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Risk-adapted intensification therapy in high-risk prostate cancer: how relevant is the role of radiation dose

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Abstract

Background/Purpose Dose escalation has demonstrated a significant improvement in biochemical recurrence in high-risk prostate cancer (HRPCa). We evaluated the impact on overall survival (OS) of dose intensification with external beam radiation therapy (EBRT) in a cohort of HRPCa patients treated in a single institution.

Methods and Materials Between January 1997 and January 2024, a total of 1451 consecutive localized PCa patients were treated with primary EBRT alone as part of a prospective institutional program for risk-adapted dose-intensification radiotherapy. For the present analysis, we specifically selected a cohort of 424 consecutive HRPCa patients with a minimum follow-up (FU) of 5 years. The median RT dose was 79.2 Gy (interquartile range [IQR] 74.9–80.3). Short and long-term hormones were administered in 56 (13%) and 350 (83%) of patients respectively. Kaplan–Meier curves were used to calculate overall survival (OS). Cumulative incidence of distant metastasis (DM), and cause specific survival (CSS) were estimated using competing risk regression.

Results Median patient age was 69 years (IQR 65–72) and median FU was 118 months (IQR 88.0–135.0). At the time of analysis, 54 of 424 patients (13%) had died. The leading cause of death was cardiovascular disease in 16/54 patients (4%), followed by PCa in 15 patients (3%). At 10 and 15 years, the KM estimated OS rates were 91% (95% CI 87–93) and 71% (95% CI 61–79), respectively. The corresponding rates for MFS were 87% (95% CI 83–90) and 60% (95% CI 49–68), and for CSS were 97% (95% CI 95–99) and 90% (95% CI 49–81), respectively. In multivariate analysis, when adjusted for patient age, T stage, Gleason/ISUP group, PSA and length of hormone-therapy, higher radiation dose remained significantly associated with an improved OS (HR 0.89; 95% CI 0.84–0.94), MFS (HR 0.94; 95% CI 0.90–0.98) and CSS (HR 0.89; 95% CI 0.84–0.94).

Conclusions The present study confirms that radiation dose intensification is paramount in the treatment of HRPCa with independence of duration of ADT.

Keywords High-risk prostate cancer, Radiation dose escalation, Radiotherapy, Overall survival, Metastasis-free survival, Androgen deprivation

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Introduction

High-risk localized prostate cancer (HRPCa) is characterized by substantial heterogeneity and a lack of predictive models to facilitate an individualized, risk-adapted therapeutic approach. Multimodal therapy, incorporating high-dose RT (RT) combined with long-term androgen deprivation therapy (LADT), is currently recognized as a widely accepted standard-of-care treatment. Additionally, for patients with very high-risk or locally advanced disease, the inclusion of abiraterone is considered to further enhance treatment efficacy [1].

The importance of RT dose intensification in PCa has been demonstrated in several randomized controlled trials [2–5]. These studies have proved that dose escalation improves biochemical recurrence outcomes. However, they have failed to establish a significant benefit in overall survival (OS). Only one trial conducted in the 1990s, which included patients across all risk groups, reported a sustained improvement in PCa-specific mortality after a median follow-up of 14 years [6]. Recently, the GETUG-AFU18 trial, presented at the ASCO 2024 meeting, revealed that escalating the dose to 80 Gy in patients with HRPCa was associated with improved OS and cancer-specific survival (CSS) (HR 0.61) compared to 70 Gy, without a concomitant increase in long-term toxicity [7].

In this study, we aimed to determine how relevant is the impact of EBRT dose escalation on key endpoints, such as OS, metastasis-free survival (MFS), CSS and late toxicity, in a prospective cohort of HRPCa patients treated in a real-world setting and with a minimum FU of 5 years.

Patients and methods

Patients and treatment characteristics

Between January 1997 and January 2024, a total of 1451 consecutive male patients with localized PCa were treated with primary EBRT alone as part of a prospective institutional program for risk-adapted dose-intensified RT. For the present analysis, we specifically selected a cohort of 424 consecutive HRPCa patients, defined according to the National Comprehensive Cancer Network (NCCN) criteria and the following eligibility requirements: histological diagnosis of acinar adenocarcinoma, no evidence of regional nodal or distant disease on conventional imaging, a radiation dose exceeding 66.0 Gy, no prior, concomitant or adjuvant treatment with chemotherapy or novel androgen receptor pathway inhibitors (ARPIs), no combined treatment with brachytherapy, and a minimum follow-up (FU) period of five years. Exclusion criteria included the presence of other histologies, T4 or N1 tumours.

Pre-treatment diagnostic evaluations included blood chemistry analysis, digital rectal examination, transrectal ultrasound, magnetic resonance imaging (MRI) of prostate since 2007, and conventional imaging for clinical staging (computed tomography of the thorax, abdomen and pelvis, and bone scan).

Treatment

All patients were treated with EBRT alone within a framework of a continuous and progressive dose-intensification institutional program. The median RT dose was 79.2 Gy (interquartile range [IQR]: 74.9–80.3 Gy). Treatment was delivered in daily fractions of 1.8–2.0 Gy in 407 cases, while alternative moderated fractionation schemes were employed in 17 cases. The first 274 patients (65%) received treatment with three-dimensional conformal RT (3D-CRT). From 2007 onward, the subsequent 150 patients (35%) were treated with intensity-modulated/image-guided RT (IMRT/IGRT), using intra-prostatic gold fiducial markers to enhance the RT dose prescription to 80.0 Gy. The techniques for simulation, treatment planning, and delivery for both 3D-CRT and IMRT have been described in detail elsewhere [8]. The clinical target volume primarily included the prostate gland and the proximal two-thirds of the seminal vesicles. Given the controversy regarding the role of prophylactic pelvic radiotherapy at the time, elective pelvic node radiotherapy (ENRT) was at the discretion of the physician and administered to 117 patients at doses of 45.0–50.0 Gy. Androgen deprivation was given as part of two consecutive multi-institutional trials [10, 11]. Short term ADT (6 months, STADT) and LADT (24–36 months) were administered in 56 (13%) and 350 (83%) of patients respectively. Table 1 summarizes the patient and treatment characteristics.

All patients were continuously monitored from the time of treatment completion, and the duration of FU was calculated from the date of diagnosis. FU visits, including digital rectal examinations, PSA measurements, and assessments of specific genitourinary (GU) and rectal morbidity, were conducted every 3–6 months for four years, and annually thereafter. CT, bone scans, and chest X-rays were scheduled for re-staging following PSA failure.

Outcomes and definitions

OS was defined as the time from diagnosis to death from any cause or censoring at the date of the last contact. MFS was defined as the time from diagnosis to metastasis or death from any cause, whichever occurred first, or as censored at the date of the last follow-up. CSS included all deaths from PCa or treatment-related complications, as well as deaths from unknown causes in patients with active cancer, excluding those with only biochemical

Table 1 Summary of patients' and treatment characteristics

	N	N = 424
Follow-up (months)	424	
Median [Q1, Q3]		118 [88, 135]
Patient age (years)	424	
Median [Q1, Q3]		69 [65, 72]
> 65		303 (71%)
≤ 65		121 (29%)
Clinical T stage	424	
T1		29 (7%)
T2		124 (29%)
T3		271 (64%)
PSA at diagnosis (ng/mL)	422	
Median [Q1, Q3]		18.70 [9.38, 33.50]
< 10		111 (26%)
10–20		109 (26%)
> 20		202 (48%)
Missing		2
Gleason score/ISUP grade groups	419	
1		138 (33%)
2		93 (22%)
3		67 (16%)
4		81 (19%)
5		40 (10%)
Missing		5
Number of risk factors	418	
One factor		274 (66%)
Two factors		118 (28%)
Three factors		26 (6%)
Missing		6
Radiation dose (Gy) (1.8–2/Fraction)	407	
Median [Q1, Q3]		[74.9–80.3]
≤ 74 Gy		120 (29%)
> 74 Gy		287 (71%)
Not evaluated (2.7 Gy/Fraction)		17
IMRT/IGRT		150/424 (35%)
Elective pelvic node radiotherapy		117/424 (28%)
Androgen deprivation therapy	424	
No		18 (4%)
STADT		56 (13%)
LTADT		350(83%)

**ISUP* International society of urological pathology; #*IMRT/IGRT* Intensity modulated radiotherapy/image guided radiotherapy; $*STAD* Short-term androgrendeprivation therapy; &: Long-term androgen deprivation therapy

failure. The cause of death was recorded by the treating physician and reviewed in clinical records if necessary.

Late toxicity assessments (occurring > 90 days after RT and graded according to the RTOG/EORTC late radiation morbidity scheme, were performed at each follow-up visit. The Common Terminology Criteria for Adverse Events (CTCAE) scoring system was used for specific conditions, such as urethral stenosis, incontinence, rectal bleeding, and haematuria. The highest recorded acute and chronic urinary toxicity for each patient was used in the analysis.

Statistics

Quantitative variables were expressed as mean and standard deviation (SD) or median and interquartile range (IQR) for the variables with non-normal distribution. For qualitative variables, frequency and proportions were used.

The OS analysis was done using Kaplan–Meier curves, and the treatment groups were compared using the log-rank (Mantel-Cox) test and the Cox proportional-hazards model to compute hazard ratios (HRs). The cumulative incidence curves of MFS and CSS were assessed using competing risk regression. For cancer-specific death and MFS, comparisons between groups were conducted using the Fine and Gray model to account for the competing risk of non-PCa mortality and estimate sub-distribution hazard ratios (HRs). Death from any cause was considered a competing risk [9].

Univariate and multivariate Cox regression analysis (MVA) was performed to assess the association between clinical outcomes and treatment, adjusting for predefined relevant clinical and demographic factors. The variables included in the analysis were patient age (both continuous and categorical), T stage, pre-treatment PSA (continuous and categorical), Gleason score -empirically adapted to International Society of Urological Pathology (ISUP) groups-, duration of ADT, and radiation dose (continuous and categorical). Patients treated with ENRT (117) were not excluded from the analysis. Variables with a p-value < 0.1 in univariate analysis, as well as those with $p \geq 0.1$ but deemed clinically relevant, were included in the MVA. Two-sided p-values < 0.05 were considered statistically significant. Statistical analyses were conducted using R v.4.3.2

Outcomes

The median patient age was 69 years (IQR 65–72), and the median FU was 118 months (IQR 88–135). At the time of analysis, 54 out of 424 patients (13%) had died. The leading cause of death was cardiovascular disease in 16 of 54 patients (4%), followed by PCa in 15 patients (3%) and other malignancies in 9 patients (2%). Biochemical failure (BF) (nadir + 2 criteria) occurred in 101 patients (24%), with a median time to event of 112 months (IQR 80–130). Of the 101 patients with BF, 97 received salvage therapy, primarily with hormone therapy (51 patients, 53%). Distant metastasis developed in 41 patients (10%), with a median time to event of 113 months (IQR 87–139).

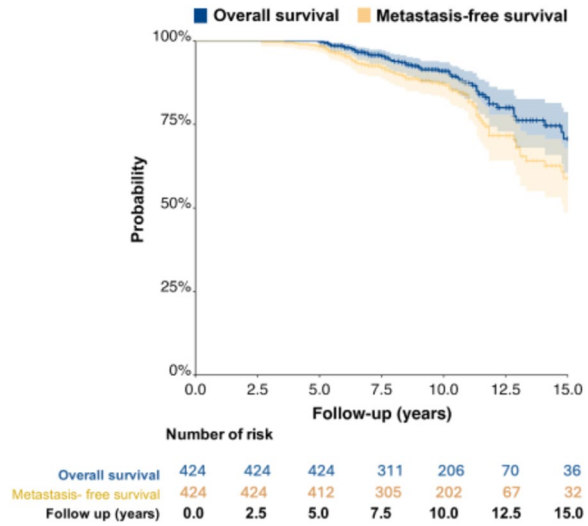


Fig. 1 Kaplan Meier curves for overall survival and metastasis-free survival

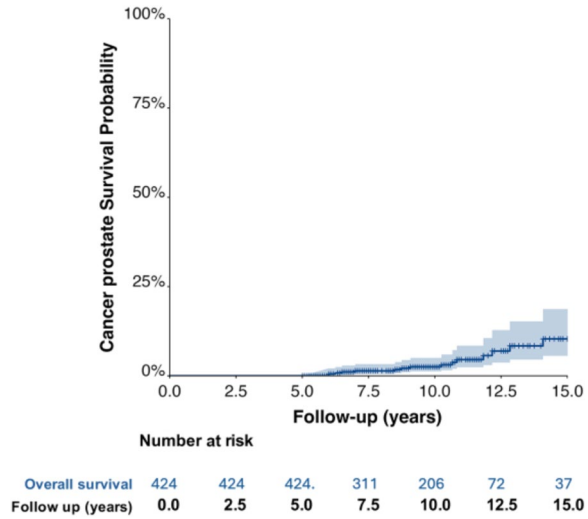


Fig. 2 Cumulative incidence of cause specific mortality from the Fine and Gray models

Local metastasis-directed therapy (MDT) combined with hormone therapy was administered in 8 patients, while salvage doublet therapy with docetaxel or androgen receptor pathway inhibitors (ARPIs) was administered as part of a clinical trial to 10 patients.

At 10 and 15 years, the Kaplan–Meier estimated OS rates were 91% (95% CI 87–93) and 71% (95% CI 61–79), respectively. The corresponding rates for MFS were 87% (95% CI 83–90) and 60% (95% CI 49–68), while those for CSS were 97% (95% CI 95–99) and 90% (95% CI 49–81), respectively (Figs. 1 and 2). The 10-year estimated incidence of grade ≥2 late urinary complications was 13%, while that of grade ≥2 late rectal toxicity was 10%. There were only nine cases (2%) of grade 3 genitourinary (GU) toxicity and two cases of grade 4 GU complications. Regarding gastrointestinal (GI) toxicity, there were four cases (0.9%) of grade 3 toxicity, with no cases of grade 4 toxicity reported.

The results of the univariate and MVA are summarized in Tables 2 and 3 and Appendices 1 and 2. For clarity, we decided to exclude from the radiation-dose analysis the 17 patients treated with a fractionation different from 1.8–2 Gy per fraction. The univariate analysis for OS showed that higher radiation dose (as continuous variable, HR 0.89, 95% CI 0.85–0.93, $p < 0.001$), low patient age (HR 1.07, 95% CI 1.02–1.12, $p = 0.010$), and LTADT (HR 0.26, 95% CI 0.12–0.58, $p < 0.001$) were significantly associated with an improvement in OS, whereas T stage, PSA levels, and Gleason/ISUP grade groups were not. Unexpectedly, patients treated with ENRT experienced significantly more events than those who did not receive ENRT ($p < 0.001$). This finding was deemed a bias-related artifact (patients with poorer prognosis and lower radiation dose) and was therefore excluded from the MVA.

In the MVA, when adjusted for patient age and length of hormone-therapy, higher radiation dose remained significantly associated with an improved OS (HR 0.89, 95% CI 0.84–0.94).The 10-year OS was 95% for patients receiving RT at doses >74 Gy, compared to 81% for those receiving lower RT doses (supplementary information in Appendix 1 and 2). With regard to MFS, higher radiation dose was also associated with a significant improvement in MFS, in both univariate and MVA (HR 0.94, 95% CI 0.90–0.98), together to Gleason/ISUP grade groups 4–5 (HR 1.66, 95% CI 1.01–2.73) (Figs. 3 and 4, Appendices 1 and 2).

Finally, although the number of events was low, we also observed a significant improved CSS with higher radiation doses (HR: 0.84; 95% CI 0.84–0.94) (Fig. 5, Appendix 1).

Discussion

The results of the present study provide new evidence highlighting the critical role of dose intensification with EBRT in treating HRPCa in a real-world setting, beyond the controlled selection criteria of clinical trials. In this long-term analysis (median FU of 118 months) of a prospective cohort of HRPCa patients, we proved a significant benefit of dose-escalation with EBRT on MFS, OS and CSS. This survival benefit was irrespective of ADT length, patient age and other tumour related factors, without compromising urinary or rectal function. The late GU and GI toxicity rates remained low, probably due to the incorporation of IMRT/IGRT techniques to intensify the RT dose from 76.0 to 80.0 Gy.

Table 2 Univariate and multivariate Cox analysis for overall survival

Variables	N	Univariate analysis		Multivariate analysis	
		***p* value**	**HR (95% CI)**	***p* value**	**HR (95% CI)**
Patient age continuous	424	0.010	1.07 (1–02-1.12)	0.059	1.05 (0.99–1.10)
Radiation dose (Gy) continuous	407	< 0.001	0.89 (0.85–0.93)	< 0.001	0.89 (0.84–0.94)
ADT	424				
No	18	–	–		–
STAD	56	0.22	0.58 (0.24–1.38)	0.37	0.67 (0.28–1.60)
LTAD	350	< 0.001	0.26 (0.12–0.58)	0.12	0.52 (0.23–1.19)
PSA ng/ml continuous	424	0.65	0.99 (0.99–1.00)		
Gleason/ISUP grade group	419				
1–2	231	-	-		
3	67	0.87	0.93 (0.38–2.26		
4–5	121	0.22	1.47 (0.80–2.68)		
T stage	424				
T1	29	-	-		
T2	124	0.41	1.86 (0.43–8.07)		
T3	271	0.60	1.47 (0.35–6.14)		

**HR* Hazard ratio; #*CI* Confidence interval; ***ADT* Androgen deprivation therapy; ¢*STADT*: Short-term androgen deprivation therapy; €*LTADT* Long-term androgen deprivation therapy; ***ISUP* International society of urological pathology

Table 3 Univariate and multivariate Cox analysis for metastasis-free survival

Variables		Univariate analysis		Multivariate analysis	
		***P*value**	**HR (95% CI)**	***P* value**	**HR (95% CI)**
Patient age Continuous	424	0.36	0.1.08 (0.98–1.05)	–	
Radiation dose (Gy) Continuous	407	0.003	0.94 (0.91–0.98)	0.003	0.94 (0.90–0.98)
ADT	424				
No	18	–	–	–	
STAD	56	0.49	0.74(0.32–1.71)		
LTAD	350	0.06	0.48 (0.23–1.02)		
PSA ng/ml Continuous	424	0.54	0.99 (0.99–1.0)	-	
Gleason/ISUP Grade	419				
1–2	131	–	–	–	–
3	67	0.42	1.30 (0.68–2.50)	0.24	1.50 (0.77–2.88)
4–5	121	0.02	1.80 (1.10–2.93)	0.05	1.66 (1.01–2.73)
T stage	424				
T1-2	153	–	–	–	
T3	271	0.76	1.07 (0.66–1.75)		

**HR* Hazard ratio; #*CI* Confidence interval; ***ADT* Androgen deprivation therapy; ¢*STADT* Short-term androgen deprivation therapy; €*LTADT* Long-term androgen deprivation therapy; ***ISUP* International society of urological pathology

To our knowledge, the MDACC dose-escalation trial, with a recent update reporting a median follow-up of 14 years, and the GETUG 18 trial, presented at the 2024 ASCO meeting, are the only phase III studies that have demonstrated a significant improvement in OS and CSS with dose escalation beyond 78 Gy. The aim of our retrospective study was to underscore the importance of high-dose EBRT, highlighting that each additional Gy (HR 0.89) contributes meaningfully to treatment outcomes in HRPCa, irrespective of the use or duration of ADT.

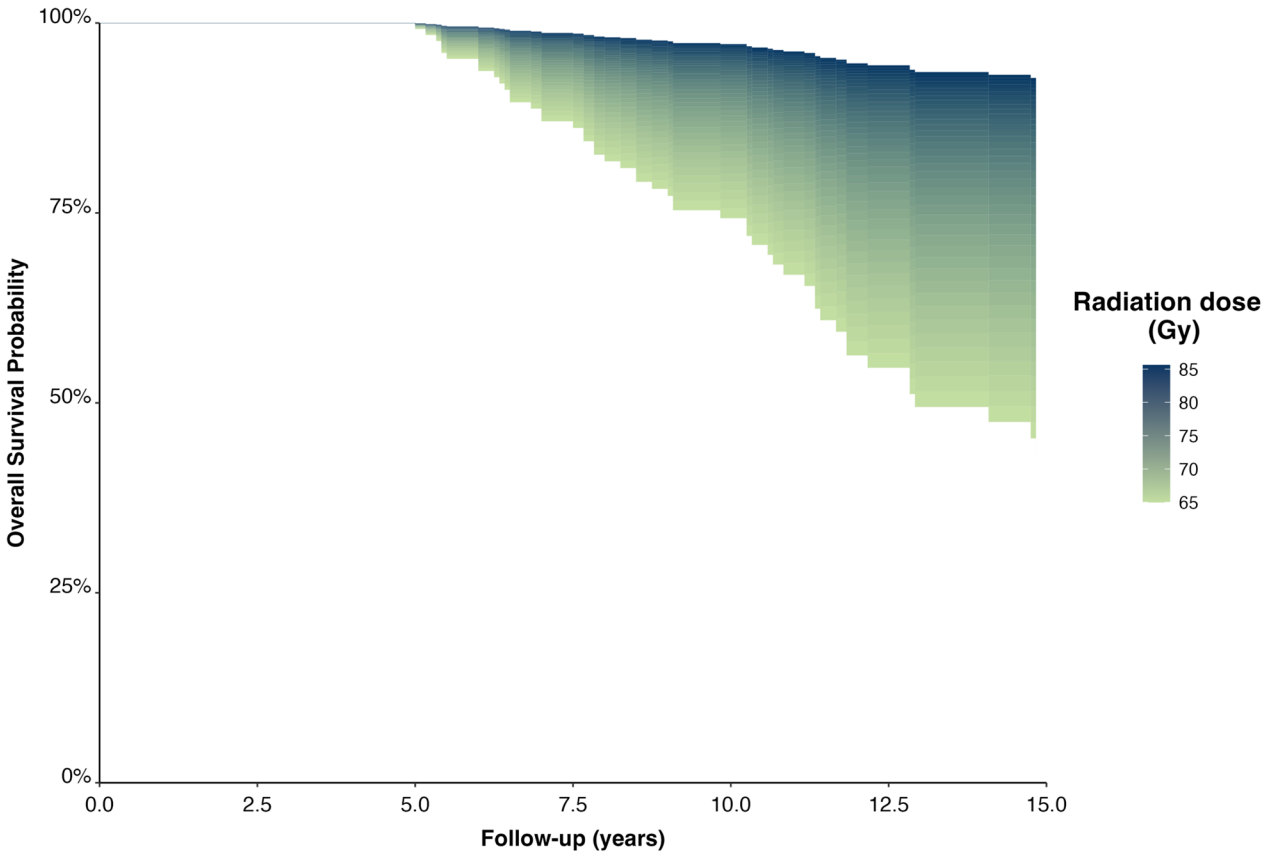


Fig. 3 Kaplan Meier curve for overall survival by radiation dose

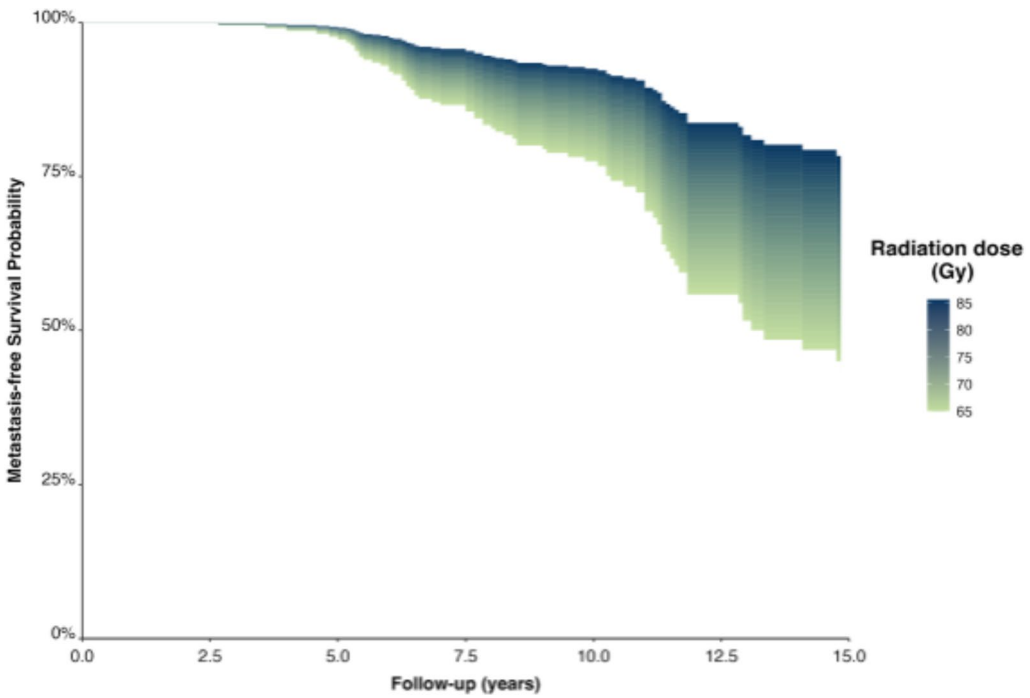


Fig. 4 Kaplan Meier curve for metastasis-free survival by radiation dose

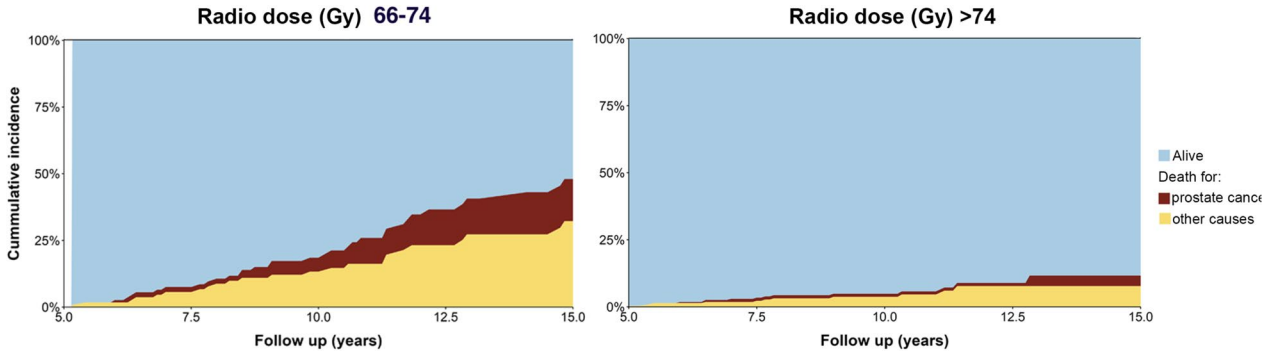


Fig. 5 Cause –specific mortality curves from the Fine and Gray models by radiation dose

Although we recognize that our data are not directly comparable, the clinical outcomes observed at 10 and 15 years in this study using EBRT alone for dose escalating, are consistent with other trials of dose intensification with EBRT, or combined therapy with a brachytherapy boost [5, 10–14]. The 10-year OS and CSS were 91% and 97%, respectively, despite only one-third of the patients received ENRT. While intuitive and rational, the impact of ENRT on the OS of HRPCa patients remains controversial. Until recently, there has been no high-level and unequivocal evidence indicating a clinically significant benefit in relevant oncologic outcomes from ENRT [15, 16]. Recently, the POP-RT trial reported a significant improvement in biochemical disease-free survival and MFS at 5-years with the addition of whole pelvic RT in 224 PET PSMA-staged patients with very unfavourable factors, although without an impact on OS [17]. Hopefully, the NRG/RTOG 0924 randomized trial will shed definitive light on the selection of patients who will benefit from ENRT.

Further refinements to intensify RT dose without a relevant increase in toxicity include hypofractionation schemes, stereotactic technics and biologically guided focal intensification. The oncological benefits of focal boosting of index lesions (ILs) was demonstrated in the phase 3 FLAME trial [18], and other studies have also reported excellent morphological and functional local control with highly selected focal radiation dose intensification [19].

Most of the evidence on ultra-hypofractionation (UHRT) is derived from studies in low- and intermediate-risk PCa, with limited data available for high-risk disease. Currently, the most extensive randomized evidence for UHRT in high-risk disease comes from the HYPO-RT-PC trial. This phase III non-inferiority clinical study that randomized 1,200 patients to receive either UHRT or conventional fractionated EBRT, including 126 high-risk patients, showed that UHRT was equally effective to conventionally fractionated radiotherapy for intermediate-to-high risk prostate cancer [20]. An individual patient meta-analysis of 344 HRPCa patients treated with stereotactic ablative body radiotherapy (SABR) has provided prospective evidence supporting favourable toxicity profile and promising efficacy of UHRT in HRPCa [21]. Prospective studies on SABR in HRPCa, with or without focal boost, have also reported encouraging preliminary results [22, 23]. Several controlled prospective studies are currently underway to validate these findings and to determine the optimal dose and biologically guided target volume in high-risk disease, particularly in combination with ENRT, ADT, and/or novel therapies [24, 25].

The incorporation of PSMA-PET imaging in staging, monitoring and biological targeting is reshaping the landscape of PCa [26, 27]. This shift is particularly significant in the high-risk and very HRPCa setting, as advanced imaging is likely to result in a more selective—and potentially more favourable—high-risk cohort. Additionally, it will lead to increased detection of low-volume oligometastatic disease requiring adjustments in management that may involve reassessing the duration of ADT, evaluating the role of ENRT versus nodal SBRT, and determining the optimal timing for integrating novel androgen receptor pathway inhibitors (ARPIs) and MDT.

Furthermore, the long-established criteria for BF following prostate RT may need to be reconsidered. The earlier—and potentially more frequent—detection of oligorecurrent and low-volume metastatic disease at low PSA levels presents new treatment challenges, particularly in defining PSA failure [28]. However, the full clinical impact of this"prognostic shift"on OS, as well as the optimal integration of PSMA-PET imaging into treatment protocols and definitions, remains under investigation and requires further phase III clinical trials [29]. Given that a substantial proportion of high-risk patients treated with LTADT (with or without ARPIS) and high-dose RT achieve long-term survival, there remains a need for earlier surrogate endpoints for OS. Emerging

biological imaging techniques are expected to play a significant role in this context.

Treatment strategies should be individualized (intensification vs de-escalation) based on emerging predictive tools. Multimodal artificial intelligence (AI) models, including those based on histopathology or imaging, as well as genomic platforms, are expected to play a pivotal role in the future of personalized PCa management. Several ongoing trials evaluating the addition of second-generation antiandrogens and/or poly(ADP-ribose) polymerase (PARP) inhibitors in combination with radiotherapy (RT) and androgen deprivation therapy (ADT) for localized HRPCa have incorporated these novel predictive tools into their study designs.

This study has several strengths, including a long-term follow-up, a low rate of missing data and a non-selective patient population treated outside of clinical trials. We analysed radiation dose as both a continuous and categorical variable, thereby enhancing the reliability of our 10-year outcome estimates. Furthermore, the use of CSS as an endpoint offers certain advantages over OS and contributes to the consistency of the results.

We acknowledge several key limitations, primarily related to the retrospective design of the study. First, the extended treatment period during which technological advancements were progressively implemented. Second, substantial variability existed in the timing, indications, and reporting methods for re-staging with conventional imaging following biochemical failure, as well as in the frequent use of early salvage hormone therapy in this context.

In summary, the findings of the present study confirm that radiation dose intensification is paramount in the treatment of HRPCa, irrespective of the duration of ADT. Dose escalation with EBRT, using IMRT/IGRT technologies, achieves excellent 10-year OS rates with low toxicity, consistent with outcomes observed in combined approaches incorporating EBRT and brachytherapy boost. The integration of novel advancements in SBRT delivery guided by predictive models is currently being evaluated in clinical trials with promising results. These innovations are expected to substantially improve treatment outcomes and, ultimately, enhance the quality of life for patients with HRPCa.

Appendix 1

See Tables 4, 5, 6, 7, 8, 9 and 10.

Table 4 Univariate and multivariate Cox analysis for overall survival

Variables	N	Univariate analysis		Multivariate analysis	
		***p* value**	**HR (95% CI)**	***p* value**	**HR (95% CI)**
Patient age continuous	424	0.010	1.07 (1–02-1.12)	0.059	1.05 (0.99–1.10)
Radiation dose (Gy) continuous	407	< 0.001	0.89 (0.85–0.93)	< 0.001	0.89 (0.84–0.94)
≤ 74 Gy [(1)]	120				
> 74 Gy [(2)]	287	< 0.001	0.24 (0.13–0.43)	< 0.001	0.29 (0.15–0.55)
ADT	424				
No	18	–	–		-
STAD	56	0.22	0.58 (0.24–1.38)	0.37	0.67 (0.28–1.60)
LTAD	350	< 0.001	0.26 (0.12–0.58)	0.12	0.52 (0.23–1.19)
Gleason/ISUP grade group	419				
1–2	231	–	–		
3	67	0.87	0.93 (0.38–2.26		
4–5	121	0.22	1.47 (0.80–2.68)		
T stage	424				
T1	29	–	–		
T2	124	0.41	1.86 (0.43–8.07)		
T3	271	0.60	1.47 (0.35–6.14)		

**HR* Hazard ratio; #*CI* Confidence intervale; ¢*STADT* Short-term androgen deprivation therapy; €*LTADT* Long-term androgen deprivation therapy; ***ISUP* International society of urological pathology. [(1) (2)] Median FU of 123 months (95% CI 95–154) and 115 months (95% CI 87–139) respectively

Table 5 Univariate and multivariate Cox analysis for metastasis-free survival

Variables		Univariate analysis		Multivariate analysis	
		***P* value**	**HR (95% CI)**	***P* value**	**HR (95% CI)**
Patient age Continuous	424	0.36	0.1.08 (0.98–1.05)	–	
Radiation dose (Gy) Continuous	407	0.003	0.94 (0.91–0.98)	0.003	0.94 (0.90–0.98)
≤ 74 Gy(1)	120				
> 74 Gy(2)	287	0.002	0.48 (0.30–0.75)	0.002	0.47 (0.30–0.76)
ADT	424				
No	18	–	–	–	
STAD	56	0.49	0.74(0.32–1.71)		
LTAD	350	0.06	0.48 (0.23–1.02)		
PSA ng/ml Continuous	424	0.54	0.99 (0.99–1.0)	–	
Gleason/ISUP Grade	419				
1–2	131	–	–	–	–
3	67	0.42	1.30 (0.68–2.50)	0.24	1.50 (0.77–2.88)
4–5	121	0.02–	1.80 (1.10-2.93)	0.05	1.66 (1.01-2.73=
T stage	424				
T1-2	153	–	–	–	
T3	271	0.76	1.07 (0.66–1.75)		

**HR* Hazard ratio; #*CI* Confidence intervale; ¢S*TADT* Short-term androgen deprivation therapy; €*LTADT* Long-term androgen deprivation therapy; ***ISUP* International society of urological pathology. (1) (2) Median FU of 123 months (95% CI 95–154) and 115 months (95% CI 87–139) respectively

Table 6 Univariate and multivariate Cox analysis for cause-specific survival

Variables	N	Univariate analysis		Multivariate analysis	
		***p* value**	**HR (95% CI)**	***p* value**	**HR (95% CI)**
Patient age continuous	424	0.460	0.97 (0.89–1.06)	–	–
Radiation dose (Gy) continuous	415	0.002	0.88 (0.81–0.95)	< 0.001	0.89 (0.84–0.94)
≤ 74 Gy (1)	120				
> 74 Gy(2)	287	0.01	0.26 (0.09–0.74)	< 0.024	0.25 (0.08–0.83)
ADT (suppress hormone therapy)					
No	18	–	–		–
STAD	56	0.59	1.78 (0.21–14.8)	–	–
LTAD	350	0.84	0.81 (0.11–6.2)	–	
PSA ng/ml continuous	424	0.57	0.99 (0.34–7.22)		
Gleason/ISUP grade group	419				
1–2	231	–	–		
3	67	0.66	1.43 (0.29–6.98)		
4–5	121	0.07	2.70 (0.91–7.95)		
T stage	424				
T1	29	–	–		
T2	124	< 0.001	11.11 (2.53–48.7)	< 0.001	10.34 (1.79–59.92)
T3	271	< 0.001	31.54 (15.3–66.1)	< 0.001	49.38 (11.5–212.2)

**HR* Hazard ratio; #*CI* Confidence intervale; ¢S*TADT* Short-term androgen deprivation therapy; €L*TADT* Long-term androgen deprivation therapy; ***ISUP* International society of urological pathology. (1) (2) Median FU of 123 months (95% CI 95–154) and 115 months (95% CI 87–139) respectively

Table 7 Univariate and multivariate Cox analysis for biochemical disease-free survival

Variables	N	Events	Univariate analysis		Multivariate analysis	
		101	*p* value	HR (95% CI)	*p* value	HR (95% CI)
Patient age continuous	424	101	0.60	0.99 (0.96–1.02)	–	–
Radiation dose (Gy) continuous	407	101	0.04	0.96 (0.93–0.99)	0.04	0.96 (0.93–0.99)
≤ 74 Gy (1)	120	47				
> 74 Gy (2)	287	52	0.04	0.65 (0.43–0.98)	0.05	0.66 (1.0–0.43)
Missing		2				
ADT	424					
No	18	8	–	–		–
STAD	56	16	0.22	0.58 (0.24–1.38)	0.37	0.67 (0.28–1.60)
LTAD	350	30	< 0.001	0.26 (0.12–0.58)	0.12	0.52 (0.23–1.19)
PSA ng/ml continuous	424	101	0.81	0.99 (0.99–1.00)	–	
Gleason/ISUP grade group	419					
1–2	231	48	–	–		
3	67	17	0.096	0.93 (0.91–2.81)	0.04	1.8 (1.03–3.21)
4–5	121	34	0.006	1.86 (1.19–2.91)	0.025	2.16 (1.36–3.44)
T stage	424					
T1	29	5	–	–	–	–
T2	124	24	0.82	1.12 (0.45–2.94)		
T3	271	72	0.59	1.29 (0.52–3.10)		

**HR* Hazard ratio; #*CI* Confidence intervale; ¢S*TADT* Short-term androgen deprivation therapy; €*LTADT* Long-term androgen deprivation therapy; ***ISUP* International society of urological pathology. (1) (2) Median FU of 123 months (95% CI 95–154) and 115 months (95% CI 87–139) respectively

Table 8 Impact of biochemical failure on overall survival

Characteristic	N	Death event	HR	95% CI	p-value
Biochemical Failure (nadir + 2 ng/ml)					
No	323	23	—	—	
Yes	101	29	2,42	1.37–4.29	0,002

HR Hazard Ratio, *CI* Confidence Interval

Table 9 Impact of biochemical failure on metastasis-free survival

Characteristic	N	MTS event	HR	95% CI	p-value
Biochemical Failure (nadir + 2 ng/ml)					
No	323	24	—	—	
Yes	101	30	0.33	0.01–0.11	< 0,001

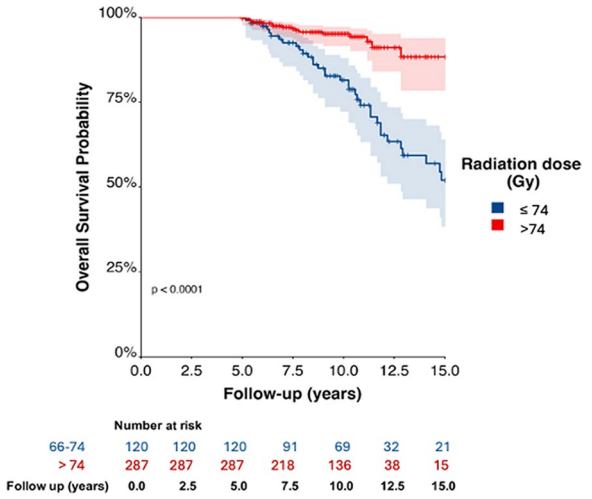
HR Hazard Ratio, *CI* Confidence Interval

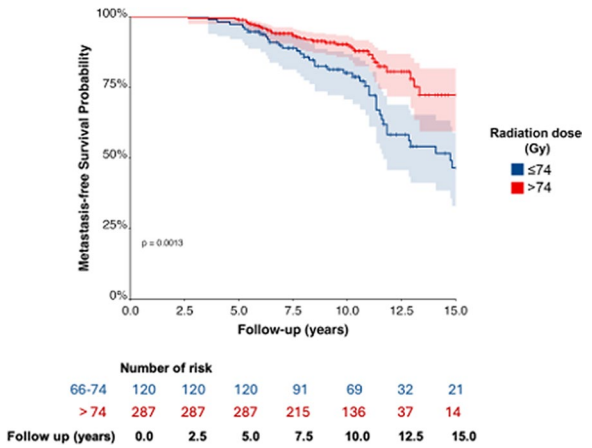
Table 10 Subgroups according to number of risk factors

Number and type of risk factors	
ISUP4-5	51 (12%)
ISUP4-5 & PSA > 20	14 (3.3%)
PSA > 20	85 (20%)
T3	138 (33%)
T3 & ISUP4-5	12 (2.9%)
T3 & ISUP4-5 & PSA > 20	26 (6.2%)
T3 & PSA > 20	92 (22%)

Appendix 2

Figures.





Author contributions

A. Z: Conceptualization, methodology, validation, investigation, data curation, Write the main manuscript text—Review & Editing of manuscript, supervision M. R: Methodology, investigation, data curation, Review & Editing of manuscript C. M.V.: Investigation, methodology Review & Editing of manuscript P. C.: Methodology, investigation, data curation, Review & Editing of manuscript N. M.: Methodology, formal statistical analysis, preparation of figures, data curation, validation, review & Editing of manuscript A MD. Cruz Conde MD: Investigation, methodology, Review & Editing of manuscript Laura Fernández-Banda MD: Investigation, methodology, Review & Editing of manuscript Laura Zaragoza MD: Investigation, methodology, Review & Editing of manuscript Sara Carroceda MD: Investigation, methodology, Review & Editing F. García Vicente PhD: Methodology, validation, investigation, data curation, Writing—Review & Editing, supervision.

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Availability of data and materials

Research data are stored in an institutional repository and will be shared upon request to the corresponding author.

Declarations

Ethics approval and consent to participate

Not applicable. This is retrospective analysis of a prospective cohort, not a clinical trial. But, all patients signed an ICF prior to radiation therapy as clinical practice in all cases.

Consent for publication

Not applicable. The clinical research of the present manuscripts comply with international and national standards for such work (such as the Declaration of Helsinki)

Competing interests

The authors declare no competing interests.

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