10-yr Results of Moderately Hypofractionated Postoperative Radiotherapy for Prostate Cancer Focused on Treatment Related Toxicity

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Abstract

This retrospective study on postoperative hypofractionated RT for prostate cancer (110 patients, 103-month follow-up) reveals low rates of severe toxicities. Ten-year survival rates are encouraging (77.3% overall, 53.3% biochemical recurrence-free, 76.7% metastasis-free). These results suggest that hypofractionated RT is a safe and effective alternative, offering convenience and reduced workload compared to conventional RT.

Introduction: To retrospectively report long term outcomes following postoperative hypofractionated radiotherapy (RT) for prostate cancer, emphasizing treatment related toxicity. **Material and Methods:** Patients for whom adjuvant or salvage RT was indicated after prostatectomy were treated with a course of moderate hypofractionation consisting in the delivery of 62.5 Gy in 25 fractions (2.5 Gy per fraction) on the prostate bed in 5 consecutive weeks ($EQD2_{1.5} = 70$ Gy) by means of 3D-CRT in most of them. Androgen deprivation therapy (ADT) was allowed at physician's discretion. Patients were evaluated for urinary and rectal complications according to the Common Terminology Criteria for Adverse Events v4 (CTCAE v.4). Overall survival (OS), biochemical recurrence free survival (bRFS), and metastasis-free survival (MFS) were estimated using the Kaplan–Meier method. **Results:** One hundred and ten patients with a median age of 67 years (range 51-78) were enrolled. The majority of them (82%) had adverse pathologic features only, while 31 (28%) had early biochemical relapse. Median PSA level before RT was 0.12 ng/mL (range 0-9 ng/mL). Median time from surgery was 4 months (range 1-136 months). Twenty-eight patients (25.4%) also received ADT. At a median follow up of 103 months (range 19-138 months), late Grade 3 and Grade 4 rectal toxicity were 0.9% (1 case of hematochezia) and 0.9% (1 case of fistula), respectively, while late Grade 3 GU side effects (urethral stenosis) occurred in 9 cases (8%). No late Grade 4 events were observed, respectively. Ten-year OS, b-RFS and MFS were 77.3% (95%CI: 82.1%-72.5%), 53.3% (95%CI: 59.9%-47.6%), and 76.7% (95%CI: 81.2%-72.2%), respectively. **Conclusion:** Our study provides long term data that a shortened course of postoperative RT is as safe and effective as a long course of conventionally fractionated RT and would improve patients' convenience and significantly reduce RT department workloads.

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Introduction

Major randomized controlled trials of moderate hypofractionation for prostate cancer (PCa) have shown similar efficacy and toxicity to conventionally fractionated regimens,[1-4] and current guidelines now recommend moderate hypofractionation for the vast majority of patients. Unlike for the intact disease, such strategy is slow to be adopted in the postoperative setting due to concerns that too high of a radiation dose to the clinical target volume (CTV) encompassing the bladder neck and vesicourethral anastomosis may lead to tissue injury,[5] resulting in an increased risk of severe late toxicities, especially genito-urinary (GU), such as incontinence, hematuria and urethral stenosis, which may significantly affect patients' quality of life.

Conversely, since the alpha/beta ratio for PCa has estimated to be as low as 1.5 Gy[6-8] — significantly lower than the 3 Gy value estimated for late complications[9] — the delivery of the same equiv-

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alent total dose at 2 Gy per fraction using a hypofractionation regimen should have a sparing effect on late responding normal tissues also postoperatively, apart from the practical benefits of reducing the treatment costs and number of sessions.

As a matter of fact, despite the use of advanced techniques, such as intensity-modulated radiation therapy (IMRT) and image-guided radiation therapy (IGRT), late toxicities after radiation therapy (RT) to the prostate bed are not uncommon[10-12] even when a conventionally fractionated regimen is the preferred option. Moreover, the incidence of late side effects, and especially GU, continues to raise with time after postoperative RT and long-term data from studies with mature follow-up are lacking. Although a number of predictive factors has been associated to the risk of late GU toxicity, such as the total dose,[13,14-16] the elderly population,[17] and a high-dose region in the bladder,[10] the effects of hypofractionation on late toxicity remain unclear. We herein reported on a long-term bi-institutional data on postoperative RT using a moderately hypofractionated schedule, emphasizing the treatment related toxicity.

Methods

Eligibility

Patients eligible for this study must have had adenocarcinoma of the prostate treated with radical prostatectomy (any type of radical prostatectomy was permitted, including retropubic, perineal, laparoscopic or robotically assisted). Additional factors were required as inclusion criteria, such as adverse pathologic features (pathologic T3/T4 disease with or without positive surgical margins) and/or a rising prostate-specific antigen (PSA) level > 0.1 ng/mL on at least 2 consecutive measurements; and no distant metastases at conventional imaging. Androgen deprivation therapy (ADT) was allowed, and its prescription was left at the physician's discretion. The study was approved by the IRB of the participating centers and all patients provided written informed consent prior to the treatment in agreement with the Declaration of Helsinki.[18]

Radiotherapy plan

Postoperative RT was mainly delivered with image-guided three-dimensional conformal RT (3D-CRT) to a total dose of 62.5 Gy in 25 fractions (2.5 Gy per fraction) on the prostate bed in five consecutive weeks [Equivalent Dose in 2Gy Fractions considering an α/β of 1.5Gy ($EQD2_{1.5}$)= 70 Gy]. All patients underwent computed tomographic (CT) simulation with a full bladder and empty rectum, in the supine position placed in an appropriate device (Combifix, Civco Medical Solutions, Coralville, IA, USA). The CTV was delineated as per the Radiation Therapy Oncology Group (RTOG) Consensus Guideline and the planning treating volume (PTV) was obtained by adding 1 cm margins, except posteriorly, at rectum interface, where 5 mm was used. The optimization was driven with the aim of delivering the prescribed dose to at least 95% of the PTV according to International Commission on Radiation Units 50/62 guidelines. In 103 (93.7%) patients, the treatment was performed with a 3D-CRT technique with photons from Linear Accelerator 6-15 MVs, 6 fields, Multileaf collimator. Daily portal imaging, matched with digitally reconstructed radiographs, was used to check the anatomical reproducibility. Seven patients (6.3%) were treated with Volumetric Modulated Arc Therapy (VMAT) consisting of two 6 MV or 10 MV full arcs optimized to ensure that the 95% isodose covered at least 95% of the PTV.

Endpoints

The primary endpoints of the study were acute and late gastrointestinal (GI) and GU toxicities. Secondary endpoints were biochemical control, metastasis-free survival (MFS) and overall survival (OS). Patients were evaluated prior to radiation, weekly during treatment and at 3-months interval during the first 2 years of follow up and every 6 months thereafter. GI and GU toxicity monitoring was assessed by Common Terminology Criteria for Adverse Events v4. Any increase in grade from baseline was considered toxicity related to treatment and calculated for the acute (90 days from the start of RT) and late phase (beyond 90 days). Evaluation of incontinence was incorporated in the GU toxicity following the Common Criteria Toxicity. Death of any cause was considered for overall survival (OS). Patients were censored at the time of the specific event.

Statistical Analysis

We calculated logistic regression for the predictors of acute toxicity. Conversely, Kaplan-Meier curves were used to calculate the actuarial rates of the late events. If an event exceeded the incidence of 3%, the univariate Cox proportional-hazards regression survival analysis was performed. Factors with $P \leq .20$ in the univariate analyses were included in the multivariate Cox regression. MedCalc® v22.009 (MedCalc Software Ltd, Ostend, Belgium; https://www.medcalc.org; 2022) was used for statistical analysis. We considered a P-value $< .05$ for statistical significance.

Results

Between January 2011 and June 2017, a total of 110 patients with a median age of 67 years (range 51-78) were enrolled at 2 institutions. The majority of them (82%) had adverse pathologic features only, while 31 (28%) showed early biochemical relapse. Median PSA level before prostatectomy and RT was 8.6 ng/mL (range 0.3-47 ng/mL) and 0.12 ng/mL (range 0-9 ng/mL), respectively. The median PTV was 150 cc (range 68-364.8 cc). Median time from surgery was 4 months (range 1-136 months). Twenty-eight patients (25.4%) also received ADT. Patients and treatment characteristics are summarized in Table 1.

At a median follow up of 103 months (range 19-138 months), late Grade 3 and Grade 4 rectal toxicity were 0.9% (one case of hematochezia) and 0.9% (one case of fistula), respectively, while late Grade 3 GU side effects (urethral stenosis) occurred in 9 cases (8%). No late Grade 4 events were observed, respectively (Table 2). The cumulative rate of 5- and 10-year late ≥Grade 2 GU toxicity was 0.9% (95%CI: 0%-1.8%) and 19.4% (95%CI: 14.5%-24.3%), respectively. The same features for 5- and 10-year late ≥Grade 2 GI toxicity were 2.9% (95%CI: 1.3%-4.5%) and 6.8% (95%CI: 4.1%-9.5%), respectively. On multivariate analysis a statistically significant correlation was found between a time interval from surgery to postoperative RT <12 months and late ≥Grade 2 GI and GU side effects, and between the number of removed lymphnodes and late ≥Grade 2 GU toxicity (Table 3).

Table 1 Patient and Treatment Characteristics

Age at RT (year)	**67 (51-78)**
Gleason score	**Median 7 (3-9)**
≤6	27
7	60
8–10	23
Pathological T stage	
≤T2c	35
T3a	43
T3b	32
Surgical margin +	**73 (66%)**
Fraction dose (Gy)	**2.5**
Total dose (Gy)	**62.50**
Total dose in $EQD2_{1.5}$ (Gy)	**71.4**
Time from RP to RT (month)	**Median 4 (1-136)**
Preoperative initial PSA (ng/ml)	**Median 8.6 (0.3-47)**
Postoperative PSA (ng/ml)	**Median 0.09 (0-2.8)**
PSA at BCR after RP (ng/ml)	**Median 0.12 (0-9)**
Follow-up time (month)	**Median 103 (19-138)**
ADT use	**28 (25%)**
Patients with BCR after SRT	**44 (40%)**
Salvage ADT	**23 (21%)**

ADT, Androgen Deprivation Therapy; BCR, BioChemical Recurrence; $EQD2_{1.5}$, Equivalent Dose in 2Gy Fractions considering an α/β, 1.5Gy; PSA, Prostate Specific Antigen; RT, Radiation Therapy; RP, Radical Prostatectomy; SRT, Salvage Radiation Therapy.

Median PSA following RT was 0.09 ng/mL (95%CI: 0-2.8). Five and 10-years OS was 94.5% (95%CI: 96.1%-92.4%) and 77.3% (95%CI: 82.1%-72.5%), respectively. Five and 10-years biochemical-Relapse-Free Survival was 70.5% (95%CI: 74.9%-66.1%) and 53.3% (95%CI: 59.9%-47.6%), respectively. Five and 10-years MFS was 88.8% (95%CI: 91.8%-85.8%) and 76.7% (95%CI: 81.2%-72.2%), respectively. The recurrence pattern was characterized by progression in 10 lymph nodal sites and 8 bone sites.

Discussion

To our knowledge, this study has the longest follow up among those reporting on outcomes of patients treated with postoperative hypofractionated RT. The benefit of a hypofractionated radiation course to the prostate bed appears to span the whole cohort irrespective of the adjuvant or salvage setting. Notably, the radiation planning technique used for most of the patients was 3D-CRT, rather than the safer and newer IMRT and IGRT established in current guidelines.[19-20] Moreover, the wide planning margins around the CTV to account for uncertainties due to organ motion would be considered large by the present standards, thus potentially resulting in higher absolute rates of toxicity than what would be expected with modern treatment techniques. Overall, our findings could be seen as a proof of the radiobiologic premise underlying hypofractionation for PCa, which appears to hold value in the postoperative setting. Indeed, the incidence of late complications – and namely late ≥Grade 2 GU toxicity – did not exceed the toxicity rates reported with conventional fractionation by means of advanced techniques,[13,21-23] suggesting that these radiobiological assumptions are in fact valid, and likely matters as much as the use of modern and contemporary treatment planning and delivery. Similarly, one of the landmark randomized trials in the setting of intact PCa, known as HYPO-RT-PC,[24] used 3D-CRT to deliver extremely hypofractionated RT in 80% of the enrolled patients and demonstrated the oncologic non-inferiority and the lack of differences in late toxicity compared to normofractionated RT, thus emphasizing the radiobiological rationale behind the use of ultra-hypofractionation, rather than a direct assessment of modern and more precise stereotactic body radiotherapy (SBRT).

Few data are available on the independent value of fractional doses on late toxicities when hypofractionated RT is applied postoperatively: a large pooled retrospective series employed a daily fraction of 2.0 Gy,[25] and most of large retrospective studies did not clarify

Table 2 Late Genitourinary (GU) and Gastrointestinal (GI) Toxicities Among 110 Patients After Postoperative Hypofractionated RT

Late GU toxicity	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**
	N (%)	**N (%)**	**N (%)**	**N (%)**
Hematuria		8 (7.2%)	1 (0.9%)	
Urinary incontinence	25 (22.5%)	2 (1.8%)	1 (0.9%)	
Urinary tract obstruction	3 (2.7%)		6 (5.4%)	
Urinary frequency	11 (9.9%)			
Non-infectious Cystitis	1 (0.9%)			
Sexual Disfunction	15 (13.5%)	1 (0.9%)	1 (0.9%)	
Total	55 (49.5%)	11 (9.9%)	9 (8.1%)	0 (0%)
Late GI toxicity	**N (%)**	**N (%)**	**N (%)**	**N (%)**
Fistula				1 (0.9%)
Hematochezia	4 (3.6%)	3 (2.7%)	1 (0.9%)	
Tenesmus/ Proctitis	1 (0.9%)			
Fecal Incontinence		1 (0.9%)		
Unknown	3 (2.7%)		1 (0.9%)	
Total	8 (7.2%)	4 (3.6%)	2 (1.8%)	1 (0.9%)

Table 3 Univariate and Multivariate Analyses of Late Grade ≥2 Events After Postoperative Hypofractionated RT

	Predictor	Univariate	*P*-value	Multivariate	*P*-value
		HR (95%CI)		HR (95%CI)	
Genitourinary	N° of removed lymph nodes	0,86 (0,73 to 1,00)	0,0592	0,82 (0,70 to 0,97)	**0,0210**
	OTT	0,88 (0,73 to 1,05)	0,1806	1,05 (0,84 to 1,30)	0,6604
	Time from surgery to RT ≤ 12 months	0,22 (0,08 to 0,66)	**0,0065**	0,07 (0,02 to 0,29)	**0,0002**
Gastrointestinal	N° of removed lymph nodes	0,80 (0,63 to 1,02)	0,0825	0,99 (0,80 to 1,22)	0,9584
	Cardiovascular Disorders	0,29 (0,05 to 1,8)	0,1879	0,11 (0,01 to 1,57)	0,1050
	Time from surgery to RT ≤ 12 months	0,08 (0,02 to 0,37)	**0,0012**	0,05 (0,00 to 0,71)	**0,0278**

CI, confidence interval; HR, hazard ratio; OTT, overall treatment Time; RT, radiation therapy.

the doses per fraction.[25-30] A systematic review on postoperative hypofractionated RT for PCa, including 1,208 patients from 17 eligible studies with a median follow-up of 30 months, showed conflicting results in late GU toxicity, and concluded that further evidence was needed before implementing this approach in clinical practice.[31] Recent prospective and retrospective trials have reported reasonable rates of late side effects when postoperative hypofractionated regimens were delivered using modern techniques.[32-37] Other studies have attempted to compare toxicity and efficacy outcomes in contemporaneous PCa patient cohorts treated with hypofractionated or conventional post-prostatectomy RT:[38,39] Tandberg et al.[38] examined 461 patients with a median follow-up of 38.6 months and found that the former schedule was not associated with late Grade ≥2 GU toxicity on multivariate analysis. Similarly, an analysis of a large single-centre cohort treated with hypofractionation with advanced RT techniques compared with conventional fractionation revealed that the shorter regimen did not yield different outcomes in terms of biochemical control and toxicities at a median follow-up of 23 months.[39] Overall, the short follow-up, typically limited to less than 5 years in all these studies, prevents from reaching any firm conclusions about the long-term safety of this strategy. A non-randomized, exploratory analysis of the RADICALS-RT trial,[40] where 634 patients were planned for adjuvant RT with either 66 Gy in 33 fractions over 6.5 weeks or 52.5 Gy in 20 fractions over 4 weeks, did not show severe toxicity nor significant differences in toxic effects or in patient-reported outcomes between the 2 schedules at a median follow up of 4.9 years. Our findings clearly show that a longer observation is required, given the potential for continued increases in late toxicities, especially GU, far beyond this timepoint.

A recent retrospective study showed higher than anticipated rate of late GI and GU toxicity of post-prostatectomy radiobiologically dose-escalated hypofractionated radiotherapy in 16 daily fractions.[41] Similar findings were reported in another retrospective study[42] in which a marked increase in the rate of 5-year severe late GU toxicity was observed as the daily dose per fraction was increased from 1.80 to 2.35 Gy and then to 2.55 Gy. In both the studies however, no information about the doses received by the bladder was provided, although it is well known that the risk of late severe bladder toxicity is related to the maximal dose as well as the dose received to subvolumes of the bladder receiving some given dose level (for example, the volume receiving 65Gy and 70Gy should be <50% and 35%).[43] Furthermore, a significant number of patients in the aforementioned studies received whole pelvis irradiation, which might have potentially accumulated the dose received by the bladder, and then the potential risk of GU toxicity. Noteworthy, our analysis shows that a time interval from surgery to postoperative RT ≤12 months significantly lessened the risk of late ≥G2 GI and GU side effects, thus confirming that adjuvant RT (when indicated) could be safely administered within 1-year post-prostatectomy after side effects have stabilized or improved, as recommended in current guidelines.[19-20] Unexpectedly, the number of removed nodes seemed to have a protective effect on late ≥Grade 2 GU toxicity.

Our study is not devoid of limitations: the practice of treating the prostate bed-only in this cohort dates back to the publication of the RTOG 0534 SPPORT trial,[44] which showed that extending salvage RT to treat the pelvic lymphnodes in combination with short-term ADT resulted in meaningful reductions in progression for patients with a detectable or rising PSA after prostatectomy. Similarly, the use of an $EQD2_{1.5}$ >70 Gy was based on the assumption that postoperative dose escalation was independently associated with progression-free survival[45] until recent level 1 evidence proved otherwise.[46,47] Likewise, the increasing use of more prostate-specific positron emission tomography imaging tracers in the current clinical practice might have helped in excluding distant metastases even at low PSA levels, thus affecting treatment recommendations. Ultimately, the inherent retrospective nature of this study along with the limited patients' cohort and the use of non-contemporary radiation techniques, as well as the absence of patients' self-assessment questionnaires to evaluate health-related quality of life, which might have turned out in an overall underestimation of toxicity, represent clear caveats in the interpretation of the findings herein presented.

Conclusion

Our study provides long term data that a shortened course of postoperative RT is as safe and effective as a long course of conventionally fractionated RT and would improve patients' convenience and significantly reduce radiotherapy department workloads. More robust data from large non-inferiority trials are needed to confirm this strategy but will probably have a limited effect on clinical practice by the time they will be published. Indeed, a number of trials of ultra-hypofractionated RT[48-52] are ongoing and already show promising outcomes at least at early timepoints, thus enhancing the cost-effectiveness profile of hypofractionation.

Clinical Practice Points

- Major trials support moderate hypofractionation for prostate cancer, but its adoption postoperatively has been slow due to concerns about increased genitourinary toxicity. Existing knowledge endorses conventional RT but acknowledges logistical challenges and extended treatment durations.
- This long-term study, with a median follow-up of 103 months, establishes the safety and efficacy of postoperative hypofractionated RT. The research demonstrates low rates of late toxicities, particularly in genitourinary complications. Noteworthy 10-year overall survival (77.3%) and biochemical recurrence-free survival (53.3%) attest the benefits of hypofractionation.
- The findings show that postoperative hypofractionated RT is a viable, safe, and effective alternative to conventional methods. It offers equivalent safety with reduced treatment duration and associated costs. The study suggests that initiating postoperative RT within the first year after surgery is safe, particularly when late toxicities are a concern. This research has the potential to reshape clinical practices, offering a more convenient and efficient approach to postoperative RT for prostate cancer patients. Ongoing trials on ultra-hypofractionation further contribute to the evolving landscape, indicating potential advancements in cost-effective and patient-friendly treatment modalities. Continued research and integration of these findings into practice could positively impact patient outcomes and resource utilization in the near future.

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Ethics Approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

The study was approved by the IRB of the participating centers.

Informed consent was obtained from all individual participants involved in the study.

Availability of Data and Materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Disclosure

The authors have no relevant financial or non-financial interests to disclose.

CRediT authorship contribution statement

Alessandra Castelluccia: Writing – review & editing, Data curation, Conceptualization. **Francesco Tramacere:** Writing – review & editing, Data curation, Conceptualization. **Riccardo Ray Colciago:** Writing – review & editing, Formal analysis. **Marzia Borgia:** Writing – review & editing. **Alessandra Sallustio:** Writing – review & editing. **Tiziana Proto:** Writing – review & editing. **Maurizio Portaluri:** Supervision. **Prof Stefano Arcangeli:** Writing – original draft, Validation, Supervision.

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