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Stereotactic body radiotherapy of adrenal metastases—A dose-finding study

Daniel Buergy[1] | Florian Würschmidt[2] | Eleni Gkika[3] | Juliane Hörner-Rieber[4] | Stefan Knippen[5,6] | Sabine Gerum[7,8] | Panagiotis Balermpas[9] | Christoph Henkenberens[10] | Theresa Voglhuber[11] | Christine Kornhuber[12] | Steffen Barczyk[13] | Barbara Röper[14] | Ali Rashid[15] | Oliver Blanck[16] | Andrea Wittig[5] | Hans-Ulrich Herold[17] | Thomas Baptist Brunner[18] | Reinhart A. Sweeney[19] | Klaus Henning Kahl[20] | Ilja Frank Ciernik[21] | Annette Ottinger[22] | Victor Izaguirre[12] | Florian Putz[6] | Laila König[4] | Michael Hoffmann[7] | Stephanie Elisabeth Combs[11,23,24] | Matthias Guckenberger[9] | Judit Boda-Heggemann[1]

[1]Klinik für Strahlentherapie und Radioonkologie, Universitätsmedizin Mannheim, Medizinische Fakultät Mannheim, Universität Heidelberg, Mannheim, Germany

[2]Radiologische Allianz, Strahlentherapie, Hamburg, Germany

[3]Strahlenheilkunde, Universitätsklinikum Freiburg, Freiburg, Germany

[4]Universitätsklinikum Heidelberg, Klinik für Radioonkologie und Strahlentherapie, Heidelberg, Germany

[5]Universitätsklinikum Jena, Klinik für Strahlentherapie und Radioonkologie, Jena, Germany

[6]Strahlenklinik, Universitätsklinikum Erlangen, Erlangen, Germany

[7]Radioonkologie LMU München, Strahlentherapie und Radioonkologie, Munich, Germany

[8]Klinik für Radiotherapie und Radioonkologie, Paracelsus Universität Salzburg, Salzburg, Austria

[9]Klinik für Radio-Onkologie, Universitätsspital Zürich, Universität Zürich, Zürich, Switzerland

[10]Medizinische Hochschule Hannover, Klinik für Strahlentherapie und Spezielle Onkologie, Hannover, Germany

[11]Department of Radiation Oncology, Technische Universität München (TUM), Munich, Germany

[12]Universitätsklinikum Halle (Saale), Klinik für Strahlentherapie, Halle (Saale), Germany

[13]Zentrum für Strahlentherapie und Radioonkologie, Belegklinik am St. Agnes-Hospital, Bocholt, Germany

[14]DIE RADIOLOGIE, MVZ Strahlentherapie Bogenhausen—Harlaching—Neuperlach, Munich, Germany

[15]MediClin Robert Janker Klinik, Klinik für Strahlentherapie und Radioonkologie, Bonn, Germany

[16]Universitätsklinikum Schleswig-Holstein, Klinik für Strahlentherapie, Kiel, Germany

[17]Cyberknife Centrum Mitteldeutschland GmbH, Institut für Radiochirurgie und Präzisionsbestrahlung, Erfurt, Germany

[18]Universitätsklinikum Magdeburg, Klinik für Strahlentherapie, Magdeburg, Germany

[19]Leopoldina Krankenhaus Schweinfurt, Klinik für Strahlentherapie, Schweinfurt, Germany

[20]Universitätsklinikum Augsburg, Klinik für Strahlentherapie und Radioonkologie, Augsburg, Germany

[21]Staedtisches Klinikum Dessau, Radiation Oncology, Dessau Medical Center, Brandenburg Medical School Theodor Fontane, Dessau, Germany

Abbreviations: BED, biologically effective dose; DEGRO, German Society for Radiation Oncology; GTV, gross tumor volume; IGRT, image-guided radiotherapy; IMRT, intensity-modulated radiotherapy; LC, local control; LRR, local recurrence rate; OS, overall survival; PFS, progression-free survival; PTV, planning target volume; RT, radiotherapy; SBRT, stereotactic body radiotherapy; SCC, squamous cell carcinoma; SCLC, small-cell lung cancer; TCP, tumor control probability.

[22]Klinikum Darmstadt GmbH, Institut für Radioonkologie und Strahlentherapie, Darmstadt, Germany

[23]Helmholtz Zentrum München (HMGU), Neuherberg, Germany

[24]Deutsches Zentrum für Translationale Krebsforschung (DKTK), Partner Site Munich, Munich, Germany

Correspondence
Daniel Buergy, Department of Radiation Oncology, University Medical Center Mannheim, University of Heidelberg, Theodor-Kutzer-Ufer 1-3, 68167 Mannheim, Germany.
Email: daniel.buergy@umm.de

Abstract

Optimal doses for the treatment of adrenal metastases with stereotactic radiotherapy (SBRT) are unknown. We aimed to identify dose-volume cut-points associated with decreased local recurrence rates (LRR). A multicenter database of patients with adrenal metastases of any histology treated with SBRT (biologically effective dose, BED10 ≥50 Gy, ≤12 fractions) was analyzed. Details on dose-volume parameters were required (planning target volume: PTV-D98%, PTV-D50%, PTV-D2%; gross tumor volume: GTV-D50%, GTV-mean). Cut-points for LRR were optimized using the R maxstat package. One hundred and ninety-six patients with 218 lesions were included, the largest histopathological subgroup was adenocarcinoma (n = 101). Cut-point optimization resulted in significant cut-points for PTV-D50% (BED10: 73.2 Gy; $P = .003$), GTV-D50% (BED10: 74.2 Gy; $P = .006$), GTV-mean (BED10: 73.0 Gy; $P = .007$), and PTV-D2% (BED10: 78.0 Gy; $P = .02$) but not for the PTV-D98% ($P = .06$). Differences in LRR were clinically relevant (LRR ≥ doubled for cut-points that were not achieved). Further dose-escalation was not associated with further improved LRR. PTV-D50%, GTV-D50%, and GTV-mean cut-points were also associated with significantly improved LRR in the adenocarcinoma subgroup. Separate dose optimizations indicated a lower cut-point for the PTV-D50% (BED10: 69.1 Gy) in adenocarcinoma lesions, other values were similar (<2% difference). Associations of cut-points with overall survival (OS) and progression-free survival were not significant but durable freedom from local recurrence was associated with OS in a landmark model ($P < .001$). To achieve a significant improvement of LRR for adrenal SBRT, a moderate escalation of PTV-D50% BED10 >73.2 Gy (adenocarcinoma: 69.1 Gy) should be considered.

KEYWORDS
adrenal, dose-finding, oligometastases, SBRT

What's new?

Stereotactic body radiation therapy (SBRT), a method of precisely targeting tumors with radiation, has been successful in treating adrenal metastases. However, the optimal dose has not yet been established. Here, the authors retrospectively analyzed 218 lesions in 196 patients who had been treated with SBRT and for whom dose-volume parameters were available. They identified dose-volume cut points above which higher doses did not provide additional benefit. Moderate escalation to 73.2 Gy for the PTV-D50% achieved a clinically relevant improvement in recurrence rate.

1 | INTRODUCTION

Successful local therapy for adrenal metastases using surgery has been described in multiple series[1,2] and may result in long-term freedom from tumor progression.[3] More recently, with the developments of intensity-modulated radiotherapy (IMRT) and stereotactic body radiotherapy (SBRT), radiotherapy (RT) has also been successfully applied as a local treatment modality for adrenal metastases.[4-16] Conventionally fractionated or low-dose approaches can be used successfully[17] in patients in a palliative setting. However, SBRT offers the option to treat metastases with steep dose gradients and a high-precision set-up,[18-22] facilitating the possibility to increase tumor doses without enhancing normal tissue toxicity. Therefore, SBRT has been used in many studies published more recently.[15,17,23] Interestingly, local control (LC) rates seem to differ between involved metastatic sites treated with SBRT; for example, in lung metastases, 1-year

LC was 90%[24] whereas in liver and adrenal metastases, 1-year LC rates of 77% and 80.8% have been reported.[17,25]

SBRT planning for adrenal metastases is often a challenge due to anatomic proximity of serial risk organs such as the duodenum, small bowel and stomach.[26] Violating dose constraints can lead to life-threatening complications[27-29] making a complex planning process, image-guided RT (IGRT), and appropriate motion management strategies necessary.[30] To avoid violating risk organ tolerance, compromises in the target dose can be necessary resulting in heterogenous dose and fractionation schedules.[17]

Several studies have reported on SBRT of adrenal metastases[31,32]; however, the optimal dose to treat adrenal metastases is unknown and sufficiently powered multicenter series and/or systematic analyses did not use the actually applied doses but the prescribed doses and detailed prescription patterns were often unavailable.[15,23] Therefore, dose-coverage with regard to the planning target volume (PTV) and the actual gross tumor volume (GTV) are unknown as they depend on prescription patterns and might vary between different plans with the same nominal prescription dose especially in series before the ICRU-91 dose reporting recommendations.[33]

We therefore conducted this analysis using a retrospective cohort of patients with adrenal metastases within the framework of the SBRT database initiative of the Working Group Radiosurgery and Stereotactic Radiotherapy of the German Society for Radiation Oncology (DEGRO). Results for safety and efficacy of the overall patient cohort have been published elsewhere[17]; for this analysis, we identified patients who were treated with SBRT and for whom dose-volume parameters were available to identify optimal cut-points for dose-volume parameters associated with a decreased local recurrence rate (LRR).

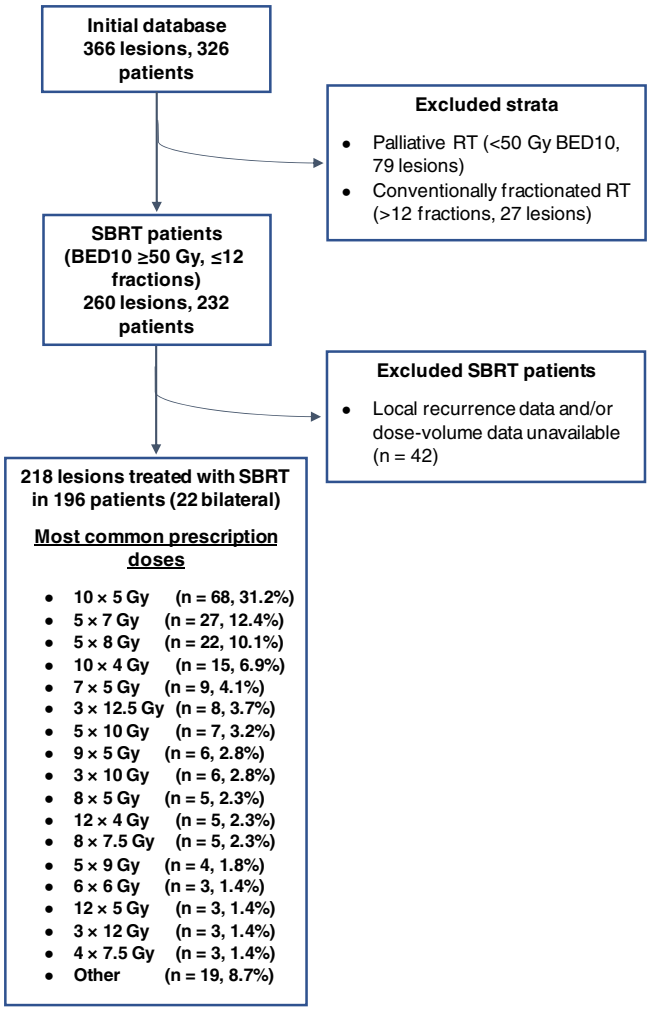

FIGURE 1 CONSORT diagram and fractionation regimens of patients and lesions included in the analysis [Color figure can be viewed at wileyonlinelibrary.com]

2 | PATIENTS AND METHODS

2.1 | Patient characteristics and data collection

Data from a multicenter retrospective cohort study of patients with adrenal metastases were analyzed after ethics approval had been obtained in the coordinating study center (2018-853R-MA) and in participating centers in accordance with local standards. All patients had at least one adrenal metastasis of any histological subtype which had been treated with SBRT. For comparison of heterogeneous dose prescription patterns and fractionation schedules, the linear-quadratic model was used with an assumed α/β of 10 Gy to convert absolute doses to biologically effective doses (BED10) for each treated lesion.[33] Details on the patient cohort, including patterns of care, outcomes on LC, overall survival (OS), and toxicity have been reported previously.[17] Briefly, the database includes three strata: (a) SBRT[19] patients treated with a prescribed BED10 of at least 50 Gy in maximal 12 fractions, (b) patients treated with palliative intent (BED10 < 50 Gy), and (c) patients treated with conventionally fractionated RT (>12 fractions). For this analysis, we included lesions treated with SBRT (≤12 fractions, prescribed BED10 ≥50 Gy); furthermore, details on one or more of the following dose-volume parameters was required for inclusion: PTV-D98%, PTV-D50%, PTV-D2% GTV-D50%, GTV-mean (GTV mean dose).[34]

2.2 | Follow up, survival- and statistical analysis

Statistical analyzes were performed using R (version 3.6.3; The R Foundation for Statistical Computing, Vienna, Austria).[35] We used a cumulative incidence function to calculate a competing risk-adjusted LRR using Gray's test to compare groups.[36] The alpha level was set at .05. To identify cut-points for minimum doses required to achieve local control, we used the method proposed by Lausen et al[37] as implemented in the R maxstat package.[38] To avoid strong numerical imbalances between high- and low-dose groups, the lower quantile of the covariate distribution was predefined at 25%. Such an approach results in optimized cut-points located between the 25% and the 75% quantiles. In each figure, high-dose and low-dose group refers to the group above and below the cut-point for the parameter, respectively.

TABLE 1 Patient, tumor and treatment characteristics of adrenal metastases included in the database

Patient, tumor and treatment characteristics		
Lesions	n	218
Patients	n	196
Pathohistology (lesions)	Adenocarcinoma, n (%)	101 (46.3)
	-NSCLC, n	82
	-Colorectal, n	12
	-Other[a], n	7
	SCLC, n (%)	29 (13.3)
	SCC, n (%)	27 (12.4)
	-NSCLC, n	24
	-Other, n	3
	Melanoma, n (%)	12 (5.5)
	Hepatocellular, n (%)	9 (4.1)
	Renal cell, n (%)	9 (4.1)
	Breast cancer, n (%)	6 (2.8)
	Other[b], n (%)	22 (10.1)
	Unknown, n (%)	3 (1.4)
Side[c]	Left/right, n (%)	105 (48.2)/113 (51.8)
Intrafractional motion management	Abdominal compression, n (%)	65 (29.8)
	Breath-hold, n (%)	43 (19.7)
	Gating, n (%)	22 (10.1)
	Tracking, n (%)	4 (1.8)
	Free breathing, n (%)	63 (28.9)
	-With 4D-CT, n	46
	- No or unknown 4D-CT, n	17
	Data on motion management unavailable, n (%)	21 (9.6)
	-With 4D-CT, %	19
	-No or unknown 4D-CT, %	2
GTV	Mean (95% CI), mL	39.9 (33.7-46.2)
PTV	Mean (95% CI), mL	87.4 (77.1-97.7)
BED10 PTV-D98	Mean (95% CI), Gy	65.5 (63.3-67.7)
BED10 PTV-D50[d]	Mean (95% CI), Gy	83.6 (80.7-86.5)
BED10 PTV-D2	Mean (95% CI), Gy	96.1 (92.2-100.1)
BED10 GTV-mean[d]	Mean (95% CI), Gy	88.7 (85.2-92.3)
BED10 GTV-D50[d]	Mean (95% CI), Gy	89.7 (86.0-93.3)

Abbreviations: BED10, biologically effective dose, $\alpha/\beta = 10$ Gy; CI, confidence interval; D2, dose to 2% of the volume; D50, median dose; D98, dose to 98% of the volume; GTV, gross tumor volume; NSCLC, nonsmall-cell lung cancer; PTV, planning target volume; SCC, squamous cell carcinoma; SCLC, small-cell lung cancer.

[a]Other primary tumors contributing to adenocarcinoma were unknown primary (n = 4), gastroesophageal (n = 2), and one breast cancer lesion which had been classified as an adenocarcinoma (n = 1).

[b]Other histologies include lesions with sarcoma, mixed type carcinoma, large cell carcinoma, thyroid (papillary) carcinoma, neuroendocrine carcinoma, thymic carcinoma, Merkel cell carcinoma, cholangiocellular carcinoma, prostate carcinoma, ovarian carcinoma, and extramedullary anaplastic plasmacytoma.

[c]Numbers include 22 bilateral lesions.

[d]Inclusion criterion was the prescribed dose by each treating center (BED10 >50 Gy). Due to the retrospective manner and different prescription methods of some centers the cohort included 3, 2, and 2 lesions which received a PTV-D50, GTV-mean, and GTV-D50 below 50 Gy (BED10), respectively.

Progression-free survival (PFS) and OS were calculated by using the Kaplan-Meier method. PFS was defined as the time from the end of the RT to any in- or out-of-field disease progression (according to Response Evaluation Criteria in Solid Tumors: RECIST 1.1) or death. For the PFS analysis, two analyses were performed: for the first model, we excluded patients with bilateral lesions (due to the

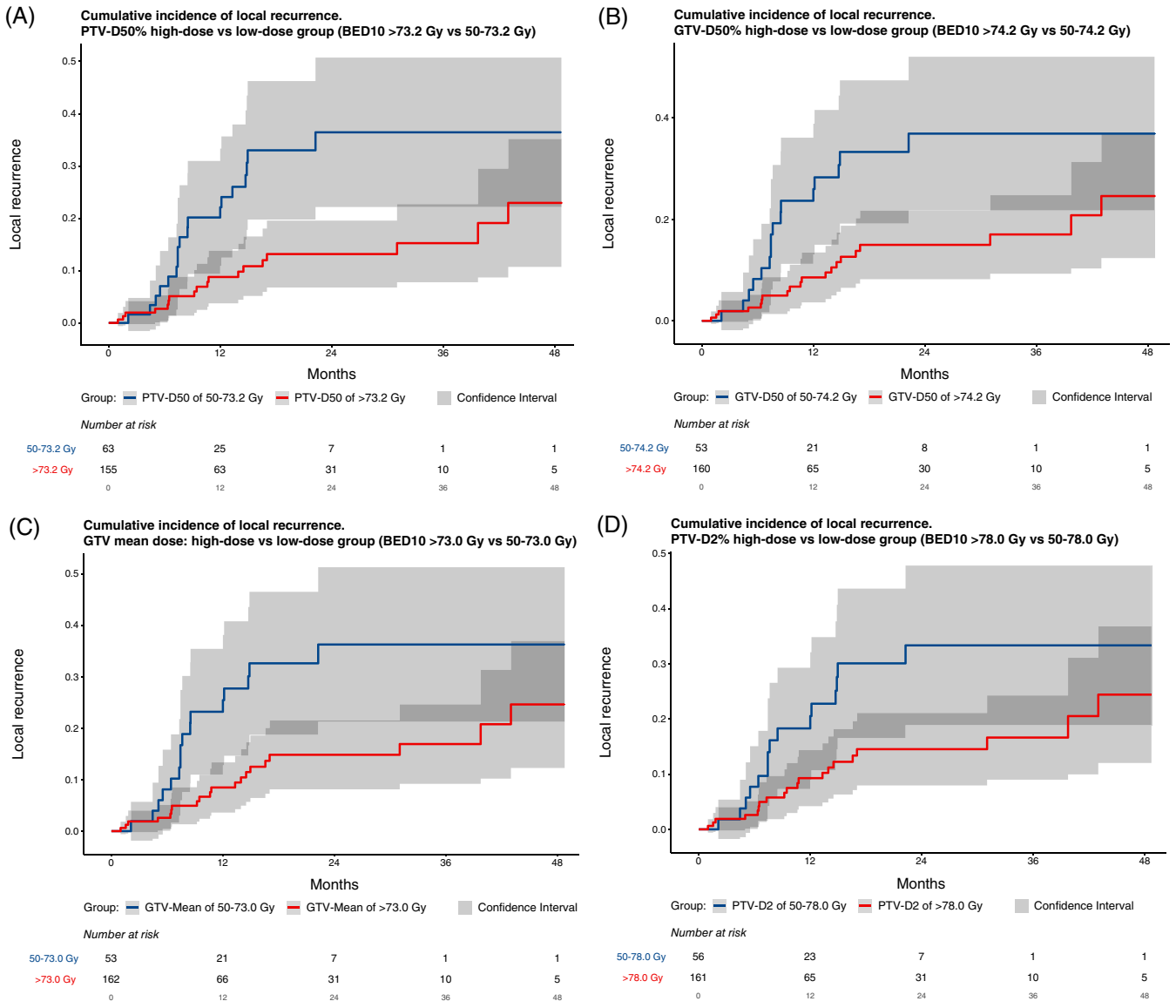

FIGURE 2 (A-D) Cumulative incidence of local recurrences using the optimized cut-points for the (A) PTV-D50% (BED10: 73.2 Gy; $P = .003$), the (B) GTV-D50% (BED10: 74.2 Gy; $P = .006$), the (C) GTV-mean (BED10: 73.0 Gy; $P = .007$), or the (D) PTV-D2% (BED10: 78.0 Gy; $P = .02$). In all cases, the 12- and 24 months recurrence rates for the higher doses were less than half the recurrence rate of the lower doses. For panels with additional graphs for informative censoring, see Figure S2a-d. Different numbers at risk are due to missing dosimetric information [Color figure can be viewed at wileyonlinelibrary.com]

guaranteed recurrence status; that is, all patients with subsequent bilateral lesions would be counted as having PFS events after the interval until the second lesion occurred), the second model includes patients with bilateral lesions. OS was defined as the interval from the end of RT to the day of death or censoring. For the OS analysis, patients with bilateral lesions were allowed, if the RT completion dates of both lesions were similar (ie, interval below 1 month/28 days).

Survival curves were truncated at 48 months for the regular figures; in the Supplementary Material, curves up to 60 months are shown. A landmark analysis was done to compare OS between patients with unilateral lesions who were alive at 12 months with or without local recurrence; patients with bilateral lesions were excluded for this analysis.

3 | RESULTS

In total, 232 patients with 260 adrenal lesions were treated with SBRT. Dose-volume parameters and/or LRR/survival data were unavailable for 42 lesions, the remaining 218 lesions in 196 patients (22 with bilateral SBRT) were included in this analysis (Figure 1). Characteristics of the irradiated lesions are detailed in Table 1; briefly, mean GTV of the treated lesions was 39.9 mL (95% CI: 33.7-46.2 mL), the largest histopathological subgroups were adenocarcinoma (n = 101 lesions, NSCLC: 81.2%, colorectal: 11.9%, other: 6.9%), small-cell lung cancer (n = 29 lesions, SCLC), and squamous cell carcinoma (SCC, n = 27 lesions, 88.9% NSCLC, 11.1% other). 61.5% of patients were irradiated with intrafraction motion

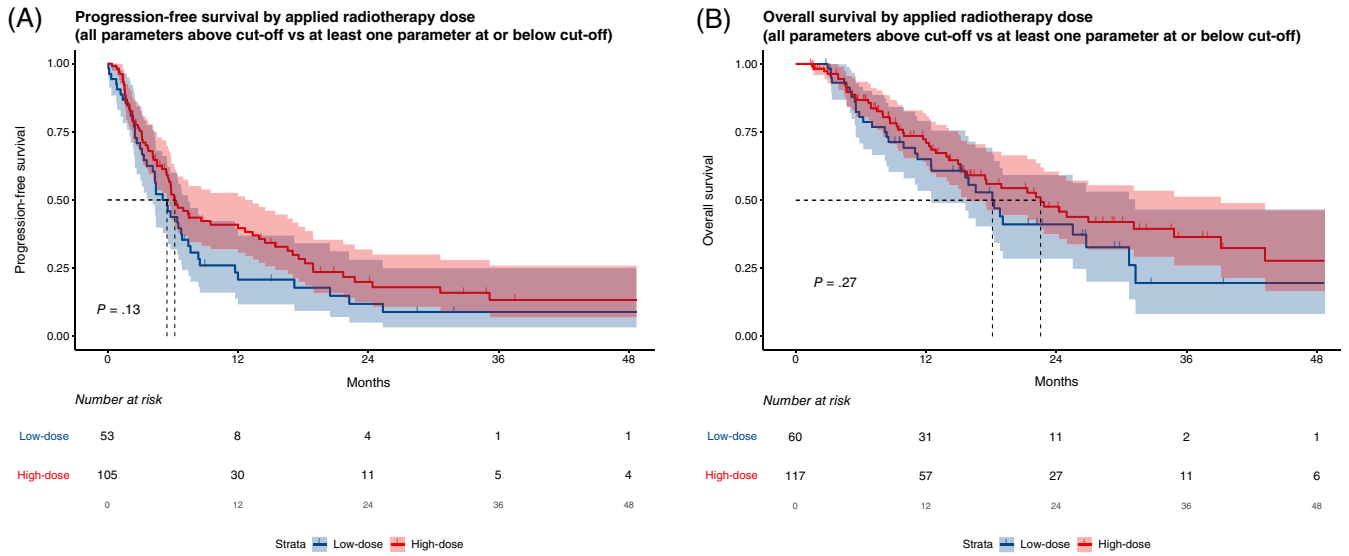

FIGURE 3 Kaplan-Meier panel for PFS (A) in patients whose lesions were irradiated with higher doses (ie, all significant cut-points surpassed), compared to patients with lesions which were irradiated with lower doses (median: 6.2 vs 5.5 months; $P = .13$). Patients with bilateral lesions were excluded for this model; however, results were robust when such patients were included (6.2 vs 5.2 months; $P = .12$, graph not shown). The Kaplan-Meier graph for OS is shown in (B). Aside from a numerical trend, we did not observe a significant difference between patients who surpassed all cut-points vs lower-dose patients (median: 22.5 vs 18.1 months; $P = .27$). Patients with missing PFS data (n = 13) and with at least one missing dosimetric dataset were excluded for this analysis [Color figure can be viewed at wileyonlinelibrary.com]

management, mostly abdominal compression, breath-hold, or gating. Out of the patients who were irradiated in free-breathing (including unknown), the majority had received a 4D-CT prior to RT; the remaining 19 patients (8.7%) were irradiated in free-breathing without 4D-CT. Distributions of prescribed doses are depicted in Figure S1.

We identified dose cut-points which separated two groups with statistically significant LRR (Gray's test) for the PTV-D50% (BED10: 73.2 Gy; $P = .003$; Figure 2A), the GTV-D50% (BED10: 74.2 Gy; $P = .006$; Figure 2B), the GTV-mean (BED10: 73.0 Gy; $P = .007$; Figure 2C), and the PTV-D2% (BED10: 78.0 Gy; $P = .02$; Figure 2D); no significant cut-off value could be identified for the PTV-D98% ($P = .06$). The corresponding cumulative LRR curves with additional graphs for competing risks (ie, death in patients without local recurrence) are shown in Figure S2a-d. We additionally compared lesions in which all significant parameters were above the cut-off values to those with at least one lower-dose parameter. This analysis also showed a significant difference ($P = .02$; Figure S3) but the separation of the curves was not more pronounced compared to the comparisons shown in Figure 2A-D.

Differences in LRR were also clinically relevant (12- and 24-months LRR more than doubled for all cut-points in Figure 2A-D that were not achieved).

Numerical improvements were also consistently observed in PFS and OS of patients who surpassed the cut-points; however, the difference was not significant for any of the tested cut-points. Curves for lesions which were irradiated with doses that surpassed all cut-points compared to those who missed at least one cut-point are shown in Figure 3A for PFS (median: 6.2 vs 5.5 months; $P = .13$), and in Figure 3B for OS (median: 22.5 vs 18.1 months; $P = .27$). Durable control (1 year or more) of irradiated metastases was associated with an improvement of OS in a 12-months landmark analysis ($P < .001$; Figure S4; bilateral lesions excluded).

Subgroup analyses for LRR were in line with the overall cohort for patients with adenocarcinoma lesions (n = 101 in 93 patients, Figure S5a-d), we observed significant differences for aforementioned cut-points in case of PTV-D50% ($P = .012$), GTV-D50% ($P = .012$), and GTV-mean ($P = .02$) resulted in significant improvements in LRR; the cut-point for the PTV-D2% was associated with a numerical improvement which was not statistically significant ($P = .09$). Additionally, a separate cut-point optimization was done for the adenocarcinoma subgroup. The difference to the initially identified cut-points was 5.6% (absolute difference: 4.1 Gy, 69.1 Gy vs 73.2 Gy (BED10)) for the PTV-D50%; all other differences were below 2%, detailed information is given in Table S1. The second largest subgroup were patients with small-cell lung cancer (SCLC; 29 lesions in 27 patients): we observed a significant improvement for the PTV-D50% cut-point ($P = .019$; Figure S6); all other aforementioned cut-points showed trends toward an improved LRR but those were not significant in the small subgroup. Due to the small number of lesions, we did not perform another separate cut-point optimization. In the third largest histopathological group, (SCC; 27 lesions in 23 patients), we did not observe any recurrences. Six patients in this group were treated with doses below the cut-off values.

For all lesions who had received doses above aforementioned cut-off values in the overall cohort, we analyzed if further dose increases would be associated with further improvements in LRR. We did not observe further statistical or numerical improvements in LRR for higher doses; as an example, Figure 4 shows the LRR for patients with PTV-D50% values of 73.2-85.9 Gy (BED10) compared to doses above 85.9 Gy ($P = .9$).

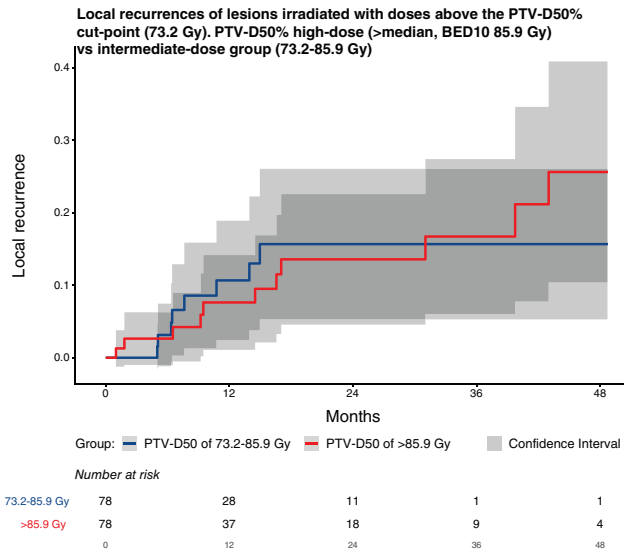

FIGURE 4 Cumulative incidence function for local recurrences of lesions which were irradiated with intermediate PTV-D50% doses (BED10: 73.2-85.9 Gy) compared to lesions which were irradiated with very high doses (>85.9 Gy); we did not observe a difference between the groups ($P = .9$). Further dose escalation steps were analyzed and none were associated with lower LRR if lesions were irradiated with doses which surpassed the cut-points detailed in Figure 2A-D [Color figure can be viewed at wileyonlinelibrary.com]

To evaluate if interactions with tumor size and localization (right-sided vs left-sided) may have confounded our results, we analyzed the following parameters:

1. We compared lesion sizes of metastases which were treated with doses above aforementioned GTV/PTV cut-off values vs patients treated with lower doses: This analysis showed no significant difference. There was, however, an imbalance between right-sided and left-sided lesions: Right-sided lesions were significantly more often treated with higher doses compared to left-sided lesions ($P < .05$ in all cases). As an example, the PTV-D50% high-dose group included 59.4% right-sided lesions compared to 50% in the lower-dose group and 51.8% in the overall cohort.
2. Due to this potential imbalance, we additionally calculated LRR in patients with right-sided vs left-sided lesions as well as larger vs smaller GTVs. Both analyses did not show an increased LRR in patients with left- or right-sided lesions and also no significant (or nonsignificant but numerically relevant) difference between larger and smaller lesions (Figure S7a,b).
3. Finally, multivariate Fine-Gray models for each dose-volume cut-point in the overall population with GTVs and localization as additional variables were calculated. None of the Fine-Gray models showed a significant association of GTV size or side of the lesion with LRR and all models confirmed the aforementioned significance of the univariate LRR models (hazard ratio [95% CI] and *P*-values as follows: PTV-D50%: 0.39 [0.2-0.75]; $P = .005$; GTV-D50%: 0.42 [0.21-0.82]; $P = .011$; GTV-mean: 0.41 [0.21-0.81]; $P = .01$; PTV-D2%: 0.47 [0.23-0.94]; $P = .033$).

4 | DISCUSSION

To the best of our knowledge, this is the largest analysis to determine dose-/volume cut-points using individual patient data for the treatment of adrenal metastases. It has been shown by three large studies that higher prescribed doses are associated with improved outcomes: In an Asian individual-patient analysis, which includes 75 patients, Zhao et al identified a prescription dose of ≥80 Gy (BED10) to be associated with an improved local control.[23] Detailed PTV/GTV dose-/volume data were not analyzed and local control was not corrected for competing risks.[39] The second study is the metaanalysis of case series published by Chen et al[15] which included 1006 patients; the authors observed that prescribed doses above 60, 80, and 100 Gy (BED10) resulted in an improved local control in the higher-dose groups[15]; however, they noted that confounding variables of the included studies were not consistently reported and could not be analyzed. Finally, Stumpf et al recently published a tumor control probability (TCP) model which incorporated data from 2008-2017; the authors estimated that a dose of 116.4 Gy (BED10) would lead to a 1-year local control of 95%[40]; furthermore, they noted that most underlying studies were small and potentially affected by competing risks. Data on histology were not incorporated and the largest underlying study[12] included 48 patients in whom two recurrences had been observed but only seven patients were alive after 2 years.

The strength of our analysis lies in the detailed dosimetric and volumetric information which were available for all included lesions. We identified cut-points which led to a highly significant separation according to the individual lesions' (or patient's) risk of recurrence. When cut-points for the PTV-D50% (73.2 Gy), the GTV-D50% (74.2 Gy), the GTV-mean (73.0 Gy), or the PTV-D2% (78.0 Gy) dose were surpassed, the risk of local recurrence during the patient's follow-up was significantly and clinically relevantly lower compared to the lower-dose group: Twelve- and 24-month LRR data showed that recurrence risks more than doubled in each analysis if aforementioned cut-points were not reached (see Figure 2A-D). Our database does not yet include information on local treatment of other metastases. Therefore, it is not surprising that we did not identify a significant difference in PFS and OS in patients who received doses surpassing the cut-points as many patients might have had untreated metastases aside from the adrenal lesion which limits the power to detect a PFS or OS difference based on dose escalation of just one metastasis. Nevertheless, we observed consistent numerical trends with regard to both endpoints (Figure 3A,B); additionally, sustained local control was associated with OS outcomes as demonstrated by the landmark analysis (Figure S4).

Our cut-points for PTV-D50%, GTV-D50%, and GTV-mean but not for PTV-D2% showed a significant separation of the LRR curves in the largest homogenous histopathological subgroup of patients with adenocarcinoma lesions. A separate optimization for the adenocarcinoma patient cohort resulted in minimal numerical differences compared to the overall cohort for most cut-points; only for the PTV-D50% the cut-point was lower in patients with adenocarcinoma lesions (BED10: 69.1 Gy vs 73.2 Gy; Table S1). This indicates that a

slightly lower PTV-D50% might be acceptable in this subgroup. Additionally, the (73.2 Gy) PTV-D50% cut-point was the only one which led to a significant separation of LRR curves in lesions with SCLC. Until further data become available for the small subgroups, our data indicate that it may be preferable to aim at the PTV-D50% cut-point of 73.2 Gy (BED10) for all adrenal metastases with the exception of adenocarcinoma which might be sufficiently treated with 69.1 Gy (BED10). Analyses of potentially confounding variables showed that neither GTV size, nor lesion side were associated with LRR in univariate models. Consequentially, multivariate models which included these factors confirmed the results from the univariate models.

Our cut-points are slightly lower compared to the cut-point of a prescribed dose of 80 Gy proposed by Zhao et al[23] which were not adjusted for competing risks and may therefore overestimate the recurrence risk.[39] Surprisingly, we could not identify any further dose-response effect in patients who had surpassed the cut-points for aforementioned PTV/GTV parameters. This is in contrast to some of the previously mentioned analyses[15,40] and might be explained by the limited power to detect a small difference in the LRR due to the limited OS of the population which leads to a high number of competing events. As an example: In the dataset of Casamassima et al,[12] which is the largest retrospective analysis underlying the TCP model by Stumpf et al,[40] only seven patients (14.6%) were at risk of local recurrence at 2 years. This was exactly in line with our dataset: There were 38 lesions at risk (14.6%), that is, controlled lesions in patients who were alive and uncensored at 2 years. This underscores the need for even larger datasets to actually detect which doses or approaches lead to long-term LC rates in potential long-term survivors.

Another limitation of our dataset is the low overall number of patients who received very high doses: 38 patients had a PTV-D50% of 100 Gy or more; out of these patients five had a local recurrence over time. Therefore, the power to detect a difference between high and very high dose escalation with our dataset was low.

Despite these shortcomings, our data clearly indicate a benefit of moderately escalated SBRT doses in patients with adrenal metastases. For all-comers, based on our data, we would suggest a PTV-D50% dose of 73.2 Gy (BED10); if possible without violating serial risk organ tolerances. In our study, this was achieved by using 50 Gy in 10 fractions, 37.5 Gy in three fractions, and 50 Gy in five fractions, among others (prescribed BED10: 75, 84.4, and 100 Gy, respectively). Patients with adenocarcinoma lesions were sufficiently treated with 69.1 Gy (BED10), which was achieved in our study by 40 Gy in five fractions (among others).

The wide variety of prescription patterns and doses in our study indicates that it will be important to obtain interinstitutional and intertechnology consistency in future prospective studies in the oligometastatic setting. A harmonization of planning, dose prescription, technological requirements and reporting is necessary and has already been published for example, lung metastases.[41] Such contouring and planning benchmarking is missing for adrenal metastases and is subject to further research. For SBRT in critical localizations in proximity to serial risk organs, further knowledge about detailed risk organ constraints and technological improvements such as advanced motion management strategies[30,42] may help to reach doses ensuring local control as found in this series.

5 | CONCLUSION

Moderate escalation of SBRT BED10 using cut-off values of 73.2, 74.2, 73.0, and 78 Gy for the PTV-D50%, the GTV-D50%, the GTV-mean, and the PTV-D2% lead to significant and clinically relevant improvements of the LRR. In adenocarcinoma lesions, the optimal cut-point for the PTV-D50% was slightly lower (69.1 Gy) with other values similar to the overall cohort. Further dose escalation was not associated with improvements of the LRR in our dataset. There was no significant direct association of dose escalation with PFS or OS; however, durable LC was significantly associated with an improvement in OS in a landmark analysis.

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CONFLICT OF INTEREST

Daniel Buergy reports personal fees from NB Capital ApS, personal fees from Nordic Biotech, personal fees from Siemens AG, personal fees from b.e. Imaging GmbH, outside the submitted work; Juliane Hörner-Rieber received speaker fees and travel reimbursement from ViewRay Inc, as well as travel reimbursement form IntraOP Medical and Elekta Instrument AB and grants from IntraOP Medical and Varian Medical Systems outside the submitted work; Florian Putz received research grants and speaker fees from Siemens Healthcare AG outside the submitted work; Laila König received speaker fees and travel reimbursement from Accuray and Novocure outside the submitted work; Klaus Henning Kahl is on the advisory board of Bristol Myers Squibb (BMS), MSD, and AstraZeneca; received travel and speakers fees from Varian, Elekta, Zeiss Meditec, Merck, Bristol Myers Squibb (BMS), AstraZeneca and fees from Medical Intelligence outside the submitted work. All the other authors reported no potential conflicts of interest.

AUTHOR CONTRIBUTIONS

Daniel Buergy and Judit Boda-Heggemann conceived the study, performed the main analysis and wrote the original draft and edited the final version after input of all authors. Matthias Guckenberger provided assistance in writing the protocol. Daniel Buergy conducted the analysis and retrieved the data. All other authors contributed data from their respective institutions and provided input for protocol generation. The work reported in the study has been performed by the authors, unless clearly specified in the text. All authors read and approved the article.

ETHICS STATEMENT

Patient and tumor characteristics, patterns of care and clinical outcomes were collected after institutional review board approval of the leading study center (Mannheim, 2018-853R-MA) and subsequent

ethics considerations in each center. Ethics approval was obtained according to local guidelines. Overall approval for the analysis was obtained in the study center Mannheim (2018-853R-MA). Informed consent was only obtained if required by local standards in line with recommendations of local ethics committees.

DATA AVAILABILITY STATEMENT

The data used and generated in this work will be available from the corresponding author upon request under ethical and data protection considerations and following approval of the lead institution on an individual basis.

ORCID

Daniel Buergy https://orcid.org/0000-0001-5913-3332
Judit Boda-Heggemann https://orcid.org/0000-0002-5831-0197

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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