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Original Research Article

Prospective results for 5-year survival and toxicity of moderately hypofractionated radiotherapy with simultaneous integrated boost (SIB) in (very) high-risk prostate cancer

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A B S T R A C T

Purpose: High-risk (HR) prostate cancer patients usually receive high-dose radiotherapy (RT) using a two-phase sequential technique, but data on a simultaneous integrated boost (SIB) technique are lacking. We prospectively evaluated the long-term results of urinary (GU) and digestive (GI) toxicity and survival data for high-dose RT using a SIB technique in HR and very high-risk (VHR) prostate cancer.

Methods: Patients were treated using an SIB technique in 34 fractions, at a dose of 54.4 Gy to the pelvis and seminal vesicles and 74.8 Gy to the prostate, combined with 36 months of androgen-depriving therapy in a prospective multicenter study. Acute and late GU and GI toxicity data were collected. Overall survival (OS), biochemical-relapse-free survival (bRFS), loco-regional-relapse-free survival (LRRFS), metastasis-free-survival (MFS) and disease-free-survival (DFS) were assessed.

Results: We recruited 114 patients. After a median follow-up of 62 months, very few patients experienced acute (M0-M3) (G3-4 GU = 3.7 %; G3-4 GI = 0.9 %) or late (M6-M60) severe toxicity (G3-4 GU = 5.6 %; G3-4 GI = 2.8 %). The occurrence of acute G2 + GU or GI toxicity was significantly related to the consequential late G2 + toxicity ($p < 0.01$ for both GU and GI). Medians of OS, bRFS, LRRFS, MFS and DFS were not reached. At 60 months, OS, bRFS, LRRFS, MFS and DFS were 88.2 % [82.1; 94.7], 86.0 % [79.4 %;93.2 %], 95.8 % [91.8 %;99.9 %], 87.2 % [80.9 %;94.0 %] and 84.1 % [77.2 %;91.6 %] respectively.

Conclusion: SIB RT at a dose of 54.4 Gy to the pelvis and 74.8 Gy to the prostate is feasible, leading to satisfying tumor control and reasonable toxicity in HR and VHR prostate cancer.

Introduction

Intensity modulated radiation therapy (IMRT) combined with 3-year androgen deprivation therapy (ADT) has been an established treatment option for high-risk (HR) prostate cancer [1–6]. Dose escalation studies have brought conventional fractionation regimens to 76–80 Grays (Gy) using 1.8 to 2.0 Gy fractions [7–12]. Whole pelvic RT (WPRT) in HR localized prostate cancer is discussed and often recommended. It has

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been shown to improve biochemical failure-free survival and disease-free survival compared to prostate-only radiotherapy [13,14].

Delivering elective pelvic nodal irradiation historically involves a two-phase sequential IMRT (S-IMRT) technique using sequentially shrinking fields with the same fraction size throughout the entire course of treatment. Phase 1 delivering 45–50 Gy in 1.8–2 Gy fractions to the pelvic nodes and prostate. Phase 2 'boosting' the prostate to a total dose of 76–80 Gy in 1.8–2 Gy fractions. Overall treatment time is usually 8 weeks.

Another IMRT technique is the simultaneous integrated boost (SIB-IMRT), using multiple radiation beams to simultaneously irradiate the tumor target and adjacent areas at different doses during a single treatment session. The result is a higher dose per fraction (2.0–3.0 Gy) with moderate hypofractionation for the prostate, and lower doses per fraction (1.5–2 Gy) for the pelvic nodes.

SIB-IMRT requires one treatment plan and is more conformal [15] compared to S-IMRT. Moreover, a dosimetric study illustrated the superiority of the SIB-IMRT with regards to dose conformality to the prostate and pelvic nodes together, with better sparing of critical structures compared with S-IMRT [16].

Many studies have evaluated an SIB approach to deliver elective pelvic nodal irradiation together with moderate hypofractionation to the prostate [14,17–32]. The consistent conclusion from all the published studies is that it is safe with a very acceptable toxicity profile. However, these studies have either small numbers (less than 65 patients) [18–20,27,29], or a short median follow-up (less than 5 years) [23,27,29–31], or the data are retrospective [24,33,25,26]. Only 4 studies present toxicity and survival data on a significant number of patients (≥100) and with a median follow-up of over 5 years (Murthy et al. [14], Faria et al. [21,22], Ekanger et al. [28], Di Muzio et al. [32]).

We conducted a prospective phase 2 study comparing the toxicity and cost-effectiveness of different modalities of pelvic IMRT techniques [34]. We now present the long-term results of urinary (GU) and digestive (GI) toxicity and survival data for moderately hypofractionated RT using an SIB technique in high-risk and very high-risk prostate cancer.

Materials and methods

Patients with histologically proven high-risk (HR) and very-high risk (VHR) prostate cancer according to NCCN [35] were prospectively included in a French multicenter study "RCMI pelvis", (NCT01325961), a micro-costing study, whose results have previously been published [34]. Fourteen academic or private centers participated in this study. Three years of androgen deprivation therapy (ADT) were combined with whole pelvic and prostate radiotherapy. A dose of 54.4 Gy (1.6 Gy/fraction) was delivered to the pelvis and seminal vesicles, with a simultaneous hypofractionated integrated boost (SIB) to the prostate at the dose of 74.8 Gy (2.2 Gy/fraction) in 34 fractions. The prescription on PTVs followed the recommendations of the ICRU 83 report [36]. The organ at risk (OAR) dose constraints were as follows: peritoneal cavity: V20 < 550 cm3, V50 < 100 cm3; rectum: V60 < 50 %, V70 < 25 %, V74 < 5 %; bladder: V60 ≤ 50 %, V70 ≤ 25 %; femoral heads: V55 < 5 %.

Acute (during and up to 3 months after treatment) and late (between months 6 and 60 of follow-up) genito-urinary (GU) and gastro-intestinal (GI) toxicity data were prospectively collected by physicians, using the Common Terminology Criteria for Adverse Events (CTCAE version 3.0) grading scale. Toxicity results are those of cumulative toxicity, that is, the worst grade presented by the patient for each category and for all times included in the category.

Biochemical recurrence-free survival (bRFS), loco-regional-relapse-free survival (LRRFS), disease-free survival (DFS), metastasis-free survival (MFS) and overall survival (OS) were assessed using the Kaplan-Meier method. Disease-free survival corresponded to the first recorded relapse, whether locoregional, biological or metastatic. Metastasis-free survival events were defined as the occurrence of metastases on conventional imaging with computed tomography (CT) and bone scans.

Table 1
Patients' characteristics.

Clinical parameter	Patients treated with the SIB technique (n = 114)
Age (years)	
mean (sd)	70 (8)
Performance status	
0	91 (83.5 %)
1 or 2	18 (16.5 %)
missing data	5 (-)
cT stage	
cT1	14 (12.5 %)
cT2	33 (29.5 %)
cT3	61 (54.5 %)
cT4	4 (3.6 %)
missing data	2 (-)
N stage	
cN0	90 (84.9 %)
cN1	16 (15.1 %)
missing data	8 (-)
PSA (ng/ml); capped values	
mean (sd)	16 (12)
Risk group	
High-risk	37 (32.5 %)
Very high-risk	77 (67.5 %)

Biochemical progression-free survival events were defined as a PSA level > nadir + 2.0 ng/mL. Patients without relapse were censored at their date of last news or death.

Results

Patients

Our study is based on the prospective micro-costing study RCMI pelvis, in which 155 patients with prostate cancer were included. Our work involved only patients with high-risk and very-high risk prostate cancer, treated with simultaneous integrated boost (n = 120). However, 6 were excluded from the final analyses because they were wrongly included (intermediate risk n = 4) or their risk could not be assessed (missing data n = 2). One hundred and fourteen patients (37 high-risk; 77 very high-risk) were thus included between 2011 and 2015. Patients' characteristics are summarized in Table 1.

Toxicity

Toxicity data were available for 108 patients (/114).

Acute GU toxicity rates were as follows: G0 = 13.0 %, G1 = 45.4 %, G2 = 38.0 %, G3 = 3.7 %, no G4. Acute GI toxicity rates were: G0 = 20.4 %, G1 = 54.6 %, G2 = 24.1 %, G3 = 0.9 %, no G4. Very few patients experienced acute severe toxicity. For acute G3 GU toxicities, there was one case of ureteral lithiasis, one case of dysuria, one case of renal colic on lithiasis and one case of urinary urgency. All these toxicities disappeared at M3, except for the case of urinary urgency. Regarding acute G3 GI toxicities, one patient reported G3 diarrhea during radiation therapy.

For late GU toxicity, about 1/4 of the patients had no toxicity and more than 2/3 of the patients had moderate toxicity; very few patients had severe late toxicities (G0 = 24.1 %, G1 = 42.6 %, G2 = 27.8 %, G3 = 4.6 %, G4 = 0.9 %). Regarding late G3-4 GU toxicities, half were hematuria, with one G4 at M36. Other toxicities reported were urinary incontinence, dysuria, bladder polyps or unclassified toxicity.

For late GI toxicity, nearly half of the patients had no symptoms and half had moderate symptoms; in the same way, very few patients had severe late toxicities (G0 = 43.5 %, G1 = 34.3 %, G2 = 19.4 %, G3 = 2.8 %, no G4). Regarding late G3 GI toxicities, all the patients concerned had rectorrhagia.

There is a strong association between the occurrence of acute G2 +

Table 2
Two-way table showing the association between G2 + acute and late toxicity.

Toxicity	Late toxicity G < 2	Late toxicity G ≥ 2	P-value*
GU toxicity			0.0017
Acute toxicity, G < 2	50 (69.4 %)	13 (36.1 %)	
Acute toxicity G ≥ 2	22 (30.6 %)	23 (63.9 %)	
GI toxicity			0.0027
Acute toxicity, G < 2	69 (82.1 %)	12 (50.0 %)	
Acute toxicity G ≥ 2	15 (17.9 %)	12 (50.0 %)	

* (Fisher exact test).

toxicity and late G2 + toxicity. This relationship is found for both GU (p = 0.0017) and GI (p = 0.0027) toxicity. Table 2.

Fig. 1**a and 1b** are Sankey diagrams to visually illustrate this relationship and reported rates of toxicity at different times.

Survival

All 114 patients were included in the survival analyses.
The median follow-up was 62 months (CI95%: [61.3; 62.5]).
Medians of overall survival (OS), biochemical-relapse-free survival (bRFS), loco-regional-relapse-free survival (LRRFS), metastasis-free-survival (MFS) and disease-free-survival (DFS) were not attained. A relevant comparative analysis of survival between HR and VHR was not possible because of an insufficient number of events.

Overall survival (OS) was 88.2 % [82.1; 94.7] at 60 months.

Biochemical-relapse-free survival (bRFS) was 86.0 % [79.4 %;93.2 %] at 60 months. 18/114 patients (HR: n = 7, VHR: n = 11) had a biochemical relapse. The Kaplan-Meier curve for bRFS is presented in Fig. 2**A.**

Loco-regional-relapse-free survival (LRRFS) was 95.8 % [91.8 %;99.9 %] at 60 months.

Metastasis free survival (MFS) was 87.2 % [80.9 %;94.0 %] at 60 months, 13/114 patients (HR: n = 3, VHR: n = 10) experienced metastatic relapse. The Kaplan Meier curve for MFS is presented in Fig. 2**B.**

Disease-free survival (DFS) was 84.1 % [77.2 %;91.6 %] at 60 months, with 20 patients experiencing a recurrence (HR: n = 7, VHR: n = 13). The Kaplan Meier curve is presented in Fig. 2**C.**

Discussion

Selecting the best simultaneous integrated boost technique for the

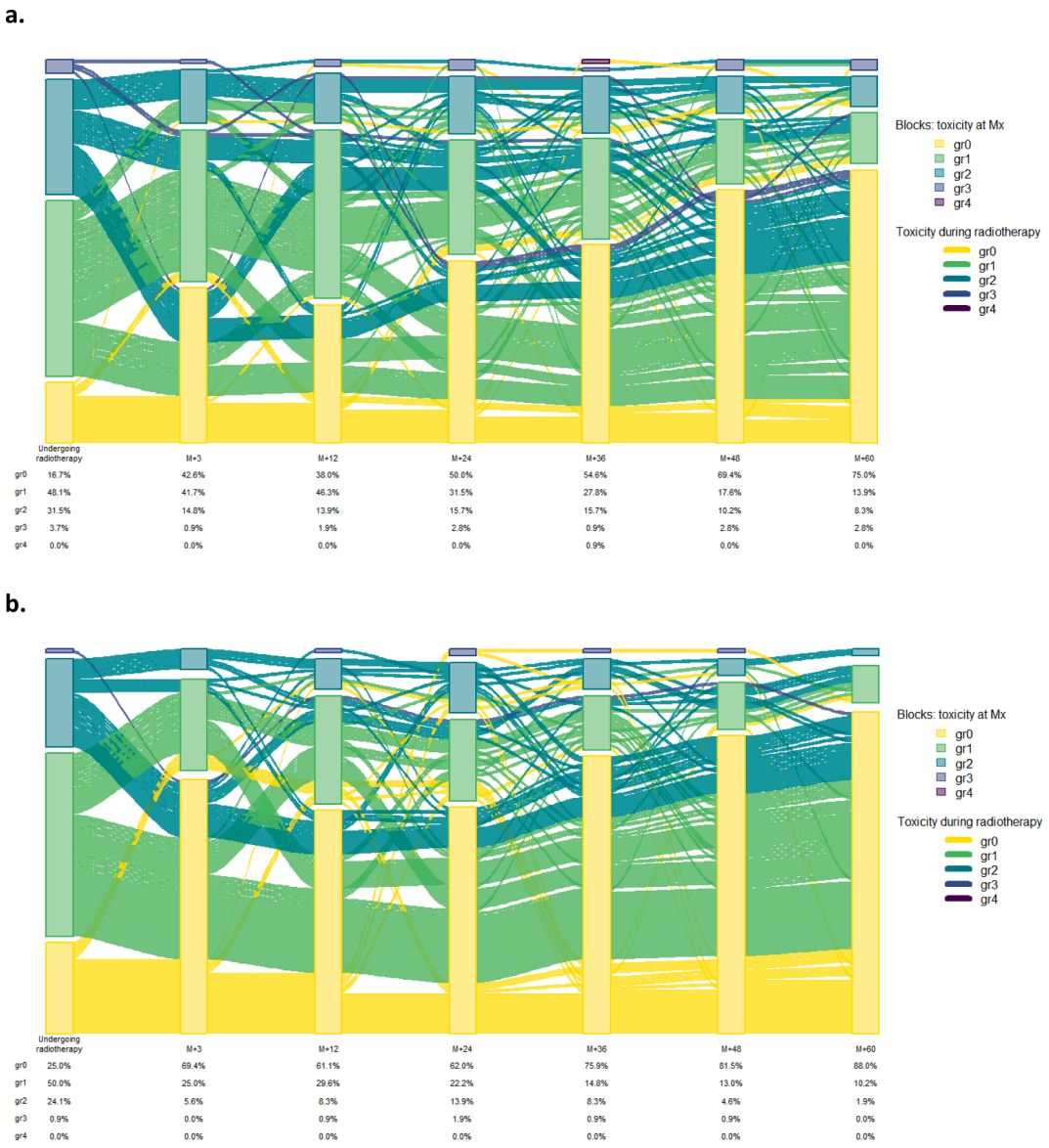

Fig. 1. Sankey diagram representing the evolution of urinary (a) and digestive toxicity (b). The width of each arrow is proportional to the patient flow represented.

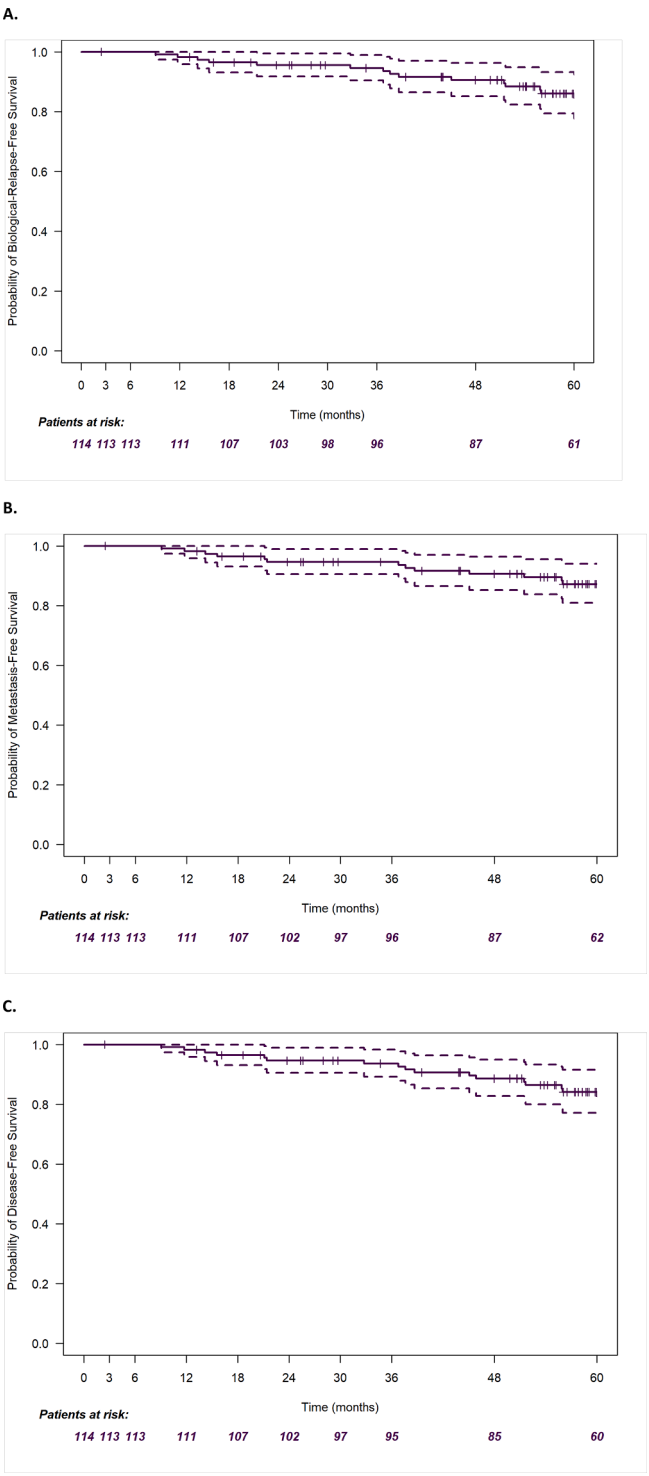

Fig. 2. Kaplan-Meier curve for biochemical-relapse-free survival (A), metastasis-free survival (B) and disease-free survival (C).

treatment of the prostate and pelvis lymph nodes is challenging, with limited prospective evidence. Our prospective, multicenter trial evaluated the impact of elective pelvic nodal irradiation combined with a moderately hypofractionated IMRT simultaneous integrated boost to the prostate in HR and VHR prostate cancer. The results showed satisfactory long-term disease outcomes and low rates of late grade $\geq$ 2 GU and GI toxicities. Our SIB fractionation scheme is therefore a validated option for the treatment of high-risk prostate cancer.

In our study, despite high doses to the prostate and pelvic lymph nodes, acute GU and GI toxicity rates were low (less than 5 % of grade 3) which is consistent with previous trials [21,23–25]. However, the cumulative incidence of late grade $\geq$ 2 GU (33.3 %) and GI (22.2 %) toxicities was higher in the present study, compared with other reports. Table 3 summarizes all prospective publications that have evaluated an SIB approach to delivering elective pelvic nodal irradiation together with moderate hypofractionation to the prostate in patients with high-risk localized prostate cancer. Regarding cumulative GU toxicity, the results are very different between studies. Compared to ours, the Gliksman study [17] reported a higher rate, the Platin trial [20], and the Adkison [27] and Di Muzio [32] studies, a similar rate and the POP-RT [14], CHiRP [29], Magli [18], Ekanger [28], Quon [23], Niazi [30], Faria [22], Pervez [19] and Jorgo [31] studies much lower rates. Our high percentage of cumulative GI toxicity could be explained by a higher EQD2 (49 Gy) to lymph nodes than most other studies, even though, in POP RT - which has an EQD2 to lymph nodes at 50 Gy - only 8.2 % of cumulative late grade $\geq$ 2 GI toxicities were reported [14]. Similarly, in the Magli study, which had an EQD2 to the lymph nodes at 50 Gy, only 2.4 % of grade $\geq$ 2 GI late toxicities were found [18]. Despite these higher cumulative results, at 60 months, we described lower toxicity rates than in the Pervez [19] and Gliksman [17] studies.

The *meta*-analysis by Viani et al. [37], on 1,745 patients, includes many of the previously cited prospective studies of elective pelvic nodal irradiation with moderate hypofractionation in high-risk prostate cancer. It also includes retrospective studies. The median follow-up was similar to our study (61 months). Concerning acute cumulative toxicity, our results are higher for grade 2 toxicity (GU: 38 % versus 22 %, GI: 24.1 % versus 16 %) and slightly higher for grade 3 toxicity (GU: 3.7 % versus 1.5 %, GI: 0.9 % versus 0 %) with no grade 4 in either. Similarly, for late toxicity, we reported more grade 2 (GU: 27.8 % versus 7 %, GI: 19.4 % versus 5 %) and grade 3 (GU: 4.6 % versus 1 %, GI: 2.8 % versus 1 %) late cumulative toxicity, as well as 1 grade 4 (GU: 1 patient (0.9 %) versus 0). Several hypotheses may explain the higher toxicity in our study: different IGRT systems and frequencies, the optional nature of prostatic fusion MRI, and different PTV margins.

However, even if all the studies reported very different results, they all found a very low rate of severe long-term toxicity, including our own.

We provided evidence that acute toxicity is a significant predictor of late GI and GU toxicity. This link had already been reported in different studies [32,38–40]. These results may lead to closer monitoring of side effects in patients who have experienced acute grade $\geq$ 2 toxicities.

In our patient cohort, the 5-year bRFS of 86 % supports the high efficacy of hypofractionated primary radiotherapy with SIB for high-risk and very high-risk prostate cancer. The Platin-1 trial [20] (83.6 % bRFS at 5 years), the *meta*-analysis by Viani et al. [37] (90 % bRFS at 5 years) and Di Muzio [32] et al. (90.1 % bRFS at 5 years, but with a mix with unfavorable intermediate-risk) found the same results. [20]. In contrast, the rates of 5-year biochemical recurrence were higher in the present study (14 %) compared to POP-RT (5 %) [14]. This apparent difference may be due to factors such as a larger proportion of VHR patients in our study (67.5 % versus 48 %) and better patient selection with use of the staging PSMA PET scan in approximately 80 % of patients in POP-RT [14].

This study has certain limitations. The first is the limited number of patients and the mid-term follow-up, with the risk of underestimating long-term toxicity. However, Di Muzio et al. showed a decrease in grade $\geq$ 3 GU and GI toxicities at 10 years [32]. Toxicity results may also have been underestimated by the lack of patient self-assessment of both acute and late side-effects, as well as a prospective quality of life evaluation. No additional boost to lymph nodes was given to the N + patients (15 % of patients), as the protocol did not specify a dose for N + lymph nodes, which may modify toxicity and survival results. Another limitation is the non-use of the new standard of care for VHR patients, which is the association of ADT and abiraterone acetate with prednisolone since the STAMPEDE trial demonstrated a significantly higher rate of metastasis-free survival [41]. This study was published in January 2022, long after

Table 3
Late toxicity results from published prospective studies of a simultaneous integrated boost approach.

Reference	No. Patients	No. Fractions	Dose to pelvic nodes	EQD2 pelvic nodes	Dose to prostate	EQD2 prostate	Median follow-up	Late GU	Late GI
Our study	114	34	54.4 Gy	49	74.8 Gy	78.5	5.1 years	cumul G2 = 27.8 % cumul G3 = 4.6 % cumul G4 = 0.9 % M60 G2 = 8.3 % M60 G3 = 2.8 % M60 G4 = 0 %	cumul G2 = 19.4 % cumul G3 = 2.8 % no cumul G4 M60 G2 = 1.9 % M60 G3 = 0 %
Adkison et al. 2012 [27]	53	28	56 Gy	56	70 Gy	78.8 Gy	2.1 years	cumul G2 = 25 % cumul G3 = 2 %	cumul G2 = 8 % no G3
Ekanger et al. 2020 [28]	97	25	50 Gy	50	67.5 Gy	79.3	10.1 years	cumul G2 = 8 % cumul G3 = 1 %	cumul G2 = 1 % no G3
Quon et al. 2012 [23]	97	25	45 Gy	42.75	67.5 Gy	79.3	3.25 years	cumul G2 = 5 % cumul G3 = 3 % cumul G4 = 1 %	cumul G2 = 7 % cumul G3 = 0 %
Glicksman et al. 2021 [17]	230	25	45 Gy	42.75	67.5 Gy	79.3	11 years	cumul G2 = 46.2 % cumul G3 = 7.5 % M60 G2 = 18.4 % M60 G3 = 2.2 %	cumul G2 = 14.2 % cumul G3 = 2.3 % M60 G2 = 2.7 % M60 G3 = 0.4 %
Niazi et al. 2023 [30]	164*	25	45 Gy	42.75	68 Gy	80.2	3.4 years	M24 G2+ = 1.8 % M24 G3 = 0.6 % No M24 G4	M24 G2+ = 9 % M24 G3 = 2 % No M24 G4
Di Muzio et al. 2021 [32]	152*	28	51.8 Gy	49.9	74.2 Gy	86.3	8.0 years	cumul G2 = 15.6 % cumul G3 = 11.2 % cumul G4 = 1.3 %	cumul G2 = 8.0 % cumul G3 = 8.5 % no cumul G4
Murthy et al. 2021 [14]	110*	25	50 Gy	50	68 Gy	80.2	5.6 years	cumul G2 = 18.2 % cumul G3 = 1.8 %	cumul G2 = 6.4 % cumul G3 = 1.8 %
Faria et al. 2020 [22]	105	20	44 Gy	46.2	60 Gy	75	6.1 years	cumul G2 = 7.6 % cumul G3 = 1.9 % M40 G2 = 5 % M40 G3 = 0 %	cumul G2 = 4.8 % cumul G3 = 1.9 % M40 G2 = 3 % M40 G3 = 0 %
Pervez et al. 2017 [19]	60	25	45 Gy	42.75	68 Gy	80.2	5.2 years	M60 G2 = 17.1 % M60 G3 = 2.4 %	M60 G2 = 2.4 % M60 G3 = 0 %
Wang et al. 2021 [29]	50 *	25	45 Gy	42.75	68 Gy	80.2	3.1 years	cumul G2 = 14 % cumul G3 = 2 %	cumul G2 = 10 % cumul G3 = 6 %
Magli et al. 2018 [18]	41	25	50 Gy	50	67.5 Gy	79.3	5.4 years	cumul G2 = 9.8 % cumul G3 = 0 %	cumul G2 = 2.4 % cumul G3 = 0 %
Koerber et al. 2019 [20]	38	34	51 Gy	44.6	76.5 Gy	81.3	5.9 years	cumul G2 = 26.3 % cumul G3 = 2.6 %	cumul G2 = 2.6 % cumul G2 = 0 %
Jorgo et al. 2020 [31]	78*	28	50.4 Gy	47.9	70 Gy	78.8	2.5 years	cumul G2 = 13 % cumul G3 = 4 %	cumul G2 = 6 % cumul G3 = 5 %

EQD2 = Equivalent dose in 2 Gy fractions for an alpha/beta ratio at 2 Gy.
Cumul = cumulative; G2 = Grade 2; G3 = Grade 3; G4 = Grade 4; M60 = at 60 months; M24 = at 24 months; M40 = at 40 months.
* Number of patients in the study with high-risk or very high-risk prostate cancer who received moderately hypofractionated radiotherapy with SIB.

the design of our protocol.

Conclusion

The SIB radiotherapy at a dose of 54.4 Gy (1.6 Gy/fraction) to the pelvic lymph nodes and seminal vesicles and 74.8 Gy (2.2 Gy/fraction) to the prostate accomplished low rates of long-term toxicity, especially of GI toxicity and achieved high rates of long-term biochemical control and survival. Our study adds strong evidence supporting the use of moderately hypofractionated radiotherapy to the prostate with simultaneous elective pelvic nodal irradiation for patients with high-risk localized prostate cancer.

CRediT authorship contribution statement

Ingrid Masson: Methodology, Investigation, Writing – original draft, Writing – review & editing, Visualization, Project administration. **Laurène Larriviere:** Writing – original draft, Writing – review & editing, Visualization. **Marc-André Mahé:** Conceptualization, Methodology, Funding acquisition, Resources. **David Azria:** Resources. **Pascal Pommier:** Resources. **Nathalie Mesgouez-Nebout:** Resources. **Philippe Giraud:** Resources. **Didier Peiffert:** Resources. **Bruno Chauvet:** Resources. **Philippe Dudouet:** Resources. **Naji Salem:** Resources. **Georges Noël:** Resources. **Jonathan Khalifa:** Resources. **Igor Latorzeff:** Resources. **Catherine Guérin-Charbonnel:** Methodology, Software, Formal analysis, Data curation, Writing – review & editing, Visualization. **Stéphane Supiot:** Conceptualization, Methodology, Resources, Writing – review & editing, Supervision, Project administration.

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Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: IM, LL, MAM, PP, NMN, PG, DP, BC, PD, NS, GN, JK, IL, CGC, SS: none. DA declares conflicts of interest with Novagray, which has nothing to do with this study.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ctro.2023.100702.

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