Aus der Klinik für Radioonkologie und Strahlentherapie
der Medizinischen Fakultät Charité – Universitätsmedizin Berlin

DISSERTATION

Postoperative Bestrahlung von Patienten mit Prostatakarzinom unter Verwendung eines risikoadaptierten Boost mittels des Tomotherapie-Bestrahlungssystems.

zur Erlangung des akademischen Grades
Doctor medicinae (Dr. med.)

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von

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aus Gunzenhausen

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INHALTSVERZEICHNIS

Postoperative Bestrahlung von Patienten mit Prostatakarzinom unter Verwendung eines risikoadaptierten Boost mittels des Tomotherapie-Bestrahlungssystems.

Abstrakt

Einleitung: Sowohl die postoperative adjuvante Bestrahlung bei Vorliegen eines Prostatakarzinoms im Stadium T3 und/oder eines R1-Resektionsstatus als auch die Salvage-Bestrahlung im Falle eines postoperativen biochemischen Rückfalls des Prostatakarzinoms stellen etablierte Standardbehandlungsverfahren dar. Durch eine Dosiseskalation bei der postoperativen Bestrahlung konnten in früheren Studien überlegene biochemische Kontrollraten erzielt werden bei jedoch zeitgleich erhöhten Nebenwirkungsraten. In unserer Studie untersuchten wir ein neues risikoadaptiertes dosiseskaliertes Bestrahlungsschema. **Methodik:** Es erfolgte eine retrospektive Analyse aller Patienten, welche zwischen 04/2012 und 04/2015 eine postoperative Bestrahlung nach radikaler Prostatektomie am Tomotherapie-Bestrahlungssystem erhalten haben. Die postoperative Bestrahlung wurde unter Verwendung eines simultan-integrierten Boost (SIB) im Risikobereich (37 Bestrahlungsfraktionen mit einer Einzeldosis von 1,9 Gy, Gesamtdosis von 70,3 Gy) und mit einer Dosis von 66,6 Gy (37 Bestrahlungsfraktionen mit einer Einzeldosis von 1,8 Gy) im Gebiet der Prostataloge appliziert. Das Risikogebiet wurde anhand histopathologischer Befunde (T3- bzw. R1-Region) und in einzelnen Fällen unter Zuhilfenahme von erweiterter Bilddiagnostik definiert. Als primärer Endpunkt wurde die akute und späte urogenitale wie auch gastrointestinale Nebenwirkungsrate festgelegt. Sekundäre Endpunkte waren die vom Patienten mittels „International Prostate Symptom Score“ (IPSS) und „International Consultation on Incontinence questionnaire“ (ICIQ) Fragebogen berichteten Symptome, sowie die mittels „prostate cancer specific Quality of Life questionnaire“ (QLQ-PR25) festgehaltene Beeinflussung der Lebensqualität. Außerdem stellte die biochemische Kontrolle einen sekundären Endpunkt dar. **Ergebnisse:** Insgesamt konnten 69 Patienten in die Auswertung eingeschlossen werden, wobei 16 Patienten eine adjuvante und 53 Patienten eine Salvage-Bestrahlung erhalten hatten. Bei einem medianen Nachbeobachtungszeitraum von 20 Monaten (8-41 Monate) zeigten sich bei 7 Patienten (10,1%) akute urogenitale Nebenwirkungen 2.Grades und bei 4 Patienten (5,8%) akute gastrointestinale Nebenwirkungen 2.Grades, während keine höhergradigen akuten Nebenwirkungen auftraten. An späten Nebenwirkungen konnten außer bei 2 Patienten (2,9%) festgestellte urogenitale Beschwerden 2.Grades keine weiteren zweit- oder

höhergradigen urogenitalen oder gastrointestinalen Nebenwirkungen registriert werden. Im Vergleich zu den Ausgangswerten vor Beginn der Bestrahlung zeigten sich am Ende des Beobachtungszeitraums keine statistisch signifikanten Veränderungen der patientenberichteten Symptome (IPSS, p=1,0), (ICIQ, p=0,87) und ebenfalls keine signifikante Veränderung der berichteten Lebensqualität. Insgesamt entwickelten 7 Patienten (10,1%) einen biochemischen Rückfall und somit ergibt sich ein 2-jähriges biochemisch progressions-freies Überleben von 91%. **Schlussfolgerung:** Das untersuchte neue postoperative risikoadaptierte dosiseskalierte Bestrahlungsschema bei Patienten mit Prostatakarzinom zeigte eine geringe Rate an akuten und späten urogenitalen und gastrointestinalen Nebenwirkungen ohne einhergehende signifikante Beeinflussung von IPSS-, ICIQ-Werten und der Lebensqualität. Außerdem konnte ein vielversprechendes biochemisch progressions-freies Überleben beobachtet werden.

Risk adapted dose-intensified postoperative radiation therapy in prostate cancer patients using a simultaneous integrated boost technique applied with helical Tomotherapy.

Abstract:

Background: Postoperative adjuvant radiation therapy (ART) in T3 and R1 prostate cancer as well as salvage radiation therapy (SRT) in case of postoperative biochemical failure (BF) are established treatments. Dose-intensified postoperative radiation therapy (RT) schemes have shown superior biochemical control accompanied by increased toxicity rates. In our study we evaluate a novel risk adapted dose-intensified postoperative RT scheme. **Methods:** A consecutive series of prostate cancer patients receiving postoperative RT after radical prostatectomy using helical Tomotherapy between 04/2012 and 04/2015 was analyzed retrospectively. RT was administered using a simultaneous integrated boost (SIB) to the area at risk (37 fractions of 1.9 Gy, total dose: 70.3 Gy) being defined based on histopathological findings (T3/R1 region) and in few cases according to additional diagnostic imaging. The whole prostate bed was treated with a dose of 66.6 Gy (37 fractions of 1.8 Gy). Primary endpoints were acute and late genitourinary (GU) and gastrointestinal (GI) toxicities. Secondary endpoints included patient reported outcome as assessed by the International Prostate Symptom Score (IPSS), the International Consultation on Incontinence questionnaire (ICIQ) and prostate cancer specific Quality of Life questionnaire QLQ-PR25, as well as rates of BF. **Results:** A total of 69 patients were analyzed. Sixteen patients underwent ART and 53 patients SRT, respectively. The median follow-up was 20 months (range, 8-41 months). Seven (10.1%) and four (5.8%) patients experienced acute grade 2 GU and GI toxicity. Two patients (2.9%) had late grade 2 GU toxicity, whereas no late grade 2 GI nor any grade 3 acute or late GU or GI events were observed. When compared to the baseline IPSS scores (p=1.0) and ICIQ scores (p=0.87) were not significantly different at the end of follow-up. Patient reported Quality of life (QoL) showed also no significant difference. A total of seven patients (10.1%) experienced a biochemical recurrence with the 2-year biochemical progression-free survival (bPFS) being 91%. **Conclusions**: Postoperative RT for prostate cancer patients with a risk adapted dose-intensified SIB using helical tomotherapy is feasible and associated with favorable acute and late GU and GI toxicity rates, no significant change of IPSS-, ICIQ scores and patient reported QoL and results in promising bPFS rates.

Eidesstattliche Versicherung

„Ich, Marcus Beck, versichere an Eides statt durch meine eigenhändige Unterschrift, dass ich die vorgelegte Dissertation mit dem Thema: „Postoperative Bestrahlung von Patienten mit Prostatakarzinom unter Verwendung eines risikoadaptierten Boost mittels des Tomotherapie-Bestrahlungssystems“ selbstständig und ohne nicht offengelegte Hilfe Dritter verfasst und keine anderen als die angegebenen Quellen und Hilfsmittel genutzt habe.
Alle Stellen, die wörtlich oder dem Sinne nach auf Publikationen oder Vorträgen anderer Autoren beruhen, sind als solche in korrekter Zitierung (siehe „Uniform Requirements for Manuscripts (URM)“ des ICMJE -*www.**icmje**.org*) kenntlich gemacht. Die Abschnitte zu Methodik (insbesondere praktische Arbeiten, Laborbestimmungen, statistische Aufarbeitung) und Resultaten (insbesondere Abbildungen, Graphiken und Tabellen) entsprechen den URM (s.o) und werden von mir verantwortet.
Mein Anteil an der ausgewählten Publikation entspricht dem, der in der untenstehenden gemeinsamen Erklärung mit dem Betreuer, angegeben ist. Sämtliche Publikationen, die aus dieser Dissertation hervorgegangen sind und bei denen ich Autor bin, entsprechen den URM (s.o) und werden von mir verantwortet.
Die Bedeutung dieser eidesstattlichen Versicherung und die strafrechtlichen Folgen einer unwahren eidesstattlichen Versicherung (§156,161 des Strafgesetzbuches) sind mir bekannt und bewusst.“

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Datum Unterschrift

<u>Ausführliche Anteilserklärung an der erfolgten Publikation</u>

Publikation: [Beck M, Wust P, Barelkowski T, Kaul D, Thieme AH, Wecker S, Wlodarczyk W, Budach V, Ghadjar P], [Risk adapted dose-intensified postoperative radiation therapy in prostate cancer patients using a simultaneous integrated boost technique applied with helical Tomotherapy], [Radiation Oncology], [2017;12(1):125]

Beitrag im Einzelnen:

Beck M. führte die Erhebung der Daten (Aktenstudium und Follow-Up Untersuchungen) und die Aufbereitung der Daten (Anlegen von Excel und SPSS Tabellen) durch. Mit Unterstützung durch den Doktorvater Ghadjar P. erfolgte die Analyse der Daten und deren statistische Auswertung (Excel und SPSS). Beck M. führte die Bewertung der Ergebnisse im Kontext der vorhandenen Literatur (ausführliches Literaturstudium) durch. Nach obigen Schritten erfolgte dann die Anfertigung der Publikation. Zunächst wurde von Beck M. die Einleitung in Kenntnis der aktuellen Literatur erstellt. Die in der Methodik beschriebenen Schritte der Datenerhebung wurden ebenfalls durch Beck M. durchgeführt. Wie vorab beschrieben wurde durch Beck M. mit Unterstützung des Doktorvaters Ghadjar P. die Auswertung der Daten durchgeführt welche im Ergebnisteil dargestellt sind. Alle Tabellen und die Abbildung wurden von Beck M. erstellt. Die kritische Diskussion der Ergebnisse und die Schlussfolgerung wurden ebenfalls durch Beck M. erstellt. Der gesamte Publikationstext wurde von Beck M. verfasst und von Ghadjar P. kritisch überprüft und bearbeitet. Fragestellungen zu den physikalischen Grundlagen und der Interpretation der Bestrahlungspläne wurden gemeinsam mit Wust P. und Wlodarczyk W. bearbeitet. Barelkowski T. half bei Fragen zur Aufbereitung der Daten (Word, Excel). Wust P., Barelkowski T., Kaul D, Thieme AH, Wecker S, Wlodarczyk W und Budach V. überprüften das fertige Manuskript kritisch und brachten wenn nötig Verbesserungsvorschläge ein. Vor endgültiger Publikation gaben alle Koautoren ihr Einverständnis zur Veröffentlichung.

Unterschrift, Datum und Stempel des betreuenden Hochschullehrers

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Unterschrift des Doktoranden

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Auszug aus der Journal Summary List (ISI Web of Knowledge[SM])

Journal Data Filtered By: **Selected JCR Year: 2016** Selected Editions: SCIE,SSCI Selected Categories: **"RADIOLOGY, NUCLEAR MEDICINE and MEDICAL IMAGING"** Selected Category Scheme: WoS
Gesamtanzahl: 126 Journale

Rank	Full Journal Title	Total Cites	Journal Impact Factor	Eigenfactor Score
1	JACC-Cardiovascular Imaging	6,895	10.189	0.027050
2	RADIOLOGY	50,983	7.296	0.066140
3	EUROPEAN JOURNAL OF NUCLEAR MEDICINE AND MOLECULAR IMAGING	14,019	7.277	0.024910
4	Circulation-Cardiovascular Imaging	4,472	6.803	0.019120
5	JOURNAL OF NUCLEAR MEDICINE	24,977	6.646	0.037540
6	NEUROIMAGE	85,630	5.835	0.173210
7	JOURNAL OF CARDIOVASCULAR MAGNETIC RESONANCE	4,349	5.601	0.014950
8	SEMINARS IN RADIATION ONCOLOGY	2,232	5.356	0.003910
9	INVESTIGATIVE RADIOLOGY	5,925	5.195	0.011230
10	INTERNATIONAL JOURNAL OF RADIATION ONCOLOGY BIOLOGY PHYSICS	44,068	5.133	0.060060
11	ULTRASOUND IN OBSTETRICS & GYNECOLOGY	11,611	4.710	0.019350
12	HUMAN BRAIN MAPPING	18,139	4.530	0.041900
13	RADIOTHERAPY AND ONCOLOGY	15,639	4.328	0.028040
14	MEDICAL IMAGE ANALYSIS	5,539	4.188	0.010720
15	EUROPEAN RADIOLOGY	16,381	3.967	0.033340
16	IEEE TRANSACTIONS ON MEDICAL IMAGING	15,215	3.942	0.019660
17	JOURNAL OF NUCLEAR CARDIOLOGY	3,021	3.930	0.003920
18	MAGNETIC RESONANCE IN MEDICINE	29,816	3.924	0.035960
19	CLINICAL NUCLEAR MEDICINE	4,008	3.640	0.006470
20	SEMINARS IN NUCLEAR MEDICINE	2,056	3.630	0.002800
21	AMERICAN JOURNAL OF NEURORADIOLOGY	21,720	3.550	0.032180
22	MOLECULAR IMAGING AND BIOLOGY	2,228	3.466	0.005880
23	ULTRASCHALL IN DER MEDIZIN	1,907	3.452	0.003930

24	RADIOGRAPHICS	10,286	3.427	0.009660
25	Biomedical Optics Express	6,187	3.337	0.021610
26	Contrast Media & Molecular Imaging	1,131	3.307	0.002810
27	INTERNATIONAL JOURNAL OF HYPERTHERMIA	3,030	3.262	0.003810

Rank	Full Journal Title	Total Cites	Journal Impact Factor	Eigenfactor Score
28	Journal of Cardiovascular Computed Tomography	1,331	3.185	0.004220
29	JOURNAL OF MAGNETIC RESONANCE IMAGING	15,073	3.083	0.029170
30	Journal of the American College of Radiology	2,690	2.993	0.006840
31	NMR IN BIOMEDICINE	6,766	2.872	0.014560
32	JOURNAL OF VASCULAR AND INTERVENTIONAL RADIOLOGY	8,371	2.780	0.012840
33	AMERICAN JOURNAL OF ROENTGENOLOGY	31,676	2.778	0.035740
34	PHYSICS IN MEDICINE AND BIOLOGY	22,873	2.742	0.034390
35	STRAHLENTHERAPIE UND ONKOLOGIE	2,687	2.735	0.004990
36	Clinical Neuroradiology	433	2.618	0.001550
37	MEDICAL PHYSICS	22,942	2.617	0.037250
38	Radiation Oncology	4,358	2.568	0.013680
39	RADIATION RESEARCH	8,394	2.539	0.007920
40	JOURNAL OF BIOMEDICAL OPTICS	12,700	2.530	0.024520
41	JOURNAL OF NEURORADIOLOGY	792	2.526	0.001310
42	ULTRASOUND IN MEDICINE AND BIOLOGY	9,759	2.494	0.012640
43	QUARTERLY JOURNAL OF NUCLEAR MEDICINE AND MOLECULAR IMAGING	1,030	2.481	0.001800
44	CLINICAL RADIOLOGY	5,717	2.478	0.008540
45	EUROPEAN JOURNAL OF RADIOLOGY	11,328	2.462	0.026500
46	NUCLEAR MEDICINE AND BIOLOGY	3,918	2.426	0.006210
47	CANCER IMAGING	1,008	2.404	0.001930
48	RADIATION AND ENVIRONMENTAL BIOPHYSICS	1,468	2.398	0.002460

49	ULTRASONICS	5,752	2.327	0.008130
50	Diagnostic and Interventional Imaging	957	2.277	0.002420
51	MAGNETIC RESONANCE IMAGING	6,465	2.225	0.011370
52	CARDIOVASCULAR AND INTERVENTIONAL RADIOLOGY	4,859	2.191	0.008890
53	KOREAN JOURNAL OF RADIOLOGY	1,941	2.156	0.003730
54	ACADEMIC RADIOLOGY	4,804	2.128	0.009150
55	NEURORADIOLOGY	5,191	2.093	0.007520
56	Dose-Response	671	2.088	0.001310
57	Brachytherapy	1,442	2.082	0.003540
58	BRITISH JOURNAL OF RADIOLOGY	7,990	2.050	0.011760
59	EJNMMI Research	844	2.033	0.003380

Rank	Full Journal Title	Total Cites	Journal Impact Factor	Eigenfactor Score
60	ACTA RADIOLOGICA	4,199	2.011	0.006600
61	JOURNAL OF THORACIC IMAGING	1,265	2.010	0.002550
62	INTERNATIONAL JOURNAL OF RADIATION BIOLOGY	4,417	1.992	0.004350
63	Physica Medica-European Journal of Medical Physics	1,385	1.990	0.003530
64	INTERNATIONAL JOURNAL OF CARDIOVASCULAR IMAGING	2,742	1.896	0.007940
65	RADIOLOGIC CLINICS OF NORTH AMERICA	2,330	1.890	0.002560
66	Diagnostic and Interventional Radiology	1,029	1.886	0.002530
67	International Journal of Computer Assisted Radiology and Surgery	1,474	1.863	0.003300
68	ABDOMINAL IMAGING	3,246	1.842	0.006240
69	Radiologia Medica	1,881	1.795	0.003430
70	JOURNAL OF RADIATION RESEARCH	2,270	1.788	0.004620
71	ULTRASONIC IMAGING	1,040	1.780	0.000750
72	COMPUTERIZED MEDICAL IMAGING AND GRAPHICS	1,800	1.738	0.002530
73	SKELETAL RADIOLOGY	5,263	1.737	0.009010
74	MAGNETIC RESONANCE MATERIALS IN PHYSICS BIOLOGY AND MEDICINE	1,391	1.718	0.002840
75	CANCER BIOTHERAPY AND RADIOPHARMACEUTICALS	1,567	1.689	0.002330
76	Radiology and Oncology	604	1.681	0.001500

77	JOURNAL OF NEUROIMAGING	1,772	1.664	0.004420
78	JOURNAL OF RADIOLOGICAL PROTECTION	974	1.657	0.001970
79	DENTOMAXILLOFACIAL RADIOLOGY	2,076	1.594	0.003040
80	JOURNAL OF ULTRASOUND IN MEDICINE	6,094	1.547	0.007920
81	Zeitschrift fur Medizinische Physik	450	1.531	0.001220
82	Journal of Contemporary Brachytherapy	332	1.496	0.000630
83	Molecular Imaging	1,135	1.479	0.001900
84	NUCLEAR MEDICINE COMMUNICATIONS	2,752	1.472	0.004640
85	PEDIATRIC RADIOLOGY	5,489	1.465	0.007820
86	Magnetic Resonance Imaging Clinics of North America	870	1.446	0.001490
87	ROFO-FORTSCHRITTE AUF DEM GEBIET DER RONTGENSTRAHLEN UND DER BILDGEBENDEN VERFAHREN	1,428	1.418	0.002530

Rank	Full Journal Title	Total Cites	Journal Impact Factor	Eigenfactor Score
88	JOURNAL OF DIGITAL IMAGING	1,518	1.407	0.002650
89	ANNALS OF NUCLEAR MEDICINE	1,980	1.396	0.003440
90	JOURNAL OF COMPUTER ASSISTED TOMOGRAPHY	5,549	1.394	0.005280
91	SEMINARS IN MUSCULOSKELETAL RADIOLOGY	705	1.374	0.001340
92	Journal of Applied Clinical Medical Physics	1,775	1.338	0.004390
93	NEUROIMAGING CLINICS OF NORTH AMERICA	1,017	1.325	0.001350
94	HEALTH PHYSICS	4,176	1.276	0.003730
95	CANADIAN ASSOCIATION OF RADIOLOGISTS JOURNAL-JOURNAL DE L ASSOCIATION CANADIENNE DES RADIOLOGISTES	489	1.266	0.000890
96	Journal of Medical Imaging and Radiation Oncology	945	1.189	0.002740
97	SEMINARS IN INTERVENTIONAL RADIOLOGY	863	1.150	0.001480
98	Magnetic Resonance in Medical Sciences	606	1.141	0.001160

99	SEMINARS IN ULTRASOUND CT AND MRI	828	1.130	0.001240
100	APPLIED RADIATION AND ISOTOPES	7,005	1.128	0.008660
101	Journal of Innovative Optical Health Sciences	355	1.120	0.000810
102	Medical Ultrasonography	492	1.118	0.001330
103	NUKLEARMEDIZIN-NUCLEAR MEDICINE	534	1.087	0.000970
104	BMC MEDICAL IMAGING	592	1.060	0.001490
105	SURGICAL AND RADIOLOGIC ANATOMY	2,583	1.051	0.003240
106	Hellenic Journal of Nuclear Medicine	347	1.048	0.000570
107	CLINICAL IMAGING	1,684	1.015	0.003420
108	Japanese Journal of Radiology	797	0.982	0.002260
109	Medical Dosimetry	687	0.957	0.001110
110	Revista Espanola de Medicina Nuclear e Imagen Molecular	386	0.951	0.000720
111	Cancer Radiotherapie	780	0.930	0.001060
112	RADIATION PROTECTION DOSIMETRY	5,723	0.917	0.007160
113	JOURNAL OF CLINICAL ULTRASOUND	2,012	0.906	0.001950
114	Ultrasound Quarterly	461	0.902	0.000790
115	INTERVENTIONAL NEURORADIOLOGY	900	0.739	0.001590
116	SEMINARS IN ROENTGENOLOGY	423	0.667	0.000500

Rank	Full Journal Title	Total Cites	Journal Impact Factor	Eigenfactor Score
117	Journal of Medical Imaging and Health Informatics	401	0.621	0.000670
118	Iranian Journal of Radiology	193	0.554	0.000590
119	Journal of Medical Ultrasonics	243	0.455	0.000410
120	RADIOLOGE	498	0.404	0.000480
121	RADIOPROTECTION	285	0.388	0.000380
122	Current Medical Imaging Reviews	269	0.308	0.000580
123	JBR-BTR	262	0.252	0.000470
124	International Journal of Radiation Research	57	0.250	0.000110
125	Journal of the Belgian Society of Radiology	5	0.027	0.000010
126	Abdominal Radiology	64	Not Available	0.000000

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Radiation Oncology

RESEARCH Open Access

Risk adapted dose-intensified postoperative radiation therapy in prostate cancer patients using a simultaneous integrated boost technique applied with helical Tomotherapy

Marcus Beck*, Peter Wust, Tomasz Barelkowski, David Kaul, Alexander-Henry Thieme, Sascha Wecker, Waldemar Wlodarczyk, Volker Budach and Pirus Ghadjar*

Abstract

Background: Postoperative adjuvant radiation therapy (ART) in T3 and R1 prostate cancer as well as salvage radiation therapy (SRT) in case of postoperative biochemical failure (BF) are established treatments. Dose-intensified postoperative radiation therapy (RT) schemes have shown superior biochemical control accompanied by increased toxicity rates. In our study we evaluate a novel risk adapted dose-intensified postoperative RT scheme.

Methods: A consecutive series of prostate cancer patients receiving postoperative RT after radical prostatectomy using helical Tomotherapy between 04/2012 and 04/2015 was analyzed retrospectively. RT was administered using a simultaneous integrated boost (SIB) to the area at risk (37 fractions of 1.9 Gy, total dose: 70.3 Gy) being defined based on histopathological findings (T3/R1 region) and in few cases according to additional diagnostic imaging. The whole prostate bed was treated with a dose of 66.6 Gy (37 fractions of 1.8 Gy). Primary endpoints were acute and late genitourinary (GU) and gastrointestinal (GI) toxicities. Secondary endpoints included patient reported outcome as assessed by the International Prostate Symptom Score (IPSS), the International Consultation on Incontinence questionnaire (ICIQ) and prostate cancer specific Quality of Life questionnaire QLQ-PR25, as well as rates of BF.

Results: A total of 69 patients were analyzed. Sixteen patients underwent ART and 53 patients SRT, respectively. The median follow-up was 20 months (range, 8–41 months). Seven (10.1%) and four (5.8%) patients experienced acute grade 2 GU and GI toxicity. Two patients (2.9%) had late grade 2 GU toxicity, whereas no late grade 2 GI nor any grade 3 acute or late GU or GI events were observed. When compared to the baseline IPSS scores ($p = 1.0$) and ICIQ scores ($p = 0.87$) were not significantly different at the end of follow-up. Patient reported Quality of life (QoL) showed also no significant difference. A total of seven patients (10.1%) experienced a biochemical recurrence with the 2-year biochemical progression-free survival (bPFS) being 91%.

Conclusions: Postoperative RT for prostate cancer patients with a risk adapted dose-intensified SIB using helical tomotherapy is feasible and associated with favorable acute and late GU and GI toxicity rates, no significant change of IPSS-, ICIQ scores and patient reported QoL and results in promising bPFS rates.

Keywords: Prostate cancer, Radiation therapy, Postoperative, Salvage, Boost, Dose intensified

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Background

Prostate cancer is the most common male cancer in developed countries and is the fifth most cause of death from cancer worldwide [1]. Radical prostatectomy (RP) offers good long-term control rates and survival in patients with cancer confined to the prostate [2]. However, 15 to 40% of patients develop biochemical failure (BF) after RP within 5 years [3–5]. In patients with high risk disease (extracapsular spread, seminal vesicle invasion or positive surgical margins) adjuvant radiation therapy (ART) improves biochemical progression-free survival (bPFS), overall survival (OS) and distant metastasis-free survival (DMFS) [6–9]. In the case of BF after RP, salvage radiation therapy (SRT) is the only potential curative treatment [10–12]. Moreover, dose-intensified radiation therapy (RT) showed a further improvement of biochemical relapse-free survival in the postoperative radiation setting [13–15]. Recently published data confirmed the benefit of dose escalation in SRT. Tendulkar et al. detected a significant reduction of BF after SRT with an applied dose ≥66 Gy vs. < 66Gy when analyzing a cohort of 2460 patients [16]. In addition, Stish et al. evaluated data of 1106 patients with SRT and registered a significantly reduced risk of BF when doses ≥68 Gy were used [17]. On the other hand, postoperative RT is also associated with genitourinary (GU) and gastrointestinal toxicity (GI), especially in dose-intensified radiation schemes. [13–15]. However, the increasing implementation of modern radiation techniques was reported to be associated with a decrease in toxicity, even in dose intensified radiation schemes [13, 18, 19]. Otherwise, the first report of the prospective randomized SAKK 09/10 trial showed a significantly increased patient reported genitourinary symptom burden in the dose intensified SRT arm (70 Gy) compared to the patients in the 64 Gy arm, irrespective of the applied radiation technique [20]. With the objective of combining the benefit of dose escalated RT with an assumed lower GU and GI toxicity rate using confined dose intensified radiation volumes, we used the helical tomotherapy for postoperative prostate cancer RT with a risk adapted dose-intensified simultaneous integrated boost (SIB).

Methods

Between 04/2012 and 04/2015, 76 consecutive prostate cancer patients who received postoperative RT after RP were analyzed retrospectively. After exclusion of 7 patients due to either macroscopic lymphnode metastasis accompanied by a prostate-specific antigen (PSA) > 4 ng/ml (n = 5), bone metastasis (n = 1) or being lost to follow-up (n = 1) the remaining 69 patients were analyzed. Patients received ART [treatment 1–3 month after RP] (n = 16) or SRT [treatment >3 month after RP or persistent PSA after RP] (n = 53) using the tomotherapy treatment system. ART was performed in high risk patients with extracapsular spread, seminal vesicle invasion or positive surgical margins (pT3, R1). SRT was administered in patients with evidence of BF with two confirmed rises over a PSA value of 0.2 ng/ml or in patients with persistent PSA after RP, respectively. Furthermore, in some cases the SRT was indicated in patients with two consecutive rises of PSA with final PSA > 0.1 ng/ml or three consecutive rises according to the definition of BF in the SAKK 09/10 trial protocol [21]. Additional androgen deprivation therapy (ADT) was administered based on risk factors according to the discretion of the referring urologist.

Computed tomography (CT) based treatment planning was performed in supine position with comfortably filled bladder and empty rectum. Clinical target volume (CTV) P comprised the prostate bed, CTV S comprised the SIB-region and in the case of pelvic lymph node radiation a CTV L contained this area. The planning target volume (PTV) P (prostate bed) was defined as the CTV P plus 5 mm in all directions. PTV S (SIB-region) was defined as the CTV S plus 2 mm in all directions and PTV L contained CTV L with a margin of 5 mm. The posterior PTV P and PTV S margin differed from other directions with a width of 3 mm. For delineation of the SIB-volume the high risk region of the prostate bed was defined considering the histological reports of prostatectomy (R1 region, T3 region of infiltration or the tumor-bearing area). Due to pN1 status and patients need for security some patients also received radiation of pelvic lymph nodes.

A prostate bed dose (PTV P) of 66.6 Gy (37 fractions of 1.8 Gy, 7.4 weeks) and a SIB (PTV S) of 70.3 Gy (37 fraction of 1.9 Gy, 7.4 weeks) to the risk region of the prostate bed was administered in helical tomotherapy technique. A concurrent radiation of pelvic lymph nodes (PTV L) was applied with a dose of 45 Gy in 11 patients, 50.4 Gy in 4 patients and 54 Gy in one case.

For the delineation European Organization for Research and Treatment of Cancer (EORTC) guidelines were considered. As additional information in 8 cases a prostate specific membrane antigen gallium 68Ga labeled positron emission tomography/computed tomography (68Ga PSMA-PET/CT), in 2 cases a magnetic resonance imaging (MRI) and in 2 cases a choline positron emission tomography/computed tomography (choline PET/CT) was used.

The GU and GI toxicities were classified using the National Cancer Institute Common Terminology Criteria version 4.0 (CTCAEv4.0). Acute toxicity events were defined as symptoms during treatment and up to 3 months after the end of RT. After >3 month the symptoms were defined as late toxicities. Toxicity events were defined as symptoms increasing in grade over the respective baseline symptoms. Further monitoring of GU symptoms was

performed using the International Prostate Symptom Score (IPSS) and the International Consultation on Incontinence questionnaire (ICIQ). The Quality of Life (QoL) was detected with the IPSS-QoL score and EORTC Quality of Life Questionnaire prostate cancer specific module PR25 (QLQ-PR25). The QLQ-PR25 module was used to measure symptom scales (urinary symptoms, bowel symptoms) and functional scales (sexual activity, sexual functioning). The GU and GI toxicities were assessed in three time periods using CTCAEv4.0 classification: baseline (before start of radiation therapy), acute (during and at end of RT) and late (>3 month after RT). IPSS, ICIQ, IPSS-Qol and QLQ-PR25 were assessed before beginning of RT and at the end of follow-up.

BF after completed RT was defined as any PSA exceeding 0.4 ng/ml and rising. In case of BF further diagnostics like 68Ga PSMA-PET/CT were applied to investigate the localization of recurrence.

The primary objective was to determine the rates of acute and late GU and GI toxicities. Secondary objectives were to document patient related outcomes as assessed by the IPSS and the ICIQ, measure patient reported QoL and to describe the rate of bPFS. Differences in IPSS sums, ICIQ sums and QLQ-PR25 scores between baseline and post-treatment were compared performing the students *t*-test. Actuarial bPFS rates were estimated using the Kaplan-Meier method. Time to event was calculated from the first day of treatment until biochemical recurrence or the last follow-up visit. Influence factors for bPFS were analyzed using the Cox-regression method. Two-sided p values <0.05 were considered statistically significant. The data were analyzed in SPSS (SPSS Inc., Chicago, IL, version 24.0).

The internal institutional review board approved a waiver for research authorization.

Results

Patient characteristics

The patient characteristics were summarized in Table 1 and the median follow-up was 20 month (range 8–41 months). Before RP patients had a median PSA level of 10 ng/ml. RT was delivered after a median of 10 months after RP (range, 1–155 months). PSA levels prior to RT ranged from 0 to 2.05 ng/ml with a median of 0.21 ng/ml. 23 patients (33.3%) were treated with an ADT. In the last follow up survey still 12 patients (17.4%) received an ADT. The ADT was given according to the discretion of the referring urologist. The 23 patients with ADT met one or more of the following treatment criteria: Either a PSA doubling time < 3 months, a symptomatic local disease, a pN1 status or a high PSA value > 0.7 ng/ml before start of RT. In 15 patients a concurrent radiation of pelvic lymph nodes due to pN1 status and in one case by reason of patients need for security was applied.

Table 1 Patient characteristics

Variable	(*N* = 69) *n* (%)
PSA before prostatectomy (ng/mL), median (range)	10.0 (0.8, 84.0)
Resection margins	
R0	31 (44.9%)
R1	38 (55.1%)
Gleason score	
≤ 7	40 (58.0%)
≥ 8	28 (40.6%)
missing	1 (1,4%)
Tumor classification	
pT2a	4 (5.8%)
pT2b	1 (1.4%)
pT2c	16 (23.2%)
pT3a	21 (30.4%)
pT3b	26 (37.7%)
pT4	1 (1.4%)
Lymphadenectomy performed	
No	9 (13.0%)
Yes	60 (87.0%)
Lymphnode classification	
N0	51 (73.9%)
N1	18 (26.1%)
Number of lymph nodes removed, median (range)	13.0 (1.0, 51.0)
Persistent PSA 4–12 weeks after prostatectomy	
< 0.1 ng/mL	46 (66.7%)
≥ 0.1 ng/mL	15 (21.7%)
< 0.5 ng/ml	54 (78.3%)
≥ 0.5 ng/ml	7 (10.1%)
missing	8 (11.6%)
PSA at start of RT	
< 0.5 ng/mL	57 (82.6%)
≥ 0.5 ng/mL	12 (17.4%)
Age at start of RT median (range) in years	66 (45, 78)
Time from surgery to RT start, median (range) in months	10.0 (1.0, 155.0)
ECOG performance status at treatment start	
0	12 (17.4%)
1	57 (82.6%)
RT technique	
Tomotherapy	69 (100%)
ADT during RT	
No	46 (66.7%)
Yes	23 (33.3%)
Pelvic nodal RT	
No	53 (76.8%)
Yes	16 (23.2%)

Abbreviations: *PSA* prostate specific antigen, *RT* radiation therapy, *ECOG* Eastern Cooperative Oncology Group, *ADT* androgen deprivation therapy

Acute toxicity

At the baseline (before onset of RT) 56 patients had grade 1, 8 patients had grade 2 GU and no patients suffered from GI toxicities. The acute toxicity was assessed during and at the end of postoperative RT. During treatment 7 patients (10.1%) experienced grade 2 GU and 4 patients (5.8%) grade 2 GI toxicity. In detail the acute GU toxicity was described as grade 2 dysuria in 3 patients and a grade 2 increase of urinary frequency in 4 patients. In all 3 cases of dysuria a complete remission was observed at the late toxicity follow-up, whereas one of these patients developed a late grade 2 change of urinary frequency. In addition, in the 4 reported cases of acute grade 2 variation of urinary frequency, symptoms alleviated to grade 1 urinary frequency level in the late follow-up. Furthermore, the 4 patients that suffered from grade 2 acute GI toxicity all had a transient grade 2 diarrhea with a reported remission in the late toxicity follow-up. No acute grade 3 or higher GU and GI toxicity was detected. Table 2 provides a detailed overview of acute GI and GU toxicity.

Late toxicity

Only 2 patients (2.9%) suffered from grade 2 late GU toxicity, whereas no late grade 2 GI or any other grade 3 or higher toxicity was documented. One patient with former acute grade 2 dysuria experienced a late grade 2 urinary frequency variation and one patient who reported grade 1 baseline and acute incontinence developed a late grade 2 incontinence. See Table 2 for detailed information of late GU and GI toxicity.

IPSS, QoL and ICIQ

The evaluation of the IPSS of 69 patients showed a baseline IPSS sum with a mean of 7.7 (standard deviation (sd) of 6.2) and IPSS sum of 7.5 (sd 5.6) at the last late follow up after RT. No statistical significant difference of IPSS was detected (p = 1.0). The IPSS measures were depicted in Table 3. The comparison of baseline IPSS sum or sum group and last late IPSS sum or sum group values showed a considerable worsening (≥5 of IPSS) in 10 patients and a considerable improvement (≥5 of IPSS) in 7 patients [22, 23]. The subgroup of patients with a (≥5 of IPSS) aggravation showed in 8 cases a change from the mild to moderate IPSS symptoms group (mild 0–7, moderate 8–19, severe 20–35) and in 2 cases from the moderate to severe group. The patients who reported a significant IPSS improvement switched in four cases from moderate to mild IPSS sum group, in two cases from severe to moderate group and in one case from the severe to the mild sum group. Figure 1 depicts all IPSS group changes, including changes of IPSS sum groups without a sum difference of ≥5 IPSS.

Table 2 Acute and late genitourinary and gastrointestinal toxicity

GU Toxicity	CTCAE highest grade[a]	During/End of RT (N = 69) n (%)	End of Follow-up (N = 69)[b] n (%)
Dysuria	0	60 (87.0%)	65 (94.2%)
	1	6 (8.7%)	3 (4.3%)
	2	3 (4.3%)	0 (0.0%)
Hematuria	0	69 (100.0%)	66 (95.7%)
	1	0 (0.0%)	2 (2.9%)
Urinary frequency	0	59 (85.5%)	59 (85.5%)
	1	6 (8.7%)	8 (11.6%)
	2	4 (5.8%)	1 (1.4%)
Urinary incontinence	0	68 (98.6%)	57 (82.6%)
	1	1 (1.4%)	10 (14.5%)
	2	0 (0.0%)	1 (1.4%)
Urinary retention	0	67 (97.1%)	57 (82.6%)
	1	2 (2.9%)	11 (15.9%)
Urinary urgency	0	57 (82.6%)	61 (88.4%)
	1	12 (17.4%)	7 (10.1%)
Highest grade of GU symptoms	0	44 (63.8%)	34 (49.3%)
	1	18 (26.1%)	32 (46.6%)
	2	7 (10.1%)	2 (2.9%)
	3	0 (0.0%)	0 (0.0%)
GI Toxicity	CTCAE highest grade[a]	During/End of RT (N=69) n (%)	End of Follow-up (N=69) n (%)
Anal or rectal hemorrhage	0	67 (97.1%)	68 (98.6%)
	1	2 (2.9%)	1 (1.4%)
Diarrhea	0	45 (65.2%)	67 (97.1%)
	1	20 (29.0%)	2 (2.9%)
	2	4 (5.8%)	0 (0.0%)
Rectal pain	0	65 (94.2%)	69 (100%)
	1	4 (5.8%)	0 (0.0%)
Highest grade of GI symptoms	0	45 (65.2%)	66 (95.7%)
	1	20 (29.0%)	3 (4.3%)
	2	4 (5.8%)	0 (0.0%)
	3	0 (0.0%)	0 (0.0%)

Abbreviations: *GU* genitourinary, *GI* gastrointestinal, *CTCAE* Common Terminology Criteria of Adverse Events, *RT* radiation therapy

[a]toxicity events were defined as symptoms increasing in grade over the respective baseline symptoms

[b]one patient with no End of Follow up GU toxicity due to bladder resection in bladder cancer

The patient reported QoL (IPSS-QoL score) was assessed before start of RT and at the end of follow-up. 64 patients reported their QoL using the IPSS-QoL score which is scaled from 0 = delighted to 6 = terrible. For analysis the score was dichotomized as 0–2 (satisfied) and 3–6 (dissatisfied) [22]. Overall 18

Table 3 Baseline and late IPSS, ICIQ and IPSS-QoL assessment

Variable	Baseline		Last Follow-up		
	n (%)	mean (sd)	*n* (%)	mean (sd)	*p*-value[#]
IPSS:					
IPSS value	69 (100%)	7.7 (6.2)	68 (98.6%)	7.5 (5.6)	1.000
missing	0		1 (1.4%)		
IPSS grouped:					
Mild (0–7)	40 (58.0%)		38 (55.1%)		
Moderate (8–19)	25 (36.2%)		28 (40.6%)		
Severe (20–35)	4 (5.8%)		2 (2.9%)		
ICIQ:					
ICIQ value:	64 (92.8%)	5.8 (4.7)	68 (98.6%)	5.6 (4.2)	0.874
missing	5 (7.2%)		1 (1.4%)		
ICIQ grouped:					
No incontinence (0)	15 (21.7%)		15 (21.7%)		
Mild incontinence (1–5)	18 (26.1%)		20 (29.0%)		
Moderate incontinence (6–10)	21 (30.4%)		24 (34.8%)		
Severe incontinence (≥11)	10 (14.5%)		9 (13.0%)		
IPSS-QoL score grouped:[a]					
Satisfied (0–2)	47 (68.1%)		49 (71.0%)		
dissatisfied (3–6)	18 (26.1%)		19 (27.6%)		
missing	4 (5.8%)		1 (1.4%)		

Abbrevations: *sd* standard deviation, *IPSS* International Prostate Symptom Score, *ICIQ* International Consultation on Incontinence questionnaire, *QoL* quality of life
[#]by paired t-Test
[a]IPSS-QoL-Score: 0 = delighted to 6 = terrible

patients were dissatisfied before RT and 19 patients were dissatisfied after RT (Table 3). Further patient reported QoL measures were detected using the EORTC QQL-PR25 questionnaire. Patients reported no significant changes in urinary symptoms (p = 0.349), bowel symptoms (p = 0.888), sexual activity (p = 0.794) and sexual functioning (p = 1.000) at last follow compared to the baseline assessment. See Table 4 for details.

The ICIQ data of 64 patients showed an ICIQ sum with a mean of 5.8 (sd 4.7) before beginning and a mean of 5.6 (sd 4.2) at the last follow up. The distribution to the different ICIQ groups (0 = no incontinence, 1–5 = mild incontinence, 6–10 = moderate incontinence, ≥11 = severe incontinence) is depicted in Table 3. The comparison of ICIQ sum before and after RT showed no statistical significant worsening of ICIQ score after RT (p = 0.874).

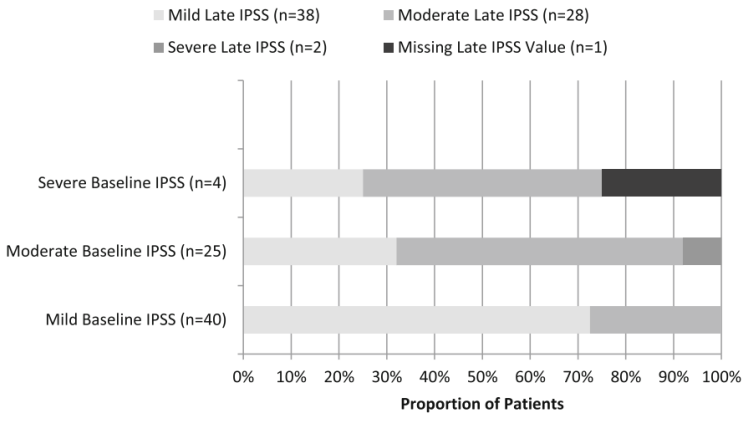

Fig. 1 Late IPSS sum groups stratified by baseline IPSS sum groups. Abbreviations: IPSS = International Prostate Symptom Score

Table 4 Baseline and late patient reported quality of life scores (QLQ-PR25)

QLQ-PR25	Baseline		Last Follow-up		
	Number of respondents	mean (sd)	Number of respondents	mean (sd)	*p*-value[#]
Symptom Scales:[a]					
Urinary symptoms (PRURI)	41	26.9 (17.0)	68	25.1 (17.1)	0.349
Bowel symptoms (PRBOW)	40	5.8 (10.9)	67	5.6 (10.2)	0.888
Functional Scales:[b]					
Sexual activity (PRSAC)	34	57.4 (28.8)	51	57.2 (31.0)	0.794
Sexual functioning (PRSFU)	15	48.9 (15.1)	23	48.9 (14.7)	1.000

Abbreviations: *QLQ-PR25 EORTC* quality of life prostate cancer module PR25, *sd* standard deviation
[#]by paired t-Test
[a]Range 0–100, with a positive score indicating a worsening
[b]Range 0–100, with a positive score indicating an improvement

Biochemical control

Within a follow-up period of median 20 month 7 patients (10.1%) experienced BF. The time from RT to BF ranged from 4 to 40 month with a median of 16 month. To differ between local recurrence and distant failure further diagnostic was applied following the diagnosis of BF. In one patient the localization of recurrence was shown as bone metastasis in a bone scintigraphy. Further, in three patients a 68Ga PSMA-PET/CT scan detected a recurrence in the iliac lymph node region and the fifth patient suffered from a recurrence in the iliac and paraaortic lymph node region, also verified by a 68Ga PSMA-PET/CT scan. The other two patients with BF refused the further diagnostic procedures.

Thus, considering these findings, in 5 of the 7 patients with biochemical failure no local prostate bed recurrence was detected. In the other two cases there is no information available on the pattern of recurrence.

In our cohort a 2-year bPFS of 91% was observed. Additional analysis showed no significant factors for the development of a biochemical failure in multivariate cox regression. In univariate cox regression a persistent PSA ≥ 0.5 mg/ml after RP was associated with decreased bPFS ($p = 0.046$) and a presurgery PSA of >10 ng/ml showed a trend towards worsening of bPFS ($p = 0.082$, Table 5).

Discussion

The results of this retrospective analysis in prostate cancer patients who received risk adapted dose-intensified RT after RP showed low rates of relevant acute and late GU and GI toxicity, no significant worsening of symptoms burden (IPSS, ICIQ), no significant change in QoL and comes along with promising biochemical control rates.

The reported minor rates of acute GU and GI toxicities, appeared during and at the end of RT, with 10.1% grade 2 GU toxicity and 5.8% grade 2 GI toxicity in absence of any

Table 5 Univariate and multiple Cox regression analysis of factors associated with biochemical recurrence-free survival

Factor	RR	CI	*p*
Univariate Cox regression:			
Age: ≤65 versus >65 (years)	1.004	0.224–4.495	0.995
ECOG performance status: 0 versus >1	0.898	0.105–7.692	0.922
Lymphnode involvement: N0 versus N1	0.476	0.057–3.956	0.492
Gleason score: ≤7 versus ≥8	2.224	0.496–9.976	0.297
Surgical margins: R0 versus R1	0.558	0.125–2.496	0.445
Androgen deprivation therapy: no or yes	0.91	0.175–4.741	0.911
Pelvic nodal RT: no or yes	0.635	0.076–5.288	0.674
Presurgery PSA: ≤10 versus >10 (ng/ml)	6.537	0.785–54.411	0.082
PSA Persistance after surgery: <0.5 versus ≥0.5 (ng/ml)	4.623	1.029–20.781	0.046
PSA at start of RT <0.5 versus ≥0.5 (ng/ml)	2.980	0.659–13.473	0.156
Multivariate Cox regression:			
Presurgery PSA: ≤10 versus >10 (ng/ml)	4.402	0.474–40.891	0.192
PSA Persistance after surgery: <0.5 versus ≥0.5 (ng/ml)	2.724	0.556–13.337	0.216

Abbreviations: *RR* relative risk, *CI* 95% confidence intervals, *RT* radiation therapy, *p* *p*-value, *ECOG* Eastern Cooperative Oncology Group, *PSA* prostate specific antigen

grade 3 or higher acute toxicity were favorably comparable with and even were slightly below toxicity rates of already published postoperative RT trials. In addition, the low number of observed late toxicity with 2.9% of grade 2 GU toxicity and no other late ≥ grade 2 toxicity demonstrated a good tolerability of the administered dose-intensified postoperative RT. Several previous published retrospective studies showed remarkable toxicity rates associated with dose escalated RT. Administering a SRT (2D and 3D conformal techniques) with a median dose of 72 Gy Cozzarini et al. reported ≥ grade 2 late GU toxicity in 23.7 and 10% grade 3 late GU toxicity [CTCAEv3.0; median follow-up 99 month] [24]. Furthermore, Ost et al. observed 22% late ≥ grade 2 GU toxicity and 3% late grade 3 GU toxicity in patients who received a SRT in intensity-modulated radiation therapy (IMRT) technique with a median dose of 76 Gy [CTCAEv3.0; median follow-up 5 years] [13]. A comparison of three-dimensional (3D) versus IMRT SRT with doses between <66 Gy up to ≥70Gy, published by Goenka et al., showed a rate of ≥ grade 2 late GI toxicity in 1.9% of patients treated with IMRT versus 10.2% when treated with 3D conformal techniques. Aside from the 8.3% reduction of late GI toxicity using IMRT no significant difference in ≥ grade 2 late GU toxicity between both techniques was seen with an overall rate of 16.3% ≥ grade 2 late GU toxicity [CTCAEv3.0; median follow-up 60 month]. In the cohort treated with IMRT the IPSS was assessed and the average IPSS of patients was 5.24 (range 0–19) before SRT and the average maximum after SRT was 7 (range 0–30) [18, 25]. Whereas, the above mentioned studies all applied dose-intensified RT to the whole prostate bed, a trial published by Zilli et al. described the SRT (3D conformal technique and a minority treated with IMRT) with a boost to the suspected relapse regions visualized by aid of endorectal magnetic resonance imaging (eMRI) with 74 Gy and a prostate bed dose of 64 Gy. Acute Grade 2 GU and GI toxicities were reported in 12.3 and 19.3%. Furthermore, 1.8% of patients experienced acute grade 4 urinary obstruction and 6.4% of patients suffered from late grade 2 GU toxicity and grade 2 GI toxicity. Late Grade 3 GU toxicity was also observed in 6.4% and late grade 3 GI toxicity was reported in 1.8% [Radiation Therapy Oncology Group (RTOG) scoring and CTCAEv3.0] [26]. Our results show a lower rate of acute and late GU and GI toxicities, using a dose-intensified risk adapted boost of 70.3 Gy in a prostate bed partial volume and a dose of 66.6 Gy for the whole prostate bed. The smaller volume with a moderate intensified dose is assumed to cause the better tolerability. Moreover in our study all patients were treated with helical tomotherapy treatment technique, ensuring sufficient sparring of risk organs. However, concerning the late toxicity results it must be noted that the median follow-up of 20 month depicts a limitation of our study, because particularly late GU toxicities are even reported to occur up to 10 years after RT.

The to date only prospective dose intensified SRT trial (SAKK 09/10) recently reported comparable, but also slightly higher acute toxicity rates, using a similar intensified dose for radiation of the whole prostate bed. This trial observed 13% acute grade 2 GU toxicity and 0.6% grade 3 GU toxicity in the 64 Gy arm compared to 16.6% acute grade 2 toxicity and 1.7% grade 3 GU toxicity when 70 Gy were applied. Acute grade 2 GI toxicity occurred in 16%, grade 3 GI toxicity in 0.6% treated with 64 Gy compared to 15.4 and 2.3% acute grade 2 and 3 GI toxicity after 70 Gy, respectively [CTCAEv4.0]. No significant differences in acute toxicities between both arms were detected. Interestingly, the trial was also stratified for radiation technique (3D vs. IMRT/rotational RT) and in contrast to former mentioned studies no significant influence on acute toxicity was monitored. Furthermore, a significantly increased patient reported genitourinary symptom burden was observed in the 70 Gy arm [20].

In this context, it was assumed that high dose RT to urethra and vesico-urethral anastomosis as applied in dose escalated whole prostate bed RT schemes results in similar GU toxicity regardless of RT technique [27]. From that point of view the partial prostate bed SIB-volume could be supposed to explain the low GU toxicity rates in our study.

To discuss the toxicities it is also worth mentioning, that physician-assessed toxicity scoring systems like CTCAEv.4.0 may underestimate the patients symptoms burden and may neglect important problems of the patient [20, 28].

Therefore it is important to consider patient reported toxicity scoring systems like IPSS or ICIQ as well as patient reported QoL. In our study patients reported their urinary symptoms (IPSS questionnaire) and incontinence symptoms (ICIQ questionnaire) before the beginning of RT and at the end of follow-up. Comparing these surveys, both scores showed no statistical significant difference, neither worsening nor improvement (Table 3). Consequently, the patients' evaluation of the treatment also showed a good long term tolerability of the applied postoperative radiation scheme. Comparable IPSS values where registered by Geonka et al. in dose intensified SRT using IMRT [18]. Another important evaluation of the treatment is the patients' perception of their QoL. Patients assessment of their QoL before RT and at the end of follow-up showed no statistical significant difference. Thus, no long term variation of QoL could be detected (Tables 3 and 4).

Within a median follow-up of 20 month 7 patients (10.1%) developed a BF and the calculated 2-year bPFS was 91%. With the aid of further diagnostics (ga-68

PSMA-PET/CT and bone scintigraphy) in five cases a local recurrence in the prostate bed was excluded, confirming a promising local control. For the remaining two patients the localization of recurrence is unknown. These data of biochemical control represent a first hint that our applied postoperative radiation scheme seems to be a promising treatment option, whereas the short follow up period is a limitation. Further analysis of the data showed a persistent PSA ≥ 0.5 mg/ml after RP was significantly associated with decreased bPFS in the univariate analysis and a presurgery PSA >10 ng/ml showed also a trend for a decrease in bPFS: Whereas, further established risk factors showed no trend or significant influence in our cohort (Table 5). The limited follow-up and the size of the cohort are assumed to be reasons for these results.

However, it should be taken into account that approximately one-third of patients in our study received an additional ADT. Consequently it may have influenced the biochemical outcome as well as toxicity and QoL. For example, data of two randomized studies combining SRT and ADT were recently published. The GETUG-AFU 16 trial observed a significant improvement in 5-year progression-free survival for combination of 66 Gy SRT with additional 6 month goserelin versus 66 Gy SRT alone (80% versus 62%; $p < 0.0001$). No significant difference in overall survival (OS) was reported. In the combined treatment arm more acute < grade 3 toxicities were registered than in SRT alone [29]. RTOG 9601 trial applied either SRT with 64.8 Gy plus 24-month bicalutamide or SRT with 64.8 Gy alone. The authors reported a significant OS benefit for combined treatment after 12 years with 76.3% versus 71.3% (HR 0.77; 95% CI, 0.59–0.99; $p = 0.04$). Subgroup analysis showed particularly an OS benefit for patients with PSA levels of 0.7–1.5 ng/ml (HR 0.61; 95% CI, 0.39–0.95; $p = 0.03$) and PSA > 1.5 ng/ml (HR 0.45; 95% CI, 0.25–0.81; $p = 0.007$). Notable differences in toxicity between both arms were a rate of 70% gynecomastia in the bicalutamide group versus 11% in the SRT only group [30]. Nevertheless, it is important to bear in mind that ADT is associated with multiple short and long term side effects like bone loss, hot flashes, metabolic changes and gynecomastia [31]. Thus, considering these results and the reported toxicities it has not been finally clarified whether in postoperative treatment schemes like ours, all or neither patients should receive ADT, what kind of ADT should be applied and for which duration. Surely it remains an individual decision taking into account the patients risk factors.

As an additional limitation of our study, it must be kept in mind that the risk adapted SIB volume was, as described in the methods section, mainly defined considering histological findings and only in some cases additional diagnostic information (68Ga PSMA-PET/CT, MRI, choline-PET/CT) was applied. Consequently it is possible that in some cases the boost volume doesn't reflect the whole high risk relapse region of the prostate bed and the postulated additional effect of the dose-intensified radiation would be missed. This limitation could be optimized by using additional information like 68Ga PSMA-PET/CT or MRI for the delineation procedure [32–35]. However, all patients received a dose of 66.6 Gy to the whole prostate bed and therefore a sufficient dose for potential control of the relapse region.

Taking into account the reported limitations (e.g. the short follow up) our presented treatment scheme with a risk adapted dose-intensified SIB using the tomotherapy treatment system and the reported low rate of toxicity, no variation of QoL and a favorable biochemical recurrence free outcome depicts an option for a modern well tolerated treatment in case of BF after RP or in high risk postoperative situations (T3, R1). However these retrospective findings should be verified in prospective trials. A future treatment scheme could be improved by using 68Ga PSMA-PET/CT and MRI additional to histological findings for definition of risk adapted SIB volumes in all treated patients. Otherwise, an early initiation of treatment (PSA <0.5 ng/ml) in the SRT setting should be considered in a future trial.

Conclusions

With a low rate of relevant acute and late GU and GI toxicity, no significant worsening of symptoms burden (IPSS, ICIQ) and no significant change in QoL the postoperative prostate cancer RT with a dose-intensified risk adapted SIB applied in our study seems to be a favorable and well tolerable therapy that comes along with promising biochemical control rates. However as main limitations the short follow-up, the moderate size of the cohort and the retrospective design should be considered and thus our approach should be verified in a future prospective trial.

Abbreviations

3D: Three-dimensional; 68Ga PSMA-PET/CT: Prostate specific membrane antigen gallium 68Ga labeled positron emission tomography/computed tomography; ADT: Androgen deprivation therapy; ART: Adjuvant radiation therapy; BF: Biochemical failure; bPFS: Biochemical progression-free survival; choline PET/CT: Choline positron emission tomography/computed tomography; CT: Computed tomography; CTCAEv4.0: National Cancer Institute Common Terminology Criteria version 4.0; CTCAEv4.0: National Cancer Institute Common Terminology Criteria version 4.0; CTV: Clinical target volume; DMFS: Distant metastasis-free survival; eMRI: Endorectal magnetic resonance imaging; EORTC: European Organization for Research and Treatment of Cancer; GI: Gastrointestinal; GU: Genitourinary; ICIQ: International Consultation on Incontinence questionnaire; IMRT: Intensity-modulated radiation therapy; IPSS: International Prostate Symptom Score; MRI: Magnetic resonance imaging; OS: Overall survival; PSA: Prostate-specific antigen; PTV: Planning target volume; QLQ-PR25: EORTC Quality of Life Questionnaire prostate cancer specific module PR25; QoL: Quality of Life; RP: Radical prostatectomy; RT: Radiation therapy; RTOG: Radiation Therapy Oncology Group; SIB: Simultaneous integrated boost; SRT: Salvage radiation therapy

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Availability of data and materials
The datasets generated and analyzed during the current study are not publicly available due to protection of privacy but are available from corresponding author on reasonable request.

Authors' contributions
MB and PG performed the analysis and drafted the manuscript. MB, PG, TB, WW and PW participated in the design of the study or made substantial contributions to acquisition, analysis and interpretation of the data. VB, WW, AT, SW and DK provided critical review of the manuscript for important intellectual content. All authors read and approved the final manuscript.

Ethics approval and consent to participate
The retrospective study was approved by the institutional review board (Charité's Ethics Committee-Universitätsmedizin Berlin).

Consent for publication
Patients gave written consent for data collection and analysis.

Competing interests
The authors declare that they have no competing interests.

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