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Stereotactic or conformal radiotherapy for adrenal metastases: Patient characteristics and outcomes in a multicenter analysis

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Abbreviations: 3DCRT/IMRT, highly conformal fractionated (>12) intensity-modulated radiotherapy; AKI, acute kidney injury; BED, biologically effective dose; CRA-LRR, competing risk-adjusted local recurrence rate; CT, computed tomography; CTCAE, Common Terminology Criteria for Adverse Events; D50, median dose; DEGRO, German Society for Radiation Oncology; Dmax, maximum dose; Dmean, average dose; FFLP, freedom from local progression; GTV, gross tumor volume; IGRT, image guided radiotherapy; KPS, Karnofsky performance status; LC, local control; OS, overall survival; Pall-RT, palliative radiotherapy; PFS, progression-free survival; PTV, planning target volume; SBRT, stereotactic body radiotherapy.

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Abstract

To report outcome (freedom from local progression [FFLP], overall survival [OS] and toxicity) after stereotactic, palliative or highly conformal fractionated (>12) radiotherapy (SBRT, Pall-RT, 3DCRT/IMRT) for adrenal metastases in a retrospective multicenter cohort within the framework of the German Society for Radiation Oncology (DEGRO). Adrenal metastases treated with SBRT (≤12 fractions, biologically effective dose [BED10] ≥ 50 Gy), 3DCRT/IMRT (>12 fractions, BED10 ≥ 50 Gy) or Pall-RT (BED10 < 50 Gy) were eligible for this analysis. In addition to unadjusted FFLP (Kaplan-Meier/log-rank), we calculated the competing-risk-adjusted local recurrence rate (CRA-LRR). Three hundred twenty-six patients with 366 metastases were included by 21 centers (median follow-up: 11.7 months). Treatment was SBRT, 3DCRT/IMRT and Pall-RT in 260, 27 and 79 cases, respectively. Most frequent primary tumors were non-small-cell lung cancer (NSCLC; 52.5%), SCLC (16.3%) and melanoma (6.7%). Unadjusted FFLP was higher after SBRT vs Pall-RT (P = .026) while numerical differences in CRA-LRR between groups did not reach statistical significance (1-year CRA-LRR: 13.8%, 17.4% and 27.7%). OS was longer after SBRT vs other groups (P < .05) and increased in patients with locally controlled metastases in a landmark analysis (P < .0001). Toxicity was mostly mild; notably, four cases of adrenal insufficiency occurred, two of which were likely caused by immunotherapy or tumor progression. Radiotherapy for adrenal metastases was associated with a mild toxicity profile in all groups and a favorable 1-year CRA-LRR after SBRT or 3DCRT/IMRT. One-year FFLP was associated with longer OS. Dose-response analyses for the dataset are underway.

KEYWORDS
adrenal, oligometastases, outcome, patterns of care, SBRT

1 | INTRODUCTION

Patients with oligometastatic cancer, which is defined by a limited number of metastases[1,2] may potentially reach long-term freedom of disease and overall survival (OS). OS for oligometastatic patients might be prolonged by an effective local treatment in addition to systemic therapy.[3-7] For stereotactic body radiation therapy (SBRT), biologically high radiation doses are delivered in a few fractions under high precision and generally with multidirectional steep dose gradients and high-precision patient setup.[8-12] Image-guided, three-dimensional conformal radiotherapy or intensity-modulated radiotherapy (IGRT, 3DCRT, IMRT) and/or SBRT can be delivered to metastatic sites as an individualized treatment. Results of randomized Phase II studies indicate an increased OS in patients who received local treatment using surgery, radiofrequency ablation, IMRT or SBRT.[3,5-7] Larger, well-powered studies are ongoing in the oligometastatic setting with varying cutoff values for the total number of metastases, ranging from up to three (NCT03862911) and up to five lesions (NCT02089100). Clinical outcomes of SBRT appear to differ between involved organ systems: SBRT of lung metastases achieves excellent 1-year local control

What's new?

When added to systemic therapy, does local treatment reduce recurrence or overall survival (OS) for patients with limited metastases? In this study, the authors found that, in patients with adrenal metastases, both stereotactic body radiotherapy (SBRT) and highly conformal, intensity-modulated radiotherapy (3DCRT/IMRT) were associated with a decreased local recurrence rate and a mild toxicity profile. Local control at 12 months was, in turn, associated with increased OS.

(LC)-rates of 90%,[13] whereas results appear worse for liver metastases with 1-year LC rates of 77%.[14]

Metastases to the adrenal glands can occur in various solid tumors, especially the lung, breast, gastric and renal cancer.[15] Adrenal metastases are symptomatic in approximately 4% of affected patients[15] requiring palliative local treatment modalities such as resection, invasive ablation or radiotherapy (RT), all with the risk of treatment-related toxicities, potentially compromising quality of life.[16-18] However, for isolated adrenal metastases, local therapy can also result in a long-term freedom of progression.[19] Surgical resection of adrenal metastases in the oligometastatic setting has been described in some series[20,21]; however, the evidence is limited and there is no consensus on the optimal local treatment approach.

SBRT of adrenal metastases has been evaluated by several groups in mostly monocentric and retrospective cohort studies with promising results.[16,22-33] Larger analyses include a retrospective database analysis conducted in Asian patients (n = 75) reporting 1-year LC rate of 83%.[34] Furthermore, multiple prospective and retrospective monocentric studies were included in a recent meta-analysis conducted by Chen et al, which reported a pooled 1-year LC rate of 82% with a strong association of prescribed doses and LC rates.[32]

We conducted this multicenter database analysis of patients with adrenal metastases treated with SBRT or fractionated highly conformal RT (3DCRT/IMRT) within the framework of the SBRT database initiative of the Working Group Radiosurgery and Stereotactic Radiotherapy of the German Society for Radiation Oncology (DEGRO). Patterns of care and outcomes by means of toxicity, LC and OS are detailed in this report.

2 | PATIENTS AND METHODS

2.1 | Patient characteristics, data collection and patterns of care

Data of a retrospective multicenter patient cohort with adrenal metastases irrespective of the primary cancer were analyzed. The selection criterion for this cohort was at least one adrenal metastasis treated by RT of any histologically proven solid tumor. For comparison of heterogeneous dose prescriptions 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.

Due to the multi-institutional, multi-platform and retrospective nature of the study, different strata based on prescribed dose and fractionation were defined as follows:

1. SBRT: $\leq$12 fractions, BED10 $\geq$ 50 Gy,
2. 3DCRT/IMRT: > 12 fractions, BED10 $\geq$ 50 Gy, and
3. Palliative RT (Pall-RT): any fractionation using low prescription doses (BED10 < 50 Gy).

Highly conformal RT planning and delivery approaches were mandatory in all arms.

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]

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). OS was defined as the interval from the end of RT to the day of death or censoring; survival curves were truncated at 60 months. Freedom from local progression (FFLP) was defined as the time from the end of the RT to the radiologically diagnosed local relapse (in-field and/or penumbra). We also calculated FFLP using the Kaplan-Meier method (unadjusted FFLP); however, due to the high number of cases with informative censoring (deaths without local relapse, that is, competing events), which were also unevenly distributed between the arms, the unadjusted Kaplan-Meier approach may be characterized by larger inaccuracy.[36,37] Therefore, we used a cumulative incidence function to calculate a competing risk-adjusted local recurrence rate (CRA-LRR) using Gray's test to compare groups.[38] The alpha level was set at .05. For the landmark analysis, we used a 12-months cut point.

2.3 | Toxicity

Acute toxicity (gastrointestinal tract and any other toxicity, including adrenal insufficiency) of patients was defined as toxicity occurring up to 90 days post-treatment, late toxicity as occurring after more than 90 days. We recorded toxicity grade 3/4 (Common Terminology Criteria for Adverse Events [CTCAE] V5.0[39]) and/or any toxicity which required treatment. Doses to the adrenal glands and organs at risk (average dose [Dmean] and median dose [D50] to the kidneys; maximum dose [Dmax] to stomach/duodenum, and Dmean to the liver) were collected only in case aforementioned toxicity criteria were met.

3 | RESULTS

3.1 | Patient/tumor characteristics and patterns of care

Data of 326 patients (36.2% female, mean ± SD age 64.8 ± 10.5 years) with 366 adrenal metastases treated between 2006 and 2019 were included from 21 German and Swiss centers (13 universities, 2 public and 6 private centers). The median follow-up interval was 11.7 (mean: 15.9) months. In case of exclusion of deceased patients, the median follow-up interval was 15.8 (mean: 20.3) months. The median number of patients and lesions per institution was 13 and 15, respectively. 260, 27 and 79 adrenal metastases met the criteria of SBRT, 3DCRT/IMRT and Pall-RT, respectively. Most frequent primary tumors were non-small-cell lung cancer (52.5%), small-cell lung cancer (16.3%) and melanoma (6.7%). At the time of RT, the median

TABLE 1 Patient and tumor characteristics of patients with adrenal metastases included in the database

Patient and tumor characteristics		All	SBRT	3DCRT /IMRT	Pall-RT
Lesions	n	366	260	27	79
Patients	n	326	232	26	68
Gender M/F	%	63.8/36.2	65.8/34.1	53.8/46.2	63.2/36.8
KPS	Median (range), %	90 (50-100)	90 (60-100)	90 (50-100)	90 (50-100)
	>80% (%)	47.2	44.8	53.8	52.9
	≤80% (%)	39.3	41.4	26.9	36.8
	Unknown (%)	13.5	13.8	19.2	10.3
Primary tumor	NSCLC, %	52.5	53.4	61.5	45.6
	SCLC, %	16.3	14.2	11.5	25
	Melanoma, %	6.7	6	3.8	10.3
	Colorectal, %	4.3	5.6	0	1.5
	HCC/CCC, %	3.4	3.9	3.8	1.5
	Other[a], %	16.9	16.8	19.2	16.2
Biopsy of adrenal metastasis	%	5.2	5.8	7.4	2.5
Systemic therapy	4 weeks prior/after RT, %	16.9	17.7	18.5	13.9
	Paused on RT days, %	10.4	8.1	0	21.5
	Continued during RT, %	3.6	3.1	7.4	3.8
Drugs continued during RT or only paused on RT days	Chemotherapy, %	19.6	20.7	0	20
	Targeted therapy, %	29.4	24.1	100	30
	Immunotherapy, %	47.1	51.7	0	45
	Combination, %	3.9	3.4	0	5
Interval from initial tumor diagnosis to adrenal metastasis	Months, median (quartiles, Q_1, Q_3)	9.8 (0.2-21.9)	9.9 (0.4-21.9)	12.8 (2.1-25.6)	8.6 (0-20.9)
Side	Left/right, %	55.2/44.8	50/50	74.1/25.9	65.8/34.2
Primary tumor controlled at time of RT	Yes/no, %	81.3/17.5	81/17.2	80.8/19.2	82.4/17.6
	Unknown, %	1.2	1.7	0	0
Number of metastases at the time of RT (including the adrenal lesion), %	1 (adrenal only)	32.8	36.2	19.2	26.5
	2-3	23.0	24.1	23.1	19.1
	4-5	10.1	6.9	11.5	20.6
	>5	24.5	22.0	26.9	32.4
	Unknown	9.5	10.8	19.2	1.5
Number of organ sites with metastases at the time of RT (including the adrenal site), %	1 (adrenal only)	33.1	36.6	19.2	26.5
	2-3	43.3	41.8	53.8	44.1
	4-5	11.7	9.5	7.7	20.6
	>5	2.8	1.3	0	8.8
	Unknown	9.2	10.8	19.2	0
Adrenal metastasis symptomatic?	Yes/no	7.1/89.3	4.3/91.8	15.4/73.1	13.2/86.8
	Unknown	3.7	3.9	11.5	0

Abbreviations: 3DCRT/IMRT, highly conformal RT with >12 fractions and a BED10 ≥50 Gy; CCC, cholangiocellular carcinoma; HCC, hepatocellular carcinoma; KPS, Karnofsky performance status; NSCLC, non-small-cell lung cancer; Pall-RT, palliative radiotherapy with a BED10 ≤50 Gy; RT, radiotherapy; SBRT, stereotactic body radiotherapy using ≤12 fractions and a BED10 of ≥50 Gy; SCLC, small-cell lung cancer.

[a]Other tumors include breast cancer, renal cell carcinoma, prostate carcinoma, sarcoma, gastric cancer, malignant thymoma, Merkel cell carcinoma, urethral carcinoma, ovarian cancer, thyroid carcinoma, squamous cell skin cancer, cancer of unknown primary, esophageal carcinoma and anaplastic extramedullary plasmacytoma.

Karnofsky performance status (KPS) was 90% (range, 50%-100%) with no clinically relevant or statistically significant differences between the three groups (Table 1).

Biopsies of the adrenal lesions had been performed in 5.2%; systemic therapy had been administered prior to RT in 30.9% of patients, consisting of 16.9% with a pause of more than 4 weeks prior and after RT, 10.4% with a shorter break and 3.6% with concurrent treatment on RT days. In cases with no treatment interruption or only short interruptions, most patients had received immunotherapy (47.1%; mostly immune checkpoint inhibitors; one patient had received interleukin-2), followed by targeted agents (29.4%), chemotherapy (19.6%) and combinations (3.9%).

Irradiated lesions were more often right-sided in the SBRT group compared to both other groups (both $P < .05$). Side distribution did not differ significantly between the 3DCRT/IMRT group and the Pall-RT group. Bilateral RT was performed in 40 patients out of whom 28, 1 and 11 were in the SBRT, 3DCRT/IMRT and Pall-RT groups, respectively.

At the time of RT, the primary tumor was controlled in 81.3% of patients. The treated adrenal metastasis was the only metastatic site in 32.8% of the patients, 23.0% of patients had an oligometastatic situation with 2 to 3 lesions, 10.1% of patients had four to five lesions in total and 24.5% of patients had more than five lesions (9.5% unknown). Patients who had received SBRT were more likely to have no other metastatic lesions in total compared to the other strata combined ($P = .032$; Table 1).

Lesions were more often symptomatic in the Pall-RT group and in the 3DCRT/IMRT group compared to the SBRT group (both $P < .05$; Table 1).

The median time interval between the diagnosis of the adrenal metastasis and the initiation of RT was 3.5 months (mean: 7.7 months), without relevant or significant differences between the three subgroups. Imaging prior to RT was performed with computed tomography (CT) or positron emission tomography CT scans in most cases (Table 2).

Immobilization for RT positioning was performed using a vacuum mold, a breast board or a wing step breast board in 54.9%, 21.3% and 5.5% of lesions, respectively. Multiple techniques were used in 14.8% of patients (unknown in 0.5%; no immobilization was used in 3% of lesions). Daily IGRT was mostly performed using cone-beam CT (77.3%) followed by stereoscopic kilovoltage imaging (16.1%), and megavoltage fan-beam CT (3%); all other modalities taken together were used in 3.3% of patients (unknown in 0.3%). Any kind of motion management was applied in 59.8% of patients (unknown: 9.6%; free-breathing in 30.6%). If motion management was applied, abdominal compression was preferred (24.9%), followed by breath-hold techniques (22.7%), gating (10.4%) and tracking (1.9%; Table 2).

The mean gross tumor volume (GTV) size was 49.8 mL (median: 24.8 mL) resulting in an average planning target volume (PTV) size of 103.7 mL (median: 64.6 mL) with safety margins depending on institutional protocols (quartiles and parameters for each group are shown in Table 2). The GTV size was smaller in the SBRT group compared to the other groups combined ($P < .05$ for SBRT vs 3DCRT/IMRT and Pall-RT; there were no further significant between-group differences).

The most common fractionation schedules were 50 Gy in 10 fractions (19.7%), 25 Gy in 5 fractions (7.7%), 35 Gy in 5 fractions (7.4%) and 40 Gy in 5 fractions (6.6%); multiple other dosing regimens were used in the rest of patients (58.7%; see Table 2 for subgroups).

The mean prescription BED10 to the PTV was 64.2 Gy (±18.9 Gy); the mean PTV-D98 (BED10) was 59.8 Gy (±20 Gy), the mean PTV-D50 was 76.3 Gy (±29.7 Gy). The mean PTV-D2 was 88 Gy (±37.4 Gy) and the average GTV dose (GTVmean, BED10) was 81.4 Gy (±34.2 Gy).

3.2 | Local control

The median unadjusted FFLP for all patients was 39.7 months. The proportions of patients who were free from local recurrence after 12 months for SBRT, 3DCRT/IMRT and Pall-RT were 80.8%, 60.6% and 57.7%, respectively (Supplementary Figure S1); after SBRT, FFLP was significantly higher compared to Pall-RT ($P = .026$). No statistically significant difference in FFLP was observed after 3DCRT/IMRT compared to SBRT or after 3DCRT/IMRT compared to Pall-RT (both $P > .05$).

CRA-LRR was numerically higher after Pall-RT but the difference was not statistically significant in the adjusted model ($P = .140$ for SBRT vs Pall-RT); additionally, there was no significant difference between the other groups (both comparisons: $P > .05$). Numerically, the 12-months rate of local recurrences for the whole cohort was 17.7%. In the subgroups, CRA-LRR was 13.8%, 17.4% and 27.7% after SBRT, 3DCRT/IMRT and Pall-RT, respectively (Figure 1A). After 24 months, the CRA-LRR was 27.0% for the overall dataset and 24.5%, 21.7% and 35.9% after SBRT, 3DCRT/IMRT and Pall-RT, respectively. Further details on deaths without local recurrences and confidence intervals of the cumulative incidence model are shown in a multiple panel analysis in Figure 1B for each stratum.

3.3 | Progression-free survival

The median PFS after SBRT, 3DCRT/IMRT and Pall-RT was 5.9, 4.1 and 3.7 months, respectively. After 12 months, the PFS rate was 30.9%, 24.3% and 16.5% after SBRT, 3DCRT/IMRT and Pall-RT, respectively, the 24-months values were 16.1%, 19.5% and 5.9% (Figure 2).

The SBRT group had a significantly longer PFS compared to the Pall-RT group ($P = .0019$). There was no significant difference between the 3DCRT/IMRT group and the Pall-RT group; furthermore, there was no significant difference in PFS between the SBRT group and the 3DCRT/IMRT group (both $P > .05$).

3.4 | Overall survival

The median OS rates after SBRT, 3DCRT/IMRT and Pall-RT were 19.1, 5.7 and 17.1 months; the 12-month OS rates were 67.1%,

TABLE 2 Treatment characteristics of lesions included in the dataset

RT characteristics		All	SBRT	3DCRT/IMRT	Pall-RT
Interval between diagnosis adrenal metastasis to RT-initiation	Months, median (quartiles, Q_1, Q_3)	3.5 (1.3-9.1)	3.4 (1.3-9.1)	5.5 (1.5-9.0)	3.4 (1.4-9.1)
Pre-SBRT diagnostic modality in addition to planning CT (%)	None	1.1	1.2	0	1.3
	CT (without other modalities)	42.3	43.5	33.3	41.8
	MRI (±CT)	7.7	6.5	14.8	8.9
	PET (±other modalities)	40.4	38.8	33.3	48.1
	Unknown	8.5	10.0	18.5	0
4D-CT	Yes/no (%)	65.8/33.1	67.3/31.5	51.9/48.1	65.8/32.9
	Unknown (%)	1.1	1.2	0	1.3
Motion management (%)	No management/free breathing	30.6	28.5	29.6	38
	Abdominal compression	24.9	26.2	29.6	19
	Breath-hold	22.7	26.5	29.6	7.6
	Gating	10.4	9.2	0	17.7
	Tracking	1.9	1.5	0	3.8
	Unknown	9.6	8.1	11.1	13.9
Most common fractionation schedules/fraction count x single dose, (%)	Most common (%)	10 × 5 Gy (19.7)	10 × 5 Gy (27.7)	13 × 3 Gy (51.9)	5 × 5 Gy (35.4)
	2nd (%)	5 × 5 Gy (7.7)	5 × 7 Gy (10.4)	13 × 4 Gy (14.8)	5 × 6 Gy (29.1)
	3rd (%)	5 × 7 Gy (7.4)	5 × 8 Gy (9.2)	15 × 3 Gy (11.1)	5 × 4 Gy (6.3)
	4th (%)	5 × 8 Gy (6.6)	12 × 4 Gy (8.1)	14 × 3 /15 × 4 Gy (each: 7.4)	6 × 5 Gy (5.1)
	Further regimens (%)	58.7	44.6	7.4	24.1
GTV	Median in mL (quartiles, Q_1, Q_3)	24.8 (12.6-51.3)	22.9 (12.3-46.0)	51.1 (27.5-164.9)	30.9 (10.8-57.0)
PTV		64.4 (39.4-116.5)	60.3 (38.3-102.7)	116.3 (63.1-206.1)	71.9 (40.7-132.7)
Prescribed dose (BED10)	Mean ± SD, Gy	64.2 ± 18.9	72 ± 15.6	58.9 ± 11.1	40.4 ± 6.5
BED10 PTV D98		59.8 ± 20	66.9 ± 18.5	47.2 ± 10.2	40.8 ± 1 0
BED10 PTV D50		76.3 ± 29.7	86.4 ± 29.7	54.2 ± 11.8	51.8 ± 12.6
BED10 PTV D2		88 ± 37.4	99.4 ± 37.6	60 ± 17.6	61 ± 17.6
BED10 GTV mean		81.4 ± 34.2	91.6 ± 35	56.1 ± 13.7	57.8 ± 16.1

Abbreviations: 3DCRT/IMRT, highly conformal RT using >12 fractions and a BED10 ≥50 Gy; BED10, biologically effective dose, α/β = 10 Gy; D2, dose to 2% of the volume; D98, dose to 98% of the volume; D50, median dose; GTV, gross tumor volume; Pall-RT, palliative radiotherapy with a BED10 ≤50 Gy; PTV, planning target volume; RT, radiotherapy; SBRT, stereotactic body radiotherapy using ≤12 fractions and a BED10 of ≥50 Gy.

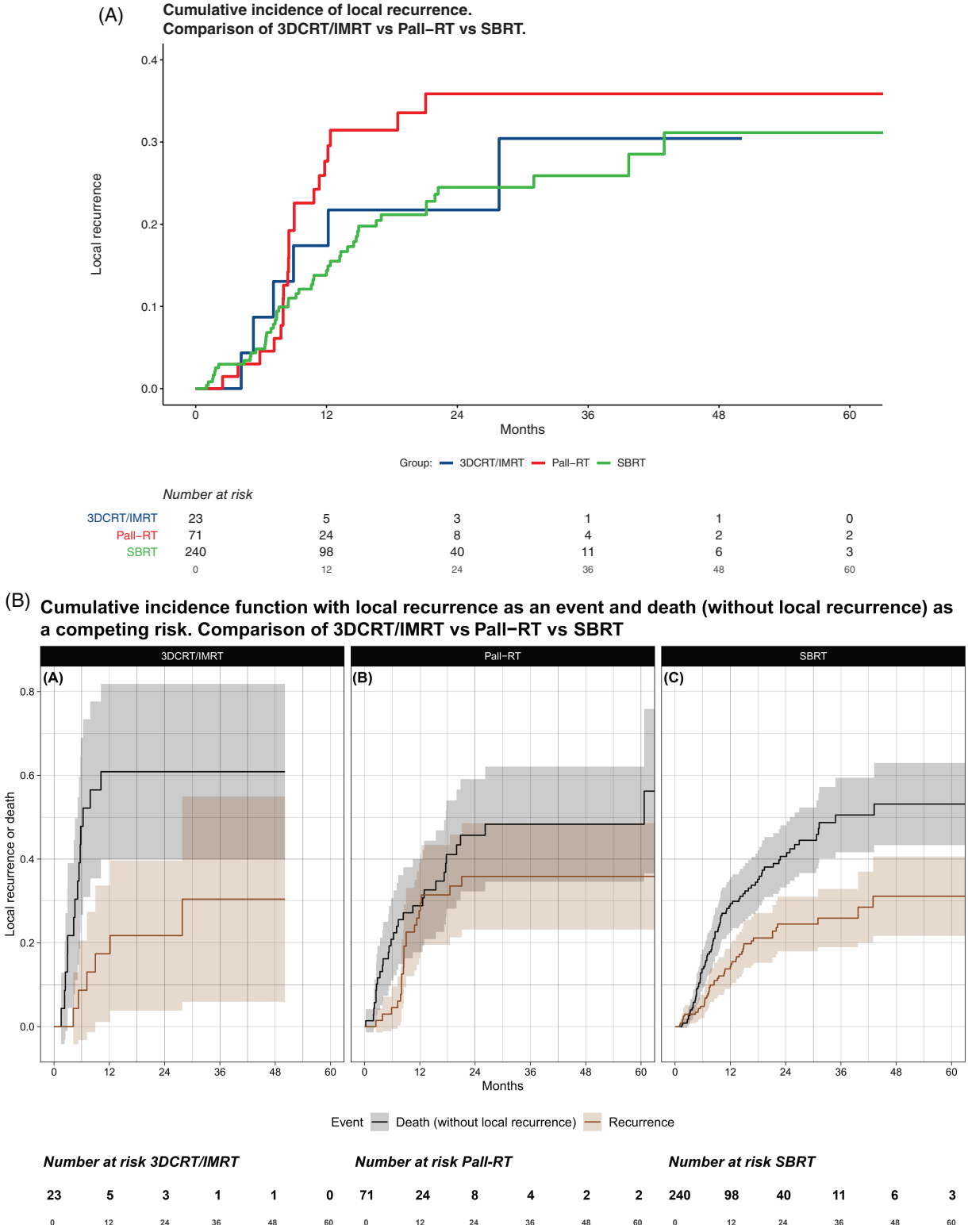

FIGURE 1 A, Cumulative incidence function of local recurrences corrected for competitive events (not shown). 3DCRT/IMRT (blue), Pall-RT (red) and SBRT (green). The differences between the groups were not significant (Gray's test; all $P > .05$). Interestingly, the Kaplan-Meier model which is not corrected for competitive events showed a significant difference between the SBRT group and the Pall-RT group (Log-rank, $P = .026$; Supplementary Figure S1). B, Cumulative incidence function as described in A; however, this figure includes curves for competitive events, depicts the groups in multiple panels (A-C) and shows the 95% confidence intervals; the comparison of competitive events between the groups showed that in the 3DCRT/IMRT group, deaths without local recurrences occurred significantly more frequently compared to the SBRT group (Gray's test; $P = .027$) [Color figure can be viewed at wileyonlinelibrary.com]

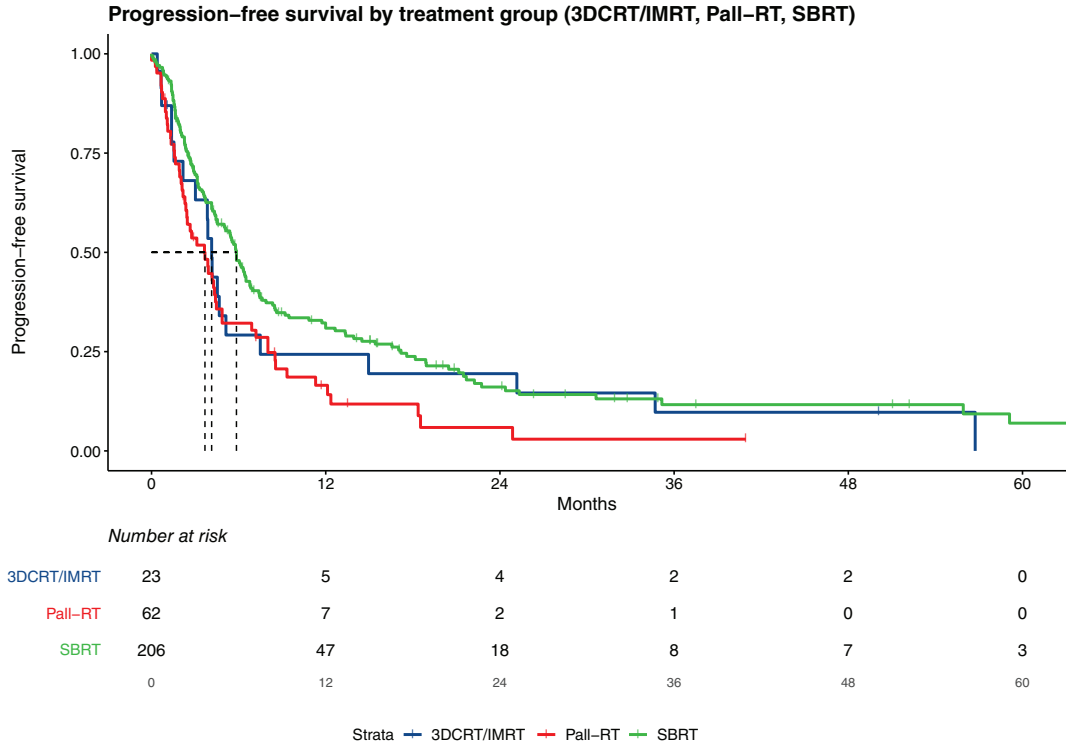

FIGURE 2 This figure shows progression-free survival (PFS) curves for 3DCRT/IMRT (blue), Pall-RT (red) and SBRT (green); differences were significant for the comparison of the SBRT group compared to the Pall-RT group (P = .0019) [Color figure can be viewed at wileyonlinelibrary.com]

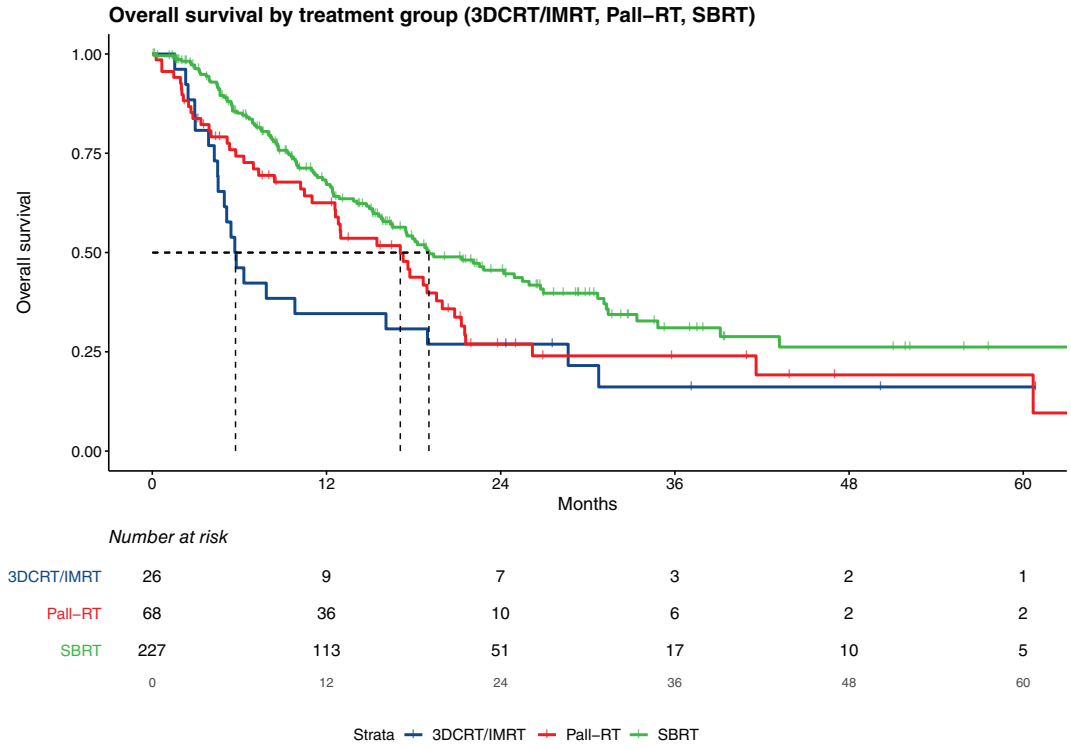

FIGURE 3 Overall survival (OS) curves for 3DCRT/IMRT (blue), Pall-RT (red) and SBRT (green) are shown in this figure. Differences between groups are significant for the comparison of SBRT vs Pall-RT (P = .041) and also for the comparison of SBRT vs 3DCRT/IMRT (P = .0028) but not for the difference of 3DCRT/IMRT vs Pall-RT. Details on direct comparisons between the groups are shown in Supplementary Figures S2-S4 [Color figure can be viewed at wileyonlinelibrary.com]

34.6% and 62.5%, and the 24-month OS rates were 45.6%, 26.9% and 27.0% for SBRT, 3DCRT/IMRT and Pall-RT, respectively (Figure 3). Differences between groups were significant for the comparison of SBRT v. Pall-RT (P = .041; Supplementary Figure S2) and for SBRT v. 3DCRT/IMRT (P = .0028; Supplementary Figure S3); no significant difference was observed between the 3DCRT/IMRT group and the Pall-RT group (Supplementary Figure S4).

3.5 | Univariate associations of other factors with FFLP and survival

We did not observe a difference between right-sided or left-sided lesions in terms of FFLP or OS (both P > .05). Patients who had no other metastases aside from the adrenal lesion showed a longer OS and a longer PFS compared to patients with more metastases (both P < .05). Data on local treatment of metastases other than the adrenal lesion were not available; however, patients with ≤3 lesions in total (including the treated lesion) showed no significant difference in terms of OS but there was an improved PFS compared to the other patients; the same was true for patients who had only up to three organs affected by metastases (irrespective of the number of metastases in each organ). Patients with ≤5 lesions did not show an improvement in OS or PFS compared to those with more lesions; again, patients with up to five affected organ systems did not show an OS or PFS benefit compared to patients with more organ systems affected at the time of RT. Patients with symptomatic adrenal metastases had a worse OS compared to asymptomatic patients (P = .007; median: 18.3 vs 9.9 months).

Finally, a landmark analysis was performed at 12 months to compare OS outcomes of patients who were alive at 12 months with or without local recurrence. Patients with a locally controlled adrenal metastasis at 12 months had a significantly longer OS compared to patients whose adrenal metastasis was not locally controlled at 12 months (P < .0001; median OS: 78.1 vs 19.1 months; see Figure 4).

3.6 | Specific toxicity—adrenal insufficiency

Four cases with adrenal insufficiency occurred out of which two were observed in patients after unilateral treatment and two were observed after bilateral treatment. A case-by-case analysis was performed for all affected patients: The first patient required hormone replacement

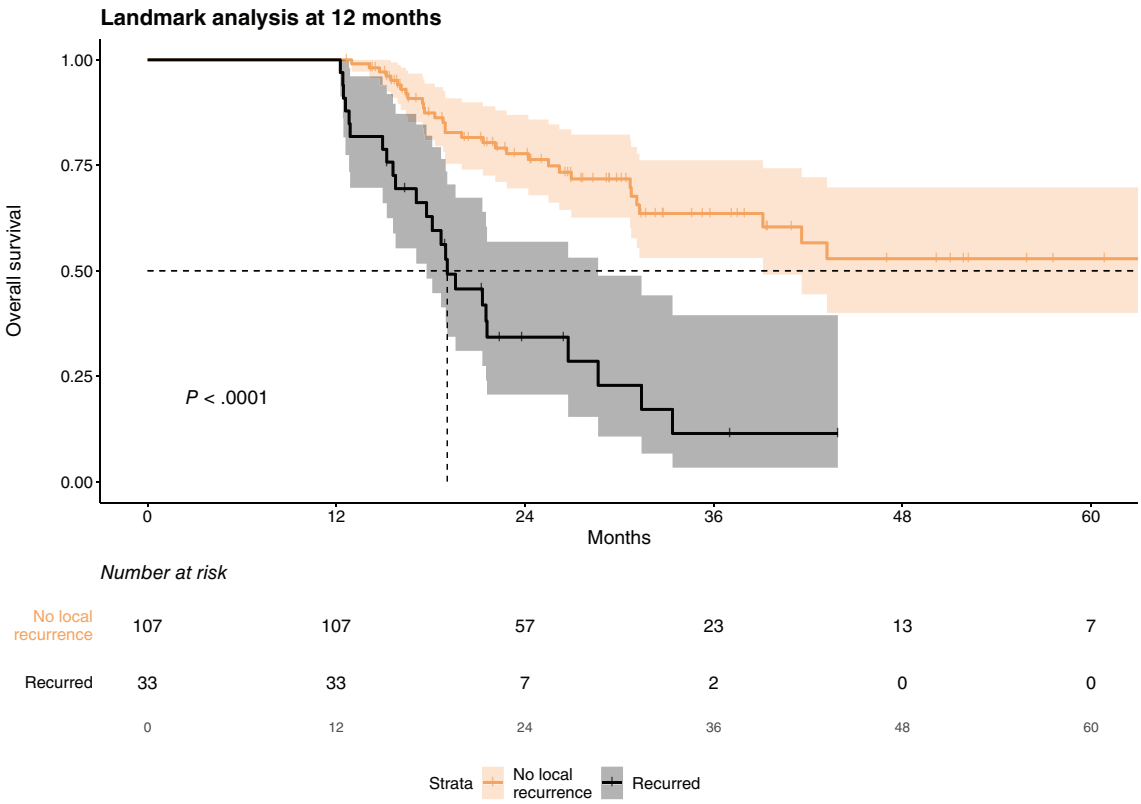

FIGURE 4 This figure shows a landmark analysis of the whole patient cohort for the comparison of patients who developed a local recurrence during the first year of follow-up vs patients who were alive at 1 year but remained locally controlled. The difference between the curves was significant (P < .0001), indicating that in our cohort, occurrence of a local recurrence during the first year of follow-up was associated with a worse OS. Patients with bilateral lesions were included in this analysis using the first lesion which was mentioned by the referring center as a reference lesion and censoring the contralateral site; the analysis was repeated after exclusion of all patients with bilateral lesions with similar results and similar between-group differences (P < .0001) [Color figure can be viewed at wileyonlinelibrary.com]

therapy due to late-onset adrenal insufficiency 10 months after bilateral RT; he was in the Pall-RT group and had received moderate RT doses to both adrenal glands (25 Gy in five fractions; PTV-D2(BED10) was 48.7 and 49.5 Gy for right- and left-sided RT, respectively). The second patient with adrenal insufficiency after bilateral RT experienced acute onset of symptoms. He had received RT with a PTV-D2 (BED10), right and left: 116.4 and 101.6 Gy, respectively; he required hormone substitution until death 10 months after RT (unknown reason; however, diffuse distant progression had occurred 1 month post-RT.

Two further cases were noted after unilateral RT; both happened in conjunction with systemic therapy: The first patient had a PTV-D2(BED10) of 38.1 Gy concurrently with interleukin-2 for metastatic melanoma. A mild adrenal insufficiency occurred 1 month after RT; it is unclear if this was primarily caused by one-sided RT, or happened as a side effect of interleukin-2 [40] or if an immune response was triggered by the combination of RT and immune therapy.

The second patient with an adrenal insufficiency after unilateral RT had received nivolumab due to metastatic kidney cancer. Nivolumab had to be stopped 2 months prior to RT due to immune-related colitis (Grade 3) which was treated with corticosteroids; tumor treatment was switched to cabozantinib (administered continuously during RT). Although bilateral adrenal metastases were present, only the right side was planned for treatment with a PTV-D2(BED10) of 77.9 Gy. Shortly after treatment was initiated acute kidney injury (AKI) and hormone dysfunction were diagnosed, presumably caused by discontinuation of corticosteroids prior to symptom onset. The patient was readmitted 10 days after completion of RT with another episode of AKI and Addison's crisis; he died 1 month later due to pneumonia, ascites, AKI and sepsis. Although an RT-related toxicity cannot be ruled out, the likelihood of an immunotherapy-related side effect[41] and/or a tumor-triggered deterioration was deemed more likely.

3.7 | Acute and chronic gastrointestinal and other toxicity

Acute gastrointestinal toxicity (≥2° or in need of therapy) occurred in a range of 2 to 53 days post-RT and was rare: nausea and vomiting requiring antiemetic therapy, but no hospital admission, occurred in 4.6% (n = 15) of patients. One case with a duodenal stenosis and pain (Grade 3) was observed; the patient had tumor infiltration of the retroperitoneal plexus and onset of symptoms was only 1 month after SBRT; therefore, tumor-related symptoms were deemed more likely although RT-related toxicity could not be ruled out. Fatigue was observed in 9.8% of patients. Electrolyte imbalances in patients without proven adrenal insufficiency were rare (<1%; n = 1 hyperkalemia, n = 1 hyponatremic dehydration).

One gastric ulceration occurred 6 months after RT in a patient who had received a Dmax of 31 Gy in 5 fractions to the stomach; other than that, no Grade 2 late gastrointestinal toxicity was reported. Flank pain occurred in <1% of the patients. No other (eg, hepatic, renal or skin) toxicities were reported.

4 | DISCUSSION

To the best of our knowledge, this is the largest retrospective multicenter study on the radiotherapeutic treatment of adrenal metastases which has been conducted to date. This patterns-of-care analysis showed a wide range of fractionation schedules for RT treatment of adrenal metastases. Most patients were treated with SBRT which required a BED10 of at least 50 Gy in 12 fractions or less.[9] Patients with symptomatic lesions and patients with larger lesions were preferentially treated with lower "palliative" doses (Pall-RT group) or with more than 12 fractions (3DCRT/IMRT group); likewise, patients who were treated with SBRT were more likely to have a solitary or a right-sided lesion. Taken together, baseline factors indicated an imbalance between the SBRT stratum compared to 3DCRT/IMRT- and Pall-RT strata with SBRT patients having a more favorable risk profile. Furthermore, there was a lack of standardization which is most likely explained by the very limited evidence about best-practice radiotherapy for adrenal metastases and strongly indicates the need for increased efforts into retrospective and especially prospective studies.

The risk of death without local recurrence was also unevenly distributed between the arms with an increased risk after 3DCRT/IMRT compared to SBRT. In all strata, the risk of death without local recurrence was numerically more frequent than local recurrence events; therefore, the unadjusted (Kaplan-Meier) LC estimate in this setting was considered inaccurate.[36,37] Despite this assumption, we decided to report on both the adjusted and the unadjusted numbers. This was done to facilitate comparability with other studies which mostly used unadjusted values.[30,34,42]

The unadjusted LC differed between the arms and was in line with the two other larger datasets: after prescribed doses of 100, 80 and 60 Gy (BED10), Chen et al[32] found in their meta-analysis 1-year LC rates of 92.9%, 84.8% and 70.5%; Zhao et al[34] calculated an unadjusted 1-year LC estimate of 83.8% after an average BED10 of 79.6 Gy. In our cohort, the unadjusted 1-year FFLP-estimates were 80.8%, 60.6% and 57.7%, after average prescribed BED10 doses of 72.0 Gy (SBRT), 58.9 Gy (3DCRT/IMRT) and 40.4 Gy (Pall-RT), respectively. As expected, the adjusted recurrence rates were considerably higher with CRA-LRR of 13.8%, 17.4% and 27.7% in the SBRT, 3DCRT/IMRT and Pall-RT groups, respectively. The lack of statistical significance may be explained by several factors: despite the size of the overall cohort, patient numbers in the subgroups of Pall-RT and 3DCRT/IMRT were limited and statistical differences in FFLP might have been obscured by differences in histology, lesion size and systemic treatments. Furthermore, the minimum BED10 in the SBRT group was 50 Gy, a dose which is well below the BED10 of 100 Gy which is typically considered ablative, for example, in lung cancer which was the largest subgroup.[43]

Although there was a numerical difference between the groups, differences in CRA-LRR did not reach statistical significance. This may be explained by confounders such as distribution of radiosensitive tumors or our dataset might have been underpowered; finally, our cutoff values to define SBRT and/or 3DCRT/IMRT may be lower than the dose that is required to achieve durable tumor control. Dosimetric analyses of the dataset are ongoing with preliminary results indicating that dose escalation was associated with LC in this cohort albeit at higher cutoff values.

Additionally, dose coverage and prescription patterns differed between centers. More detailed subgroup analyzes about the impact of prescription patterns, dose coverage and higher dose escalation in the SBRT group are ongoing.

PFS data in our study showed improved outcomes after SBRT compared to Pall-RT; OS was also longer after SBRT compared to both other groups; it is likely that both observations were partially explained by aforementioned imbalances. We observed a strong association between FFLP at 12 months and OS in a landmark analysis, indicating that long-term FFLP was also associated with OS. Furthermore, improved OS and PFS outcomes were observed in patients who had only one lesion (or one affected organ) compared to those with more metastatic lesions or sites. Patients with ≤3 lesions had an improved PFS compared to other patients but not an improved OS. However, we did not observe better outcomes in patients with ≤5 lesions compared to patients with multiple metastases. Unfortunately, our analysis on oligometastatic patients does not yet include treatment data on lesions other than the adrenal sites; therefore, the informative value of the comparisons is limited. As shown by the landmark analysis, patients who were free from local recurrences and alive after 1 year had a longer OS compared to patients who were alive but not free from local failures. This indicates that LC might be associated with OS in this setting; however, such an analysis cannot distinguish between treatment effects or effects caused by confounding factors. Most recently, data from the long-term analysis of the SABR-COMET Phase II trial were published. The results suggest that SBRT for oligometastatic solid tumors might not only result in an improved PFS but is also associated with an OS benefit.[44]

In our study, gastrointestinal toxicities were mild and rare. Adrenal insufficiency was rare; however, occurred after relatively low doses (25 Gy in five fractions). Cutoff doses could not be determined due to the limited number of patients at risk. As indicated by surgical series, adrenal function might recover if 15% to 30% of healthy tissue is left after adrenalectomy.[45] Nevertheless, even unilateral adrenalectomy was associated with adrenal insufficiency in 22% of cases.[46] The risk of adrenal insufficiency after unilateral treatment in our study was low and possibly associated with concomitant medication. Nevertheless, considering the results of surgical series and our data, all patients should be informed about the risk of adrenal insufficiency and laboratory screening should be performed during follow-up.[46]

To sum up, both unilateral and bilateral RT of the adrenal glands is associated with acceptable rates of adrenal insufficiency, especially considering that untreated bilateral adrenal metastases are also associated with a 3% to 8% risk of adrenal insufficiency.[47]

Major limitations of our study are the retrospective approach and the inhomogeneity of the cohort in terms of RT approaches and tumors.

5 | CONCLUSION

Adrenal RT was associated with an acceptable FFLP in all arms and a favorable FFLP after SBRT. Aside from sporadic cases of adrenal insufficiency, toxicity was generally mild. Follow-up visits should include monitoring for adrenal insufficiency and patients should be informed about the potential risk. Solitary adrenal metastases and 1-year FFLP were associated with a longer OS. Dose-response analyses for the dataset are underway.

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CONFLICT OF INTEREST

None of the authors had direct conflicts 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 outside the submitted work; Florian Putz received research grants and speaker fees from Siemens Healthcare AG outside the submitted work; Matthias Guckenberger received grants from Viewray, Varian and AstraZeneca outside the submitted work; Klaus Henning Kahl received travel and speakers fees from Varian, Elekta, Zeiss Meditec MDS, Bristol Myers Squibb, Astra Zeneca and Medical Intelligence outside the submitted work. All the other authors reported no potential conflicts of interest.

DATA AVAILABILITY STATEMENT

Data used and generated in this work are available from the corresponding author upon reasonable request.

ETHICS STATEMENT

Patient and tumor characteristics, patterns of care and clinical outcomes were collected retrospectively after institutional review board approval of the leading study center (Mannheim, 2018-853R-MA) and subsequent ethics considerations in each center. Due to the retrospective design of the study no informed consent was needed.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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