diagnostic imaging such as multiparametric MRI and prostate specific membrane antigen (PSMA) positron emission tomography (PET) may allow better

identification of patients at high-risk of harbouring adverse pathological features^{16,17}, enhance tumor delineation¹⁷, and improve regional and distant staging¹⁸⁻²⁰. In turn, these advances could enable tailored PreORT approaches based on overall and anatomically-mapped risk quantifications.

To our knowledge, only one additional modern-era study has explored PreORT in PCa. Koontz et al. evaluated long-course PreORT (with doses between 39.6-54 Gy in 1.8 Gy per fraction) followed by RadP within 4-8 weeks in a phase I trial of 13 men with high-risk disease²¹. At median follow-up of 46 months, 42% of patients developed chronic grade 2+ GU toxicity and 17% developed a symptomatic urethral stricture requiring dilatation²¹. We observed similarly high crude rates of G2+ GU toxicity (53.3%; 8 out of 15 patients). Nonetheless, all of our G2+ events presented in the first 2 years after treatment, with continuously decreasing prevalence to 38% and 33% at 5- and 10-years of follow-up, respectively.

There are a number of limitations of this study. First, the small cohort size, reflecting the pilot nature of the study, limits the generalizability of the findings. Second, the study was conducted when modern RT techniques (i.e. IMRT) were not established as standard-of-care. Therefore, 93% of patients received conformal RT, now known to be associated with higher toxicity rates²². Third, the study included unfavourable intermediate- and high-risk patients, selected based on poorer prognostic indices and high likelihood of requiring PORT, likely accounting for the oncologic results observed. Last, combinatorial hormonal therapy has shown to improve oncologic outcomes in patients with similar features treated with radical RT²³ or PORT²⁴, however was not included in this protocol as per *status quo* in patients managed with RadP.

In summary, we report the long-term toxicity and oncologic outcomes of a PreORT phase I study for unfavourable localized PCa. We observed considerable rates of G2-3 late GU toxicity. Future studies are needed to judiciously determine the optimal RT technique, dose and schedule, in order to define the potential role of pre-operative approaches in patients with locally aggressive PCa.

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Figures:

Figure 1. Cumulative incidence of G2+ genitourinary toxicity (1A) and prevalence of genitourinary toxicity within 2 years to 14 years following radiotherapy (1B); cumulative incidence of G2+ gastrointestinal toxicity (1C) and prevalence of gastrointestinal toxicity within 2 years to 14 years following radiotherapy (1D).

Figure 2. Oncologic outcomes. Kaplan-Meier curves of biochemical relapse-free survival (2A) and metastasis-free survival (2B).

Table 1. Baseline patient characteristics.

Case ID number	Age	Surgery		ISUP grade group	PSA (ng/mL)		Stage		Pre-op NCCN risk category	SM
		RP	LND		Pre-op	Post-op	Pre-op #	Post-op		
1	56	Yes	Yes	2*	13.67	<0.05	cT2b	pT3aN0	UI	+
2	60	Yes	No	4*	7.51	0.08	cT2b	pT2bNx	H	-
3	69	Yes	Yes	3*	47.5	0.28	cT2b	pT3bN0	H	+
4	68	Yes	Yes	2*	26.02	<0.05	cT1c	pT3bN0	H	+
5	66	Yes	Yes	2*	24.09	<0.05	cT2b	pT3bN0	H	+
6	60	Yes	Yes	3	31.4	<0.05	cT2a	pT3bN0	H	-
7	57	Yes	Yes	2*	8.41	<0.05	cT2a	pT2aN0	UI	-
8	74	Yes	Yes	3*	38.93	<0.05	cT2a	pT3bN0	H	+
9	62	Yes	Yes	2*	26.91	<0.05	cT1c	pT2cN0	H	-
10	64	Yes	Yes	2*	28.9	0.93	cT2a	pT3aN0	H	-
11	61	No	No	3*	18.1	0.7	cT2b	pTxN1	UI	NA
12	64	Yes	Yes	2*	22.23	0.02	cT2b	pT3bN1	H	+
13	58	Yes	Yes	3*	11.25	<0.05	cT2a	pT2cN0	UI	-
14	63	Yes	Yes	3*	15.78	0.14	cT2a	pT3aN1	UI	+
15	62	Yes	Yes	3*	17.8	<0.05	cT1c	pT2cN0	UI	-

RP, radical prostatectomy; PLA, pelvic lymphadenectomy; SM, surgical margins; NA, not assessed; NCCN, national comprehensive cancer network; UI, unfavorable intermediate risk; H, high risk; # all cases staged as N0M0 based on bone scan and CT abdomen-pelvis. * $\geq 50\%$ of cores involved with adenocarcinoma.

Table 2. Late genitourinary toxicities and interventions details.

Case ID number	Late GU toxicity grade	Late GU toxicity	Intervention for late GU toxicity
1	G2	Urinary urgency; urge incontinence	Cystoscopy; metal surgical clip found in bladder neck (removed); urge incontinence managed with solifenacin, oxybutynin
2	G3	VUA stricture	Three VIUs
3	G0	n/a	n/a
4	G1	Mild incontinence	None
5	G0	n/a	n/a
6	G1	Mild incontinence	None
7	G1	Mild incontinence	None
8	G3	Incontinence	Sling procedure
9	G3	VUA stricture, incontinence	Two VIUs, three cystoscopies with bladder neck dilatation
10	G2	Bladder neck contracture, urge incontinence	Cystoscopy; no dilatation
11	G0	n/a	n/a
12	G1	Mild incontinence	None
13	G3	Incontinence	Sling procedure, insertion of artificial urinary sphincter
14	G3	Incontinence	Dorsal slit procedure, one VIU, urethral dilatation
15	G3	VUA stricture, urinary retention	Two VIUs, one TURBT

VUA, vesicourethral anastomotic; VIU, visual internal urethrotomy; TURBT, transurethral resection of a portion of the bladder.

Table 3. Oncologic outcomes.

Case ID number	BCR	Time to BCR (months)	ADT	Second generation hormonal therapies	Metastases	Time to metastases (years)	CRPC	Vital status
1	No	-----	-----	-----	-----	-----	-----	Alive
2	Yes	14	Yes	No	Yes	7.9	Yes	Alive
3	Yes	31	Yes	No	Yes	9.0	Yes	Alive
4	Yes	62	Yes	Yes	Yes	11.4	Yes	Dead*
5	No	-----	-----	-----	-----	-----	-----	Alive
6	No	-----	-----	-----	-----	-----	-----	Alive
7	No	-----	-----	-----	-----	-----	-----	Dead
8	No	-----	-----	-----	-----	-----	-----	Dead
9	Yes	72	Yes	Yes	Yes	10.9	Yes	Alive
10	Yes	3	Yes	No	No	-----	No	Alive
11	Yes	3	Yes	No	Yes	7.0	Yes	Alive
12	No	-----	-----	-----	-----	-----	-----	Alive
13	Yes	122	No	No	No	-----	No	Alive
14	Yes	101	Yes	No	Yes	10.8	Yes	Dead*
15	No	-----	-----	-----	-----	-----	-----	Alive

BCR, biochemical relapse; ADT, androgen deprivation therapy; CRPC, castrate-resistant prostate cancer; *PCa-related death.

2A

2B

Summary

We report the long-term results of a phase I pilot study assessing short-course pre-operative radiotherapy (PreORT) followed by radical prostatectomy in 15 unfavourable intermediate and high-risk prostate cancer (PCa) patients. With median follow-up of 12 years, the incidence of grade 2+ genitourinary and gastrointestinal toxicity were 53.3% and 6.7%, respectively. Biochemical and metastatic disease recurrence occurred in 53.3% and 40% of patients, respectively. Future studies must cautiously select PreORT technique and dose schedule.