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European Association of Urology

Platinum Priority – Prostate Cancer

Editorial by Sophia C. Kamran on pp. 316–318 of this issue

Dose-intensified Versus Conventional-dose Salvage Radiotherapy for Biochemically Recurrent Prostate Cancer After Prostatectomy: The SAKK 09/10 Randomized Phase 3 Trial

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Article info

Article history:
Accepted May 26, 2021

Associate Editor:
T Morgan

Abstract

Background: Salvage radiotherapy (SRT) is utilized for biochemical progression of prostate cancer after radical prostatectomy (RP).
Objective: To report the outcomes of the SAKK 09/10 trial comparing conventional and dose-intensified SRT.
Design, setting, and participants: SAKK 09/10 was a randomized, multicenter, phase 3 trial that recruited men with biochemical progression after RP.
Intervention: Patients were randomly assigned to conventional-dose (64 Gy) or dose-intensified SRT (70 Gy) to the prostate bed without hormonal therapy.

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https://doi.org/10.1016/j.eururo.2021.05.033

Keywords:
Prostate cancer
Biochemical progression
Salvage radiotherapy

Outcome measurements and statistical analysis: The primary endpoint was freedom from biochemical progression (FFBP). Secondary endpoints included clinical progression-free survival (PFS), time to hormonal treatment, overall survival (OS), acute and late toxicity (Common Terminology Criteria for Adverse Events v4.0), and quality of life (QoL).
Results and limitations: Between February 2011 and April 2014, 350 patients were randomly assigned to 64 Gy ($n = 175$) or 70 Gy ($n = 175$). Median prostate-specific antigen at randomization was 0.3 ng/ml. After median follow-up of 6.2 yr, the median FFBP was 8.2 yr in the 64 Gy arm and 7.6 in the 70 Gy arm (log-rank $p = 0.4$), with a hazard ratio of 1.14 (95% confidence interval 0.82–1.60). The 6-year FFBP rates were 62% and 61%, respectively. No significant differences in clinical PFS, time to hormonal treatment, or OS were observed. Late grade 2 and 3 genitourinary toxicity was observed in 35 (21%) and 13 (7.9%) patients in the 64 Gy arm, and 46 (26%) and seven (4%) in the 70 Gy arm, respectively ($p = 0.8$). Late grade 2 and 3 gastrointestinal toxicity was observed in 12 (7.3%) and seven patients (4.2%) in the 64 Gy arm, and 35 (20%) and four (2.3%) in the 70 Gy arm, respectively ($p = 0.009$). There were no significant differences in QoL.
Conclusions: Conventional-dose SRT to the prostate bed is sufficient in patients with early biochemical progression of prostate cancer after RP.
Patient summary: The optimal radiation therapy dose for patients who have increased tumor markers after surgery for prostate cancer is unclear. We found that administering a higher dose only increased the gastrointestinal side effects without providing any benefits to the patient.
This clinical trial is registered on ClinicalTrials.gov as NCT01272050.

1. Introduction

Biochemical progression after radical prostatectomy (RP) for prostate cancer (PC) can be common, depending on risk factors for locally recurrent or distant metastatic disease [1–3]. The only potentially curative treatment at the earliest signs of biochemical progression is salvage radiation therapy (SRT) to the prostate bed ± the pelvic nodes [4–6]. Dose-intensified SRT may be more effective in reducing biochemical progression than conventional-dose SRT [4,5,7–10], but data from well-designed, prospective randomized trials are lacking.

To address this question, the SAKK 09/10 prospective, open-label, multicenter, randomized phase 3 trial was initiated [11]. The aim of the study was to demonstrate that dose-intensified SRT is superior to conventional-dose SRT with respect to freedom from biochemical progression (FFBP).

2. Patients and methods

2.1. Trial design and participants

We conducted a prospective, open-label, multicenter, randomized phase 3 trial (SAKK 09/10) of dose-intensified versus conventional-dose SRT in PC patients with biochemical progression without macroscopic disease at 28 hospitals in three European countries (14 in Switzerland, 11 in Germany, and 3 in Belgium). Patients with evidence of biochemical progression (two consecutive rises in prostate-specific antigen [PSA] with final PSA >0.1 ng/ml, or 3 consecutive rises) and PSA ≤2 ng/ml at randomization were eligible.

Further inclusion criteria were written informed consent; lymph node–negative prostate adenocarcinoma treated with RP at least 12 wk before randomization; tumor stage pT2a–3b, R0-1, pN0, or cN0 according to the 2009 International Union Against Cancer TNM staging system, with Gleason score available; World Health Organization performance status 0–1; age 18–75 yr; and a completed baseline quality-of-life (QoL) questionnaire.

The exclusion criteria were PSA persistently >0.4 ng/ml 4–20 wk after RP; any hormonal treatment; a palpable prostatic fossa mass suggestive of macroscopic local recurrence, unless ultrasound-guided biopsy showed nonmalignancy; pre-SRT pelvic lymph-node enlargement >1 cm in short-axis diameter (cN1), unless the enlarged lymph node was histologically negative; or evidence of macroscopic local recurrence or metastatic disease on pre-SRT magnetic resonance imaging (MRI) or multislice computed tomography (CT) of the abdomen and pelvis within 16 wk before randomization. The full inclusion and exclusion criteria can be found at ClinicalTrials.gov (NCT01272050). The ethics committee at each center reviewed and approved the protocol.

2.2. Randomization and masking

Randomization was performed online using the password-protected Sinatras data management system. Patients were randomly assigned in a 1:1 ratio and stratified according to Gleason score (≥8 vs 7 vs ≤6), tumor classification (pT3b vs others), lymphadenectomy (no [cN0] vs positive [pN0]), persistent PSA after surgery (≥0.1 vs <0.1 ng/ml), PSA at randomization (>0.5 vs ≤0.5 ng/ml), center, and SRT technique (three-dimensional conformal radiotherapy [3D-CRT] vs intensity-modulated radiotherapy [IMRT]/rotational techniques) using the minimization method with 90% allocation probability. Owing to the different treatment durations, patients and physicians could not be masked to allocation.

2.3. Treatment and follow-up procedures

RP was performed at least 12 wk before randomization and was not part of this trial. All RP techniques were permitted. Within 16 wk before randomization, either MRI (recommended) or CT of the abdomen and pelvis was mandatory to exclude macroscopic local recurrence or lymph node metastases. SRT was administered to a total dose of 64 Gy in 32 fractions (2 Gy over 6.4 wk in the standard arm (arm A) and to 70 Gy in 35 fractions (2 Gy over 7 wk) in the experimental arm (arm B).

CT simulation of treatment planning was required. Patients were positioned in the supine position and treated with a comfortably full bladder and empty rectum.

The prostate bed, clinical target volume (CTV), and planning target volume (PTV) were contoured according to the European Organisation for Research and Treatment of Cancer (EORTC) guidelines. PTV was defined as CTV + 10-mm margins in all directions except for an 8–10-mm margin posteriorly. Margins were reduced to a minimum of 5 mm for centers using image-guided SRT.

Dose prescription was at the median dose (D50%) for the PTV. Dose variation in the PTV was required to be within +7%/−5% of the prescribed dose; in other words, the 95% isodose encompassed the PTV.

Organs at risk (OAR) included the bladder, rectum, and femoral heads. The rectum was contoured from the anus to the rectosigmoid flexure or the caudal part of the sacroiliac joint. Besides whole-organ delineation, the bladder wall (BW) and rectal wall (RW) were contoured using a 5-mm internal margin. OAR constraints were as follows: RW, volume at 60 Gy (V60Gy) ≤50% and V70Gy ≤20%; BW, V65Gy ≤50%; and femoral heads, V50Gy ≤10%. Megavoltage equipment with nominal photon energy ≥6 MV was required. The protocol allowed use of 3D-CRT, IMRT, and rotational techniques, including tomotherapy and the volumetric modulated arc technique [12].

2.4. Endpoints and sample size

The primary endpoint was FFBP, defined as the time from randomization to biochemical progression, clinical progression, or death due to clinical progression, whichever occurred first. Biochemical progression was defined as post-SRT occurrence of an absolute serum PSA ≥0.4 ng/ml, rising compared to the previous value. The trial was designed as a two-arm phase 3 superiority trial, assuming a median FFBP of ≤3.8 yr for the null hypothesis and ≥5.8 yr for the alternative hypothesis (hazard ratio [HR] 0.6526), based on an estimated increase in FFBP of 2.5% per 1-Gy increment in dose intensification. The one-sided type I error was 5% with 80% power. The number of events required for the primary analysis was 139, and the sample size was 350 patients.

Secondary endpoints included clinical progression-free survival (PFS), time to hormonal treatment, overall survival (OS), acute and late toxicity, and QoL. Clinical PFS was defined as the time from randomization to the first record of local, regional, or distant recurrence (all detected via imaging according to the choice of the treating center); the start of hormonal treatment; or death due to any cause. Time to hormonal treatment was defined as the time from randomization until the start of hormonal treatment. OS was defined as the time from randomization until death due to any cause. Acute and late gastrointestinal (GI) and genitourinary (GU) toxicity was assessed according to Common Terminology Criteria for Adverse Events (CTCAE) v4.0. Acute toxicity events were defined as those occurring during treatment or within 3 mo thereafter. Late events were those occurring ≥3 mo after treatment.

Rapid biochemical progression was defined as a rising PSA level at any time within 6 mo after completion of SRT.

The baseline PSA doubling time after RP was calculated from the natural log of 2, divided by the slope of the relationship between the time of PSA measurement and the log of PSA using linear regression for each patient for all PSA measurements from RP until randomization.

QoL was assessed using the EORTC QLQ-C30 v3 questionnaire [13], the PC module QLQ-PR25 [14], and an adapted instrument for overall treatment burden [15]. The urinary symptoms score (QLQ-PR25) at 3 yr after SRT completion was defined as the primary QoL endpoint. The symptom and function scales and single items of the QLQ-C30 and the QLQ-PR25 were scored and linearly transformed to a scale of 0–100 (EORTC manual). A higher score for symptom scales and items indicates a worse condition, while a higher score for functional scales or global health status/QoL indicates a better condition. The indicator for overall burden was linearly transformed to a scale of 0–100, with higher scores indicating a greater burden. Clinically meaningful changes were defined for the QLQ-C30 according to reference data [16,17] and for the QLQ-PR25 and overall burden according to a distribution-based measure [18] as ≥3.3 points in either direction; we considered the cutoff for changes in QLQ-PR25 defined in the trial protocol (ie, 10 points) as too conservative [17]. Submission rates were defined as the percentage of completed versus expected questionnaires.

2.5. Statistical analysis

Analysis was based on the intention-to-treat (ITT) population (defined as all patients without major eligibility deviations who started SRT) for all efficacy endpoints, and on the safety population (defined as all patients who started SRT) for all safety endpoints. Sensitivity analyses based on the per-protocol population were performed for the primary endpoint.

All time-to-event endpoints are summarized as the median and corresponding 95% confidence interval (CI) using the Kaplan-Meier method and compared using log-rank tests. HRs were calculated via Cox regression. Furthermore, time-to-event endpoints were analyzed at 6 yr after randomization. Competing-risk analyses were conducted as supportive analyses.

Predefined GI and GU toxicity events are described by type, grade, frequency, and percentage by treatment arm across all time points (recording the worst grade). The occurrence of late grade ≥2 toxicity, for any increase in grade over baseline symptoms, was compared between treatment arms using Fisher's exact tests.

QoL symptom and function scales and single items are summarized at each time point using descriptive statistics. Repeated mixed models were applied to analyze the effect over time by treatment arm. The primary QoL endpoint of urinary symptoms at 3 yr after completing SRT was compared between the treatment arms using *t* tests.

Two-tailed tests with a significance level of 0.05 were used for all analyses. As no adjustment for multiple testing was made, all analyses except the primary endpoint analysis were exploratory and hypothesis-generating. All analyses were performed using SAS v9.4 (SAS Institute, Cary, NC, USA) and R v3.6.0 (The R Foundation; www.r-project.org).

3. Results

3.1. Patient characteristics

Between February 2011 and April 2014, 350 patients were assigned to receive either conventional-dose (n = 175) or dose-intensified (n = 175) SRT. Three patients (2 in the 64 Gy and 1 in the 70 Gy arm) received no SRT because of withdrawal of consent, and three (all in the 64 Gy arm) were found to be ineligible after randomization and were excluded from the ITT population. One patient from the 64 Gy arm received 70 Gy and was included in the ITT analysis for the 64 Gy arm but in the 70 Gy arm for the treatment-received analysis. This resulted in 170 (64 Gy) and 174 patients (70 Gy) in the ITT population (Fig. 1). The mean dose to the PTV was 64.0 Gy (interquartile range [IQR] 64.0–64.2) for the 64 Gy arm and 70.0 Gy (IQR 70.0–70.1) in the 70 Gy arm.

Baseline patient characteristics are summarized in Table 1. The median PSA at randomization was 0.3 ng/ml (IQR 0.2–0.5). The median PSA velocity from RP to randomization was 0.1 ng/ml/yr in both arms. The median PSA doubling time was 216.5 d (IQR 128–392) in the 64 Gy

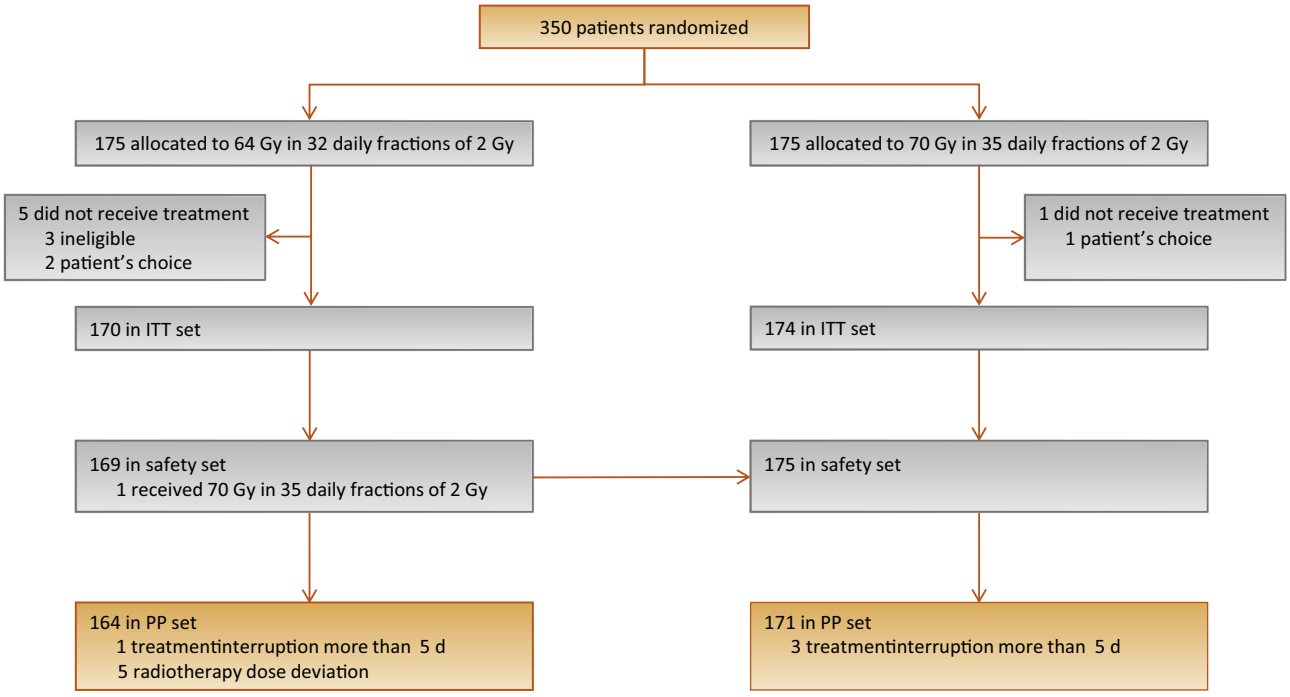

Fig. 1 – CONSORT diagram for the SAKK 09/10 randomized trial. ITT = intention to treat; PP = per protocol.

arm and 264.5 d (IQR 143–502) in the 70 Gy arm. Staging was performed via MRI in 120 patients (34.9%) and CT in 224 (65.1%). At the time of data cutoff (July 3, 2020), the median follow-up was 6.2 yr (IQR 5.5–7.2) with a total of 138 biochemical progression events, of which 65 occurred in the 64 Gy arm and 73 in the 70 Gy arm (Table 2). Median follow-up for patients without a biochemical progression event was 6.3 yr (IQR 6.1–7.2). Median FFBP was 8.2 yr in the

Table 1 – Patient characteristics for the intention-to-treat population (*N* = 344)

Variable	Arm A (64 Gy) (*N* = 170)	Arm B (70 Gy) (*N* = 174)
Median PSA before prostatectomy, ng/ml (IQR)	8.1 (5.4–11.6)	7.6 (5.3–12.7)
R0 resection margins, *n* (%)	92 (54)	98 (56)
Gleason score, *n* (%)		
≤6	25 (15)	26 (15)
7	115 (68)	115 (66)
≥8	30 (18)	33 (19)
Tumor classification, *n* (%)		
pT2a	7 (4.1)	12 (6.9)
pT2b	3 (1.8)	8 (4.6)
pT2c	93 (55)	81 (47)
pT3a	49 (29)	54 (31)
pT3b	18 (11)	19 (11)
Lymphadenectomy performed (pN0), *n* (%)	150 (88)	151 (87)
Median number of lymph nodes removed, *n* (IQR)		
Left	5 (3–8)	5 (3–7)
Right	5 (3–8)	5 (3–7)
Persistent PSA ≥0.1 ng/ml after prostatectomy, *n* (%)	35 (21)	35 (20)
PSA ≤0.5 ng/ml at randomization, *n* (%)	129 (76)	129 (74)
EAU high risk, *n* (%) [a]	129 (76)	121 (70)
GETUG high risk, *n* (%) [b]	124 (73)	121 (70)
Median age at randomization, yr (IQR)	67 (63–71)	66 (62–70)
Median time from surgery to RT start, mo (IQR)	25.9 (14.0–42.3)	30.3 (15.8–50.8)
WHO performance status 0 at treatment start, *n* (%)	160 (94)	161 (93)
Radiation therapy technique, *n* (%)		
Three-dimensional conformal radiation therapy	74 (44)	77 (44)
IMRT/rotational techniques	96 (57)	97 (56)

PSA = prostate-specific antigen; WHO = World Health Organization; EAU = European Association of Urology; GETUG = Groupe d'Étude des Tumeurs Uro-Génitales; IMRT = intensity-modulated radiation therapy.
[a] EAU high risk: PSA doubling time ≤1 yr or Gleason score ≥8.
[b] GETUG high risk: Gleason score ≥8, or negative surgical margins, or PSA doubling time at relapse of ≤6 mo, or seminal vesicle involvement (pT3b).

Table 2 – Type of events for time-to-event endpoints

Variable	Patients (*n*)	
	Arm A (64 Gy) (*N* = 170)	Arm B (70 Gy) (*N* = 174)
Freedom from biochemical progression event	65	73
Biochemical progression	63	71
Clinical progression	2	2
Clinical progression-free survival event	51	51
Local recurrence [a]	9	2
Local and regional recurrence	2	2
Local and distant recurrence	0	1
Regional recurrence	11	17
Regional and distant recurrence	4	2
Distant recurrence	11	12
Hormonal treatment	4	9
Death	10	6
Initiation of hormonal treatment	30	32
Reason for administering hormonal treatment		
Evidence of metastatic disease	11	13
Gleason score 8–10	1	1
Lymph node progression	3	2
Prostate-specific antigen doubling time <12 mo	14	17
Rising prostate-specific antigen	2	5
Other	2	0

[a] Of the local recurrences, ten were deemed to be in-field, three were marginal, two were out-of-field, and one was unknown (no imaging).

64 Gy arm and 7.6 yr in the 70 Gy arm (log-rank $p = 0.4$; Fig. 2), with a HR of 1.14 (95% CI 0.82–1.60). Competing-risk analyses revealed similar results (HR 1.17, 95% CI 0.61–1.20; $p = 0.4$; Supplementary Fig. 1). The estimated FFBP rate at 6 yr was 62% in the 64 Gy arm and 61% in the 70 Gy arm.

Clinical PFS, time to hormonal treatment, and OS did not significantly differ between the two arms (Fig. 2, Table 2).

3.2. *Late GU and GI toxicity*

Late grade 2 and 3 GU toxicity was observed in 35 (21%) and 13 (7.9%) patients treated with 64 Gy, and 46 (26%) and seven (4%) patients treated with 70 Gy, respectively (odds ratio [OR] for grade ≥2 GU toxicity 1.06, 95% CI 0.66–1.73; $p = 0.8$). No patient experienced grade 4 late GU toxicity.

Late grade 2 and 3 GI toxicity was observed in 12 (7.3%) and seven (4.2%) patients treated with 64 Gy, and 35 (20%) and four (2.3%) patients treated with 70 Gy, respectively (OR for grade ≥2 GI toxicity 2.20, 95% CI 1.21–4.00; $p = 0.009$). No grade 4 late GI toxicities were noted.

Late grade 3 erectile dysfunction did not differ significantly between the two arms (27% vs 30%; OR 1.19, 95% CI 0.75–1.92; $p = 0.5$).

No significant differences in late GI toxicity between the IMRT/rotational techniques and 3D-CRT were observed (OR 0.95, 95% CI 0.54–1.68; $p = 0.9$). For late GU toxicity, the grade ≥2 incidence was higher for 3D-CRT (35%) than for IMRT/rotational techniques (26%), but the difference did not reach conventional statistical significance (OR 0.64, 95% CI 0.40–1.03; $p = 0.073$).

3.3. *Quality of life*

The questionnaire submission rate was 99% at baseline, 94% at 3 mo, 88% at 1 yr, 84% at 2 yr, 78% at 3 and 4 yr, and 70% at 5 yr. Completed questionnaires had few missing data, with the exception of sexual functioning and overall burden (Supplementary Table 1). The baseline global health status/QoL results showed particular impairment of emotional functioning, urinary symptoms, problems with an incontinence aid (conditional), sexual activity and functioning, and overall burden (Table 3).

At 3 yr after SRT completion, there was no significant difference in urinary symptoms compared to baseline between the two arms, with mean worsening of 3.5 points ($n = 112$, standard deviation [SD] = 13.1) for the 64 Gy arm and 6.6 points ($n = 103$, SD = 15.6) for the 70 Gy arm (primary QoL endpoint; mean difference between the arms 3.1 points, 95% CI −0.78 to 6.9; $p = 0.12$; Fig. 3). This worsening was clinically significant for both arms according to our criterion (ie, changed metric from the protocol). Over the whole observation period, urinary symptoms deteriorated over time ($p = 0.001$) independent of the treatment arm (interaction: $p = 0.4$).

There was no significant treatment difference for the other QoL domains over time and no treatment-by-time interaction (Supplementary Table 2). In particular, the difference in late grade 2 and 3 GI toxicity observed was not reflected in the patient-reported QoL scores. Overall, the changes from baseline were small across the treatment groups (Fig. 3). Bowel symptoms showed marginal improvement. Over time, there was minor worsening of physical ($p = 0.003$) and cognitive ($p = 0.001$) functioning, dyspnea ($p = 0.003$), hormonal treatment–related symptoms ($p = 0.046$), and overall burden ($p = 0.01$; Supplementary Table 2). A substantial minority of patients reported a clinically meaningful improvement in emotional functioning and sexual activity over the entire observation period (Fig. 3).

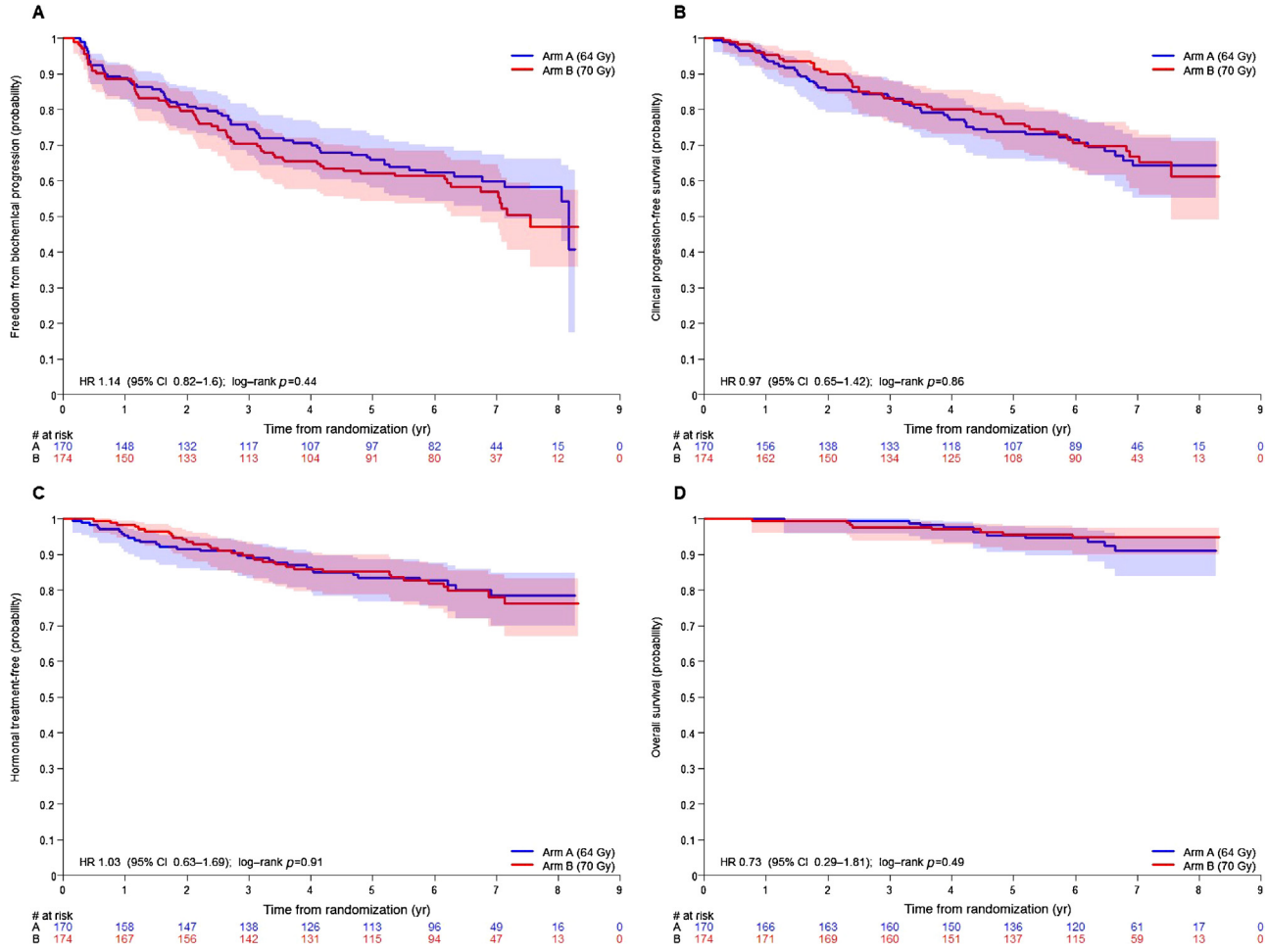

Fig. 2 – Kaplan-Meier analysis of (A) biochemical progression–free, (B) clinical progression–free, (C) hormonal treatment–free, and (D) overall survival. HR = hazard ratio; CI = confidence interval.

Regarding the change in urinary symptoms at 3 yr, there was no significant difference between shorter (≤12 mo) and longer time (>12 mo) from RP to treatment start (mean difference 2.2 points, 95% CI −2.9 to 7.3; $p = 0.5$) or between the 3D-CRT and IMRT/rotational radiation techniques (mean difference 2.0 points, 95% CI −1.9 to 5.8; $p = 0.3$).

4. Discussion

The SAKK 09/10 trial delivered three main results: (1) dose-intensified SRT for biochemically relapsed PC was not superior to conventional-dose SRT regarding FFBP; (2) SRT-related late GI toxicity was higher after dose-intensified SRT; and (3) dose intensification had no significant impact on patient-reported symptom burden.

In our cohort of patients with median PSA of 0.3 ng/ml at randomization, including approximately 75% with PSA ≤0.5 ng/ml without additional hormonal therapy or elective radiation of the pelvic lymph nodes, the 6-yr FFBP rates compare favorably with large multi-institutional cohorts [4,5]. After a median SRT dose of 68 Gy, 5-yr FFBP rates of 63% for patients with PSA 0.21–0.50 ng/ml and 54% for those with PSA 0.51–1.0 ng/ml have been reported [4]. After a median SRT dose of 66 Gy, 5-yr cumulative incidence of biochemical progression of 49.9% was also reported [5].

A recent randomized trial compared adjuvant radiation therapy with SRT using 64 Gy without hormonal therapy or elective radiation of the pelvic lymph-nodes reported a 5-yr FFBP rate of 87% [19]. This trial included patients with lower pre-SRT PSA levels than in our cohort and used target volume specifications based on the Faculty of Radiation Oncology Genito-Urinary Group guidelines, which are significantly greater than the EORTC recommendations used in our trial [20].

A small randomized trial of 144 patients who underwent SRT (67%) and adjuvant postoperative radiation therapy compared doses of 66 Gy and 72 Gy and found no differences in biochemical PFS or acute and late GU or GI toxicities after limited follow-up [21].

The results of our trial do not support earlier findings from retrospective studies that SRT dose intensification improves tumor outcomes [4,5,7–10]. There may be various reasons for this discordant finding, including selection bias

Table 3 – Quality-of-life scores at baseline

Variable	ITT population ($N = 344$)	
	Patients (n)	Mean score (SD)
Functional scales [a]		
Physical functioning	339	95.3 (9.7)
Role functioning	339	92.8 (17.2)
Emotional functioning	336	81.6 (18.4)
Cognitive functioning	337	91.0 (13.8)
Social functioning	337	88.1 (19.3)
Sexual functioning	200	45.5 (21.2)
Sexual activity	333	57.4 (25.8)
Global health status/quality of life [a]	336	78.0 (18.4)
Symptom scales/items [b]		
Fatigue	339	11.5 (16.4)
Nausea/vomiting	339	1.2 (5.0)
Pain	339	8.8 (18.0)
Dyspnea	339	6.8 (15.7)
Insomnia	338	14.4 (20.8)
Appetite loss	338	2.4 (10.3)
Constipation	336	6.7 (16.7)
Diarrhea	337	6.1 (14.6)
Financial problems	337	6.2 (17.0)
Urinary symptoms	336	15.8 (13.1)
Bowel symptoms	335	3.6 (7.3)
Hormonal treatment-related symptoms	336	9.4 (9.8)
Incontinence aid	126	17.5 (24.1)
Overall burden	263	34.8 (25.6)

ITT = intention to treat; SD = standard deviation.
[a] Range 0–100, with a higher score indicating a better condition.
[b] Range 0–100, with a higher score indicating a worse condition.

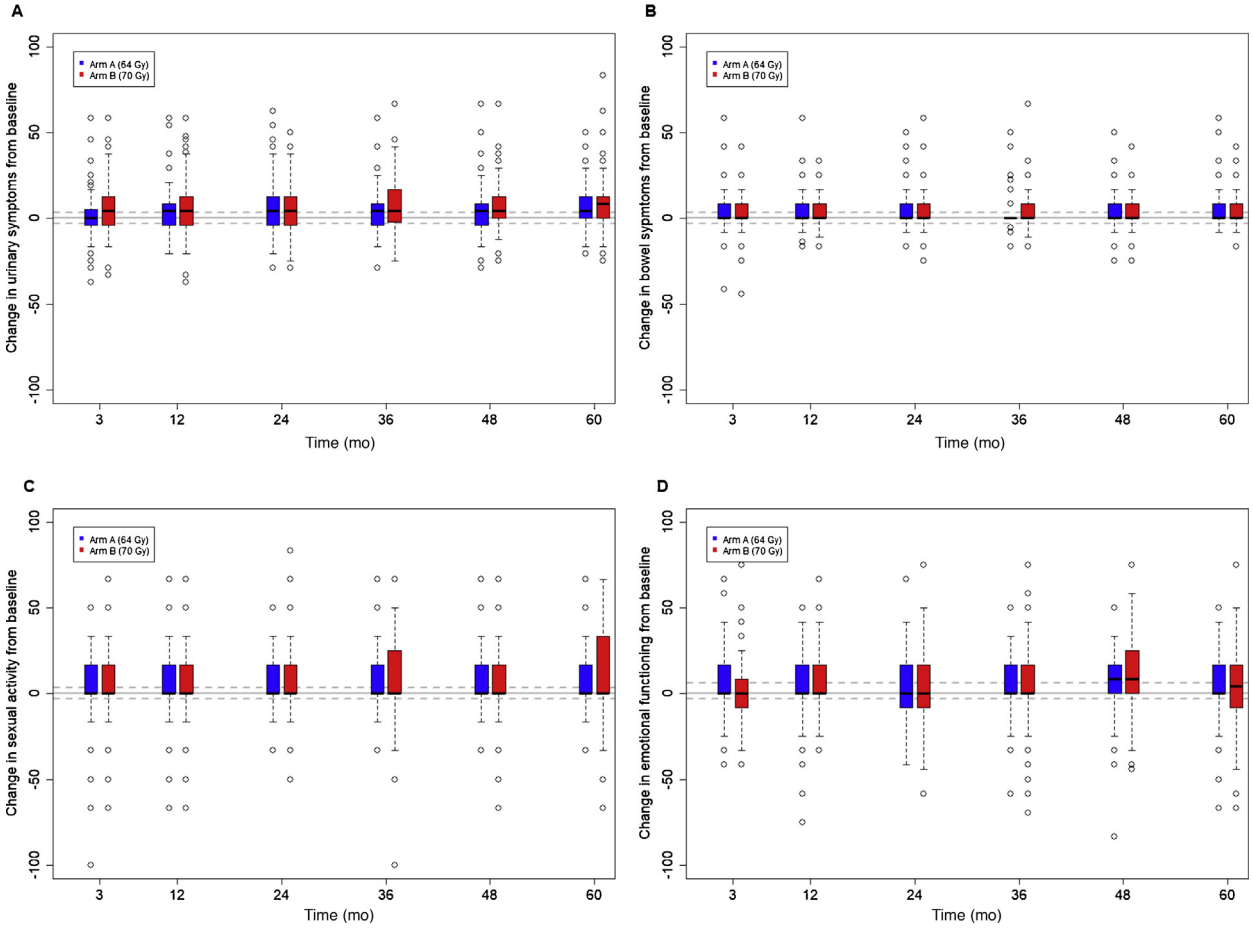

Fig. 3 – Changes from baseline in (A) urinary symptoms, (B) bowel symptoms, (C) sexual activity, and (D) emotional functioning.

in retrospective studies, as patients who received dose-intensified SRT were more likely to have been treated with more contemporary IMRT/rotational techniques with shorter follow-up, and the more stringent omission of patients with macroscopic local recurrence in our trial.

We did our best at the time of trial initiation to ensure exclusion of patients with macroscopic disease identified via conventional pelvic MRI or CT. We can only speculate whether contemporary state-of-the-art prostate-specific membrane antigen positron emission tomography/CT in our trial would have been able to detect disease outside the prostate bed or macroscopic local recurrences. The NRG Oncology/RTOG 0534 SPPORT trial has shown a 5-yr freedom from disease progression benefit with addition of elective pelvic nodal treatment to prostate bed irradiation and 4-6 mo of hormonal treatment [22]. The GETUG-AFU16 study demonstrated an improvement in 5-yr PFS when SRT was combined with 6 mo of hormonal treatment as compared to SRT alone (80% vs 62%) [23]. No comment can be made on whether elective pelvic nodal treatment and/or hormonal treatment would have changed our results. However, the fact that only 18% of the total patient cohort in our trial received hormonal treatment for biochemical or clinical progression after SRT suggests that upfront combined hormonal treatment and SRT might lead to overtreatment.

Both the EAU and GETUG have developed criteria for identification of individuals at high risk of metastatic disease among patients with biochemical recurrence [23,24], but these could not predict the effectiveness of dose-intensified SRT in our trial. Thus, new risk groups based on clinical, histopathological, or novel genomic parameters [25] are needed for precise outcome prediction.

In addition to FFBP, other endpoints such as clinical PFS, time to hormonal treatment, and OS did not differ between the two arms in our trial.

Patient-reported late GU and GI toxicity rates compared well with previously reported late grade $\geq$2 GU and GI rates after SRT of 54% and 10%, respectively [19].

The use of smaller target volumes according to EORTC recommendations and the use of IMRT/rotational techniques in approximately 50% of patients may have contributed to the good tolerability in our trial. In the primary PC radiotherapy setting, a randomized controlled trial suggested that IMRT significantly reduced both acute and late GI and GU grade $\geq$2 toxicity compared to 3D-CRT [26].

We have described a risk-adapted dose intensification approach for postoperative radiation therapy after RP in which the prostate bed is treated with a moderate dose of 66.6 Gy using a focal simultaneous integrated boost for high-risk areas of the bed up to 70.3 Gy [27]. Moreover, randomized trials are currently studying the role of hypofractionation for postoperative radiation therapy after RP using photons (NRG GU-003) or protons [28].

Overall, the impact of SRT led to minor changes in QoL over a period of 5 yr after randomization. The more pronounced early worsening of urinary symptoms among patients receiving 70 Gy [11] was not observed at subsequent assessments. The findings of GI toxicity according to CTCAE v4.0 were not reflected in a treatment-related difference in patient-reported scores for their bowel symptoms. Notably, we observed an increase in late grade 2 but not grade 3 GI symptoms after dose-intensified SRT.

It is important to acknowledge the limitations of our trial. The RW dose constraints used were rather permissive; for instance, V60Gy was required to be $\leq$50%. IMRT/rotational techniques can usually achieve lower rectal doses, and thus application of tighter rectal constraints may reduce the rate of late GI toxicity in current clinical practice. Another limitation is the relatively small proportion of patients with Gleason score >7 and pT3b disease.

5. Conclusions

In conclusion, dose-intensified SRT was not superior to conventional-dose SRT, but was associated with higher rates of late grade $\geq$2 GI toxicity, which was not reflected in QoL. To further improve outcomes for patients with biochemical progression after RP, future studies and clinical trials should improve patient selection to allow individualized SRT treatment.

Author contributions: Pirus Ghadjar had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Ghadjar, Zwahlen, Thalmann, Aebersold.
Acquisition of data: Ghadjar, Zwahlen, Hölscher, Gut, Polat, Hildebrandt, Müller, Plasswilm, Papachristofilou, Sumila, Zaugg, Guckenberger, Ost, Reuter, Bosetti, Khanfir, Gomez, Wust, Thalmann, Aebersold.
Analysis and interpretation of data: Ghadjar, Hayoz, Bernhard, Zwahlen, Thalmann, Aebersold.
Drafting of the manuscript: Ghadjar, Hayoz, Bernhard, Zwahlen, Thalmann, Aebersold.
Critical revision of the manuscript for important intellectual content: Ghadjar, Hayoz, Bernhard, Zwahlen, Hölscher, Gut, Polat, Hildebrandt, Müller, Plasswilm, Papachristofilou, Schär, Sumila, Zaugg, Guckenberger, Ost, Reuter, Bosetti, Khanfir, Gomez, Wust, Thalmann, Aebersold.
Statistical analysis: Hayoz.
Obtaining funding: Ghadjar, Zwahlen, Thalmann, Aebersold.
Administrative, technical, or material support: Hayoz, Bernhard, Schär.
Supervision: Ghadjar, Zwahlen, Thalmann, Aebersold.
Other: None.

Financial disclosures: Pirus Ghadjar certifies that all conflicts of interest, including specific financial interests and relationships and affiliations relevant to the subject matter or materials discussed in the manuscript (eg, employment/affiliation, grants or funding, consultancies, honoraria, stock ownership or options, expert testimony, royalties, or patents filed, received, or pending), are the following: None.

Funding/Support and role of the sponsor: The SAKK 09/10 trial was funded by grants provided by the Hedy and Werner Berger-Janser Foundation, Krebsforschung Schweiz (Swiss Cancer Research Foundation), Radio-Onkologie Berner Oberland AG, Switzerland, and the Swiss State Secretariat for Education, Research and Innovation (SERI). The sponsors played no direct role in the study.

Acknowledgments: We thank the patients and all the investigators and research support staff at the SAKK 09/10 participating centers.

Appendix A. SAKK 09/10 Trialists

The principal and main co-investigators of the SAKK 09/10 trial according to participating center (number of patients recruited) were as follows:

Switzerland

Kantonsspital Luzern ($n = 30$): P. Gut, P. Thum
Kantonsspital St. Gallen ($n = 20$): J. Collon, P.M. Putora, L. Plasswilm
Bern University Hospital ($n = 17$): M. Sassowsky, G.N. Thalmann, D.M. Aebersold
Hirslanden Hospital Group Zürich ($n = 15$): M. Sumila
Stadtspital Triemli ($n = 15$): H. Kranzbühler, K. Zaugg
Basel University Hospital ($n = 15$): A. Papachristofilou, F. Zimmermann
Zürich University Hospital ($n = 14$): Y. Najafi, M. Brown, M. Guckenberger
Kantonsspital Münsterlingen ($n = 13$): S. Wuttke, C. Reuter
Kantonsspital Graubünden ($n = 12$): C. Oehler, D.R. Zwahlen
Istituto Oncologico della Svizzera Italiana ($n = 12$): N.C. Azinwi, D.G. Bosetti, G. Pesce
Kantonsspital Aarau ($n = 12$): I. Tacacs, S. Bodis, S. Gomez
Hôpital du Valais ($n = 11$): K. Khanfir
Radioonkologiezentrum Biel ($n = 3$): F. Behrensmeier, K. Beer
Radioonkologie Berner Oberland ($n = 3$): P. Messer

Germany

Dresden University Hospital ($n = 41$): T. Hölscher, M. Baumann
Würzburg University Hospital ($n = 30$): B. Polat, M. Flentje
Rostock University Hospital ($n = 28$): V. Lewitzki; G. Hildebrandt
Tübingen University Hospital ($n = 26$): A.C. Müller, D. Zips
Charité Universitätsmedizin Berlin ($n = 10$): P. Ghadjar, P. Wust, V. Budach
University Munich ($n = 7$): U. Ganswindt, C. Belka
Aachen University Hospital ($n = 2$): M. Pinkawa, M.J. Eble
Essen University Hospital ($n = 2$): K. Berkovic, M. Stuschke

Belgium

University Ghent ($n = 9$): P. Ost
Ziekenhuis Netwerk Antwerp ($n = 4$): F. Vandaele

Appendix B. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.eururo.2021.05.033.

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