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

DISSERTATION

Efficacy and Safety of Single Fraction Radiosurgery versus Fractionated Stereotactic
Body Radiotherapy for Patients with Oligometastases and Primary Renal Cell
Carcinoma

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

vorgelegt der Medizinischen Fakultät
Charité – Universitätsmedizin Berlin

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Datum der Promotion: 03.12.2021

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1. *Abstract (English)*

Objectives: Stereotactic body radiotherapy (SBRT) is increasingly used to treat oligometastatic disease (OMD) or various primary tumors in inoperable patients. SBRT delivered in one fraction is called single fraction radiosurgery (SFRS) and has attracted attention owing to its shortest possible treatment time. However, there are no recommendations for the use of SFRS vs. fractionated SBRT (fSBRT). This thesis investigated whether SFRS is comparable to fSBRT regarding efficacy and safety when treating either oligometastatic prostate cancer (OPCA) or lung metastases (LM) from various solid tumors and renal cell carcinoma (RCC) in inoperable patients who are at risk of end-stage renal disease. Moreover, I analyzed whether SBRT can delay the start of androgen deprivation therapy (ADT) in OPCA patients and looked for prognostic factors for survival in OMD.

Methods: Data from 112 patients, among whom 181 lesions had been treated between 2012 and 2017, were analyzed. The primary endpoints were local control (LC), progression-free survival (PFS), overall survival (OS), and ADT-free survival (ADT-FS).

Results: Fifty, 52, and 10 patients with OPCA, LM, and RCC, respectively, were included. Sixty (80%), 45 (47.9%), and eight (62%) lesions in patients with OPCA, LM, and RCC, respectively, were treated with SFRS. The 2-year LC rates after SFRS vs. fSBRT did not differ significantly in patients with OPCA (96% vs. 100%) and RCC (100% vs. 80%). LM treated with SFRS achieved better 2-year LC rates than those after fSBRT (83% vs. 59%, p=0.026). However, LM treated with SFRS were significantly smaller in size (p<0.001). SFRS was well tolerated, with no treatment-related acute or late toxicity of grade ≥3. There was no significant change in the glomerular filtration rate in patients with RCC before SBRT (mean 51.3±19.7 mL/min) and 22 months later (mean 51.6±25.8 mL/min). ADT was initiated in 14 (28%) of the 35 ADT-naïve patients. Median ADT-FS was not reached after a median follow-up of 34 months. Longer distant metastasis-free interval (DMFI) to the first metastasis was associated with improved PFS in OPCA patients (DMFI>36 months, HR 0.5, 95% CI: 0.3–0.8, p=0.01) and OS in patients with LM (DMFI ≥12 months, HR 0.2, 95% CI: 0.1–0.7, p=0.01).

Conclusions: SFRS is a safe and efficient treatment option for select patients with OMD and inoperable RCC. LC and toxicity after SFRS were comparable to those after fSBRT. Moreover, in patients with OPCA, SBRT can postpone palliative ADT for some time. Prolonged DMFI is a positive prognostic factor in OMD.

2. Abstrakt (Deutsch)

Fragestellung: Stereotaktische Körper-Radiotherapie (SBRT) wird zunehmend zur Behandlung der oligometastasierten Erkrankung (OMD) und bei inoperablen Patienten mit unterschiedlichen Primärtumoren eingesetzt. SBRT, die in einer Fraktion verabreicht wird, bezeichnet man als Einzeit-Radiochirurgie (SFRS), und diese ist aufgrund der kürzest möglichen Behandlungszeit besonders attraktiv. Aktuell existieren keine Empfehlungen, wann die SFRS gegenüber der fraktionierten SBRT (fSBRT) zu bevorzugen ist. Meine Doktorarbeit untersucht, ob die SFRS mit der fSBRT in Bezug auf Wirksamkeit und Sicherheit bei der Behandlung von oligometastasierten Patienten mit Prostatakarzinom (OPCA) oder Lungenmetastasen (LM) von soliden Tumoren und inoperablen Patienten mit Nierenzellkarzinom (RCC) mit dem Risiko für eine terminale Niereninsuffizienz vergleichbar ist. Weitere Fragen waren, ob SBRT den Beginn einer Androgendeprivationstherapie (ADT) bei Patienten mit OPCA verzögern kann und welche prognostischen Faktoren Einfluss auf das Überleben von Patienten mit OMD haben könnten.

Methoden: Es wurden die Daten von 112 Patienten mit insgesamt 181 Läsionen analysiert, die zwischen 2012 und 2017 eine SFRS und fSBRT erhielten. Die primären Endpunkte waren lokale Kontrolle (LC), progressionsfreies Überleben (PFS) und Gesamtüberleben (OS) sowie das ADT-freie Überleben (ADT-FS).

Ergebnisse: Fünfzig, 52 und 10 Patienten hatten OPCA, LM bzw. RCC. Sechzig (80%), 45 (47,9%) und 8 (62%) Läsionen bei Patienten mit OPCA, LM und RCC wurden mit SFRS behandelt. Die 2-Jahres-LC-Raten nach SFRS vs. fSBRT waren bei Patienten mit OPCA (96% vs. 100%) und mit RCC (100% vs. 80%) nicht signifikant unterschiedlich. Mit SFRS behandelte LM erreichten bessere LC-Raten nach 2 Jahren im Vergleich zu fSBRT (83% vs. 59%, p=0,026). Allerdings waren die mit SFRS behandelten LM signifikant kleiner (p<0.001). Es gab keine akute Toxizität oder Spätnebenwirkungen von Grad ≥3. Bei RCC-Patienten war die glomeruläre Filtrationsrate prä-SBRT (Mittelwert 51,3±19,7 ml/min) zu 22 Monate posttherapeutisch (Mittelwert 51,6±25,8 ml/min) nicht signifikant unterschiedlich. ADT-Einleitung war bei 14 (28%) von 35 ADT-naiven Patienten erfolgt. Das mediane ADT-FS war auch nach 34 Monaten Nachbeobachtungszeit (im Median) noch nicht erreicht. Ein längeres metastasenfreies Intervall (DMFI) bis zur ersten Metastase verbesserte signifikant das

PFS bei OPCA-Patienten (DMFI>36 Monate, HR 0,5; 95% CI: 0,3-0,8, p=0,01) und das OS bei LM-Patienten (DMFI ≥12 Monate, HR 0,2; 95% CI: 0,1-0,7, p=0,01).

Schlussfolgerungen: Die SBRT ist eine sichere und effiziente Behandlungsoption für selektionierte Patienten mit OMD oder mit inoperablen RCC. Die LC und Toxizität nach SFRS waren mit der fSBRT vergleichbar. Zusätzlich kann die SBRT bei OPCA-Patienten zur Verzögerung einer palliativen ADT führen. Bei Patienten mit OMD ist ein längeres DMFI ein positiver prognostischer Faktor für ein verlängertes Überleben.

3. Introduction

Stereotactic body radiotherapy (SBRT) is high-precision external beam radiotherapy for the treatment of extracranial tumors and delivers a high dose of radiation in up to 12 fractions (1). SBRT is a potential curative treatment modality in patients with oligometastatic disease (OMD) (2, 3) and various primary tumors (4, 5). In addition to being minimally invasive, SBRT delivers ablative doses in only a few fractions (fractionated SBRT [fSBRT]) with excellent local control (LC) rates and minimal toxicity (6, 7). SBRT applied in only one fraction is known as single-fraction radiosurgery (SFRS) and is particularly attractive due to a single treatment session resulting in improved patient compliance, reduced need for healthcare resources, and elimination of interfraction immobilization uncertainty. Additionally, SFRS reduces patient–health care worker interaction; therefore, it could be used as a treatment of choice in circumstances such as coronavirus pandemics. Data on extracranial SFRS for oligometastases and primary tumors are limited, and there are no recommendations on when to use SFRS vs. fSBRT. The need for effective local oncological therapy applied for the shortest possible time in the outpatient setting for this vulnerable patient population currently requires a shift in favor of SFRS.

3.1 Indications for SBRT

3.1.1 Oligometastatic disease

OMD is a condition in which long-term disease-free survival or even a cure can be achieved despite tumor cell dissemination to distant organs. A certain combination of favorable clinical factors of the tumor determines a less aggressive course of the disease, resulting in only a limited number of metastases in one or a few organs. In contrast to extensively disseminated cancer, OMD can be successfully managed with local ablation rather than palliative systemic therapy alone. This paradigm-changing concept was first introduced in 1995 by Hellman and Weichselbaum (8).
The relevance of SBRT in the OMD setting was supported in four randomized phase II trials (9-12). The benefit of SBRT was translated into significantly prolonged progression-free survival (PFS) and/or overall survival (OS) compared with surveillance.

3.1.2 Oligometastatic prostate cancer (OPCA)

In advanced prostate cancer (PCA), androgen deprivation therapy (ADT) is the treatment of choice as recommended by the European Association of Urology and National Comprehensive Cancer Network (13, 14). In daily practice, however, the use of ADT is limited by the broad spectrum of side effects (sexual dysfunction, reduced bone mineral density, hot flashes), which severely impair patients' quality of life (15). Additionally, ADT is a palliative treatment option because most patients undergoing treatment will develop hormone-refractory PCA. Metastasis-directed therapy (MDT) in patients with OPCA is of particular interest, as it may delay the onset or escalation of ADT (9, 10). The development of highly specific diagnostic imaging such as Gallium-68-labeled PSMA-PET computed tomography (PSMA-PET/CT) has enabled the detection of very early metastatic disease with lesions as small as 5 mm in diameter (16). This analysis examined the LC rates after PSMA-PET/CT guided SFRS vs. fSBRT for patients with OPCA. Additionally, I investigated whether PSMA-PET/CT-guided SBRT could delay the initiation or escalation of ADT in patients with OPCA, thus preventing undesirable side effects and sparing palliative treatment in case of further progression (17).

3.1.3 Lung (oligo)metastases (LM)

Lungs are common sites of distant metastases among various solid tumors (18). Surgical resection of LM remains the standard treatment for most patients. However, the emerging use of SBRT, particularly in older patients, often considered as poor candidates for surgery due to comorbidities, revealed good LC rates comparable to those after surgery (10, 19). To the best of my knowledge, no randomized trials have compared these two treatment approaches. Although no standard SBRT schedules exist, a biologically effective dose (BED) of >100 Gy has been shown to improve LC rates (6). A further objective of this study was to compare LC rates and toxicities after SFRS vs. fSBRT in LM from different primary tumors (20).

3.1.4 Renal cell carcinoma (RCC)

The standard therapeutic approach for non-metastatic stage I, II, and III RCC is surgery. The extent of surgical treatment depends on the disease stage, patient age, and comorbidities. For patients who are poor surgical candidates, minimally invasive therapies such as radiofrequency ablation or cryoablation may be used. However, this treatment approach is mostly limited to tumors < 4 cm in

diameter and located distantly from the hilum or central collecting system (21). Owing to its low α/β ratio, RCC is considered a radioresistant tumor when treated with conventional radiotherapy five times a week for several weeks (22). Nevertheless, the use of high-dose radiotherapy administered in only a few fractions has been shown to overcome the inherent radioresistance of RCC, resulting in acceptable LC (23). Although the analysis of SBRT efficacy in the treatment of RCC is mostly limited to retrospective and phase I studies, current evidence shows excellent LC and low toxicity rates (24). This study evaluated the efficacy and safety of SFRS vs. fSBRT in RCC in inoperable patients who are at risk of end-stage renal disease (25).

3.2   Prognostic factors in OMD

Although the number of studies investigating the use of metastasis-directed therapy in OMD is growing rapidly, there is still lack of a consistent clinical definition for identifying patients who will benefit from aggressive local therapies. For instance, the number of metastases in the presence of OMD in most studies varied between 3 and 5 (9, 12). Consequently, treatment outcomes across trials are inconsistent and difficult to compare. Considering this issue, I aimed to identify prognostic clinical factors in patients with LM and OPCA treated with SBRT.

A growing body of evidence suggests that clinical criteria alone may not be sufficient to specify a true OMD and should be complemented by the use of biomarkers (10, 26, 27). However, valid biomarkers for routine diagnostics in oligometastatic settings have not yet been established. Liquid biopsy as a source of potential biomarkers, such as cell-free circulating tumor DNA and RNA, is particularly attractive, as it can be collected non-invasively. Moreover, it is a cost-efficient procedure that may replace biopsies of solid tumors or bone marrow in the future. The last goal of this study was to establish a biobank of liquid biopsies based on blood samples from patients with OMD for future assessment of prognostic biomarkers.

In this doctoral thesis, I compared outcomes and toxicities after single-dose and fractionated approaches using a Cyberknife/high-precision stereotactic linear accelerator for patients with cancer. To this end, the data of patients with OMD and RCC treated with SFRS and fSRBT to assess the advantages and disadvantages of these different techniques in terms of survival, LC, and toxicity were analyzed. Additionally, I investigated whether SBRT for all metastases detected with PSMA-PET/CT

can delay the initiation and escalation of ADT in OPCA. I also searched for prognostic factors that predicted better outcomes after SBRT in OMD.

4. *Materials and methods*

The present study consisted of two parts:

1) Retrospective data collection and analysis of patients treated with SBRT between January 2010 and December 2016 at the Department of Radiation Oncology, Charité - Universitätsmedizin Berlin for either OPCA or LM from any primary, or for patients with inoperable primary or recurrent (p/r)RCC with an increased risk of developing end-stage renal disease (17, 20, 25). Data on patient demographics, treatment and tumor characteristics, treatment outcomes, and survival data were collected.

2) Prospective collection and processing of liquid biopsies of patients with OMD from various primary tumors treated with SBRT between June 1, 2016 and May 31, 2017, at the Department of Radiation Oncology, Charité - Universitätsmedizin Berlin. Ethical approval was received from the Institutional Medical Ethics Committee of Charité-Universitätsmedizin Berlin (EA1/214/16 and EA1/233/18). Analysis of prognostic factors for OMD after collecting blood samples from 40 eligible patients is in progress. In this thesis, the results of retrospective data analysis are presented.

4.1   Inclusion criteria

The cohort with OPCA: PSMA-PET/CT-based SBRT for a maximum of five active metastatic lesions in patients with *de novo* or repeat OPCA (28); histologically confirmed PCA treated with local treatment with curative intent; hormone-sensitive and castration-resistant patients; no ADT or ADT initiated before SBRT.

The cohort with LM: SBRT for all LM in patients with *de novo* or repeat OMD from various solid tumors (28); up to 5 LM.

The cohort with p/rRCC: histologically confirmed p/r RCC; patients with an increased risk of end-stage renal disease; patients not eligible for surgery or other radical local therapies; SBRT to the primary or recurrence in the (remaining-) kidney recommended by the Multidisciplinary Uro-Oncology Board.

4.2 Treatment planning and delivery

SBRT was performed using the robotic radiosurgery system CyberKnife (CK) (Accurray®, USA) and/or a high-precision dedicated stereotactic linear accelerator Novalis Tx™ (Varian, USA). The CyberKnife Synchrony® Respiratory Motion Tracking System was used for all RCC treatments in the kidney and some lung and lymph node metastases. Before motion-tracking SBRT, a gold fiducial (1.0 mm x 5.0 mm) was implanted into the target lesion under CT guidance and local anesthesia to ensure minimal treatment volumes and optimal organ at risk sparing by on-line tracking or gating. In patients with lesions of limited movement or with contraindications for fiducial insertion, alignment to the spine using XsightSpine® Tracking (Accuracy®, USA) or ExacTrac-based spinal alignment (BrainLab®, Germany) was used. For all patients, a thin-slice (1–3 mm) planning CT of the body region of interest was performed in the supine position. Diagnostic PSMA-PET/CT for all patients with OPCA and, if indicated, magnetic resonance imaging was co-registered for precise contouring of the target tumor lesion on all axial slices of the planning CT scan. Gross tumor volume (GTV) corresponded to the tumor visible on the planning CT and co-registered diagnostic imaging. The clinical target volume was set equal to the GTV in the majority of cases. For lesions with significant motion but without gold marker implantation, an internal target volume (ITV) was generated. Planning treatment volume (PTV) was defined as GTV or ITV with additional isotropic margins of 3–7 mm depending on the tracking or gating method used for SBRT.

Treatment dose and fractionation schedules were prescribed with regard to tumor entity, tumor location, and tumor size. If dose constraints for organs at risk were met when using SFRS, SFRS was preferred over fSBRT.

4.3 Follow-up

Patients with LM or p/rRCC underwent radiological imaging every 3 months for the first 2 years and every 6 months thereafter. In patients with OPCA, prostate-specific antigen (PSA) testing was routinely performed. A continuous increase in PSA levels triggered radiological imaging.

4.4 Endpoints

All survival endpoints were calculated from the date of the first or single fraction of SBRT and the date of the event or the last follow-up. For overall survival (OS), death due to any cause was calculated as an event. PFS was defined as any local or distant tumor recurrence or death from any cause. LC

was defined as the absence of tumor re-growth within the irradiated region or an increase in tumor volume outside the GTV. Furthermore, for patients with OPCA, the following endpoints were analyzed: treatment failure-free survival (TFFS), defined as initiation of any new tumor-targeted therapy (ADT, chemotherapy, surgery, SBRT) or death from any cause; ADT-free (ADT-FS) survival; and androgen deprivation therapy escalation-free survival (ADTE-FS). The initiation or escalation of ADT or death from any cause was counted as an event.

4.5 Statistics

Data processing and statistical analysis were performed using FileMaker Pro 15 Advanced, Excel 2010, and IBM SPSS Statistics 24 (SPSS Inc., Chicago, IL, USA). Survival analyses were performed using the Kaplan-Meier method. The Cox proportional hazards model was used in univariate and multivariate analyses to calculate hazard ratios (HRs) with 95% confidence intervals (95% CI). Covariates with a p-value of ≤ 0.1, in the univariate analysis, were included in the multivariate analysis. The chi-square test was used to compare the variables. Statistical significance was set at p <0.05.

5. Results

5.1 Baseline patient and tumor characteristics

A total of 112 patients met the inclusion criteria and were included in the analysis. Fifty, 52 and 10 patients had OPCA, LM, and uni- or multifocal p/rRCC, respectively (17, 20, 25). Baseline patient and tumor characteristics are summarized in Table 1.

Table 1. Patient and tumor characteristics			
	OPCA cohort N=50	LM cohort N=52	p/rRCC cohort N=10
Age at tumor diagnosis, years			
median	66	62	72
range	47–75	26–84	48–87
Karnofsky performance index (%)			
median	90	80	80

range	80–100	60–100	70–80
Sex, n (%)			
female	0 (0)	20 (38.5)	5 (50)
male	50 (100)	32 (61.5)	5 (50)
Distant metastasis-free interval (DMFI), months			
median	37	19	–
range	1–199	0–37.9	–
No. of lesions treated with SBRT			
median	2	1	1
range	1–5	1–5	1–3
No. of affected organs per patient at SBRT (%)			
1	48 (96)	35 (67.3)	–
2	2 (4)	11 (21.2)	–
3	0	5 (9.6)	–
4	0	1 (1.92)	–

Abbreviations: OPCA *oligometastatic prostate cancer*, LM *lung oligometastases*, p/rRCC *primary/recurrent renal cell carcinoma*, SBRT *stereotactic body radiotherapy (17, 20, 25)*.

5.1.1 Cohort with OPCA

All patients with OPCA were staged with PSMA-PET/CT before SBRT. Based on the D'Amico risk classification (29), 41 (82%), three (6%), and four (8%) patients were classified as having high, intermediate, and low risk, respectively. In two (4%) cases, data on risk class were missing. In 31 (62%) patients, the primary tumor was treated with radical prostatectomy (RP) followed by adjuvant or salvage radiotherapy. Unimodal treatment with RP or radiotherapy alone was used in 15 (30%) and four (8%) cases, respectively. The median PSA value at the initial diagnosis and before the SBRT for oligometastases was 9.8 ng/mL (range: 0.54–195) and 1.9 ng/mL (range: 0.16–59.8), respectively. At the time of SBRT, 35 (70%) patients were free from ADT, whereas 15 (30%) were undergoing ADT. In 25 (50%) and 24 (48%) patients, only lymph nodes or bones were affected.

5.1.2 Cohort with LM

The most common primary tumor was colorectal cancer, which was diagnosed in 17 (32.7%) patients, followed by sarcoma in eight (15.4%), malignant melanoma in seven (13.5%), head and neck cancer in six (11.5%), RCC in five (9.6%), non-small cell lung cancer in three (5.8%), and other entities in six (11.5%) patients. Staging with FDG-PET/CT was performed in 11.5% of the cases. Forty-six (88.5%) patients received systemic therapy before the initiation of SBRT. Synchronous OMD was diagnosed in 12 patients (23.1%) with LM.

5.1.3 Cohort with p/rRCC

All patients had chronic kidney disease, which reached grade 3b in 40%, grade 2 in 30%, grade 3a in 20%, and grade 4 in 10% patients. There were 70% patients with cT1a and 30% with cT3a tumors. Two patients were diagnosed with von Hippel-Lindau syndrome. The first-line treatment in half of the patients was nephrectomy. Partial ipsilateral resection was performed in four (40%) patients and partial contralateral resection of the kidney in three (30%) patients. Radiofrequency ablation was performed in two (20%) patients. The mean ± standard deviation (SD) serum creatinine level at the baseline was 1.4 ± 0.5 mg/dL (mean ± SD glomerular filtration rate [GFR] 51.3 ± 19.7 mL/min).

5.2 Survival outcomes

5.2.1 Cohort with OPCA

The median follow-up time was 34 months (range 5–70 months) (17). The 1- and 2-year OS rates were 100% and 100% and 1- and 2-year PFS rates were 54% and 22%, respectively. Overall, four (8%) patients died. At the time of the last follow-up, only one patient (2%) was free from disease progression. The most common progression pattern was repeat OMD, observed in 32 (64%) patients, followed by polymetastatic diseases in six (12%) and biochemical progression in six patients (12%). Primary tumor recurrence occurred in three (6%) patients.

The TFFS rates at 1 and 2 years were 55.2% and 23.4%, respectively. At the time of the first progression, the second course of SBRT was the treatment of choice in 24 (48%) patients with repeat OMD. ADT was initiated in 14 (28%) ADT-naïve patients and escalated in six (12%) patients with ongoing hormone therapy. The 1- and 2-year ADT-FS rates were 76.4% and 60.5% and 1- and 2-year ADTE-FS rates were 58.2% and 33.9%, respectively. Median ADT-FS was not reached, and median ADTE-FS was 27 months (95% CI: 8.8–45.1).

5.2.2 Cohort with LM

With a median follow-up of 21 months (range: 3 – 68), the 1- and 2-year OS rates were 84% and 71%, respectively (20). A total of 21 (40.4%) patients died. Progression was observed in 42 (80.8%) patients with 1- and 2-year PFS rates of 26% and 15%, respectively.

5.2.3 Cohort with p/rRCC

The median follow-up period was 27 months (range: 15 – 54) (25). Two patients died after 15 and 16 months of age due to disease progression. The 1- and 2-year OS rate were 100% and 80%. None of the patients required hemodialysis, and all patients remained stable for renal function at the time of the last follow-up. The mean ± SD serum creatinine level at the last follow-up was 1.5 ± 0.8 mg/dL (mean ± SD GFR 51.6 ± 25.8 mL/min).

5.3 Local control rates and toxicity after SFRS and fSBRT

The total number of metastases treated was 168, of which 94 were located in the lung and 74 in either the bone or lymph nodes (17, 20). One patient with LM from OPCA was included in both cohorts. Overall, 13 primary or recurrent renal RCC lesions were treated (25). Baseline tumor and treatment characteristics are shown in Table 2.

5.3.1 Cohort with OPCA

In total, only two metastases located in the bone and treated with SFRS (20 and 21 Gy) relapsed. Median time to relapse has not yet been reached. The 1-year and 2-year LC rates after SFRS vs. fSBRT were 98% and 96% vs. 100% and 100%, respectively (Fig 1 A). No differences in LC or toxicities were observed between the two groups. Severe ≥ grade 3 toxicities were not observed.

5.3.2 Cohort with LM

The 1-year and 2-year LC rates for SFSR vs. fSBRT were 89% and 83% vs. 75% and 59%, respectively (*p*=0.026) (Fig 1 B). In total, 22 metastases relapsed, of which 72.2% were treated with fSBRT. Median time to relapse for metastases treated with fSBRT was 32 months (95% CI: 21.3–42.7). The median time to relapse for lesions treated with SFRS was not reached. Metastases treated with SFRS (median diameter = 12 mm) were significantly smaller than those treated with fSBRT (median diameter = 16 mm, p=0.003). In univariate analysis treatment with SFRS (HR 2.7; 95% CI:

1.0–7.0, p=0.04), non-colorectal histology (HR 0.2; 95% CI: 0.1–0.6, p=0.004), BED < 100 Gy (HR 2.7; 95% CI: 1.1–6.4, p=0.02), and treatment started within 12 months after metastasis diagnosis (HR 2.5; 95% CI: 1.1–6.0, p=0.03) were linked to better LC. None of these factors remained significant in multivariate analysis.
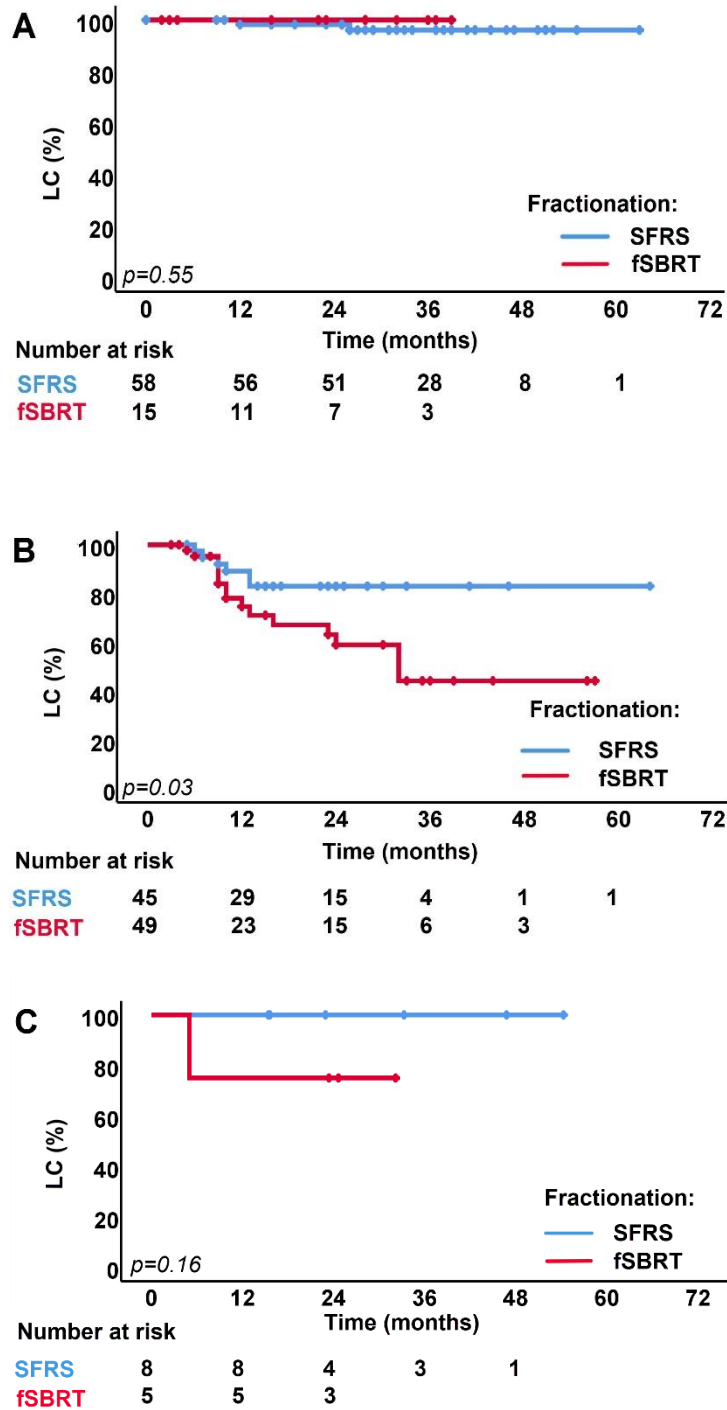
Regarding toxicities, both treatments were well tolerated, with no grade ≥3 side effects. Six patients (11.5%) had grade 1 pneumonitis. In one patient (1.9%), treatment with prednisolone was indicated owing to symptomatic grade 2 pneumonitis. Grade 1 late pulmonary fibrosis was observed in one patient (1.9%).

Table 2. Tumor and treatment characteristics

	Lung metastases		Lymph node		Bone metastases		p/rRCC	
	SFRS	fSBRT	SFRS	fSBRT	SFRS	fSBRT	SFRS	fSBRT
Number	45	49	26	13	33	2	8	5
PTV (cc)								
median	10	24	3	5	5	16	18	66
range	2–91	6–165	1–14	3–23	1–62	14–17	4–31	17–190
Number of fractions								
median	1	4	1	3	1	3	1	3
range	-	2–12	-	3–6	-	-	-	-
PTV-encompassing single dose (Gy)								
median	24	12	20	8	20	9	25	12
range	17–26	4–18	18–22	5–10	16–24	8–10	24–25	-
PTV-encompassing prescription dose (Gy)								
median	24	45	20	24	20	27	25	36
range	17–26	20–60	18–22	19–29	16–24	24–30	24–25	-
Biological effective dose to the lesion (Gy)								
α/β-ratio	**10**		**3**		**3**		**6.9**	
median	82	106	153	88	153	108	116	99
range	46–94	43–151	126–183	60–88	101–216	88–130	108– 116	99

Abbreviations: p/rRCC primary or recurrent *renal cell carcinoma in the kidney*, PTV *planning treatment volume*, SFRS *single fraction radiosurgery,* fSBRT *fractionated stereotactic body radiotherapy (17, 20, 25).*

Fig 1. Kaplan-Meier survival curves for local control (LC) by fractionation schedules single fraction radiosurgery (SFRS) vs. fractionated stereotactic body radiotherapy (fSBRT) for (A) patients with oligometastatic prostate cancer, (B) patients with lung oligometastases, (C) patients with primary/recurrent renal cell carcinoma.

5.3.3 Cohort with p/rRCC

Only one lesion (7.7%) treated with 3×12 Gy relapsed after 5 months. The 1-year and 2-year LC rates after SFRS vs. fSBRT were 100% and 100% vs. 100% and 80%, respectively (Fig 1 C). The median tumor diameter for the entire cohort was 28.8 mm. No grade 2 or higher toxicity events were observed. Grade 1 abdominal pain and grade 1 diarrhea with abdominal distention were observed in two patients (20%). No difference in toxicities was observed between SFRS and fSBRT.

5.4 Prognostic factors for patients with oligometastases

A distant metastasis-free interval (DMFI) between the diagnosis of the primary tumor and the first metastasis was linked to better outcomes in both cohorts with OMD (17, 20). Patients with OPCA with DMFI > 36 months had significantly longer PFS (HR 0.5; 95% CI, 0.3–0.8; p=0.01) and TFFS (HR 0.4; 95% CI, 0.2–0.8; p=0.01). For the cohort with LM, a DMFI of 1-year or longer predicted better OS (HR 0.2; 95% CI: 0.1–0.7, p=0.01).

In the cohort with OPCA, a lower PSA level with a cutoff of 1 ng/mL at the time of SBRT predicted longer TFFS (HR 0.4; 95% CI: 0.2–0.9, p=0.03).

Furthermore, in the group with LM, good performance status (Karnofsky index >70%) was associated with longer OS (HR 0.3; 95% CI: 0.1–0.8; p=0.03) and PFS (HR 0.4; 95% CI: 0.2–0.7; p=0.02). A higher number of metastases with a cutoff of three before SBRT was associated with worse PFS (HR 2.7; 95% CI: 1.4–5.4; p=0.003).

6. *Discussion*

In the present study, the efficacy and tolerability of SFRS were compared to those of fSBRT in the oligometastatic setting and patients with p/rRCC at risk for renal failure/dialysis (17, 20, 25). I observed that repeated SBRT might postpone the initiation and escalation of palliative ADT in OPCA. Furthermore, this work complemented the existing knowledge about prognostic factors for survival and treatment outcomes in patients with OPCA and LM.

To the best of my knowledge, no randomized trials have compared SFRS with fSBRT in the setting of OPCA. Consequently, there are no recommendations regarding which treatment schedule is preferred in this situation. Consistent with my findings, Siva et al. reported 2-year LC rates of 93% after SFRS with 20 Gy for lymph node or bone oligometastases from PCA in a prospective, non-

randomized study. The therapy was well tolerated, except for one patient with a grade 3 vertebral fracture. Recently, a published meta-analysis investigated the relationship between LC rates and BED after SBRT for 1,441 oligometastases in patients with OPCA (30). With minimal toxicity of only 1.3%, the authors found that a BED > 100 Gy was associated with significantly better LC rates (BED < 100 Gy LC=88% vs. BED > 100 Gy LC=96%). In the present study, the median BED for SFRS was >100 Gy, whereas, for fSBRT, it was only 88 Gy (range: 60.16–88 Gy). In contrast to the meta-analysis mentioned above, excellent LC rates without any difference in BED were observed. However, the present results should be interpreted with caution as only 20% of metastases were treated with fSBRT and thus received BED <100 Gy. In a retrospective series conducted by Muldermans et al., the relationship between dose escalation and LC was observed after treatment of 81 oligometastases, of which 88% were treated using SFRS. The authors found LC rates at 2 years of only 58% for metastases treated with 16 Gy compared with 95% after administration of a minimum of 18 Gy (p ≤0.001) (31). No local recurrence was observed in metastases treated with >18 Gy. No grade 2 toxicity events occurred. In the present study, two relapsed lesions were treated with SFRS > 18 Gy, and the only lesion treated with 16 Gy was controlled after 51 months of follow-up. Although no consensus on the optimal fractionation scheme can be derived from retrospective data, the current results demonstrated that SFRS is a safe and effective treatment modality for patients with oligometastases from PCA. Further randomized studies are needed to investigate the best fractionation schedules for treatment outcomes and toxicity.

The LC after SBRT for **LM** observed in the present study is consistent with results reported in the literature (6, 32, 33). Regarding fractionation regimens, SFRS with a median of 24 Gy and median BED < 100 Gy proved to be superior to fSBRT in terms of recurrence rate. In contrast to the results of some recently published studies, this study demonstrated that good LC can be achieved after SBRT with a BED <100 Gy. It should be noted that metastases treated with SFRS were significantly smaller, which may be linked to better LC, as some authors have reported an association between smaller lesions and longer recurrence-free interval (32, 34, 35). However, other studies found no correlation between LM size and LC rates (6, 36). Results from the recent phase 2 SAFRON II trial demonstrated that SFRS is safe and effective compared with fSBRT for up to 3 LM, with a 1-year LC of 93% vs. 95% and grade 3 toxicity of 5% vs. 3% (37). For additional metastases and treatment characteristics, the full publication must be awaited. The results of the present study show that small lesions with a volume of 10 cc can be effectively and safely treated with the shortest possible treatment schedule.

This analysis found that SBRT, either in a single fraction or in three fractions, is safe and efficient for patients with impaired renal function experiencing *p/rRCC*. These findings are comparable to those reported in the literature, where LC rates after 2 years range from 92.3% to 100% (23, 38, 39). Considering the small number of lesions treated, no difference was observed between SFRS and fSBRT in the present cohort. Furthermore, renal function remained unchanged after 2 years. Siva et al. conducted a prospective interventional clinical trial that demonstrated SFRS vs. fSBRT to be equally good in terms of LC after the treatment of 37 patients with unresectable T1a-T2a RCC (40). SFRS was indicated for tumors < 5 cm in diameter. Grade 3 toxicity was observed in only one patient (3%), and no grade ⩾4 toxicities were reported. In contrast to the present study, the authors observed a GFR decline of 11 mL/min at 1 year. The median PTV of patients in present study was smaller (SFRS: 17.5 cc [range: 3.8–31] and fSBRT: 66.2 cc [range: 17.4–190.3]) compared with the median PTV reported by Siva and colleagues (SFRS: 77.2 cc [range: 51.8–89.4] and fSBRT: 166.8 cc [range: 133.1–214.2]). Smaller treatment volume could be one of the factors leading to better conservation of nephrons and thus preservation of renal function. In a large retrospective series of 223 patients treated with either SFRS (n=118) or fSBRT (n=105) for RCC with a median tumor diameter of 43.6 ± 27.7 mm, the mean decline of GFR by 5.5 ± 13.3 mL/min was reported (23). Tumors treated with SFRS were significantly smaller, with a median diameter of 37.1 ± 10.6 mm. However, the authors found no association between tumor size (T1a vs. >T1a), fractionation schedule (SFRS vs. fSBRT), and renal function changes. Other factors such as pre-existing comorbidities (diabetes, cardiovascular disease, and arterial hypertension) might influence renal function after SBRT. Considering the results of this study and other retrospective and prospective phase I studies, SFRS showed excellent LC rates in smaller RCC with preservation of renal function and limited toxicities. The results of the prospective, phase II, nonrandomized FASTRACK II trial of SFRS and fSBRT in unresectable RCC are expected to validate SBRT as safe and effective in RCC (41).

Considering the role of SBRT in postponing ADT for patients with OPCA**,** several prospective trials have been conducted (9, 10, 42). Two randomized phase II studies, OREOLE and STOMP, showed that metastasis-directed therapy is superior to active surveillance, resulting in either prolonged PFS or ADT-FS (9, 10). In the present study, the median ADT-FS was not reached after 34 months of follow-up, which is notably better than in some prospective and retrospective studies (9, 30). The explanation for this inconsistency may be the use of a second SBRT line in the majority of patients with repeat oligoprogression after initial SBRT. In line with current results, Pasqualetti et al. reported a systemic

therapy-free survival of 39.7 months after performing repeated SBRT for patients with ≤ 3 oligometastases from PCA (43). The maximum number of SBRT lines administered in one patient was five. In addition to delaying the onset of ADT, SBRT might be used to eradicate hormone-resistant tumor cell clones, thus postponing the escalation of systemic therapy for further progression (44). In six of 15 patients with ongoing ADT at the time of SBRT, systemic therapy was escalated after a median time of 27 months. Triggiani et al. found that almost 50% of castration-resistant patients after SBRT to up to three oligometastases have started with second-line therapy (45). The median time to escalation was 22 months. Although the use of SBRT in patients with ongoing palliative system therapy has not been investigated in prospective trials, it might not be limited to symptomatic patients but used to control the therapy-refractory tumor burden.

It should be noted that even with novel imaging techniques such as PSMA-PET/CT, in some cases, the micrometastases are underdiagnosed and thus remain untreated. A delay in the start or escalation of systemic therapy leads to the manifestation of polymetastatic disease in these patients, which is associated with increased mortality (46). In the STOMP study, 30% of patients in the MDT arm developed polymetastases 1 year after SBRT (9). Regarding this, I observed better results, with only six (12%) patients having >5 metastases at first progression after SBRT. Similar to the current study, Bowden et al. showed a 17.6% rate of progression to polymetastatic disease within 2 years after PSMA-PET/CT-based SBRT for a maximum of five lesions (47). I hypothesize that staging with PSMA-PET/CT might lead to lower rates of polymetastases in the aforementioned and the present study. Further studies are needed to identify patients who will most likely benefit from MDT in an oligometastatic setting.

Furthermore, within my thesis, I asked the question, *"What are potential prognostic factors for OMD?"*. I found that longer DMFI significantly improved PFS and TFFS in patients with OPCA and OS in a cohort of patients with LM. The OMD is classified as synchronous or metachronous concerning the onset of the first metastasis. In synchronous OMD, the primary tumor and metastasis are diagnosed simultaneously, whereas in metachronous OMD, there is a certain disease-free interval until metastasis occurs. However, the definition of metachronous disease differs considerably in the literature, with a disease-free interval varying between 2 and 78 months (48-51). In some studies, synchronous OMD or shorter disease-free interval was associated with a more aggressive tumor subtype, leading to worse treatment outcomes (52, 53). In the present study, a longer DMFI predicted better survival in both cohorts with OMD, however, the cut-off value differed between OPCA and

LM patients, suggesting that DMFI is not a universal prognostic factor but rather specific to primary tumor type and metastatic potential. In line with current results, Franzese et al. found a DMFI of ≥ 34 months to be a prognostic factor for distant PFS in 92 patients with OPCA (54). After analyzing patients with a maximum of 5 LM from different primary tumors, Rieber et al. found that a longer time interval between primary tumor diagnosis and SBRT for metastasis predicted a significantly better OS (6). The researchers also found that patients with a prolonged interval to SBRT were enriched in the subgroups of patients with breast and colorectal cancers. Further studies are needed to determine a DMFI to predict treatment outcomes in an oligometastatic setting concerning the primary tumor type.

Another prognostic factor found in the present study was a good performance status (Karnofsky index >70%), which was observed only in the cohort with LM. Several other studies have reported performance status as an important prognostic factor in patients with lung and liver oligometastases (6, 55). This suggests that fragile patients should be considered more cautiously for curative therapies, as palliative treatment might be a better option in this case.

The major limitations of this study are its retrospective design, the bias in patient selection, and the relatively small sample size. Additionally, the number of metastases treated with SFRS in the cohort with OPCA was four times greater than that in those treated with fSBRT.

This study demonstrated that SFRS is safe and effective for the treatment of selected patients with oligometastases and p/rRCC with renal function impairment. SFRS is particularly important during a "pandemic" times by reducing patient-to-healthcare workers' exposure without compromising oncologic outcomes in a subgroup of patients.

7. References

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8. *Statutory Declaration*

"I, Goda Kalinauskaitė, by personally signing this document in lieu of an oath, hereby affirm that I prepared the submitted dissertation on the topic Efficacy and Safety of Single Fraction Radiosurgery versus Fractionated Stereotactic Body Radiotherapy for Patients with Oligometastases and Primary Renal Cell Carcinoma, independently and without the support of third parties, and that I used no other sources and aids than those stated.

All parts which are based on the publications or presentations of other authors, either in letter or in spirit, are specified as such in accordance with the citing guidelines. The sections on methodology (in particular regarding practical work, laboratory regulations, statistical processing) and results (in particular regarding figures, charts and tables) are exclusively my responsibility.

My contributions to any publications to this dissertation correspond to those stated in the below joint declaration made together with the supervisor. All publications created within the scope of the dissertation comply with the guidelines of the ICMJE (International Committee of Medical Journal Editors; www.icmje.org) on authorship. In addition, I declare that I shall comply with the regulations of Charité – Universitätsmedizin Berlin on ensuring good scientific practice.

I declare that I have not yet submitted this dissertation in identical or similar form to another Faculty.

The significance of this statutory declaration and the consequences of a false statutory declaration under criminal law (Sections 156, 161 of the German Criminal Code) are known to me."

Date   Signature

9. Detailed declaration of own contribution

Publication 1: Kalinauskaite G., Senger C., Kluge A., Furth C., Kufeld M., Tinhofer I., Budach V., Grün A., Stromberger C. 68Ga-PSMA-PET/CT-based radiosurgery and stereotactic body radiotherapy for oligometastatic prostate cancer, PLoS One, 2020. https://doi.org/10.1371/journal.pone.0240892.

Contribution according to publication 1: "Conceptualization: Goda Kalinauskaite, Markus Kufeld, Ingeborg Tinhofer, Volker Budach, Arne Grün, and Carmen Stromberger. Data curation: Goda Kalinauskaite, Carolin Senger, Markus Kufeld, Arne Grün, and Carmen Stromberger. Formal analysis: Goda Kalinauskaite, Arne Grün, and Carmen Stromberger. Funding acquisition: Goda Kalinauskaite. Investigation: Goda Kalinauskaite and Carmen Stromberger. Methodology: Goda Kalinauskaite, Ingeborg Tinhofer, Volker Budach, Arne Grün, and Carmen Stromberger. Project administration: Goda Kalinauskaite, Arne Grün. Resources: Goda Kalinauskaite, Carolin Senger, Marcus Beck, and Carmen Stromberger. Software: Goda Kalinauskaite and Anne Kluge. Supervision: Goda Kalinauskaite, Carolin Senger, Arne Grün, and Carmen Stromberger. Validation: Goda Kalinauskaite and Alexandra Hochreiter Visualization: Goda Kalinauskaite, Anne Kluge. Writing – original draft: Goda Kalinauskaite. Writing – review & editing: Goda Kalinauskaite, Carolin Senger, Anne Kluge, Christian Furth, Markus Kufeld, Ingeborg Tinhofer, Volker Budach, Marcus Beck, Alexandra Hochreiter, Arne Grün, and Carmen Stromberger."

In detail publication 1:

GK was directly involved in the initial design and setup of the study on a single-fraction radiosurgery and fractionated stereotactic body radiotherapy for patients with oligometastatic prostate cancer. She reviewed the clinical records of all patients with oligometastatic prostate cancer treated with SBRT between 2012 and 2016 at Charité Universitätsmedizin Berlin, Department of Radiation Oncology, and selected the eligible patients. She continued to build the database of clinical, treatment, and follow-up data using the FileMaker platform. To assess response after radiotherapy she reviewed treatment plans and radiologic images. GK performed data preparation by creating Excel and SPSS spreadsheets. GK performed data preparation by creating Excel and SPSS spreadsheets. GK performed the statistical data analysis using Excel and SPSS, and presented the main findings in the results section. GK interpreted the results in the context of the existing literature by means detailed literature review. After completion of the above steps, GK prepared the manuscript. All sections of the manuscript were written by GK and critically reviewed and edited by CS2. All tables and the figure were designed and created by GK, except for Fig. 1, which was prepared by AK. After final manuscript was put together IT, MK, AK, AG, VB, CS1 reviewed the draft and gave their consent for publication. Submission and revision of the publication was done by GK.

Publication 2: Kalinauskaite G.G., Tinhofer I.I., Kufeld M.M., Kluge A.A., Grün A.A., Budach V.V., Senger

C.C, Stromberger C.C. Radiosurgery and fractionated stereotactic body radiotherapy for patients with lung oligometastases. *BMC Cancer* **20,** 404 (2020). https://doi.org/10.1186/s12885-020-06892-4.

Contribution according to publication 2: "GK acquired, analyzed, and interpreted patient data, conducted statistical analysis, and drafted the manuscript. CS2, IT, and MK provided ideas for the study. CS1, CS2, and IT contributed to data interpretation and manuscript writing. AK provided technical support, preparation of figures, and a critical review of the manuscript. GK, MK, AG, VB, CS1, and CS2 were responsible for treatment, collection of patient data, and follow-up. CS1 and CS2 contributed equally to this study. All authors have read and approved the final version of the manuscript."

In detail publication 2:

GK was directly involved in the initial design and set-up of the study of a single-fraction radiosurgery and fractionated stereotactic body radiotherapy in patients with lung oligometastases. She reviewed the clinical records of all patients with lung metastases treated with SBRT between 2010 and 2016 at Charité Universitätsmedizin Berlin, Department of Radiation Oncology, and selected the eligible patients. She developed a database of clinical, treatment, and follow-up data using the FileMaker platform. To assess response after radiotherapy and to distinguish radiotherapy-associated radiologic changes from tumor progression, she reviewed treatment plans and radiologic images. GK performed data preparation by creating Excel and SPSS spreadsheets. GK performed the statistical data analysis using Excel and SPSS, and presented the main findings in the results section. GK interpreted the results in the context of the existing literature by means detailed literature review. After completion of the above steps, GK prepared the manuscript. All sections of the manuscript were written by GK and critically reviewed and edited by CS2. All tables and the figure were designed and created by GK, except for Fig. 1, which was prepared by AK. After final manuscript was put together IT, MK, AK, AG, VB, CS1 reviewed the draft and gave their consent for publication. Submission and revision of the publication was done by GK.

Publication 3: Senger C., Conti A., Kluge A., Pasemann D., Kufeld M., Acker G., Lukas M., Grün A., Kalinauskaite G., Budach V., Waiser J., Stromberger C. Robotic stereotactic ablative radiotherapy for renal cell carcinoma in patients with impaired renal function, BMC Urology, 2019. https://doi.org/10.1186/s12894-019-0531-z.

Contribution according to publication 3: "CS (Senger) acquired, analyzed, and interpreted the patient data and drafted the manuscript. AC contributed to writing of the manuscript. AK and DP provided technical support, preparation of figures, and critical review of the manuscript. MK made substantial contribution to data acquisition. ML conducted statistical analyses. GA, AG, GK, JW, and VB provided administrative support and critically revised the manuscript. CS (Stromberger) participated in the design of the study and made substantial contributions to the acquisition, analysis, and interpretation of data. CS (Senger) approved the final version of the manuscript on behalf of all the authors. All authors read and approved the final manuscript."

In detail publication 3:

GK participated in the literature review, performed proofreading of the manuscript, and provided minor suggestions.

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Signature, date and stamp of the first supervisor

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Signature of the doctoral candidate

10.   *Printed copies of selected publications*

Publication 1:

Kalinauskaite G, Senger C, Kluge A, Furth C, Kufeld M, Tinhofer I, *et al.* 68Ga-PSMA-PET/CT-based radiosurgery and stereotactic body radiotherapy for oligometastatic prostate cancer. PLOS ONE. 2020;15(10):e0240892.

https://doi.org/10.1371/journal.pone.0240892

PLOS ONE

RESEARCH ARTICLE

68Ga-PSMA-PET/CT-based radiosurgery and stereotactic body radiotherapy for oligometastatic prostate cancer

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Abstract

Background

Androgen deprivation therapy (ADT) remains the standard therapy for patients with oligometastatic prostate cancer (OMPC). Prostate-specific membrane antigen positron emission tomography/computed tomography (PSMA-PET/CT)-based stereotactic body radiotherapy (SBRT) is emerging as an alternative option to postpone starting ADT and its associated side effects including the development of drug resistance. The aim of this study was to determine progression free-survival (PFS) and treatment failure free-survival (TFFS) after PSMA-PET/CT-based SBRT in OMPC patients. The efficacy and safety of single fraction radiosurgery (SFRS) and ADT delay were investigated.

Methods

Patients with ≤5 metastases from OMPC, with/without ADT treated with PSMA-PET/CT-based SBRT were retrospectively analyzed. PFS and TFFS were primary endpoints. Secondary endpoints were local control (LC), overall survival (OS) and ADT-free survival (ADTFS).

Results

Fifty patients with a total of 75 metastases detected by PSMA-PET/CT were analyzed. At the time of SBRT, 70% of patients were castration-sensitive. Overall, 80% of metastases were treated with SFRS (median dose 20 Gy, range: 16–25). After median follow-up of 34 months (range: 5–70) median PFS and TFFS were 12 months (range: 2–63) and 14 months (range: 2–70), respectively. Thirty-two (64%) patients had repeat oligometastatic disease. Twenty-four (48%) patients with progression underwent second SBRT course. Two-year LC after SFRS was 96%. Grade 1 and 2 toxicity occurred in 3 (6%) and 1 (2%) patients,

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respectively. ADTFS and OS rates at 2-years were 60.5% and 100%, respectively. In multi-variate analysis, TFFS significantly improved in patients with time to first metastasis (TTM) >36 months (p = 0.01) and PSA before SBRT ≤1 ng/ml (p = 0.03).

Conclusion

For patients with OMPC, SBRT might be used as an alternative to ADT. This way, the start/escalation of palliative ADT and its side effects can be deferred. Metastases treated with PSMA-PET/CT-based SFRS reached excellent LC with minimal toxicity. Low PSA levels and longer TTM predict elongated TFFS.

Introduction

For stage IV prostate cancer (PCA) palliative systemic therapy with androgen deprivation and/or chemotherapy with docetaxel remains the standard of care [1]. However, some patients with a limited number of metastases have a less aggressive disease course and might be treated with metastasis directed therapy (MDT) for all tumor sites as an alternative to systemic treatment [2]. These patients represent a condition known as oligometastatic disease, which is defined as an intermediate state between localized cancer and widespread metastases [3]. In the context of oligometastatic prostate cancer (OMPC), the desired effect of MDT is to postpone the start or escalation of androgen deprivation therapy (ADT) or in some cases even to achieve long lasting remission [4]. As a result, delayed onset of ADT-associated side effects and the inevitable emergence of therapy resistant PCA can be assumed.

The advent of positron emission tomography (PET) with different tracers has improved the diagnosis of patients with OMPC by detecting early recurrence. The prostate-specific membrane antigen (PSMA) is a membrane-specific type II glycoprotein that is overexpressed in more than 80% of PCA cells and is therefore an ideal target for diagnostic imaging [5, 6]. Recently Gallium-68-labelled PSMA PET computed tomography (PSMA-PET/CT) was found to be superior in localizing actively metabolizing tumor in patients with primary diagnosis or recurrence of PCA compared to conventional imaging modalities and choline-based PET/CT [7–11]. The detection rates for PSMA-PET/CT reported in the literature vary from 46% to 97% depending on the levels of prostate-specific antigen (PSA) [12–15]. Some authors observed detection rates of >50% in patients with PSA <0.5 ng/mL [16, 17]. Such a high sensitivity allows identification of very early recurrences with lesions <5 mm in size [10].

One-year local control (LC) rates reported after fractionated stereotactic body radiotherapy (fSBRT) for patients with oligometastatic prostate cancer vary from 93–100%. Besides, no grade ≥3 adverse events have been observed [18–20]. In this regard, single fraction radiosurgery (SFRS) is particularly attractive, since LC rates seem to be equally effective but treatment is delivered in a single session [21].

The primary aim of this study was to assess progression-free survival (PFS) and treatment failure free-survival (TFFS) after PSMA-PET/CT-based SFRS or fSBRT in patients with OMPC with up to five metastases. Further endpoints included safety and efficacy of SFRS, overall survival (OS) and possible delay of ADT initiation.

Materials and methods

Study population

In this retrospective analysis men with de-novo oligometastatic PCA (synchronous oligometastatic disease or metachronous oligorecurrence or metachronous oligoprogression) who

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received curative 68Ga-PSMA-PET/CT-based SBRT for all metastases were included [22]. No more than 5 metastases in ≤3 organs were allowed. The first metastasis was diagnosed after median time of 37 months (1–199) from the initial diagnosis of PCA. All men had curative therapy for prostate cancer. Both castration sensitive and castration resistant patients were eligible for this study. The patients who started ADT and SBRT at the same time and patients with previous SBRT were excluded.

This single center study was approved by the institutional medical ethics committee of the Charité-Universitätsmedizin Berlin (EA1/214/16).
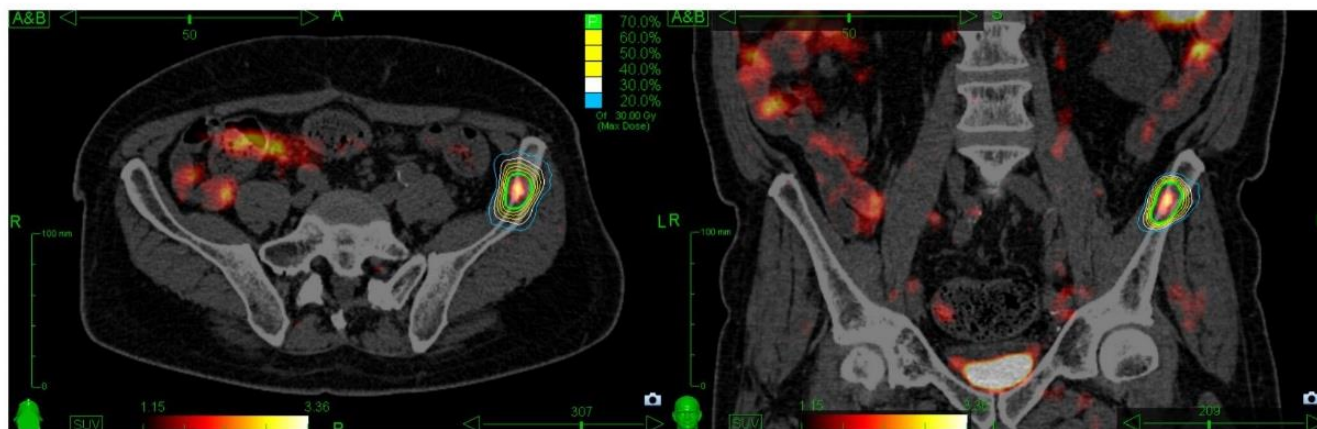
Radiotherapy

SBRT/SFRS was performed using mainly the CyberKnife (CK) Robotic Radiosurgery System (Accurray®, USA) and dedicated stereotactic linear accelerator. CK Fiducial® Tracking (Accurray®, USA) was applied if indicated (e.g. lymph nodes expected to shift independently to the bone) with one gold fiducial (1.0 mm x 5.0 mm) being placed within/close to the target under CT guidance. Otherwise, patients were aligned to the spine using XsightSpine® Tracking (Accuracy®, USA) or ExacTrac-based spine alignment (BrainLab®, Germany). A thin-slice planning CT with 1.0–2.0 mm slices in supine position was obtained. PSMA-PET/CT images were co-registered for contouring. The gross tumor volume was contoured on all axial CT slices. The clinical target volume corresponded to the gross tumor volume. The planning target volume was created by adding a 2–5 mm margin around the clinical target volume. A SFRS/fSBRT dose was prescribed to the 70–80% isodose surrounding the planning target volume (Fig 1).

The fractionation regiments were selected taking into account the location of the lesion. If the irradiated metastasis was in the immediate vicinity of the organs at risk and therefore dose restrictions could not be met, fSBRT was indicated. Otherwise, SFRS was preferred over fSBRT for patient comfort, economic and logistic advantages.

Follow-up

Follow-up was obtained every 3 months after SBRT within the first two years and half-yearly thereafter. Adverse events were scored using the National Cancer Institute Common Toxicity Criteria version 4. Additionally, patients attended routine follow-up visits at their urologist.

Fig 1. PSMA-PET/CT based radiotherapy treatment plan of CyberKnife treatment system for bone metastasis located in the left ilium.

Endpoints

Endpoints of the study were PFS, TFFS, local control (LC), ADT-free survival (ADTFS), ADT-escalation-free survival (ADTEFS) and OS calculated from the start of SBRT. PFS was defined as freedom from biochemical failure, in-field progression, distant metastases or death. For TFFS new tumor-directed therapy (e.g. repeated SBRT, start of ADT, escalation of an ongoing ADT, surgery, chemotherapy) or death were determined as events. For LC, the in-field progression was counted as an event and was defined as an increase of metastasis volume or local regrowth within the PTV. LC was assessed using conventional (CT or MRT) or functional (PSMA-PET/CT) imaging. ADTFS was the interval until onset of ADT or death, whereas ADTEFS was defined as time to ADT-escalation or death for patients with ongoing ADT. For OS death of any cause was determined as an event.

Statistical analysis

Survival analysis was conducted using the Kaplan–Meier method. The Cox proportional hazard model was used in univariate and multivariate analyses to calculate hazard ratios (HR) with 95% confidence intervals (95% CI). Covariates with a p-value ≤ 0.1 in univariate analysis were included in the multivariate analysis. The Chi-square test was performed to compare variables. A p-value of <0.05 was considered to be statistically significant. Data processing and statistical analysis were conducted using FileMaker Pro 15 Advanced, Excel 2010 and IBM SPSS Statistics 24 (SPSS Inc., Chicago, IL, USA).

Results

Between January 2012 and December 2016, 50 patients with OMPC and 75 oligometastases detected by PSMA-PET/CT were treated with SBRT to all tracer-avid metastatic lesions. Patients, metastases, and treatment characteristics are summarized in Table 1 and S1 Table. At the initial diagnosis of PCA, 41 patients (82%) were classified as high risk according to the D'Amico classification [23]. Three (6%) and 4 (8%) patients had low- and intermediate-risk PCA, respectively. In 2 (4%) patients the risk class was unknown. Fifteen patients (30%) were castration resistant. Median time from PCA diagnosis to the first metastasis (TTM) was 37 months (range: 1–199). Forty-eight (96%) patients had single organ involvement. The median number of metastases treated per patient was one (range: 1–5). SFRS with a median PTV-surrounding dose of 20 Gy (range: 16–25) was applied to 60 (80%) metastases, 13 (17.3%) received fSBRT with 24 Gy in 3 fractions (3 x 8 Gy) and 2 other schedules (2.7%) (S2 Table).

With a median follow-up of 34 months (range: 5–70), the 1-, 2-years PFS and TFFS were 54%, 22%, and 55.2%, 23.4%, respectively (Fig 2A and 2B). Median PFS and TFFS were 12 months (95% CI: 7.6–16.3) and 14 months (95% CI: 10–17.9), respectively. The TFFS significantly improved in patients with time to first metastasis >36 months (Fig 2C). Progression occurred in 49 patients (98%), with 32 patients (64%) having repeat oligometastatic disease with median two new metastases (range: 1–5). Forty-two (84%) patients underwent repeated PSMA-PET/CT due to a rising PSA. Treatment failure was observed in 46 patients (92%). Of these, 24 patients (48%) were treated with a second course of PSMA-PET/CT-based SBRT. The median time from the first to the second course of SBRT was 17 months (95% CI: 9.7–24.2). Fourteen patients (28%) started ADT, whereas in 6 patients (12%) ADT was escalated. The pattern of progression and new tumor-directed therapies is presented in Table 2. At the last follow-up, 31 (62%), 13 (26%), 3 (6%), and 1 (2%) patients had 2, 3, 4, and 5 courses of SBRT, respectively.

Local control was available for 73 lesions. The 1-, 2-year LC rates after SFRS and fSBRT were 98%, 96% and 100%, 100%, respectively (Fig 2D). There was no significant difference

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Table 1. Patients, tumor and treatment characteristics.

Characteristic	Value
Age at PCA diagnosis, years	
Median (range)	62 (47–75)
PSA at PCA diagnosis, ng/mL	
Median (range)	9.8 (0.54–159)
PSA at SBRT, ng/mL	
Median (range)	1.9 (0.16–59.8)
Gleason score, N (%)	
≤6	3 (6)
7	28 (56)
≥8	18 (36)
unknown	1 (2)
Primary tumor size (T), N (%)	
c/pT1-T2b	16 (32)
c/pT2c-T3	32 (64)
Tx	2 (4)
Regional lymph node involvement at PCA diagnosis, N (%)	
c/pN0	36 (72)
c/pN1	11 (22)
Nx	3 (6)
PCA treatment, N (%)	
RP	15 (30)
RT	4 (8)
RP and RT	31 (62)
ADT at the time of SBRT, N (%)	
no	35 (70)
yes	15 (30)
Time to metastases from diagnosis of PCA (months)	
Median (range)	37 (1–199)
Number of metastases treated at first SBRT, N (%)	
1	35 (70)
2	9 (18)
3	3 (6)
4	2 (4)
5	1 (2)
Primary site of metastases, N (%)	
Lymph node	24 (48)
Pelvic	15 (62.5)
Extra-pelvic	8 (33.3)
Both	1 (4.2)
Bone	23 (46)
Bone and lymph node	2 (4)
Lung	1 (2)
Maximal SUV of PSMA-PET/CT	
Median (range)	6 (2.6–42)
Fractionation schedules, N (%)	
SFRS	60 (80)
3 fractions	13 (17.3)

(*Continued*)

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Table 1. (Continued)

Characteristic	Value
other	2 (2.7)
Median dose (Gy) for SFRS (range)	20 (16–25)
Median dose (Gy) for fSBRT(range)	24 (19.2–28.8)

Abbreviations: ADT = androgen deprivation therapy; fSBRT = fractionated stereotactic body radiotherapy; PCA = prostate cancer; PSA = prostate-specific antigen; PSMA-PET/CT = prostate-specific membrane antigen positron emission tomography/computed tomography; RP = radical prostatectomy; RT = radiotherapy; SBRT = stereotactic body radiotherapy; SFRS = single fraction radiosurgery; SUV = standardized uptake value.

observed for LC in SFRS and fSBRT groups (p = 0.55). Two (2.7%) bone metastases relapsed after SFRS with 20 Gy and 21 Gy, respectively. One was repeatedly treated with fSBRT.

At the last follow-up, 42.9% (15/35) of primarily ADT-naïve patients started treatment with ADT. The 1- and 2-year rates for ADTFS were 76.4% and 60.5%, respectively. Median ADTFS was not reached. ADT escalation was performed in 73.3% (11/15) of patients, with 1- and 2-year ADTEFS rates being 58.2% and 33.9%, respectively. The median ADTEFS was 27 months (95% CI: 8.8–45.1). Four patients were dead at the time of analysis. 1-, 2- and 5-years OS rates were 100% and 100% and 80.3%. Median OS was not reached (Fig 2E). There was a trend towards better OS in patients treated with the second course of SBRT compared to patients receiving other therapy (Fig 2F).

Results of univariate and multivariate analysis of clinical prognostic factors affecting PFS and TFFS are summarized in Table 3. In multivariate testing, a TTM >36 months (p = 0.01) and PSA ≤1 ng/ml before SBRT predicted significantly longer TFFS (p = 0.03). In addition, a longer PFS in univariate analysis was observed (p = 0.01) in patients with a TTM >36 months. Multivariate analysis for PFS was not conducted because only one covariate had a p-value ≤0.1.

Acute grade 1 toxicity was observed in three (6%) patients: 1 fatigue, 1 pain within the irradiated region, and 1 subacute pneumonitis. Only 1 (2%) grade 2 fatigue was observed. No grade 3 or higher acute or any late toxicity occurred. No significant differences in terms of toxicities between SFRS and fSBRT were observed (p = .58).

Discussion

This study complements the existing literature on metastases-directed therapy (MDT) for patients suffering from OMPC in several ways. First, we analyzed a large number of metastases treated with PSMA-PET/CT based SFRS. Second, we reported outcomes after repeated use of SBRT with the intention to defer the start or escalation of palliative ADT.

To the best of our knowledge, there are only two randomized studies that examined MDT in comparison to observation for OMPC patients. In the STOMP Phase 2 trial, either SBRT with 10 Gy in 3 fractions or surgery was used after staging with choline PET/CT [2]. Lately announced 5-year follow-up results showed significantly lower rates of ADT onset in patients after MDT (34% vs 8%, p = 0.06). The most recent ORIOLE phase 2 trial investigated the progression rate at 6 months after SBRT for up to 3 metastases [24]. Although PSMA-PET/CT was performed at baseline, it was blinded to the radiation oncologist so that in some patients not all PSMA-avid lesions were treated. The intervention arm showed a significantly reduced progression rate of 19% vs 61% (p = 0.005). Furthermore, patients with no additional PSMA-avid lesions at baseline had longer distant metastasis free survival (29 months vs 6 months,

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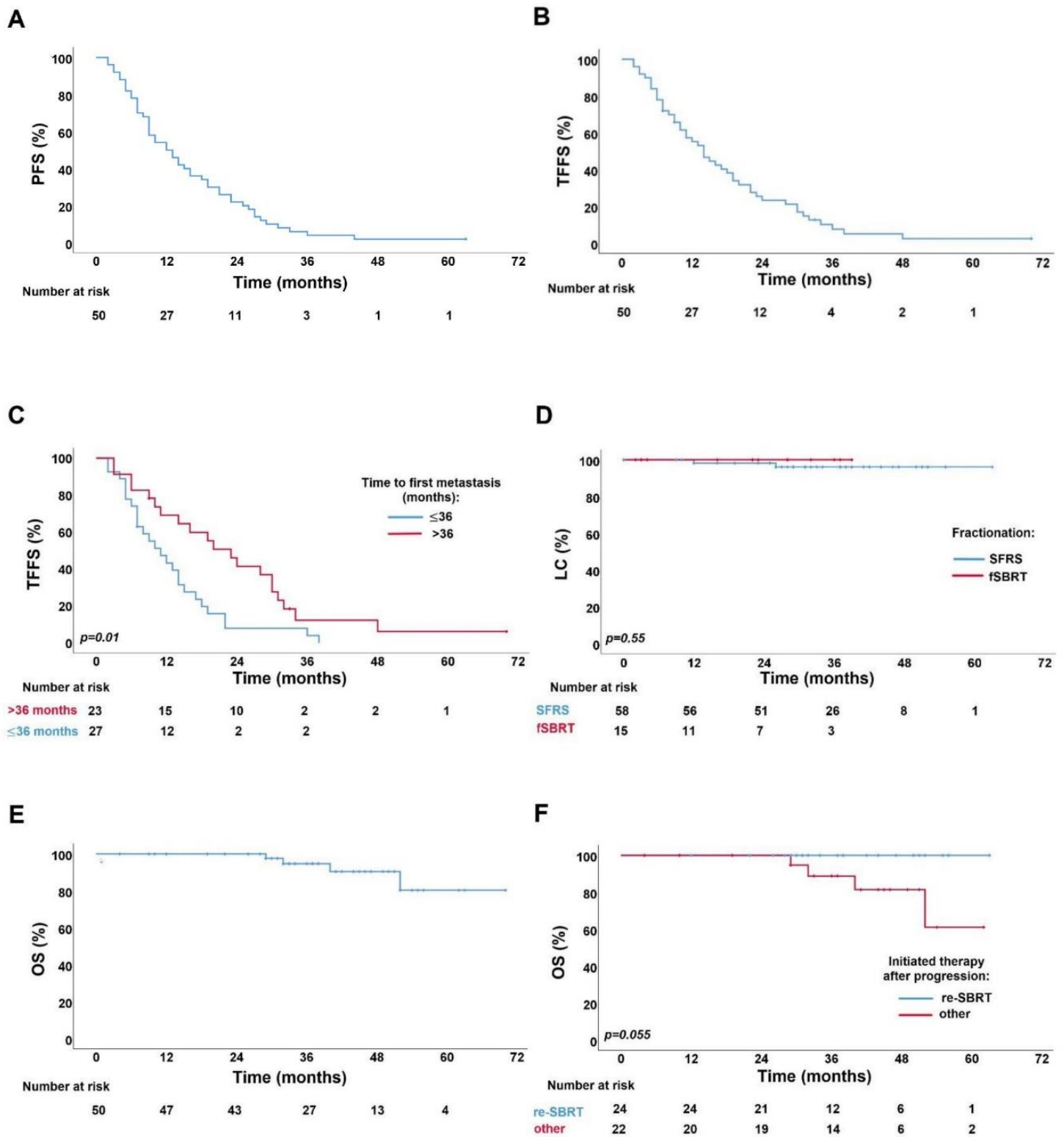
Fig 2. Kaplan–Meier survival curves for: (A) progression-free survival (PFS), (B) treatment failure-free survival (TFFS) (C) treatment failure-free survival by time from PCA diagnosis to first metastasis: >36 months vs ≤36 months, (D) local control (LC) by fractionation schedules: single fraction radiosurgery (SFRS) vs fractionated stereotactic body radiotherapy (fSBRT), (E) overall survival (OS), (F) overall survival by therapy initiated after progression: repeated SBRT (re-SBRT) vs other.

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Table 2. Progression pattern and therapy initiated in case of treatment failure in all patients.

Progression pattern	Number (%)	Therapy in case of TF	Number (%)
Repeat OMPC (5 ≤ metastases)	32 (64)		
		SBRT	22 (68.8)
		ADT initiation	7 (21.9)
		ADT escalation	1 (3.1)
		combined	1 (3.1)
		no	1 (3.1)
Polymetastatic disease (5 > metastases)	6 (12)		
		ADT initiation	4 (66.7)
		ADT escalation	2 (33.3)
Biochemical (PSA) progression	6 (12)		
		ADT initiation	3 (50)
		ADT escalation	3 (50)
In-field progression	2 (4)		
		SBRT	1 (50)
		Surgery	1 (50)
Prostate/prostatic lodge recurrence	3 (6)		
		SBRT	1 (33.3)
		no	2 (66.7)
No progression	1 (2)	no	1 (100)

Abbreviations: ADT = androgen deprivation therapy; OMPC = oligometastatic prostate cancer; PSA = prostate-specific antigen; SBRT = stereotactic body radiotherapy; TF = treatment failure.

https://doi.org/10.1371/journal.pone.0240892.t002

p = 0.0008), suggesting that PSMA-PET/CT-based SBRT may not only serve to treat existing metastases, but may also modulate course of disease.

In our analysis, the majority of patients (64%) with a progression after SBRT developed up to five new metastases and were therefore still considered to have a repeat OMPC. Other authors reported similar results, with 70–75% of patients treated with SBRT remaining oligo-progressive or oligorecurrent after distant relapse with median ≤3 metastases [25, 26]. This implies that in case of progression most patients are still eligible for further MDT.

Median PFS reported in the literature varies from 3 to 24 months (Table 4). Some authors observed a 21-month difference in median PFS in castration-sensitive versus castration-resistant patients with a maximum 3 bone metastases [20]. Furthermore, another small series found 1-year PFS rates to be 67% vs 0% in castration-sensitive compared to castration-resistant patients after radiotherapy to a maximum 3 metastases [18]. Such a difference in PFS between the groups raises the question of whether patients with progression despite hormone therapy are suitable candidates for MDT alone. However, in some castration-resistant patients, progression is limited only to a few sites, while the remaining disease is controlled by systemic therapy. In this case, the eradication of castration-resistant metastases using MDT allows a continuation of ongoing ADT and thus spares a second-line hormone or chemotherapy for further progression [27]. In contrast to the aforementioned studies, Valeriani and colleagues observed a relatively high median PFS of 18.4 months in 29 castration-resistant patients with oligoprogressive PCA treated with local radiotherapy for up to 3 metastases [28]. In present study, no differences in PFS in patients with or without ADT at the time of SBRT was observed.

In the case of repeat OMPC, multiple SBRT might be used as a bridging treatment to delay palliative system therapy. Recently, prospective analysis of 199 OMPC patients (76.4% staged

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Table 3. Univariate and multivariate analysis of factors influencing PFS and TFFS.

| | PFS | | TFFS | | | |
| | Univariable | | Univariable | | Multivariable | |
Determinant	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value
Time from PCA to first metastasis (months)						
> 36	1		1		1	
≤ 36	2.17 (1.20–3.91)	0.01	2.18 (1.18–4.02)	0.01	2.54 (1.33–4.82)	0.01
Gleason score						
≤7	1		1		N.A.	
>7	1.20 (0.66–2.17)	0.55	0.99 (0.73–1.33)	0.96		
Primary tumor size						
T ≤ 2	1		1		N.A.	
T > 2	0.98 (0.53–1.79)	0.95	0.99 (0.53–1.84)	0.99		
Regional lymph node involvement at PCA diagnosis						
N0	1		1		N.A.	
N1	1.50 (0.75–3.00)	0.25	1.66 (0.83–3.32)	0.15		
Initial PSA (ng/ml)						
≤ 10	1		1		N.A.	
> 10	0.89 (0.47–1.60)	0.65	0.91 (0.49–1.67)	0.75		
PSA (ng/ml) before SBRT						
≤ 1	1		1		1	
> 1	1.69 (0.88–3.22)	0.11	1.02 (0.99–1.05)	0.06	2.25 (1.10–4.59)	0.03
Salvage radiotherapy after prostatectomy						
Yes	1		1		N.A.	
No	1.27 (0.71–2.27)	0.43	1.27 (0.70–2.31)	0.43		
Concomitant ADT						
Yes	1		1		N.A.	
No	1.57 (0.84–2.93)	0.16	1.69 (0.88–3.25)	0.11		
Number of metastases at SBRT						
1	1		1		1	
>1	1.54 (0.84–2.83)	0.16	1.70 (0.91–3.17)	0.10	1.42 (0.73–2.73)	0.30
Number of affected organs						
1	1		1		N.A.	
>1	1.53 (0.54–4.34)	0.42	1.72 (0.61–4.90)	0.31		
Bone metastases						
No	1		1		N.A.	
Yes	0.81 (0.46–1.42)	0.46	0.84 (0.47–1.51)	0.56		
Extra-pelvic lymph node metastases						
No	1		1		N.A.	
Yes	0.75 (0.32–1.73)	0.50	0.62 (0.27–1.48)	0.29		

Abbreviations: CI = confidence interval; HR = hazard ratio; NA = not assessed; PCA = prostate cancer; PFS = progression free-survival; PSA = prostate-specific antigen; SBRT = stereotactic body radiotherapy; TFFS = treatment failure-free survival.

with PSMA-PET/CT) with ≤5 metastases after SBRT reported 31.7%, 9.5% and 4% of patients receiving second, third, and fourth courses of SBRT [29]. After a median follow-up of 35.1 months, the majority of patients (51.7%) did not require a further tumor directed therapy. In 49.3% of patients palliative systemic- or radiotherapy had been postponed for a median time of 27.1 months (95% CI 21.8–29.4). Bouman–Wammes *et al.* investigated the impact of SBRT

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Table 4. Studies on SBRT for OMPC patients.

Reference	Year	No. of patients/ met.	No. of met.	Met. location	Castration sensitivity	Radiotherapy	Treatment outcomes	
							PFS	ADTFS
Prospective								
Phillips et al. (ORIOLE) [24]	2020	54/72	≤3	LN = 33% Bone = 21%	100%	SBRT with 19.5 to 48.0 Gy in 1 to 3 fractions	Median in SBRT arm was not reached after 18.8 months of FU vs 5.8 months in observation arm	N.A.
Siva et al. [21]	2018	33/50	≤3	LN = 36.4% Bone = 60.6% Both = 3.0%	67%	SFRS with 20 Gy	1-yr: 58% 2-yr: 39%	2-yr: 48%
Ost et al. (STOMP) [2]	2017	62/116	≤3	LN = 54.8% Non-nodal = 45.2%	100%	SBRT in 80.6%	Median 10 months in MDT arm vs 6 months in surveillance arm	Median 21 months in MDT arm vs 13 months in surveillance arm
Retrospective								
Hurmuz et al. [31]	2020	176/353	≤5	LN = 34.7% Bone = 42.6% Both = 22.7%	Unknown	SBRT in 73% with median 27 Gy in median 3 fractions; Conventional RT in 27% with median 60 Gy	Median 39.3 months 2-yr: 63.1%,	N.A.
Nicosia et al. [32]	2020	109/155	≤5	LN = 100%	100%	SBRT with median 36 Gy in 4–7 fractions	Median 14.5 months 1-yr: 54.6% 2-yr: 32.8%,	Median 15 months
Oehus et al. [33]	2020	78/185	≤5	LN = 68.2% Bone = 45% Visceral = 6.5%	Unknown	SBRT in 20.5%	Median: 17.0 months 1-yr: 55.3%,	Median not reached after 16 months of follow-up
Franzese et al. [34]	2019	92/119	≤5	LN, bone and visceral	66%	SBRT with median 42 Gy in 2 to 8 fractions	Median 9.4 months 1-yr: 42.8% 3-yr: 16.7%,	N.A.
Patel et al. [20]	2019	51/64	≤3	Bone = 100%	82%	SBRT with 24 to 30 Gy in 3 or 5 fractions	Median 24 months in castration sensitive vs 3 months in castration resistant	N.A.
Valeriani et al. [28]	2019	29/37	≤3	LN = 5.4% Bones = 83.8% Other = 10.8%	0%	SBRT for 16.2%	Median 18,4 months 2-yr: 38.3% 3-yr: 8.5%,	N.A.
Ong et al. [19]	2019	20/26	≤3	LN = 75% Bone = 15% Both = 10%	100%	SBRT with 30 Gy in 3 fractions and 35 to 40 Gy in 5 fractions	1-yr: 62%	1-yr: 70%
Guler et al. [18]	2018	23/38	≤3	LN = 44.7% Bone = 55.3%	57%	Hypofractionated RT	1-yr: 51%	N.A.
Triggiani et al. [35]	2017	141/209	≤3	LN = 79% Bone = 21%	71%	SBRT with 24 to 45 Gy in 3 to 6 fractions	Median in castration sensitive 17.7 months vs 11 months in castration resistant	Median ADTFS 20.9 months in castration sensitive vs median ADTEFS 22 months in castration resistant
Bouman-Wammes et al. [30]	2017	43/54	≤4	LN = 76.6% Bone = 20.9% Both = 2.3%	100%	SBRT with 30 or 35 Gy in 3 or 5 fractions	N.A.	Median 15.6 months
Pasqualetti et al. [36]	2016	29/45	≤3	LN = 55.5% Bone = 44.5%	62%	SBRT with 24 Gy or 27 Gy in 1 or 3 fractions	N.A.	Median (systemic therapy free survival) 39.7 months

(Continued)

Table 4. (Continued)

Reference	Year	No. of patients/ met.	No. of met.	Met. location	Castration sensitivity	Radiotherapy	Treatment outcomes	
							PFS	ADTFS
Decaestecker et al. [25]	2014	50/70	≤3	LN = 54%	100%	SBRT with 30 or 50 Gy in 3 or 10 fractions	Median 19 months	Median 25 months
				Bone = 44%				1-yr: 82%
				Visceral = 2%			1-yr: 64%	2-yr: 60%
							2-yr: 35%,	
Current study	2020	50/75	≤5	LN = 48%	70%	SFRS 80% with median 20 Gy	Median 12 months	Median not reached
				Bone = 46%				
				Both = 4%			1-yr: 54%	1-yr: 76%
				Visceral = 2%			2-yr: 22%	2-yr: 60%

Abbreviations: ADTFS = androgen deprivation therapy-free survival; LN = lymph node; MDT = metastasis directed therapy; N.A. = not assessed; OMPC = oligometastatic prostate cancer; RT = radiotherapy; SBRT = stereotactic body radiotherapy; SFRS = single fraction radiosurgery.

on delaying ADT for 43 hormone-sensitive PCA patients with <5 metastases detected using choline-PET-CT [30]. The second SBRT course was applied in 16.3% of patients with a median 19.8 months between the courses, which is in line with our results. The median ADTFS observed within this group was 32.1 months (95% CI: 7.8–56.5). Furthermore, Triggiani and colleagues observed a 18% rate of repeated SBRT in 141 patients with hormone-sensitive and castration-resistant OMPC treated with SBRT for up to 3 metastases [35]. In our cohort, a second SBRT course was the treatment of choice in almost 50% of patients with progression and thus ADT initiation or escalation was delayed. The median ADTFS was not reached after 34 months follow-up. Furthermore, we observed a trend (p = 0.055) toward better OS after second SBRT course compared to other therapy initiated after progression.

The median ADTFS reported in the literature for patients with OMPC after MDT varies between 20.9 and 39.7 months, which is comparable to our results Table 4. However, the results of different studies should be compared with caution, due to diverse inclusion criteria (e.g. number of metastases), staging methods (PSMA/PET-CT, FDG/PET-CT), treatment modalities (SBRT, surgery) and different indications for ADT start used.

In our analysis SFRS showed excellent LC rates of 96% at 2 years with no grade ≥3 adverse events. Siva *et al.* prospectively analyzed safety and feasibility of SFRS with 20 Gy for bone and lymph node metastases staged with sodium fluoride PET/CT. After treating 50 lesions in 33 patients, the authors observed 1- and 2-year LC rates of 97% and 93%, respectively. Grade 3 adverse events were observed in one patient (3%) [21]. Muldermans *et al.* reported LC at 2 years of 82% after treating 69 patients with 81 metastases– 88% received SFRS with a median dose of 16 Gy (range: 16–24) [37]. Seventy percent of patients were staged with choline PET/CT. In multivariate analysis, radiation dose ≥18 Gy was associated with better LC. No grade ≥2 adverse events were observed. Although, the prescribed dose varied within the studies emerging data including our study show that SFRS can be safely used in favor of patients' convenience and provide excellent LC rates.

In our analysis a TTM of more than 36 months was found to be an independent prognostic factor for prolonged TFFS and was associated with greater PFS. Benefits might be explained by an indolent tumor biology with a lower metastatic potential. Supporting this hypothesis, analysis of a multi-institutional study on oligometastatic disease from several tumor entities showed that longer TTM using the MDT-approach resulted in improved survival [38].

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The retrospective study design, relatively small sample size including heterogeneous patients, inherent patient selection bias and lack of control group are the major limitations of our study. Furthermore, the comparison between SFRS and fSBRT group needs to be interpreted with caution due to limited number of metastases treated with fSBRT. The majority of patients had a high risk PCA, so conclusions for patients with low and medium risk of PCA should be drawn carefully. Nonetheless, we were able to show the efficacy, safety, and excellent local control rates after SFRS use in OMPC patients.

Conclusions

In conclusion, our study suggests that PSMA-PET/CT-based SFRS might be considered a valid treatment option for OMPC patients, including cases with repeat oligometastatic disease. This way, the onset or escalation of palliative ADT and its potential side effects can be avoided. Metastases treated with SFRS reached excellent local control rates with minimal toxicity. Low PSA levels and longer TTM predicts elongated TFFS. Randomized studies are needed to support our findings.

Supporting information

S1 Table. Metastases location.
(DOCX)

S2 Table. Treatment characteristic.
(DOCX)

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Publication 2:

Kalinauskaite G.G., Tinhofer I.I., Kufeld M.M., Kluge A.A., Grün A.A., Budach V.V. *et al.* Radiosurgery and fractionated stereotactic body radiotherapy for patients with lung oligometastases. *BMC Cancer* **20,** 404 (2020).

RESEARCH ARTICLE   **Open Access**

Radiosurgery and fractionated stereotactic body radiotherapy for patients with lung oligometastases

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Abstract

Background: Patients with oligometastatic disease can potentially be cured by using an ablative therapy for all active lesions. Stereotactic body radiotherapy (SBRT) is a non-invasive treatment option that lately proved to be as effective and safe as surgery in treating lung metastases (LM). However, it is not clear which patients benefit most and what are the most suitable fractionation regimens. The aim of this study was to analyze treatment outcomes after single fraction radiosurgery (SFRS) and fractionated SBRT (fSBRT) in patients with lung oligometastases and identify prognostic clinical features for better survival outcomes.

Methods: Fifty-two patients with 94 LM treated with SFRS or fSBRT between 2010 and 2016 were analyzed. The characteristics of primary tumor, LM, treatment, toxicity profiles and outcomes were assessed. Kaplan-Meier and Cox regression analyses were used for estimation of local control (LC), overall survival (OS) and progression-free survival.

Results: Ninety-four LM in 52 patients were treated using SFRS/fSBRT with a median of 2 lesions per patient (range: 1–5). The median planning target volume (PTV)-encompassing dose for SFRS was 24 Gy (range: 17–26) compared to 45 Gy (range: 20–60) in 2–12 fractions with fSBRT. The median follow-up time was 21 months (range: 3–68). LC rates at 1 and 2 years for SFSR vs. fSBRT were 89 and 83% vs. 75 and 59%, respectively ($p = 0.026$). LM treated with SFSR were significantly smaller ($p = 0.001$). The 1 and 2-year OS rates for all patients were 84 and 71%, respectively. In univariate analysis treatment with SFRS, an interval of ≥12 months between diagnosis of LM and treatment, non-colorectal cancer histology and BED < 100 Gy were significantly associated with better LC. However, none of these parameters remained significant in the multivariate Cox regression model. OS was significantly better in patients with negative lymph nodes (N0), Karnofsky performance status (KPS) > 70% and time to first metastasis ≥12 months. There was no grade 3 acute or late toxicity.

Conclusions: Longer time to first metastasis, good KPS and N0 predicted better OS. Good LC and low toxicity rates were achieved after short SBRT schedules.

Keywords: Oligometastases, SBRT, Radiosurgery, Lung metastases, CyberKnife

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Background

Metastatic progression of cancer is linked to poor prognosis and is the leading cause of cancer-related deaths [1]. Few decades ago, the diagnosis of metastatic disease was related to lethal outcomes. This paradigm has changed after Hellman and Weichselbaum introduced the concept of oligometastases: the intermediate state between non-metastatic cancer and highly palliative disseminated metastatic disease [2]. Patients with an initially limited number of metastases or with progression of only few lesions after cytoreductive therapy might be potentially cured or reach long-term survival when treated with local ablation therapy for all lesions. The search for prognostic biomarkers for discrimination of potentially oligometastatic patients is still ongoing. In some small prospective studies circulating tumor cells as well as circulating tumor DNA in liquid biopsies were able to predict treatment outcomes and response to ablative therapy [3]. However, until prognostic biomarkers will be established for routine application, the selection of patients that could benefit from local ablative therapy rather than from palliation will be based on clinical features.

The lungs are one of the most common metastatic sites for various solid tumors [4, 5]. Stereotactic body radiotherapy (SBRT) and surgical resection are frequently used treatment options for patients with a limited number of pulmonary lesions. Although SBRT compared to surgery for lung metastases have not been studied in a prospective randomized trial, retrospective data suggest that both methods achieve equal results in terms of local control and overall survival [6, 7]. Single fraction radiosurgery (SFRS) is especially attractive as an outpatient procedure in terms of patients' compliance, cost effectiveness and limited treatment time. However, up to now there is no recommendation when to administer SFRS over fractionated SBRT (fSBRT). The aim of this study was to analyze local control (LC) after SFRS and fSBRT in patients with lung oligometastases and identify prognostic clinical features for better survival outcomes.

Methods

Study design

This retrospective study was approved by the institutional medical ethics committee of the Charité - Universitätsmedizin Berlin (EA1/214/16). We identified all patients with lung metastases treated with curative intended SFRS or fSBRT between January 2010 and December 2016. Cases with an initially limited number of lung metastases from various solid tumors or with oligo-progression after systemic therapy were selected for the study. Patients with disseminated disease or with a second malignancy were excluded. The data on patients' demographics, e.g. primary tumor and metastases, disease stage as determined by computed tomography (CT), magnetic resonance imaging or positron emission tomography, treatment parameters, follow-up and LC, overall survival (OS), progression-free survival (PFS), distant metastases-free survival (DMFS) were calculated. Clinical follow-up was performed at 6 weeks after SFRS/fSBRT and at 3, 6, 12, 18, and 24 months after treatment and annually thereafter. Acute and late adverse events were scored using NCI Common Terminology Criteria for Adverse Events (CTCAE), version 4.0.

Treatment planning and delivery

SBRT was delivered using CyberKnife (CK) and Novalis systems, both dedicated stereotactic linear accelerators. For respiratory motion compensation, the CyberKnife Synchrony® Respiratory Motion Tracking System was used. In general, one gold fiducial (1.0 mm × 5.0 mm) was placed centrally within the lung metastasis under CT-guidance in local anesthesia. For lesions larger than 2 cm feasibility of X-sight lung tracking was evaluated. If motion compensation was not possible (e.g. due to patients' comorbidities or technical limitations) an internal gross tumor volume (IGTV), defined as the gross tumor volumes of all respiratory phases on a 4D CT was constructed. In these cases, patients were aligned on the spine. High-resolution thin-slice native planning CT of the chest with 1.0 to 2.0 mm slice thickness in supine position was performed.

The gross tumor volume (GTV) was delineated on all axial slices including spiculae in the lung window. The clinical target volume (CTV) was equal to the GTV. The planning target volume (PTV) was obtained by adding a 5–8 mm margin to the CTV.

For CK treatments, doses were prescribed to the 70% isodose covering the PTV and a total maximum of 100%. Novalis treatment was planned with less inhomogeneous dose distributions with the 80% isodose line of the prescribed 100% dose encompassing the PTV and allowing a maximum of up to 110% (Fig. 1).

The linear-quadratic model, assuming an alpha/beta ratio of 10 Gy for tumor, was used to calculate the biologically equivalent dose (BED) and the equivalent dose in 2 Gy fractions (EQD2) for PTV-encompassing total dose. Dose constraints to organs at risk for single fraction treatment are shown in Table 1. Treatment planning for CK was performed in Multiplan® (Accuray) using the Ray-Trace or Monte Carlo algorithm and for Novalis in iPlan® (BrainLAB) using the Pencil Beam algorithm.

Endpoints and statistical considerations

LC was defined as time from SFRS/fSBRT to tumor progression within the irradiation field or absence of

Fig. 1 Treatment plan and dose distribution for (**a**) CyberKnife, (**b**) Novalis treatment system
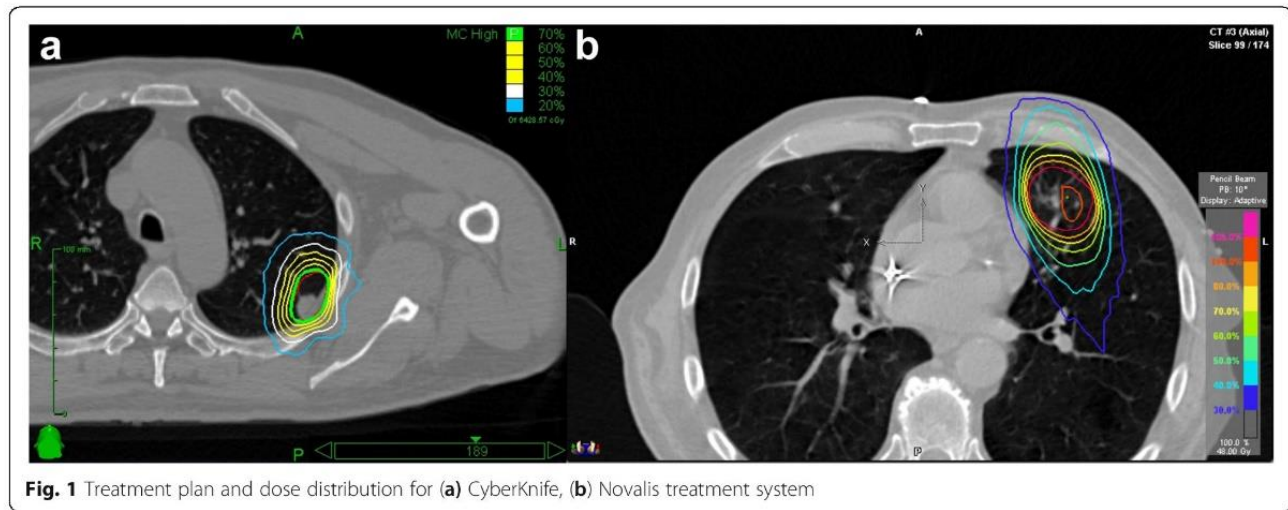
progression at last available follow-up. LC was assessed using routinely CT scans every 3 months. PET-CT and/or biopsy of irradiated metastasis was performed in cases of uncertain progression detected on CT images. OS was calculated from the beginning of SFRS or fSBRT until the death of any cause or the date of last follow-up. The time to new metastases in the lung outside of the SFRS/fSBRT field or in other organs was defined as DMFS and was calculated from the start of SFRS/fSBRT. PFS was defined as the time from the start of SFRS/fSBRT until progression of the primary tumor, development of new metastases or local failure.

LC was compared between lung metastases treated with SFRS and fSBRT. The different fractionation regimens in the same patient were allowed, thus fractionation impact on OS, PFS and DMFS could not be assessed.

OS, LC, DMFS and PFS after SFRS/fSBRT for lung metastases were calculated using the Kaplan-Meier method. Cox-regression analysis was used to obtain the Hazard Ratio (HR) and 95% confidence intervals (CI) for

Table 1 Dose constrains for organs at risk of single fraction radiosurgery

Organs at risk	Max critical volume above threshold (cm^3)	Threshold dose (Gy)	Max point dose (Gy)[a]
Spinal cord	<0.35	10.0	14.0
Esophagus	<5	11.9	15.4
Hearts/pericardium	<15	16.0	22.0
Great vessels	<10	31.0	37.0
Trachea and large bronchus	<4	10.5	20.2
Rib	<1	22.0	30.0
Ipsilateral Lung (mean)	-	9.0	-

[a]Point defined as 0.035 cm^3 or less

various covariates. Covariates with a *p*-value of ≤0.1 were included into the multivariate analyses carried out with a Cox proportional hazards model with a threshold of $p < 0.05$. The chi-squared test was performed in order to compare variables between groups. A p-value of < 0.05 was considered as statistically significant. The data processing and statistical analyses were accomplished using FileMaker Pro 15 Advanced, Excel 2010 and IBM SPSS Statistics 24 (SPSS Inc., Chicago, IL, USA).

Results

Patient and tumor characteristics
The clinical, treatment and follow-up data of 52 eligible patients were assessed. Thirty-two patients were male (61.5%) and 20 were female (38.5%) with a median age of 66 years (range: 26–84) and a median Karnofsky performance status (KPS) of 80% (range: 60–100). The most prevalent primary tumor was colorectal cancer (CRC) in 17 patients (32.7%). PET-CT staging before the SBRT for lungs was performed in 7 (13.5%) patients. Twelve patients (23.1%) had oligometastases at the time of tumor diagnosis. The median time to first metastasis was 19.5 months (range: 0–37.9). In 37 patients (71.2%) metastases were limited to the lungs. Eight patients (15.4%) had additional liver metastases and 3 patients (5.8%) had brain metastasis. Forty-six patients (88.5%) had systemic therapy prior to lung SBRT and 15 (28.8%) after lung SBRT. Seventeen patients (32.7%) received immunotherapy at any time during the disease course. Patients' and primary tumor characteristics are shown in Table 2.

Treatment characteristics
Overall, 94 lung metastases were treated using SFRS/fSBRT with a median of 2 lesions per patient (range: 1–5). Metastases and SFRS/fSBRT characteristics are shown in Table 3 and Table 4. Forty-five metastases

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Table 2 Patient and primary tumor characteristics

Characteristics	No. (%)
Age, years	
Median	66
Range	26 - 84
Gender	
Female	20 (38.5)
Male	32 (61.5)
KPS (%)	
Median	80
Range	60 - 100
Primary tumor type	
CRC	17 (32.7)
Sarcoma	8 (15.4)
Melanoma	7 (13.5)
HNC	6 (11.5)
RCC	5 (9.6)
NSCLC	3 (5.8)
Others	6 (11.5)
T-classification at initial diagnosis	
T≤2	17 (32.7)
T>2	30 (57.7)
Unknown	5 (9.6)
N-classification at initial diagnosis	
N0	18 (34.6)
N+	26 (50.0)
Unknown	8 (15.4)
M-classification at initial diagnosis	
M0	36 (69.2)
M1	12 (23.1)
Unknown	4 (7.7)
Pre-SFRS/fSBRT systemic therapy	
Yes	46 (88.5)
No	6 (11.5)
No. of LM treated with SFRS/fSBRT per patient	
Median	2
Range	1 - 5
No. of affected organs per patient	
Median	1
Range	1 - 4

KPS Karnofsky performance status, *CRC* colorectal cancer, *HNC* head and neck cancer, *RCC* renal cell carcinoma, *NSCLC* non-small cell cancer, *SFRS* single fraction radiosurgery, *fSBRT* fractionated stereotactic body radiotherapy, *LM* lung metastasis

Table 3 Metastases and treatment characteristics

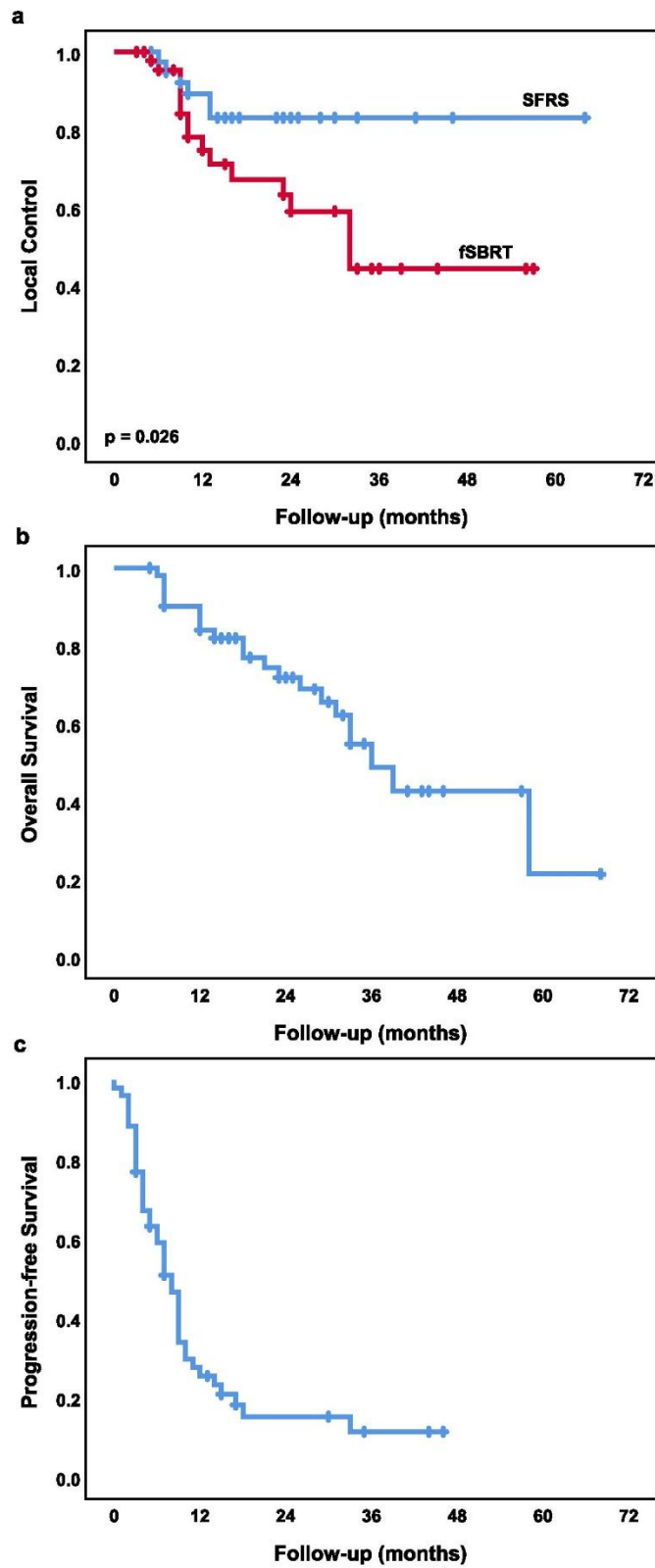| LM and treatment characteristics	SFRS (n=45)	fSBRT (n=49)	p-value
Metastasis diameter (mm)			
Median	12.0	16.0	0.003
Range	5.0-35.0	5.0-70.0	
Metastasis PTV (cm^3)			
Median	9.9	24.0	<0.001
Range	2.4-90.8	5.8-164.5	
Metastasis location			
peripheral	32	25	0.092
central	13	24	
Metastasis histology (CRC vs. non-CRC)			
CRC	8	21	0.009
Non-CRC	37	28	
PTV-encompassing prescription dose (Gy)			
Median	24	45	<0.001
Range	17-26	20-60	
PTV-encompassing single dose (Gy)			
Median	24	9.6	<0.001
Range	17-26	4-16	
Biological effective dose (Gy)			
Median	81.6	105.6	0.015
Range	45.9-93.6	42.6 – 151.2	

LM lung metastases, *SFRS* single fraction radiosurgery, *fSBRT* fractionated stereotactic body radiotherapy, *PTV* planning target volume, *CRC* colorectal cancer

central vs. 25 peripheral). Median diameter of metastases was 14.5 mm (range: 5–70), with no significant difference between centrally and peripheral located lesions. The median time from the diagnosis of lung metastases to the start of SFRS/fSBRT was 4.5 months (range: 0–

Table 4 Fractionation regimens

Fractions and PTV- encompassing single dose	No. of LM (%)	BED (Gy)	EQD2 (Gy)
1 x 22 Gy	2 (2.1)	70.4	58.7
1 x 24 Gy	20 (21.3)	81.6	68.0
1 x 25 Gy	12 (12.8)	87.5	72.9
1 x 26 Gy	5 (5.3)	93.6	78.0
3 x 12.5 Gy	3 (3.2)	84.4	70.3
3 x 15 Gy	8 (8.5)	112.5	93.8
3 x 16 Gy	9 (9.6)	124.8	104.0
4 x 12 Gy	8 (8.5)	105.6	88.0
4 x 9.6 Gy	9 (9.6)	75.3	62.7
5 x 8 Gy	2 (2.1)	72.0	60.0
other regimens	16 (17.0)		

LM lung metastases, *PTV* planning target volume, *BED* biologically effective dose, *EQD2* equivalent dose

(47.9%) were treated with SFRS of which only 12 were located centrally. Metastases treated with fSBRT were almost equally distributed with respect to location (24

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Fig. 2 Kaplan-Meier curves of (**a**) local control SFRS vs. fSBRT, (**b**) overall survival, (**c**) progression-free survival

61). Before the therapy with CK a gold fiducial was implanted in 51 metastases, whereof 37 were treated with SFRS and 14 with fSBRT using the Synchrony tracking method. A total of 14 lung metastases were treated using the X-sight lung tracking method. IGTV was used for all 29 metastases treated with Novalis. The median prescription dose for SFRS was 24 Gy (range: 17–26) compared to fSBRT with median 45 Gy (range: 20–60) delivered in 2–12 fractions. The median diameter and PTV were significantly smaller in metastases treated with SFRS compared to fSBRT: 12 mm (range: 5–35) and 9.9 cm^3 (range: 2.4–90.8) vs. 16 mm (range: 5–70) and 24.0 cm^3 (range: 5.8–164.5), respectively.

Patient outcomes

The median follow-up time was 21 months (range: 3–68). The 1-year and 2-year LC rates for SFSR vs. fSBRT were 89 and 83% vs. 75 and 59%, respectively (p = 0.026). One and 2-year LC rates for metastases from CRC vs. non-CRC were 59 and 46% vs. 90 and 80%, respectively (p = 0.001). In 5 out of 22 metastases with local progression relapse was confirmed using PET-CT and in 2 after histological examination. Eleven lesions were repeatedly treated with local therapy: either with repeated SBRT or with surgery. One and 2-year OS and PFS rates were 84, 71 and 26%, 15%, respectively. At the time of analysis 21 patients (41.4%) were dead. Disease progression occurred in 42 patients (80.8%), of which 19 patients (36.5%) developed metastases in new organs. The Kaplan-Meier LC, OS and PFS curves are shown in Fig. 2.

Treatment with SFRS, an interval of < 12 months between diagnosis of metastases and the beginning of SFRS/fSBRT as well as non-colorectal histology were significantly associated with better LC in univariate analysis (Table 5). However, none of these parameters remained significant in multivariate analysis. N0, KPS > 70% and time to first metastasis ≥12 months were significantly associated with improved OS. PFS was significantly better in patients with KPS > 70% and with maximum 3 metastases at the time of SBRT (Table 6). There was no difference regarding survival outcomes between patients with oligorecurrence and oligometastases.

Treatment related toxicity

The SFRS and fSBRT were safe and very well tolerated. No treatment-related deaths and grade ≥ 3 toxicities occurred. Six patients (11.5%) developed asymptomatic grade 1 pneumonitis (2 patients after SFRS and 4 patients after fSBRT) and one patient had grade 1 pulmonary fibrosis. Symptomatic and medical intervention requiring grade 2 pneumonitis was diagnosed in one patient (1.9%) after SFRS with 25 Gy.

Table 5 Univariate analysis of factors influencing local control

Covariate	HR (95% CI)	*p*-value
Time between diagnosis of LM and SBRT (months)		
<12	1	
≥12	2.5 (1.1-6.0)	0.027
Location of LM		
central	1	
peripheral	0.7 (0.2-1.7)	0.412
Histology		
CRC	1	
non-CRC	0.2 (0.1-0.6)	0.004
LM diameter (mm)		
≤10	1	
>10	2.2 (0.8-6.6)	0.150
PTV (cm^3)		
≤10	1	
>10	3.3 (0.9-11.3)	0.053
Fractionation regimens		
SFRS	1	
fSBRT	2.7 (1.0-7.0)	0.037
BED		
<100Gy	1	
≥100 Gy	2.7 (1.1-6.4)	0.021

HR Hazard ratio, *CI* confidence interval, *LM.* lung metastases, *SBRT* stereotactic body radiotherapy, *SFRS* single fraction radiosurgery, *fSBRT* fractionated stereotactic body radiotherapy, *PTV* Planning target volume, *BED* biologically effective dose

Discussion

This analysis represents a single-center experience in treating oligometastatic lung lesions with curative intended SFRS and fSBRT. The 1-, 2-year LC and OS rates for the entire cohort were 82, 70 and 84%, 71%, respectively. Our findings are comparable with the current findings in the literature (Table 7) [8–16].

SBRT is an attractive non-invasive treatment option providing good therapy outcomes with minimum toxicity. The BED ≥100 Gy, smaller tumor size, shorter interval between diagnosis and treatment of metastases are favorable prognostic factors influencing local control of lung metastases after SBRT [9, 17–19]. The existing data on fractionation schedules as well as dosage of SBRT for lung metastases is limited by retrospective nature or non-randomized prospective study design. Therefore, no standardized treatment regimens are yet available. The primary results of TROG 13.01 SAFRON II Phase II trial which compares SFRS to fSBRT for lung metastases are expected soon [20].

According to our data, small lung metastases (median PTV ≤ 9.9 cm^3, median diameter 12 mm) might safely be treated with SFRS applying 24–26 Gy (median D$_{max}$ of

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Table 6 Univariate and multivariate analysis of factors influencing overall and progression-free survival

Covariate	Overall survival				Progression-free survival			
	Univariate analysis		Multivariate analysis		Univariate analysis		Multivariate analysis	
	HR (95% CI)	*p*-value	HR (95% CI)	*p*-value	HR (95% CI)	*p*-value	HR (95% CI)	*p*-value
Age (years)								
>70	1				1			
≤70	1.1 (0.4-2.7)	0.81	NA	NA	0.8 (0.4-1.5)	0.56	NA	NA
Gender								
Female	1				1			
Male	1.6 (0.6-4.6)	0.31	NA	NA	1.2 (0.8-1.6)	0.25	NA	NA
Primary tumor								
non-CRC	1				1			
CRC	0.6 (0.2-1.4)	0.29	NA	NA	0.8 (0.5-1.6)	0.64	NA	NA
KPS								
≤70%	1				1			
>70%	0.4 (0.2-1.1)	0.09	0.3 (0.1-0.8)	0.03	0.5 (0.3-0.9)	0.03	0.4 (0.2-0.7)	0.02
T-classification								
T≤2	1				1			
T>2	2.4 (0.8-6.8)	0.08	1.5 (0.4-5.0)	0.48	1.4 (0.7-2.8)	0.31	NA	NA
N-classification								
N0	1				1			
N+	2.6 (0.9-7.3)	0.06	4.4 (1.2-15.6)	0.02	1.4 (0.7-2.7)	0.33	NA	NA
Time to first metastasis (months)								
<12	1				1			
≥12	0.3 (0.1-0.9)	0.03	0.2 (0.1-0.7)	0.01	0.6 (0.3-1.2)	0.14	NA	NA
No. of metastases before SBRT								
<3	1				1			
≥3	1.4 (0.6-3.3)	0.42	NA	NA	2.6 (1.3-5.1)	0.005	2.7 (1.4-5.4)	0.003
No. of affected organs								
1	1				1			
>1	1.6 (0.7-3.9)	0.24	NA	NA	1.1 (0.5-1.9)	0.97	NA	NA
Systemic therapy before SBRT								
Yes	1				1			
No	1.4 (0.3-6.3)	0.65	NA	NA	1.4 (0.5-4.1)	0.48	NA	NA

NA not assessed, *HR* Hazard ratio, *CI* confidence interval, *CRC* colorectal cancer, *KPS* Karnofsky performance status, *SBRT* stereotactic body radiotherapy

53 Gy and a median BED_{max} of 81 Gy) with excellent 1- and 2-year LC rates of 89 and 83%, implying that BED < 100 Gy using SFRS might be sufficient for durable control in small lung lesions. This observation, however, contradicts the findings of other studies, where BED < 100 Gy was found to be a negative prognostic factor for LC. Ricco et al. analyzed whether different lung metastases volumes and BED were associated with treatment outcomes [17]. In this study, lesions after SBRT with BED ≥100 Gy reached better LC rates. Moreover, in the group with BED ≥100 Gy smaller metastases (volume < 11 cm^3) were linked to improved LC and OS rates. The median number of fractions employed was 3 (range: 1–

8), how many lesions were treated with SFRS remains unclear. Other trials rarely report on the significance of BED and fractionation regimens in terms of treatment outcome for metastases according to their size [9, 12]. Nevertheless, the existing data on size-adapted SFRS for lung metastases as well as primary lung tumors is promising with 1 year LC rates varying from 89.1–93.4% [15, 21–23]. However, diverse measurement units or target volumes describing metastases size (e.g. diameter, GTV, PTV) found in the literature make it difficult to categorize lesions or to identify the optimal dose. Randomized, prospective studies are needed to determine which fractionation schedule is the most suitable for

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Table 7 Overall survival and local control rates after SFRS/fSBRT or pulmonary metastasectomy according to various studies

Reference	Study design	Year	No. Patients	Primary tumor	No. of LM	Treatment	Overall survival		Local control	
							1-year (%)	2-years (%)	1-year (%)	2-years (%)
Nuyttens et al. [8]	Phase 2 study	2015	30	Various	1 - 5	SFRS/fSBRT	-	63	79	-
Rieber J et al. [9]	Retrospective	2016	700	Various	42% single	SFRS/fSBRT	75.1	54.4	-	81.2
Navarria et al. [10]	Retrospective	2014	76	Various	1 - 5	fSBRT	84.1	73	95	89
Sharma A. et al. [11, 12]	Retrospective	2018	206	Various	1 - 5	SFRS/fSBRT	-	63	-	85
Widder J et al. [13]	Retrospective	2013	110	Various	3 - 5	fSBRT 42, PME 68	SBRT: 87 PME: 98	SBRT: 86 PME: 74	SBRT: 94 PME: 93	SBRT:94 PME: 90
Sapir et al. [14]	Retrospective	2016	78	Sarcoma	-	SBRT 26, PME 127	-	SBRT: 57.9, PME: 62.2	-	SBRT: 97.4 PME: 96.8
Filippi et al. [15]	Retrospective	2014	67	Various	1 - 5	SFRS	85.1	70.5	93	88.1
Agolli L [16]	Retrospective	2017	44	CRC	1 - 4 (61% single)	SFRS/fSBRT	-	67.7	68.8	60.2
Present study	Retrospective	2019	52	Various	Median 2	SFRS/fSBRT	84	71	SFRS 89, fSBRT 83	SFRS 83, fSBRT 59

LM lung metastases, *SBRT* stereotactic body radiotherapy, *SFRS* single fraction radiosurgery, *fSBRT* fractionated stereotactic radiotherapy

lung metastases according to the size in terms of therapy outcomes, toxicity and patient's compliance.

In the current study, 1- and 2-year LC rates for metastases from CRC compared with non-CRC were significantly worse. Recently, Jingu et al. investigated the impact of primary tumor histology on LC rates after SBRT for lung metastases in a metanalysis and systematic review. Analysis of 1920 patients (619 with CRC, 1301 non-CRC) showed that LC was significantly inferior in the CRC group ($p < 0.00001$). In addition, the dose escalation (BED > 130 Gy) was associated with decreased local recurrences [24]. Furthermore, Ahmed and colleagues concluded that lung metastases from rectal carcinoma are related with increased radio-resistance, and therefore are more likely to relapse after SBRT. The authors recommend dose escalation with BED > 100 Gy for radio-resistant tumors in order to improve treatment outcomes [25]. In the present study, the median BED for relapsed metastases from rectal cancer was 87.5 Gy (range: 56–124.8), suggesting that an insufficient dose for this histology may be responsible for lower LC rates in patients with CRC. Therefore, SBRT with BED < 100 Gy should be used with caution in patients with lung oligometastases from rectal cancer.

We found time to the first metastasis ≥12 months, KPS > 70% and N0 to be independent favorable prognostic factors for OS. Metachronous metastases with longer metastasis free interval are associated with indolent tumor histology and thus are frequently linked to better outcomes, with the favoring time to metastasis diagnose varying from ≥2 months to ≥75 months depending on the primary tumor type [26–28]. Furthermore, in agreement with our results good performance score before initiation of the SBRT was linked to better survival in

various studies [29, 30]. Absence of lymph node involvement was addressed as a prognostic factor mostly in series on oligometastatic lung cancer [27, 31]. Unlike our finding, no prognostic value of N classification was reported in studies with cohorts of heterogenous primary tumor type, therefore this finding must be interpreted carefully. Despite the small sample size, we identified two commonly reported prognostic factors that might be useful for selecting oligometastatic patients for curative SBRT.

The major limitation of this study is its retrospective design with inhomogeneous primary tumor types and the limited number of patients. Therefore, neither a subgroup analysis based on metastasis histology nor an analysis of the effects of dose escalation was performed. Treatment planning calculations with Ray-Tracing, Pencil Beam or Monte Carlo dose algorithms for lung might produce differences in dose distribution for target and organs at risk. However, there was no difference detected in the treatment outcomes in metastases planed with different treatment algorithms. Since multiple metastases in the same patient were treated with different fractionation, finding the prognostic value of SFRS vs. fSBRT for survival outcomes was not feasible.

Conclusions

KPS > 70%, longer time to first metastasis and absence of locoregional lymph node metastases were found to be positive predictive factors for OS in patients with lung oligometastases after SBRT. Long-term LC and low toxicity rates were achieved after short SBRT schedules.

Abbreviations
BED: Biologically effective dose; CRC: Colorectal cancer; CI: Confidence interval; CT: Computed tomography; CTV: Clinical treatment volume;

CK: Cyberknife; DMFS: Distant metastases-free survival; EQD2: Equivalent dose in 2 Gy fractions; fSBRT: Fractionated stereotactic body radiotherapy; GTV: Gross tumor volume; HNC: Head and neck cancer; HI: Hazard ratio; IGTV: Internal gross tumor volume; LC: Local control; non-CRC: Non-colorectal cancer; NSCLC: Non-small-cell lung cancer; OS: Overall survival; PFS: Progression-free survival; PTV: Planning treatment volume; RCC: Renal cell carcinoma; SFRS: Single fraction radiosurgery; SBRT: Stereotactic body radiotherapy

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Publisher's Note

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Publication 3:

Senger C., Conti A., Kluge A., Pasemann D., Kufeld M., Acker G. *et al.* Robotic stereotactic ablative radiotherapy for renal cell carcinoma in patients with impaired renal function. *BMC Urol* **19,** 96 (2019).

https://doi.org/10.1186/s12894-019-0531-z

BMC Urology

RESEARCH ARTICLE

Open Access

Robotic stereotactic ablative radiotherapy for renal cell carcinoma in patients with impaired renal function

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Abstract

Background: Robotic stereotactic ablative radiotherapy (SABR) is currently under investigation as a noninvasive treatment option for patients with renal cell carcinoma (RCC). For radiation therapy of RCC, tumor motion and the need for high ablative doses while preserving the remaining renal parenchyma is a challenge. We aimed to analyze the safety and efficacy of robotic radiosurgery in RCC in a specific difficult subgroup of patients with impaired renal function.

Methods: We retrospectively identified all patients with RCC, treated with robotic SABR and motion compensation in our institution between 2012 and 2017. Either single fraction SABR of 24 or 25 Gy or 3 fractions of 12 Gy prescribed to the 70% isodose line was applied. Local control, overall survival, radiation side effects were evaluated together with renal function and tumor motion.

Results: We analyzed data of 13 lesions treated in 10 patients with clear cell RCC and a mean age of 70.5 ± 13.6 years (range: 48–87). Prior to SABR, 8 patients underwent previous complete and/or partial nephrectomy, 7 patients presented with chronic kidney disease ≥ stage 3. The median of minimum, mean and maximum planning target volume doses were 23.2, 29.5 and 35.0 Gy for single fraction and 24.4, 42.5 and 51.4 Gy for the three fractions regime. Persistent local control by robotic SABR was achieved in 9 out of 10 patients (92.3% of all lesions) within a median follow-up period of 27 month (range: 15–54). One patient underwent nephrectomy due to progressive disease and sufficient renal function of the contralateral kidney. Renal function remained stable with a mean estimated glomerular filtration rate (eGFR) of 51.3 ± 19.7 ml/min at baseline and 51.6 ± 25.8 ml/min at follow-up. The largest respiratory-induced tumor motion was seen in superior-inferior direction, compensated by the CyberKnife with mean targeting errors of maximal 2.2 mm.

Conclusions: Robotic SABR is technically feasible for the treatment of RCC in preexisting kidney disease with good local tumor control at about 2 years follow-up. Robotic SABR with motion tracking offers a valid treatment option for patients, who are at increased risk for progression to end-stage renal disease due to partial nephrectomy or ablative techniques.

Keywords: CyberKnife, Radiosurgery, SABR, Renal cell carcinoma, Kidney, Motion tracking

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Background

Renal cell carcinoma (RCC) is the most common form of kidney cancer and its incidence has risen in recent years [1]. Due to increased incidental detection rates of kidney tumors, more RCC are still confined to the kidney at the time of diagnosis. The standard treatment for Stage I RCC is a partial renal resection. Radical nephrectomy is only performed for centrally located tumors or when partial resection is not feasible. Patients with bilateral tumors, contralateral recurrent tumor after unilateral nephrectomy, metastases from RCC in the contralateral kidney or preexisting chronic kidney disease are special candidates for partial nephrectomy. In these patients preserving renal parenchyma is essential to avoid chronic kidney disease.

As a possible therapeutic approach robotic stereotactic ablative radiotherapy (SABR) is currently under investigation as a non-invasive treatment option for patients with RCC. Renal cell carcinoma is frequently reported as a radio-resistant tumor. However, pathologic complete responses have been described after ablative radiotherapy previously [2]. Tumor motion and the need for high ablative radiation doses while preserving the remaining renal parenchyma, poses a major challenge. Robotic radiosurgery allows continuous tumor tracking under free breathing and therefore minimal gross tumor volume (GTV) to planning target volume (PTV) margins are needed. Robotic SABR for moving tumors is already established as a standard treatment option for patients with early stage non-small cell lung cancer [3, 4].

Although current data seem to demonstrate that SABR provides good tumor control while preserving the renal function [5, 6], most studies are limited to patients with normal renal function. In this study, we analyzed the safety and efficacy of image-guided CyberKnife (Accuray Inc., Sunnivale, USA) radiosurgery in RCC in a specific subgroup of patients with preexisting impaired renal function. Feasibility and technical aspects of robotic SABR will be provided as well.

Methods

Study design

Retrospective analysis of patient data was approved by the Ethics Committee Campus Charité Mitte (EA1/233/18). We identified all histology proven RCC patients, who were treated with robotic SABR in our center between June 2012 and April 2017. We collected data on patient characteristics regarding disease stage, preexisting kidney disease, estimated glomerular filtration rate (eGFR), clinical outcome, complications, local tumor control and overall survival. Dose-volume parameters were analyzed including prescription dose, fractionation, treatment dose (D_{min}, D_{mean}, D_{max},), GTV, PTV, new conformity index (nCI), PTV coverage, tumor motion and tracking accuracy.

Robotic SABR planning and delivery

The patients were referred to CyberKnife irradiation from the nephrology department, all at increased risk for progression to end-stage renal disease caused by further invasive treatment. The decision to perform a robotic SABR was recommended by a multidisciplinary urology board review for patients who are at increased risk for progression to end-stage renal disease due to partial nephrectomy or other ablative techniques.

One gold fiducial marker (1.0 mm × 5.0 mm) was implanted within or close to each tumor using an 18-G needle under computed tomography (CT)-guidance in local anesthesia. A tissue sample was taken in the same procedure if there was no prior pathology report available. High-resolution native thin-slice (1.0 mm) planning CT was performed within a median of 8 days (range: 1–21) after fiducial insertion to allow for fiducial settlement [7]. For accurate tumor delineation, magnetic resonance images (MRI) were co-registered with the planning CT and contouring was performed on all axial slices. The GTV was defined as the tumor volume based on CT and MR images. The clinical target volume (CTV) was equivalent to the GTV. The PTV was obtained by adding in median a 3 mm (range: 0–5 mm) isotropic margin to the GTV. Depending on tumor size or organs at risk (OAR) two different dose concepts were used, either single fraction SABR of 24 or 25 Gy, or 36 Gy in 3 fractions (12 Gy/fraction) prescribed each to the 70% isodose covering the PTV. Treatment planning and dose calculations were obtained by MultiPlan 4.6 (Accuray Inc., Sunnyvale, USA) using the Ray-tracing algorithm.

The linear-quadratic model, assuming an a/ß ratio of 2.6–6.9 Gy for RCC [8], was used to calculate the biologically equivalent dose (BED) and the equivalent dose in 2 Gy fractions (EQD2). The calculated $BED_{6.9}$ and $EQD2_{6.9}$ encompassing the PTV for single fraction were 107.5 Gy and 83.3 Gy, and 98.6 Gy and 76.4 Gy for the 3-fraction treatment.

Dose constraints for OAR for single fraction treatments were as follows: $< 5\,cm^3$ of small bowel loops could receive up to 10.0 Gy with a maximum point dose of 19.0 Gy; for the extratumoral kidney parenchyma $< 200\,cm^3$ could receive up to 8.0 Gy. The normal tissue constraints for three fractions were: $< 5\,cm^3$ could receive up to 16.0 Gy with a maximum point dose of 27.0 Gy for small bowel, and less than 33% of the remaining kidney parenchyma could receive a total of 15.0 Gy. The dose constraints for spinal cord, liver, stomach and large intestine were set according to published standard limits [9]. The nCI $[(V70\% \cdot V_{PTV})/V70\%_{PTV}^2]$, which describes

the conformity between the prescription isodose and the volume and shape of the PTV, was also used for treatment plan evaluation.

Technical aspects

The CyberKnife System installed in July 2011 in Berlin combines two systems, a lightweight linear accelerator mounted on a robotic arm with 6-MV photon energy and an image guidance system consisting of two orthogonally positioned x-ray cameras. For patient positioning, an automatic tracking algorithm compares live x-rays with digital reconstructed images from planning CT. For respiratory motion compensation, the CyberKnife Synchrony® Respiratory Motion Tracking System (MTS) was used. Thereby, the external motion of LED markers located on the chest of the patient was correlated with the internal tumor motion represented by the fiducial position and determined by the x-ray images. The individually measured correlation model is continuously updated and synchronizes the radiation beam in real time such that the beam always remains aligned with the target. An accuracy of less than 1.0 mm is technically achieved and allows clinicians to reduce safety margins significantly, while eliminating the need for gating or breath-hold techniques. During treatment, the motion patterns for each patient were recorded in logfiles.

Follow-up and statistics

Clinical and radiological follow-up with CT or MRI was frequently performed after robotic SABR and the latest available follow-up was used in this analysis. For local control the MRI scans were evaluated by the senior physician in charge to verify treatment response. Tumor response was analyzed using response evaluation criteria in solid tumors (RECIST version 1.1). The treatment response of each RCC was categorized using OsiriX MD 10.0 (Pixmeo SARL, Bernex, Switzerland) to compare baseline MRI and planning CT with the latest available follow up images in 1) complete remission (CR): no measurable lesion; 2) partial remission (PR) defined as a volume reduction ≥ 30%; 3) stable disease (SD); 4) progressive disease (PD) defined as a ≥ 20% increase in volume or ≥ 5 mm increase in size. Local control (LC) was calculated from the end of SABR until last available follow-up or PD.

Overall survival (OS) was calculated from the end of SABR until last follow-up or death. LC and OS were estimated using Kaplan-Meier curves. Common Terminology Criteria for Adverse Event V4.03 (CTCAE) for acute and late radiosurgery related side effects were recorded separately. Renal function at baseline and latest available follow up was calculated according to the chronic kidney disease epidemiology collaboration (CKD-EPI) formula at baseline and last available follow up.

Due to respiratory induced kidney motion, the motion patterns and total targeting errors between the predicted and the actual position of the tumor were evaluated. Overall, the motion pattern and targeting accuracy of 19 out of 21 treatment sessions could be extracted. Motion pattern evaluation and statistical analysis were done with MATLAB 9.3 (The MathWorks, Inc., Natick, USA).

Results

Patient characteristics

Data of 13 lesions treated in 10 patients histologically confirmed as clear cell RCC grade 1 or 2 were collected. The mean age of patients who underwent robotic SABR was 70.5 ± 13.6 years (range: 48–87). The female/male ratio was 1:1. All patients treated with robotic SABR had an ECOG performance status 1 or 2 and suffered from chronic kidney disease (CKD). The median and mean time interval between the first histological diagnosis of RCC and SABR was 7.5 and 8.4 ± 6.0 years, respectively, with a large range of 2 months to 19.7 years. Tumor characteristics are summarized in Table 1. Seven patients had T1a (≤ 40 mm) and 3 patients had larger tumors (T3a). In 3 patients it remained unclear whether the treated tumor was a metachronous RCC or a metastasis from a previously occurred contralateral RCC. The subsites of the 13 lesions were the upper, mid or lower pole in 53.8%, close to the renal pelvis or extending to the perinephric tissue in 15.4% each and infiltrating the renal vein or close to the hilum in 7.7% each.

Prior to SABR, 8 out of 10 patients underwent surgery or radiofrequency ablation (RFA) for their renal tumors, 6 of them had procedures done on both sides. Nephrectomy was carried out in 5 patients, partial ipsilateral resection in 4 patients and contralateral resection in 3 patients. Previous RFA of the SABR treated kidney was performed in 2 patients. Von Hippel-Lindau disease was diagnosed in 2 patients. One patient had a RCC in his kidney transplant. Three patients had a diabetes mellitus type 2. CKD stage 2, 3 and 4 with an eGFR level below 90, 60, 45 ml/min was diagnosed in 3, 6 and one patient, respectively (see Table 1 for preexisting kidney disease).

Treatment and Dosimetric analysis

The tumors had a median diameter of 28.8 mm (range: 9–70). Two patients had tumors larger than 40 mm with RCC extension into the renal vein or perinephric tissue. The median GTV volume was $13.3 \, cm^3$ (range: 1.3–108.4), the resulting median PTV was $22.1 \, cm^3$ (range: 3.8–190.3). Five patients received single fraction SABR of 24 or 25 Gy, 4 patients received 3 fractions of 12 Gy every other day and one patient with three lesions received both regiments. The patient's median of minimum, mean and

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Table 1 Tumor characteristics and preexisting kidney disease in patients with renal cell carcinoma

Case	Size (mm)	Primary tumor	Tumor location	Baseline CKD stage	First line treatment / Preexisting kidney disease
#1	32	cT1a/DD metastasis	close to renal pelvis	3b	Nephrectomy, RFA and embolisation ipsilateral
#2	30	cT1a/DD metastasis	mid pole	2	Nephrectomy, partial resection ipsilateral /DM type 2
#3	14 10	cT1a	upper pole mid pole	3b	Nephrectomy, partial resection ipsilateral / short term dialysis, DM type 2
#4	26	cT1a	upper pole	2	RPGN, kidney transplant
#5	70	cT3a	infiltrating renal vein	2	Partial resection contralateral
#6	36	cT1a	mid pole	4	Nephrectomy
#7	36	cT1a	lower pole	3a	partial resection contralateral, multiple RFA ipsilateral / VHL
#8	39	cT1a	close to renal pelvis	3a	partial resection ipsi- and contralateral / VHL
#9	47	cT3a	extends to perinephric tissue	3b	–
#10	9 10 15	cT3a/DD metastasis	lower pole extends to perinephric tissue close to hilum	3b	Nephrectomy, partial resection ipsilateral

RFA Radiofrequency ablation, *CKD* chronic kidney disease, *DM* diabetes mellitus, *RPGN* rapidly progressive glomerulonephritis, *VHL* von Hippel-Lindau disease

maximum PTV dose was 23.2, 29.5 and 35.0 Gy for single fraction and 24.4, 42.5 and 51.4 Gy for the three fractions regimen, respectively. Dose-volume parameters and further treatment characteristics including nCI and percentage of the PTV coverage are summarized in Table 2.

Each robotic SABR treatment was done as an outpatient procedure with delivery times between 46 min and 86 min per session. For single session treatments, the mean total treatment time was 62 ± 15 min, fractionated treatments took in total 184 ± 33 min (61 ± 11 min per fraction). All patients completed their treatment.

Tumor response

Local control (CR, PR and SD) by robotic SABR therapy was achieved in 9 out of 10 patients and 92.3% of all lesions within the median follow-up period of 27 month (range: 15–54). A representative example of the tumor response and treatment plan is shown in Fig. 1. Whereas SD was observed in 38.5% of the treated lesions, PR was observed in 30.8% and CR in 23.1% (Table 2). However, there was no difference in SD or PR between the one fraction or three fractions regiment. The only local treatment failure occurred in one lesion (7.7%) 5 month after SABR.

Four patients with metastases to other organs at time of radiosurgery or during follow-up had additional adjuvant systemic treatment. Out of 10 patients 8 were alive at the last available follow-up. Two patients with progressive metastatic disease died 15 and 16 months after SABR. Kaplan-Meier Curves for local control and overall survival are shown in Fig. 2.

Renal function and toxicity

Typical normal tissue dose constraints were within the range mentioned. Over a median follow-up period of 22

Table 2 Dose-volume and follow-up parameters for robotic stereotactic ablative body radiotherapy

Case	GTV (cm^3)	PTV (cm^3)	Margin (mm)	Dose (Gy)	PTV coverage (%)	nCI	Follow-up (month)	Local control
#1	8.2	17.9	4	1 × 24	97.8	1.07	54	SD
#2	20.4	31.0	3	1 × 25	97.8	1.06	23	PR
#3	13.5 17.0	13.5 17.0	0 0	1 × 24 1 × 24	96.8 98.5	1.13 1.13	47	CR PR
#4	14.3	24.6	3	1 × 25	99.9	1.06	33	SD
#5	108.4	190.3	5	3 × 12	92.0	1.23	25	SD
#6	13.2	22.7	3	1 × 25	99.5	1.13	15	SD
#7	9.2	17.4	3	3 × 12	98.3	1.14	32	SD
#8	45.5	88.4	5	3 × 12	86.0	1.40	30	PD
#9	44.2	66.2	3	3 × 12	98.7	1.21	23	PR
#10	1.3 9.0 2.3	3.8 21.4 5.6	3 4 3	1 × 25 3 × 12 1 × 25	99.7 82.0 98.4	1.09 1.50 1.20	16	CR PR CR

GTV Gross tumor volume, *PTV* planning target volume, *nCI* new conformity index, *SD* stable disease, *PR* partial remission, *CR* complete remission, *PD* progressive disease

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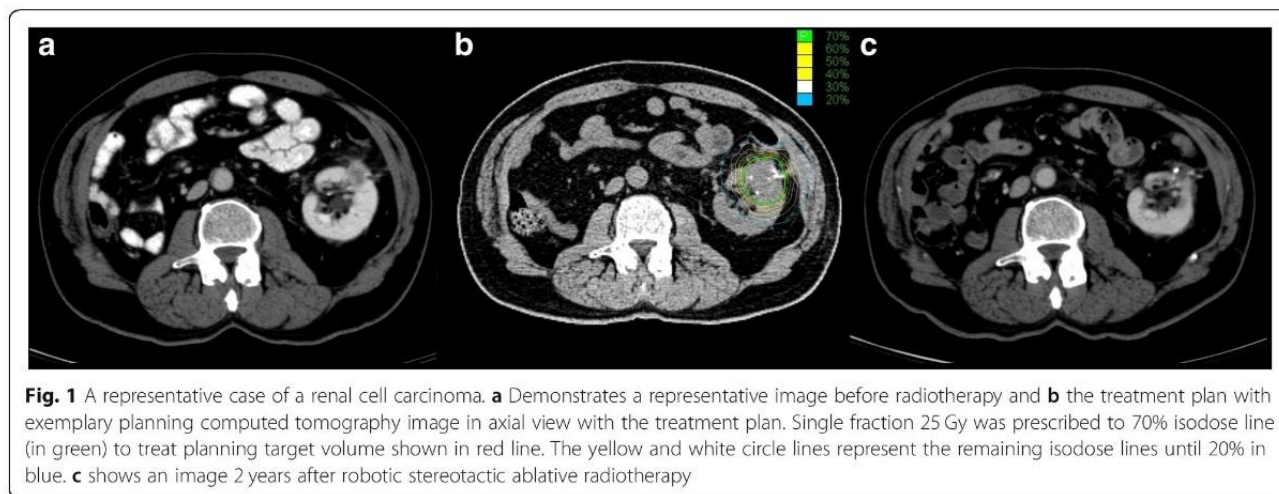
Fig. 1 A representative case of a renal cell carcinoma. **a** Demonstrates a representative image before radiotherapy and **b** the treatment plan with exemplary planning computed tomography image in axial view with the treatment plan. Single fraction 25 Gy was prescribed to 70% isodose line (in green) to treat planning target volume shown in red line. The yellow and white circle lines represent the remaining isodose lines until 20% in blue. **c** shows an image 2 years after robotic stereotactic ablative radiotherapy

month (range: 4–51) renal function remained stable with a mean serum creatinine of 1.4 ± 0.5 mg/dl (eGFR 51.3 ± 19.7 ml/min) at baseline and 1.5 ± 0.8 mg/dl (eGFR 51.6 ± 25.8 ml/min) at follow-up (Fig. 3). One patient underwent nephrectomy due to progressive disease after SABR with three fractions of 12 Gy and sufficient renal function of the contralateral kidney. One patient developed mild abdominal pain (grade 1) and another one diarrhea and abdominal distension (grade 1). All symptoms occurred in the two patients with tumors larger than 40 mm. No patient developed CTCAE grade 2 or higher toxicity or needed hemodialysis.

Tumor motion tracking

Each patient got one gold fiducial implanted per lesion. Two patients had 2 and 3 gold fiducials for multiple lesions. There were no side effects with marker placement in the kidney or difficulties with marker migration observed. To position the patient as in planning CT, he was first aligned using the bony spine structures. Afterwards the position of the fiducial was tracked. The majority of the lesions (92.3%) were treated using MTS for motion compensation. The only robotic SABR done without tumor motion tracking was performed in a kidney transplant located in the left iliac fossa where no respiratory motion was suspected. For all patients, treatment was performed in "free-breathing", the largest respiratory-induced tumor motion was seen in superior-inferior direction with magnitudes between 3.0 mm and 24.7 mm. The left/right and anterior/posterior displacements of the tumor ranged from 0.7 to 10.6 mm, and 1.6 to 14.6 mm, respectively (Fig. 4). This motion was compensated by the CyberKnife with mean targeting errors over the complete treatment time of maximal 2.2 mm.

Discussion

In this retrospective study the efficacy of robotic SABR was assessed retrospectively in 10 patients with RCC and
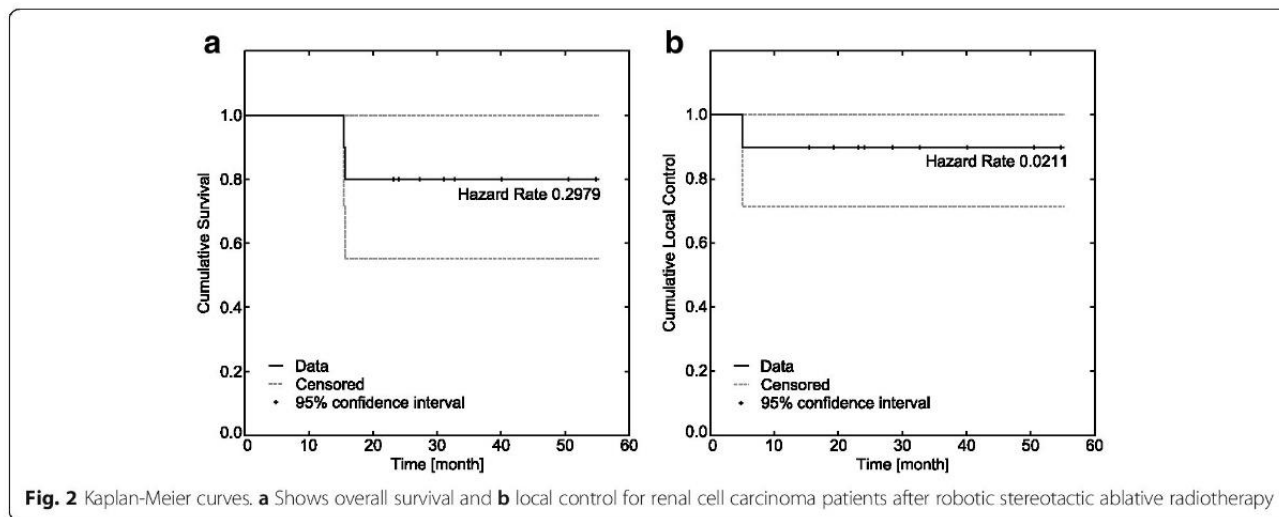
Fig. 2 Kaplan-Meier curves. **a** Shows overall survival and **b** local control for renal cell carcinoma patients after robotic stereotactic ablative radiotherapy
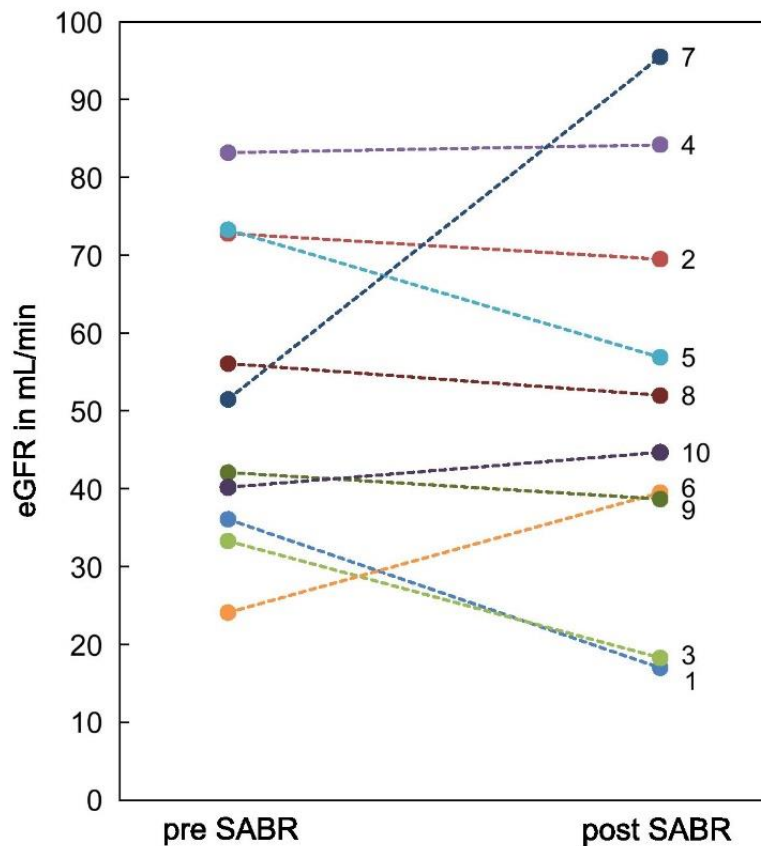
Fig. 3 Kidney function at baseline and follow-up. Estimated glomerular filtration rates (eGFR) before stereotactic ablative radiotherapy (pre SABR) and latest available follow-up (post SABR)

moderate to severe chronic kidney disease. Our study demonstrates that this minimal invasive and highly sophisticated treatment method provides good response rates and local control with negligible toxicity. SABR with motion compensation is a nephron-sparing treatment that perfectly adapts to patients with RCC and significant preexisting chronic renal failure.

Our results concerning local tumor control in 92.3% of all lesions and mild toxicity appear to be consistent with those available in the literature. A previous systematic review of 126 patients described a weighted local control rate of 94% and a grade 3 toxicity rate of 3.8% [10]. Since that study, 3 single-institution, prospective studies of 19 patients [11], 40 patients [2], and 33 patients [12] have reported similar findings, with local control rates ranging from 98 to 100% and grade $\geq$ 3 toxicity rates from 0 to 15.8%. Recently, 9 centers across Germany, Australia, the United States, Canada, and Japan formed an International Radiosurgery Oncology Consortium for Kidney and reported data of 223 patients [6]. The rates of LC, cancer-specific survival, and progression-free survival at 2 and 4 years were 97.8, 95.7, 77.4% and 97.8, 91.9, 65.4%, respectively. Multi-fraction

SABR was associated with poorer progression-free survival and worse cancer-specific survival. Grade 1 and 2 toxicities were reported for 35.6% of patients whereas grade 3 and 4 toxicities were recorded in only 1.3% [6].

In patients with bilateral tumors or contralateral tumor recurrences after unilateral nephrectomy or partial resection treatment is especially challenging. The resection of the remaining kidney consecutively leads to the progression of chronic kidney disease including the need for hemodialysis treatment. In such cases, minimally invasive ablative techniques such as cryosurgery, radiofrequency ablation and SABR are possible alternatives to nephrectomy. A 2016 systematic review and meta-analysis reporting on survival across management strategies demonstrated a 95 to 100% cancer specific survival after nephrectomy and thermal ablation with a median follow-up period of 22 to 120 months. Whereas, for tumors more than 40 mm (T1b) survival rates decrease to around 90% and for tumors more than 70 mm (T2) between 82.5 and 86.7% [13]. A mostly retrospective data analysis by Kunkle and Uzzo [14] showed local tumor progression rates of 12.9% after RFA and 5.2% after renal cryoablation. In our series, tumor progression was

Fig. 4 A diagram of motion amplitudes. Maximal motion amplitudes of all treatment sessions in inferior/superior (Inf/Sup), left/right (Lft/Rgt) and anterior/posterior (Ant/Pos) direction in mm
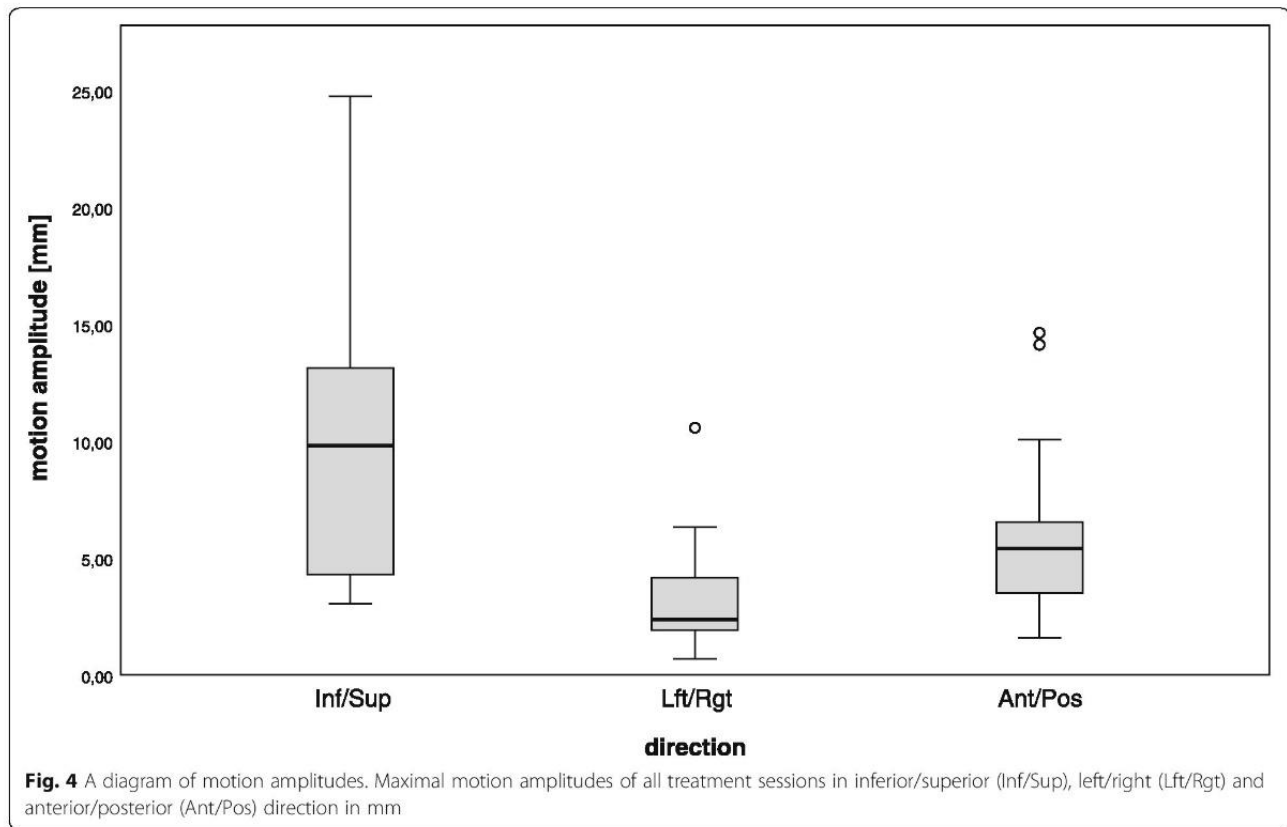
recorded in 7.7% of all lesions, accordingly in one out of 10 patients (10%). In this case the tumor size was above the median, located close to renal pelvis and the PTV coverage was less than 90%.

Notably, renal function remained stable following treatment in all patients despite the high doses of radiation delivered to the kidney. This result raises two considerations. Firstly, preservation of renal function was assumed to be due to compensatory mechanisms of the contralateral kidney and the spared ipsilateral kidney volume described as renal functional reserve [15]. These results also suggest that it might be possible to rely on a compensatory capacity of the ipsilateral kidney in patients who already had contralateral nephrectomy and that, whenever oncologically suitable, a selective approach aimed to avoid post-treatment severe chronic kidney disease should be pursued. A second point concerns the radiation tolerance of the peritumoral kidney and the reliability of tumor tracking in robotic SABR. Cassady [16] proposed a threshold dose of 15 Gy for renal injury based on data of bilateral whole kidney irradiation in 3 fractions. Nevertheless, ours and other previous studies demonstrate a good tolerance to higher doses and stable kidney function. The prescribed dose (1 × 24–25 Gy or 3 × 12 Gy prescribed to the 70% isodose) was relatively high in order to overcome the radioresistance of RCC. The fraction number and prescribed dose of the two large studies from Staehler et al. [2] and Sun et al. [17] were similar to our dose concepts. Overall, they treated 80 patients with either 25 Gy in one fraction or 38 Gy in 3 fractions prescribed to the 70 or 80% isodose line. Both studies reported only grade 1 side effects with > 90% local control in a relatively short follow-up.

Svedman et al. [18] evaluated kidney injury following 3 fractions SABR in 7 patients with primary or metastatic renal disease with only one functioning kidney. In 5 patients, kidney function remained unaffected after SABR, with a kidney volume of 37.3% receiving 15 Gy (V15), whereas 2 patients exhibited modest changes in renal function without the requirement for medical intervention or hemodialysis. In SABR patients, a V15 limited to less than one third of the normal single remaining kidney could be an appropriate dose-volume constraint in patients with preexisting kidney disease. We therefore considered this dose constraint in our series for the three-fraction regiment.

Furthermore, the high doses used and the treatment result in terms of remission, local control and sparing of renal function, demonstrate that the robotic SABR is highly reliable in terms of targeting precision and dose delivery. According to our data, the median targeting accuracy was within 2.2 mm. This provided us an important information regarding the margins to be used. In

fact, we believe that, unlike margins of up to 10 mm, as used in other studies, a moderate expansion of the tumor (i.e. 3.0 mm) is sufficient for the CyberKnife MTS. Since only one marker was implanted, rotations could neither be directly detected nor corrected. However, geometric calculations have shown that a 3.0 mm margin appears to be sufficient also if small rotations ($< 5°$) occur.

Limitations

This study has several limitations. This is a retrospective series with a limited number of cases collected and a relatively short follow-up for renal function. Nevertheless, it should be considered as a proof-of-concept study for SABR on patients with impaired renal function gaining satisfactory results and providing a low risk for treatment-related side effects.

Conclusion

Robotic SABR is technically feasible for the treatment of early stage RCC in patients with preexisting kidney disease with good local control at short term follow-up. As an outpatient procedure, it may prevent (treatment related) loss of renal function with only mild side effects. Therefore robotic SABR with motion tracking represents a valid treatment option for these patients, who are at increased risk for progression to end-stage renal disease due to partial nephrectomy or other ablative techniques. Further studies are needed but warranted to determine long-term results of this treatment.

Abbreviations

CR: Complete remission; CT: Computed tomography; CTV: Clinical target volume; eGFR: Estimated glomerular filtration rate; GTV: Gross tumor volume; LC: Local control; MRI: Magnetic resonance images; MTS: Motion Tracking System; nCI: New conformity index; OAR: Organs at risk; OS: Overall survival; PD: Progressive disease; PR: Partial remission; PTV: Planning target volume; RCC: Renal cell carcinoma; RFA: Radiofrequency ablation; SABR: Stereotactic ablative radiotherapy; SD: Stable disease

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Publisher's Note

11. *Curriculum Vitae*

My curriculum vitae is not published in the electronic version of my work for reasons of data protection.

12. *List of publications*

1. **Kalinauskaite G**, Senger C, Kluge A, Furth C, Kufeld M, Tinhofer I, Budach V, Beck M, Hochreiter A, Grün A, Stromberger C. 68Ga-PSMA-PET/CT-based radiosurgery and stereotactic body radiotherapy for oligometastatic prostate cancer. PLoS One. 2020 Oct 21;15(10):e0240892. doi: 10.1371/journal.pone.0240892. PMID: 33085712; PMCID: PMC7577453.
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2. **Kalinauskaite GG**, Tinhofer II, Kufeld MM, Kluge AA, Grün AA, Budach VV, Senger CC, Stromberger CC. Radiosurgery and fractionated stereotactic body radiotherapy for patients with lung oligometastases. BMC Cancer. 2020 May 11;20(1):404. doi: 10.1186/s12885-020-06892-4. PMID: 32393261; PMCID: PMC7216666
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Impact factor 2.57

13. Acknowledgments