

# Breathing-motion-compensated robotic guided stereotactic body radiation therapy

## Patterns of failure analysis

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### Abstract

**Purpose** We retrospectively evaluated the patterns of failure for robotic guided real-time breathing-motion-compensated (BMC) stereotactic body radiation therapy (SBRT) in the treatment of tumors in moving organs.

**Patients and methods** Between 2011 and 2016, a total of 198 patients with 280 lung, liver, and abdominal tumors were treated with BMC-SBRT. The median gross tumor volume (GTV) was 12.3 cc (0.1–372.0 cc). Medians of mean GTV BED<sub>α/β=10 Gy</sub> (BED = biological effective dose) was 148.5 Gy<sub>10</sub> (31.5–233.3 Gy<sub>10</sub>) and prescribed planning target volume (PTV) BED<sub>α/β=10 Gy</sub> was 89.7 Gy<sub>10</sub> (28.8–151.2 Gy<sub>10</sub>), respectively. We analyzed overall survival (OS) and local control (LC) based on various factors, including BEDs with α/β ratios of 15 Gy (lung metastases), 21 Gy (primary lung tumors), and 27 Gy (liver metastases).

**Results** Median follow-up was 10.4 months (2.0–59.0 months). The 2-year actuarial LC was 100 and 86.4% for primary early and advanced stage lung tumors, respectively, 100% for lung metastases, 82.2% for liver metastases, and 90% for extrapulmonary extrahepatic metastases. The 2-year OS rate was 47.9% for all patients. In uni- and multivariate analysis, comparatively lower PTV prescription dose (equivalence of 3 × 12–13 Gy) and higher average GTV dose (equivalence of 3 × 18 Gy) to current practice were significantly associated with LC. For OS, Karnofsky performance score (100%), gender (female), and SBRT without simultaneous chemotherapy were significant prognostic factors. Grade 3 side effects were rare (0.5%).

**Conclusions** Robotic guided BMC-SBRT can be considered a safe and effective treatment for solid tumors in moving organs. To reach sufficient local control rates, high average GTV doses are necessary. Further prospective studies are warranted to evaluate these points.

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**Keywords** Lung cancer · Liver metastases · Abdominal neoplasms · Overall survival · CyberKnife robotic radiosurgery

**Atembewegungskompensierte, robotergeführte stereotaktische Körperstammstrahlentherapie**  
Analyse der Rezidivmuster

### Zusammenfassung

**Zweck** Wir führten eine retrospektive Untersuchung der Rezidivmuster bei der Behandlung von Tumoren in bewegten Organen mittels robotergeführter in Echtzeit atembewegungskompensierter (EAK) stereotaktischer Körperstammstrahlentherapie (SBRT) durch.

**Patienten und Methoden** Zwischen 2011 und 2016 wurden insgesamt 198 Patienten mit 280 Lungen-, Leber- und Abdominaltumoren mit EAK-SBRT behandelt. Das mediane makroskopische Tumolvolumen (GTV) lag bei 12,3 cm<sup>3</sup> (0,1–372,0 cm<sup>3</sup>). Die mediane mittlere GTV-BED <sub>$\alpha/\beta = 10$  Gy</sub> lag bei 148,5 Gy<sub>10</sub> (31,5–233,3 Gy<sub>10</sub>; BED = biologisch effektive Dosis) und die verschriebene PTV-BED <sub>$\alpha/\beta = 10$  Gy</sub> bei 89,7 Gy<sub>10</sub> (28,8–151,2 Gy<sub>10</sub>; PTV = Planungszielvolumen). Wir analysierten das Gesamtüberleben (GÜ) und die lokale Kontrolle (LK) basierend auf verschiedenen Faktoren, einschließlich BED mit  $\alpha/\beta$ -Verhältnissen von 15 Gy (Lungenmetastasen), 21 Gy (primäre Lungentumoren) und 27 Gy (Lebermetastasen).

**Ergebnisse** Die mediane Nachbeobachtungszeit betrug 10,4 Monate (2,0–59,0 Monate). Die 2-Jahres-LK betrug 100 und 86,4 % für primäre Lungentumoren im Früh- bzw. fortgeschrittenen Stadium, 100 % für Lungenmetastasen, 82,2 % für Lebermetastasen und 90 % für extrapulmonale, extrahepatische Metastasen. Die 2-Jahres-GÜ-Rate über alle Patienten betrug 47,9 %. In der uni- und multivariaten Analyse wurde die LK vor allem durch eine zur üblichen Praxis vergleichsweise niedrige PTV-Verschreibungsdosis (äquivalent zu 3-mal 12–13 Gy) sowie durch höhere mittlere GTV-Dosen (äquivalent zu 3-mal 18 Gy) beeinflusst. Für ein hohes GÜ waren ein hoher Karnofsky-Index (100 %), das Geschlecht (weiblich) und die SBRT ohne gleichzeitige Chemotherapie prognostisch signifikant. Grad-3-Nebenwirkungen waren selten (0,5 %).

**Schlussfolgerungen** Die robotergeführte EAK-SBRT kann als eine sichere und wirksame Behandlung für solide Tumoren in beweglichen Organen angesehen werden. Für eine ausreichend hohe lokale Kontrollrate sind hohe mittlere GTV-Dosen erforderlich. Weitere prospektive Studien sind nötig, um diese Punkte zu evaluieren.

**Schlüsselwörter** Lungentumoren · Lebermetastasen · Abdominaltumoren · Gesamtüberleben · CyberKnife-robotergeführte Radiochirurgie

Stereotactic body radiation therapy (SBRT) is frequently used for treating primary lung tumors [1–4], lung metastases [4–7], liver metastases [8–11], and lately for extrapulmonary extrahepatic oligometastatic disease [12–14]. For most indications, well-defined dose–response relationships for local control have been established based on planning target volume (PTV) prescription dose and/or based on maximum gross tumor volume (GTV) and isocenter dose, respectively [1, 3–5, 7, 10, 11, 15, 16]. However, even though these data were generated with large patient and lesion numbers, the platforms used were heterogeneous and there remains doubt if the reported tumor control probabilities (TCP) can be fully applied to all treatment systems and techniques and all lesion sites.

For example, the CyberKnife system (Accuray Inc., Sunnyvale, CA, USA) [17] makes use of small noncoplanar, nonisocentric cylindrical beams which can in turn generate highly modulated dose distributions with geometrically variable maximum dose regions. The CyberKnife is also capable of real-time breathing-motion-compensation (BMC) [18] which allows the application of high radiation doses with minimal safety margins [19] resulting in very small clinical dosimetry errors [20, 21]. Therefore, robotic BMC-SBRT may not perfectly fit into current TCP modeling paradigms mostly derived from gantry-based coplanar isocentric SBRT with integrated tumor volume (ITV) concepts.

Furthermore, current developments in dose calculation accuracy (i. e., Monte Carlo simulations) and their implementation into clinical routine highlight the need for different dose prescriptions in the lung (i. e., the prescription based on GTV mean dose) [22]. Such concepts may also be warranted for larger tumors in the abdomen and may especially be important for CyberKnife BMC-SBRT [10].

Finally, advanced TCP modeling of historical data recently suggested different radiation sensitivity for various tumor histology and lesion sites (i. e., higher alpha/beta ( $\alpha/\beta$ ) ratios than 10 Gy were proposed for primary lung tumors and lung and liver metastases) [4, 11, 15, 16]. Hence, different dose concepts may be required for separate treatment systems or even for institutional techniques for each different lesion site.

The aim of this retrospective pattern-of-failure analysis was to investigate local control (LC), overall survival (OS), and toxicity for our dedicated GTV-optimized treatment approach [10] for moving lesions using robotic BMC-SBRT and to compare our results to previously published studies and common clinical practice.

## Patients and methods

This retrospective study was approved by the local ethics committees of the universities of Frankfurt (477/15), Rostock (A2016-0008), and Lübeck (13–218A).

## Patient characteristics

Between March 2011 and September 2016, a total of 198 patients (118 men, 80 women) with 280 lesions were treated with robotic BMC-SBRT at two treatment centers with homogenized treatment planning and treatment delivery protocols. All patients were considered early stage or oligometastatic having  $\leq 4$  lesions in a single organ per treatment. Most of the patients were treated for a single lesion ( $n = 156$ ) and the rest of the patients for two ( $n = 24$ ), three ( $n = 6$ ) or four and more ( $n = 12$ ) lesions, repeat

**Table 1** Patient, lesion, and treatment characteristics

		Total	%
Patients	–	198	–
Lesions	–	280	–
Gender	Male	118	59.6
	Female	80	40.4
Age	Median (range) in years	68	(34–89)
Karnofsky index	Median (range) in %	90	(60–100)
Primary lung tumor	Patients/lesions	68/70	–
	Early stage	40/42	20.2/15.0
	Advanced stage	28/28	14.1/10.0
Lung metastases	Patients/lesions	41/62	–
	Lung cancer	15/18	7.6/6.4
	Colorectal cancer	11/22	5.6/7.9
	Other primary	15/22	7.6/7.9
Liver metastases	Patients/lesions	75/131	–
	Colorectal cancer	34/62	17.2/22.1
	Breast cancer	8/12	4.0/4.3
	Other primary	32/57	16.7/20.3
Other	Patients/lesions	14/17	–
	Lymph node metastases	5/8	2.5/2.9
	Soft tissue metastases	9/9	4.5/3.2
Number of lesions treated <sup>a</sup>	1	156	78.8
	2	24	12.1
	3	6	3.0
	4 or more	12	6.1
GTV	Median (range) in cc	12.3	(0.1–372)
GTV dimension	Median (range) in cm	2.9	(0.6–8.9)
PTV prescription BED <sub>10</sub>	Median (range) in Gy	89.7	(28.8–151.2)
Plan maximum BED <sub>10</sub>	Median (range) in Gy	174.4	(38.5–275.5)
<i>GTV mean doses</i>			
All lesions BED <sub>10</sub>	Median (range) in Gy	148.5	(31.5–233.3)
Primary lung BED <sub>21</sub>	Median (range) in Gy	108.2	(35.5–147.8)
Lung metastases BED <sub>15</sub>	Median (range) in Gy	122.2	(44.3–178.9)
Liver metastases BED <sub>27</sub>	Median (range) in Gy	85.4	(22.4–99.5)

GTV Gross Tumor Volume, PTV Planning Target Volume, BED<sub>x</sub> Biological Effective Dose with alpha/beta of *x* Gy where 15 Gy (lung metastases), 21 Gy (primary lung tumors), and 27 Gy (liver metastases) where derived from [15, 16]

<sup>a</sup>Repeat treatments included (*no more than 4 lesions were treated simultaneously*)

procedures of new lesions included. The median age of the patients was 68 years (range 34–89 years) and the median baseline Karnofsky performance score was 90% (range 60–100%). Of all treated patients, 12.6% did not stop chemotherapy during the time of SBRT delivery.

Out of the 280 lesions, 131 liver metastasis were treated, the largest number originating from colorectal cancer ( $n = 62$ ). Furthermore, 132 lung lesions were treated, of which 70 lesions were primary lung tumors (42 early stage, 28 advanced stage) and 62 lesions were lung metastases, mostly originating from colorectal cancer ( $n = 22$ ) or lung cancer ( $n = 18$ ). All other lesions ( $n = 17$ ) were either lymph node metastases or soft tissue metastases in the upper abdomen.

The median GTV was 12.3 cc (range 0.1–372.0 cc) and the corresponding maximum GTV dimensions ranged from 0.6 to 8.9 cm (median 2.9 cm). A detailed description of the patient characteristics can be found in Table 1.

### Treatment planning and delivery

For all extrapulmonary and for 9/132 (6.8%) intrapulmonary lesions, either GoldAnchor™ (Naslund Medical AB, Huddinge, Sweden) or solid gold fiducial markers (IZI Medical Products, Owings Mills, MD, USA) were implanted prior to treatment as close to the lesions as possible. Treatment planning was performed on standard

computer tomography (CT) at regular end expiration breath hold with 1.5 mm slice thickness. The planning CT was fused with magnetic resonance images (MRI) for extrapulmonary or with positron emission tomography (PET) for intrapulmonary lesions, whenever available. The GTV was defined according to common standards and guidelines [2, 8, 10]. The clinical target volume (CTV) consisted of the GTV with an expansion of 5 mm for intrahepatic and 2 mm for extrahepatic lesions. The PTV included the CTV and an expansion of 3 mm in all directions to encompass the targeting uncertainties for the CyberKnife system [19–21].

Plan optimization was done with the CyberKnife MultiPlan® software (Accuray, versions 3.5 and 4.5) utilizing Sequential Multi-Objective Optimization [23] and the consensus guidelines for robotic radiosurgery treatment planning [24]. The main objective for optimization was to maximize the GTV mean dose to more than  $3 \times 18$  Gy for extrapulmonary [10],  $3 \times 20$  Gy for lung metastases, and  $3 \times 21.5$  Gy for primary lung tumors [22], while for all intrapulmonary lesions the Monte Carlo algorithm was used for dose calculation [25]. The secondary objective was to minimize the dose to all critical structures according to the ALARA (As Low As Reasonably Achievable) principle. Standard PTV prescription dose was sought to reach  $3 \times 15$  Gy according to standard practice. However, if this was not possible due to critical organ constraints [26], either the fractions were increased or the prescription dose was lowered while for both we tried to maintain high GTV mean doses [10]. Rarely, very small lung lesions were treated in a single fraction (6.8%) [27]. The final biological effective doses ( $BED_{\alpha/\beta=10 \text{ Gy}}$ ) surrounding 95% of the PTV ranged between 28.8 and 151.2 Gy<sub>10</sub> (median 89.7 Gy<sub>10</sub>) prescribed to the 40–85% isodose (median 71%), and the mean GTV  $BED_{\alpha/\beta=10 \text{ Gy}}$  ranged between 31.5 and 233.3 Gy<sub>10</sub> (median 148.5 Gy<sub>10</sub>). We also calculated the BEDs with variable  $\alpha/\beta$  ratios for 2-year TCP based on recent studies [15, 16] resulting in mean GTV  $BED_{\alpha/\beta=15 \text{ Gy}}$  of median 122.2 Gy<sub>15</sub> for lung metastases (range 44.3–178.9 Gy<sub>15</sub>),  $BED_{\alpha/\beta=21 \text{ Gy}}$  of median 108.2 Gy<sub>21</sub> for primary lung tumors (range 35.5–147.8 Gy<sub>21</sub>), and  $BED_{\alpha/\beta=27 \text{ Gy}}$  of median 85.4 Gy<sub>27</sub> for liver metastases (range 22.4–99.5 Gy<sub>27</sub>).

For all lesions, SBRT was delivered using the CyberKnife Synchrony® real-time BMC tracking system (Accuray, versions 8.5 and 9.5) [17, 18]. A custom-made vacuum mattress (HEK Medical, Germany) was used for immobilization and all patients were initially aligned using the spinal vertebra. The breathing-induced motion of the lesions was compensated for by the robot during beam-on time [17, 18] using the prediction of chest markers [28] which were correlated to either the previously implanted fiducial markers (56.1%) or to the lung lesion directly (43.9%), both detected on the orthogonal x-ray imaging [29, 30]. BMC tracking accuracy performance

was kept according to best practice guidelines [20, 21, 31]. The median fraction treatment time was 45 min (range 15–110 min), excluding setup time, and mostly depended on treatment complexity and number of treated lesions.

### Follow-up and statistical analysis

All patients were observed in time intervals of 3 months in the first year and then 6 months thereafter. We estimated LC and OS as the clinical end points with Kaplan–Meier survival curves. These endpoints were calculated from the end of treatment to the date of last contact or local progression or death, respectively. LC was evaluated using the Response Evaluation Criteria in Solid Tumors (RECIST). Suspected local progression was confirmed with biopsy or functional imaging (i. e., PET/CT). Whenever possible, we also registered the follow-up imaging to the treatment plan for determination on in-field or field-border recurrence. Patients that were still alive and had no local failure were censored at last follow-up.

To identify prognostic factors for the respective clinical endpoints, we conducted univariate analysis using the log-rank method taking into account different clinical variables—PTV prescription, GTV mean, and plan maximum dose—all three expressed as  $BED_{\alpha/\beta=x \text{ Gy}}$  with different histology-dependent  $\alpha/\beta$  ratios, lesion volume and diameter, and histology of the primary tumor as independent variables. For analyzing overall survival we used the Karnofsky performance score, age, gender, lesion site, and simultaneous chemotherapy. For the subsequent multivariate Cox regression analysis, we included all factors found to be significant in the univariate analysis. For the statistical analysis we used SPSS (Version 21.0, IBM, Amonk, NY, USA) and we considered a  $p$ -value of  $\leq 0.05$  as the limit for statistical significance.

## Results

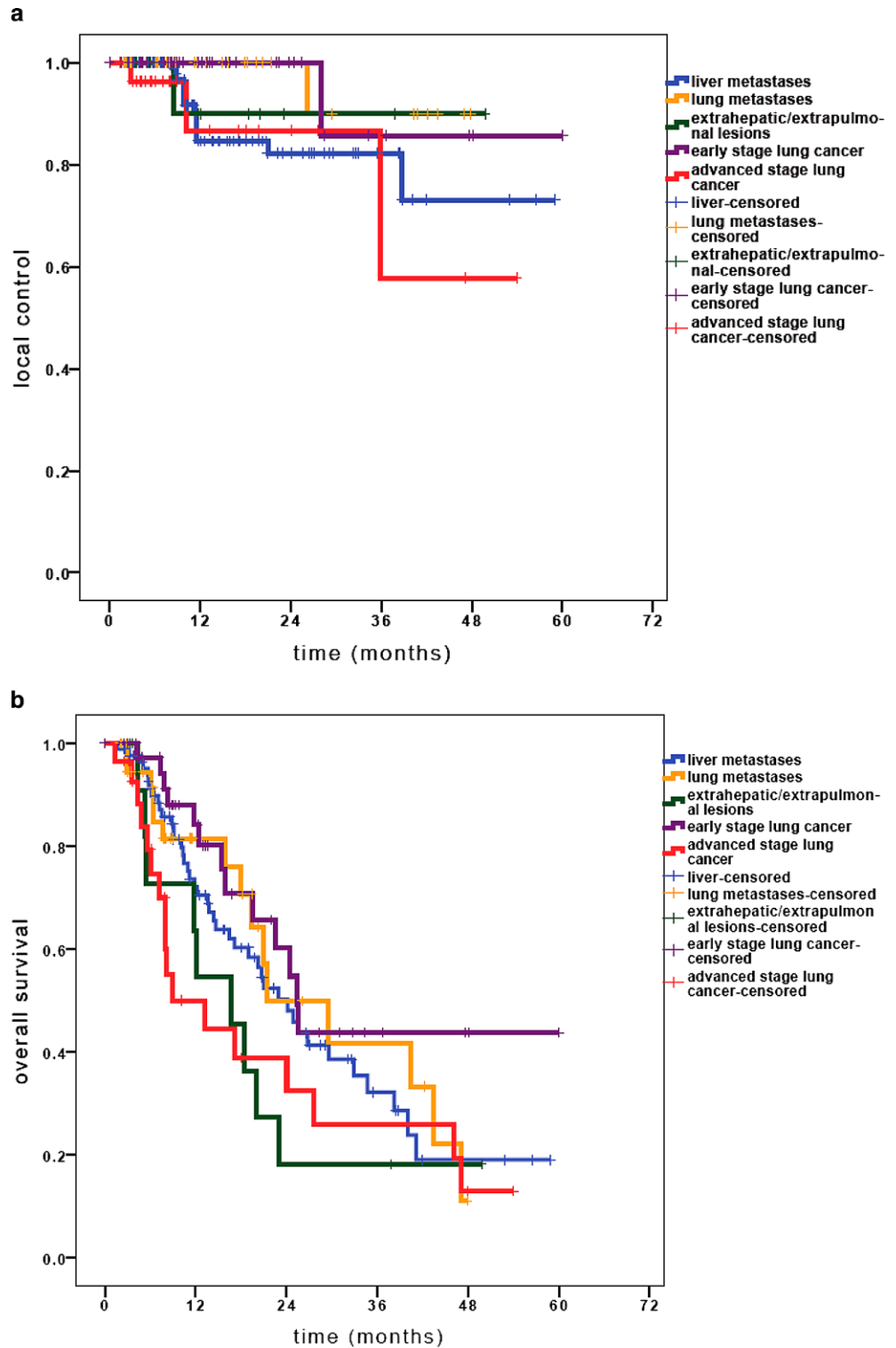
At the time of analysis, the median follow-up for all patients was 10.4 months (range 2.0–59.0 months).

### Local control

The crude LC for all lesions ( $n = 280$ ) was 92.9% at the time of analysis. The 2-year actuarial LC was 100% for early stage primary lung tumors, 86.4% for advanced stage primary lung tumors (including re-irradiation of previously treated lesions), 100% for lung metastases, 82.2% for liver metastases, and 90.0% for extrapulmonary extrahepatic metastases, respectively (Fig. 1).

In the univariate analysis for all primary lung tumors, we found a significant correlation between no prior lung

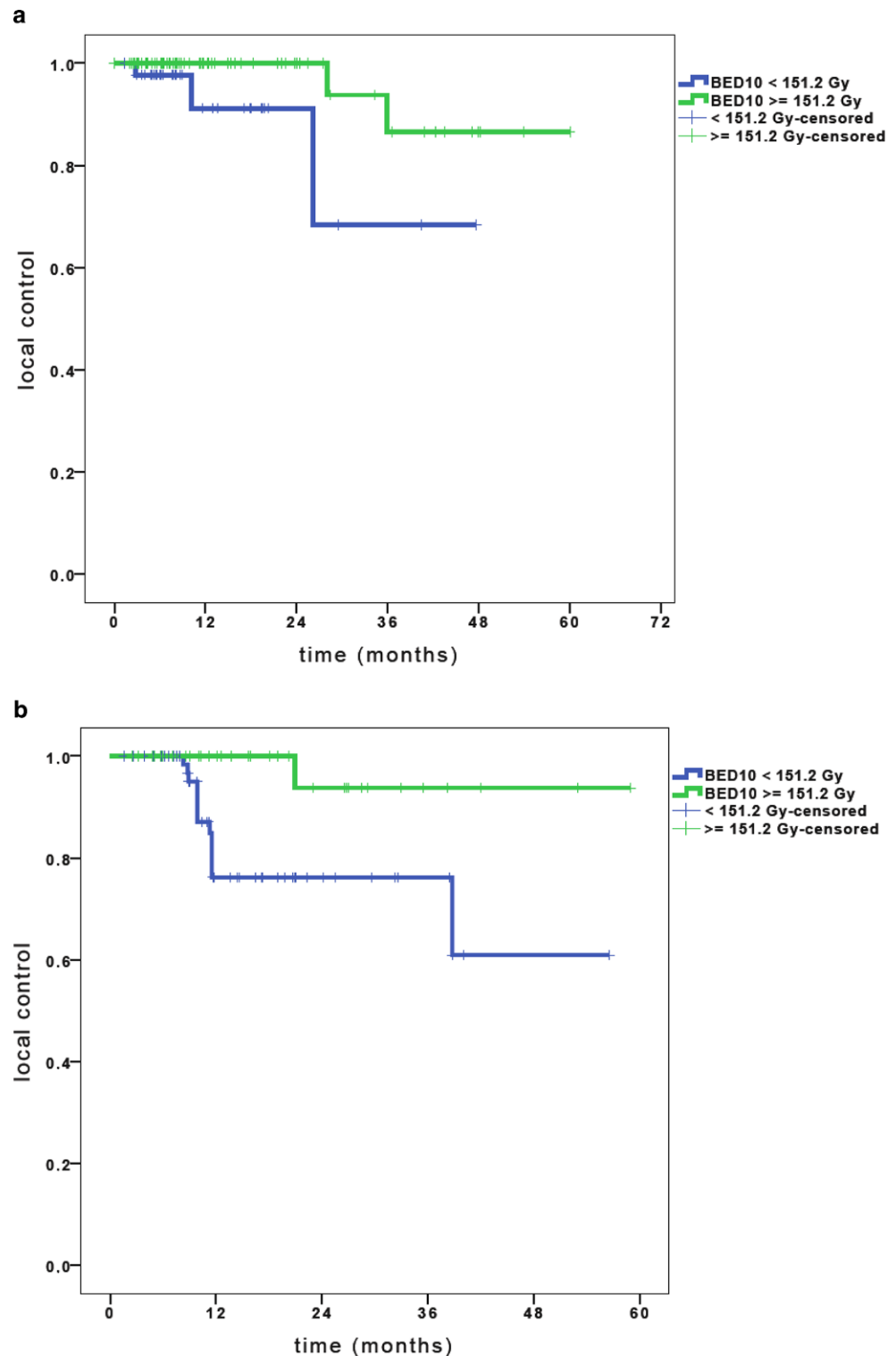
**Fig. 1** Kaplan–Meier curves for local control (a) and overall survival (b)



tumor therapy (operation, chemotherapy, radiotherapy, etc.) and better LC (hazard ratio [HR] 9.386, 95% confidence interval [CI] 0.911–96.655,  $p = 0.027$ ). For the lung metastases group, we had only one local failure in the third year after treatment; hence, we combined all lung lesions for statistical analysis for volume, dimension, number of frac-

tions and dose ( $BED_{10}$  and combined  $BED_{15}$  for metastases with  $BED_{21}$  for primary tumors, respectively). In univariate analysis for all lung lesions, a PTV prescription dose  $\geq 89.7 Gy_{10}$  (HR 0.077, 95% CI 0.012–0.503,  $p = 0.001$ ) and  $\geq 70.0 Gy_{15/21}$  (HR 0.128, 95% CI 0.021–0.801,  $p = 0.011$ ) was associated with better LC, but PTV prescrip-

**Fig. 2** Kaplan–Meier local control curves for lung (a) and liver (b) metastases based on GTV mean  $BED_{\alpha/\beta=10}$  ( $p = 0.035$  for a and  $p = 0.014$  for b). GTV gross tumor volume, BED biological effective dose



tion doses above  $3 \times 15$  Gy ( $112.5 \text{ Gy}_{10}$  and  $82.5 \text{ Gy}_{15/21}$ ) were not ( $p = 0.176$  and  $p = 0.114$ , respectively). For the GTV mean dose, a dose level  $\geq 151.2 \text{ Gy}_{10}$  (HR 0.172, 95% CI 0.028–1.074,  $p = 0.035$ ) and  $\geq 100.0 \text{ Gy}_{15/21}$  (HR 0.132, 95% CI 0.021–0.823,  $p = 0.012$ ) was associated with better LC (Fig. 2), while a maximum plan dose above  $3 \times 21.3$  Gy

presented only a trend for LC ( $p = 0.070$ ). Interestingly, univariate analysis also showed a significantly better LC with multiple fraction compared to single fraction radiosurgery ( $p = 0.042$ ), but this result has to be considered with caution as for single fraction, the PTV prescription was generally lower (by approximately 25%) and rarely used. Hence, in

**Table 2** Univariate and multivariate analysis for local control

	Univariate analysis		Multivariate analysis	
	HR (95% CI)	<i>p</i> -value	HR (95% CI)	<i>p</i> -value
<i>Only primary lung tumors</i>				
Stage (early vs. advanced)	0.193 (0.020–1.875)	0.115	–	–
Therapy (no RT vs. prior lung RT)	9.386 (0.911–96.655)	0.027	–	–
<i>Only secondary lung tumors</i>				
Histology (colorectal vs. other)	0.028 (0-Inf)	0.513	–	–
<i>Primary and secondary lung tumors</i>				
GTV (≥18.5 cc vs. <18.5 cc)	1.403 (0.232–8.465)	0.711	–	–
GTV dimension (≥2.9 cm vs. <2.9 cm)	0.576 (0.096–3.469)	0.542	–	–
Fractions (3–5 vs. 1)	5.330 (0.875–32.466)	0.042	1.804 (0.156–20.806)	0.546
PTV BED <sub>10</sub> (≥89.7 Gy vs. >89.7 Gy)	0.077 (0.012–0.503)	0.001	0.035 (0.002–0.824)	0.037 <sup>b</sup>
PTV BED <sub>15/21</sub> (≥70 Gy vs. >70 Gy)	0.128 (0.021–0.801)	0.011	0.168 (0.017–1.623)	0.123 <sup>b</sup>
GTV BED <sub>10</sub> (≥151.2 Gy vs. <151.2 Gy)	0.172 (0.028–1.074)	0.035	0.248 (0.021–2.924)	0.268 <sup>b</sup>
GTV BED <sub>15/21</sub> (≥100 Gy vs. < 100 Gy)	0.132 (0.021–0.823)	0.012	0.179 (0.019–1.660)	0.130 <sup>b</sup>
Max. BED <sub>10</sub> (≥200 Gy vs. <200 Gy)	0.166 (0.018–1.503)	0.070	–	–
<i>Secondary liver tumors</i>				
Histology (colorectal vs. other)	<0.001 (0-Inf)*	<0.001	<0.001 (0-Inf)*	0.916
GTV (≥35 cc vs. < 35 cc)	0.456 (0.102–2.039)	0.285	–	–
GTV Dimension (≥3.4 cm vs. <3.4 cm)	0.422 (0.123–1.588)	0.420	–	–
PTV BED <sub>10</sub> (≥79.2 Gy vs. <79.2 Gy)	0.329 (0.102–1.059)	0.047	0.536 (0.167–1.723)	0.295 <sup>b</sup>
PTV BED <sub>27</sub> (≥60 Gy vs. <60 Gy)	0.240 (0.053–1.077)	0.041	0.364 (0.079–1.673)	0.194 <sup>b</sup>
GTV BED <sub>10</sub> (≥151.2 Gy vs. <151.2 Gy)	0.122 (0.016–0.933)	0.014	0.109 (0.014–0.878)	0.037 <sup>b</sup>
GTV BED <sub>27</sub> (≥90 Gy vs. <90 Gy)	0.166 (0.050–0.551)	0.001	0.290 (0.085–0.995)	0.049 <sup>b</sup>
Max. BED <sub>10</sub> (≥180 Gy vs. <180 Gy)	1.415 (0.442–4.531)	0.552	–	–

RT Radiation Therapy, GTV Gross Tumor Volume, PTV Planning Target Volume, BED<sub>x</sub> Biological Effective Dose with alpha/beta of *x* Gy where 15 Gy (lung metastases), 21 Gy (primary lung tumors) and 27 Gy (liver metastases) where derived from [15, 16]; HR hazard ratio, 95% CI 95% confidence interval, *p*-value ≤0.05 was considered significant

<sup>a</sup>due the lack of events in one group no hazard ratio could be calculated

<sup>b</sup>due to multicollinearity and limited number of events only one dose parameter was used each time for multivariate analysis

the multivariate analysis only the PTV prescription BED<sub>10</sub> (*p* = 0.037 for 89.7 Gy<sub>10</sub>) reached statistical significance for LC.

For liver metastases, a clear correlation between LC and histology (*p* < 0.001) could be shown in the univariate analysis, as all local recurrences were found to have colorectal cancer as primary tumor origin. Furthermore, a PTV prescription dose ≥79.2 Gy<sub>10</sub> (HR 0.329, 95% CI 0.102–1.588, *p* = 0.047) and ≥60.0 Gy<sub>27</sub> (HR 0.240, 95% CI 0.053–1.077, *p* = 0.041) was associated with better LC, but PTV prescription doses above 3 × 14 Gy (100.8 Gy<sub>10</sub> and 63.8 Gy<sub>27</sub>) were not (both *p* = 0.089). For the GTV mean dose, a dose level ≥151.2 Gy<sub>10</sub> (HR 0.122, 95% CI 0.016–0.933, *p* = 0.014) and ≥90.0 Gy<sub>27</sub> (HR 0.166, 95% CI 0.050–0.551, *p* = 0.001) was associated with better LC (Fig. 2), while a maximum plan dose above 3 × 20 Gy was not (*p* = 0.552). In the multivariate analysis only the GTV mean doses (*p* = 0.037 for 151.2 Gy<sub>10</sub> and *p* = 0.049 for 90.0 Gy<sub>27</sub>) reached statistical significance for LC. However, the results of the multivariate analysis should be interpreted with caution due to all events occurring in colorectal cancer patients harboring the risk of

over-fitting. Noteworthy was also the fact that GTV and maximum GTV dimension for both lung and liver lesions did not affect LC in our patient cohort.

Due to the low number of cases, the extrahepatic extra-pulmonary lesions were not subjected to formal statistical analysis for LC. All treated lymph node metastases were locally controlled at the time of analysis and one of four treated adrenal gland metastases had a local recurrence after delivering a low dose of 4 × 5 Gy, restricted due to previous local radiotherapy (20 × 2 Gy) in this case. The complete statistical analysis for LC is presented in Table 2, detailed descriptions of the local recurrences can be found in Table 3, and examples of local and regional failure in Fig. 3.

**Overall survival**

The median OS at the time of analysis was 11.2 months. The 1-, 2-, and 3-year OS of all patients were 72.4, 47.9, and 34.0%, respectively (Fig. 1). Worse OS was associated with a Karnofsky performance score less than 100%

**Table 3** Case description of the local recurrences

No.	Lesion	GTV (cc)	Prior treatment	Primary Tumor	Fraction/dose	Mean GTV	Time to LF	Position/likely cause of LF	Further treatment
1	Recurrent Early Lung	1.6	OP (2x), Chemo	NSCLC	3 × 15 Gy	156 Gy <sub>10</sub>	28.0 months	FB/DD: new regional tumor	OP
2	Stage IV Lung	30.0	n/a	NSCLC	3 × 16 Gy	185 Gy <sub>10</sub>	35.8 months	IF/No adjuvant chemo, DD: regional progress	Chemo
3	Stage IV Lung	5.7	RT, Chemo	NSCLC	1 × 23 Gy	129 Gy <sub>10</sub>	10.1 months	IF/Dose	Chemo
4	Stage IV Lung	60.8	RT, Chemo	NSCLC	3 × 8 Gy	59 Gy <sub>10</sub>	2.8 months	IF/Dose	BSC
5	Lung Met	2.9	OP, Chemo	NSCLC	1 × 23 Gy	123 Gy <sub>10</sub>	26.1 months	IF/Dose	Chemo
6	Liver Met	1.5	OP, Chemo	CRC	3 × 13 Gy	142 Gy <sub>10</sub>	8.3 months	FB/DD: new regional tumor	OP
7–10	Liver Mets (4 lesions)	62.9	OP, Chemo	CRC	3 × 13 Gy	144 Gy <sub>10</sub>	11.5 months	IF (all 4)/Dose	SBRT (all four)
11	Liver Met	12.0	OP, RFA, Chemo	CRC	3 × 13 Gy	146 Gy <sub>10</sub>	14.2 months	FB/GTV definition	SBRT
12	Liver Met	103.0	OP, RT, Chemo	CRC	4 × 9 Gy	106 Gy <sub>10</sub>	38.7 months	IF/Dose	Chemo
13–16	Liver Mets (4 lesions)	19.0	OP, RT, Chemo	CRC	4 × 7 Gy	60 Gy <sub>10</sub>	9.9 months	IF/Dose	BSC
17	Liver Met	35.0	OP, RFA, Chemo	CRC	3 × 15 Gy	151 Gy <sub>10</sub>	20.9 months	FB/DD: new regional tumor	OP
18	Liver Met	5.5	OP, Chemo	CRC	3 × 8 Gy	134 Gy <sub>10</sub>	8.3 months	IF/Dose	OP
19	Adrenal Gland Met	52.0	RT, Chemo	NSCLC	4 × 5 Gy	35 Gy <sub>10</sub>	8.5 months	IF/Dose	OP

GTV Gross Tumor Volume, *Frac.* Fraction, *LF* Local Failure, *Met* Metastasis, *Mets* Metastases, *RT* Radiation Therapy, *Chemo* Chemotherapy, *OP* Operation, *BSC* Best Supportive Care, *NSCLC* Non-Small Cell Lung Cancer, *CRC* Colorectal Cancer, *FB* Field Board Recurrence, *IF* In-Field Recurrence, *DD* Differential Diagnosis

(HR 2.279, 95% CI 0.997–5.210,  $p = 0.045$ ), the administration of continuous chemotherapy during SBRT (HR 1.793, 95% CI 1.004–3.203,  $p = 0.045$ ), and interestingly a male gender (HR 1.657, 95% CI 1.071–2.566,  $p = 0.022$ ) in univariate analysis. Those parameters remained significant in multivariate analysis. Furthermore, a GTV of  $\geq 35$  cc was significantly associated with worse OS in univariate analysis (HR 1.548, 95% CI 1.021–2.346,  $p = 0.038$ ), but the lesion size was not significant in multivariate analysis ( $p = 0.085$ ). Not predictive for OS was the age of the patient at the time of first SBRT treatment ( $p = 0.135$ ). Patients with early stage lung cancer showed clear trend ( $p = 0.067$ ) for better OS (1-year OS = 100%) and patients with advanced stage lung cancer showed clear trend ( $p = 0.080$ ) for worse OS (1-year OS = 51.7%), as expected. For metastatic patients only, the primary tumor histology was not a predictive factor for OS. The detailed results of the OS analysis can be found in Table 4.

### Toxicity

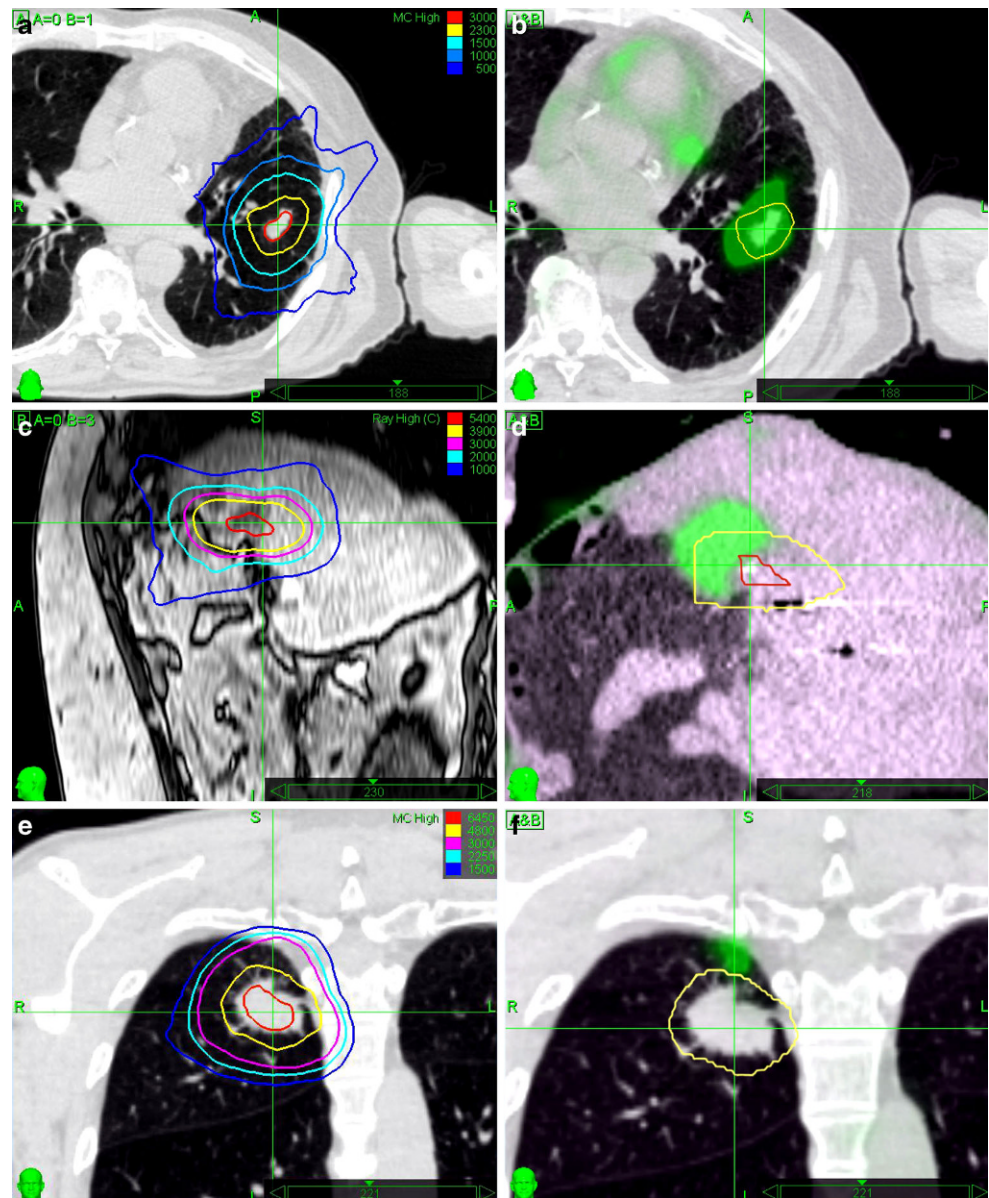
For the gold marker implantation, one extrapulmonary patient (1.1%) developed an infected encapsulated hematoma in the liver requiring antibiotics and drainage therapy and 4/9 intrapulmonary patients (44.4%) developed a self-resolving minor pneumothorax requiring observation only. Radiation treatment-related side-effects of grade III were identified only in a single patient (0.5%), requiring a stent implantation for a hepatic vein occlusion as previously reported [10].

### Discussion

We are presenting one of the largest patterns of failure studies with a single dedicated treatment planning and delivery technique for robotic real-time BMC-SBRT. Our main findings were high LC rates (82.2–100% for various tumor sites) with overall low risks of grade III side effects (0.5%)



**Fig. 3** Examples for in-field, field border, and regional failure after robotic breathing-motion-compensated stereotactic body radiation therapy (BMC-SBRT). **a** Treatment plan (1 × 23 Gy, Monte Carlo) and isodose lines for a lung metastasis from primary non-small cell lung cancer (NSCLC). **b** In-field recurrence after 26.1 months: 2-deoxy-2-[F-19]fluoro-D-glucose positron emission tomography (19FDG-PET) overlay (green) to the treatment plan (23 Gy in red). **c** Treatment plan (3 × 15 Gy, Ray Trace) and isodose lines for a liver metastasis from primary colorectal cancer (CRC). **d** Field border recurrence after 14.2 months: 19FDG-PET overlay (green) to the treatment plan (45 Gy in red). **e** Treatment plan (3 × 16 Gy, Monte Carlo) and isodose lines for a primary NSCLC. **f** New regional tumor after 8.7 months: 19FDG-PET overlay (green) to the treatment plan (48 Gy in red)



and a clear dose–response relationship for PTV prescription and GTV mean doses up to certain dose levels.

For primary non-small cell lung cancer (NSCLC), we further found that local control is significantly dependent upon whether the patient had prior lung tumor therapy (e. g., operation, chemotherapy, or radiation therapy) or not ( $p = 0.027$ ). For the retreatment of local recurrences after prior local lung radiotherapy, this may seem obvious due to dose limitations [32], but those patients were a minority in the presented cohort (4.6%) and more importantly did not show any local failure. This was also recently found in similar studies with BMC-SBRT [33]. Three of the four lung tumors that showed local failure during follow-up were classified as regional recurrent NSCLC after curative radiochemotherapy or resection with adjuvant chemotherapy

before SBRT (Table 3). It may be speculated that recurrent NSCLC especially after prior chemotherapy have a tendency to be more radioresistant and require higher doses [34], but the overall data for this hypothesis remains small. Furthermore, in comparison to local (in-field or field border) recurrences after SBRT, regional recurrences may also occur due to the small and focused treatment fields [35], but those were rare in our patient cohort (2.9%, compare Fig. 1 for one of the two cases). The treatment of local recurrences after SBRT of NSCLC is also controversial and very individualized (compare Table 3), but a recent recommendation for such specific situations [36] may help to generate guidelines in the future.

For all lung tumors combined, our LC rates were high (i. e., reaching 100%) and well in agreement with previ-

**Table 4** Univariate and multivariate analysis for overall survival

	Univariate analysis		Multivariate analysis	
	HR (95% CI)	<i>p</i> -value	HR (95% CI)	<i>p</i> -value
Karnofsky index ( $\leq 90\%$ vs. $100\%$ )	2.279 (0.997–5.210)	0.045	2.791 (1.192–6.535)	0.018
Gender (male vs. female)	1.657 (1.071–2.566)	0.022	1.685 (1.087–2.612)	0.020
Age ( $< 67$ years vs. $\geq 67$ years)	0.744 (0.497–1.114)	0.135	–	–
GTV ( $\geq 35$ cc vs. $< 35$ cc)	1.548 (1.021–2.346)	0.038	1.453 (0.949–2.225)	0.085
Early stage lung cancer (vs. other)	0.596 (0.332–1.071)	0.080	–	–
Advanced stage lung cancer (vs. other)	1.633 (0.961–2.775)	0.067	–	–
Lung metastases (vs. other)	0.894 (0.515–1.552)	0.690	–	–
Liver metastases (vs. other)	0.984 (0.656–1.476)	0.938	–	–
Other metastases (vs. other)	0.984 (0.656–1.476)	0.938	–	–
Simultaneous chemotherapy	1.793 (1.004–3.203)	0.045	2.075 (1.151–3.741)	0.015
<i>Only metastatic patients</i>				
Histology (colorectal cancer vs. other)	1.018 (0.602–1.723)	0.946	–	–
Histology (breast cancer vs. other)	0.631 (0.228–1.746)	0.370	–	–
Histology (lung cancer vs. other)	0.707 (0.301–1.660)	0.424	–	–

HR hazard ratio, 95% CI 95% confidence interval  
*p*-value  $\leq 0.05$  was considered significant

ously published large multicenter studies [1, 3–5, 7]. However, we found that the PTV prescription doses required for high LC ( $> 90\%$ ) were noticeably lower with our method compared to those previously presented. Arguably, we routinely use the Monte Carlo dose calculation algorithm and some of those studies used older pencil beam algorithms, which may significantly overestimate the dose [22, 37–40] and hence are difficult to compare [40]. But also in contrast to CyberKnife Monte Carlo data, our PTV prescription dose for high LC seem lower [37–39]. Allowance for larger inhomogeneity within the PTV and the optimization of the GTV mean dose per se, which appears to be a necessary task for the small CyberKnife beams [10], rather than only prescribing to the GTV mean dose [22] may have significantly contributed to this phenomenon. Yet of course, the evidence for this hypothesis is immature.

Nevertheless, the results concerning the liver metastases in our study also point in this direction, confirming our previous results with a larger dual-center patient cohort [10]. While again our LC rates were similar compared to other studies [41, 42], the needed PTV prescription doses for high LC ( $> 90\%$ ) were definitively lower in our study ( $3 \times 12$ – $13$  Gy compared to  $3 \times 15$  Gy or more), but of course, due to the difference in treatment planning techniques, the results remain complex to compare. However, regardless of the lack of similar studies, we did not find better LC for PTV prescription doses above  $112.5$  Gy<sub>10</sub> and  $100.8$  Gy<sub>10</sub> for lung and liver lesions, respectively. This may, different to previous publications [3, 7, 9, 37–39, 41, 42], suggest an efficacy plateau for our technique concerning the PTV prescription dose, while at the same time higher GTV mean

doses above  $151.2$  Gy<sub>10</sub> still increase the likelihood of local control significantly.

A similar finding, i. e., better correlation of maximum dose to LC compared to prescription dose, was noticed recently in the working group Stereotactic Radiotherapy of the Deutsche Gesellschaft für Radioonkologie (DEGRO) evaluation of lung and liver SBRT [4, 11]. However, most of the data originated from static field isocenter treatments which naturally links maximum dose with GTV mean dose (i. e., the maximum dose is centrally located and directly influences the GTV mean dose), whereas the maximum dose for robotic SBRT is geometrically flexible (e. g., it can even easily be located outside the GTV for larger tumors [10]) due to the small nonisocentric noncoplanar beam arrangement. Therefore, it is no surprise that the maximum dose in our analysis did not significantly impact LC, though there was a small trend identified in the lung lesion group likely explained due to the build-up effects in the lung which naturally moves the maximum dose further into the GTV center.

Another finding of our study was a significant correlation between histology (i. e., primary colorectal cancer) and LC for liver metastases, whereas for lung metastases no correlation between histology and LC was found. While for the lung metastases group, the statistical analysis has to be taken with caution due to the minimal number of events ( $n = 1$ ), both findings concerning histology are well in agreement with published multicenter studies [4, 5, 11]. Looking more closely at the local failures in the liver metastases group (compare Table 3), we found that all patients received prior chemotherapy which could point to a de-

crease in radiosensitivity, hence, requiring higher SBRT doses for those lesions, as very recently demonstrated in the aforementioned multicenter study [11]. Interestingly, we also found no correlation between tumor volumes or tumor dimensions with LC seemingly overcoming the limitations of ablation techniques as recently published for larger liver tumors [43]. The literature remains very controversial on this topic [3, 5, 7, 11, 41, 43–45], as on one hand, patients with larger tumor volumes have a tendency for lower overall survival and likely do not reach the time point for local recurrences and, on the other hand, are more often treated with lower doses due to critical organ limitations. With our GTV-optimized PTV dose-reduction technique in larger volume SBRT (5–9 cm), we however believe that at least the dose limitation effects can be overcome to achieve high local tumor control within 3–5 years. Whether or not the BMC technology also had an impact on LC remains to be seen and may likely be only relevant in heavily moving tumors in the lower lung and abdomen [11, 46], but regardless, further studies including advanced biological modeling approaches [15, 16, 47, 48] are clearly needed to investigate the GTV dose–volume effects in greater detail.

Overall survival of 60.2, 41.3, 50.0, and 50.2% at 2 years for early and late stage NSCLC and for lung and liver metastases was comparable to published literature [1, 3, 5–7, 32, 44]. As expected, patients with early stage NSCLC had a trend for better OS compared to patients with advanced stage NSCLC, although the result was not statistically significant (Table 3). For metastatic patients only, primary tumor histology was not a predictive factor for OS in our patient cohort. Histology may be a predictive factor for patients with lung metastases [7, 45], but for liver metastases it remains unclear [9, 10, 42] and our patient numbers are too small to render any final conclusion in this regard. Furthermore, patients with a high Karnofsky performance score had a better OS, as previously noted for lung metastases [45]. A Karnofsky performance score of 90% is still quite high but there was only a relatively low number of patients with a Karnofsky score lower than 90% in our cohort (the median score was 90%). Even so we think that this statistically significant difference shows the impact of performance score for oncological outcomes and should be always taken into account also in trials examining SBRT. Interestingly, the simultaneous combination of chemotherapy and BMC-SBRT had a significant negative influence on OS in both uni- and multivariate analysis, which may likely point to the fact that those patients had further underlying systemic disease spread as compared to the typical early stage or oligometastatic cancer patient where chemotherapy is either paused or not administered at all.

The limitations to our study are inherent to its retrospective nature with inhomogeneous patients and lesions, even though we treated all patients according to strict study-like

institutional guidelines with a single dedicated treatment technique. Furthermore, we identified a low number of local recurrences which may not allow drawing any definitive conclusions from the multivariate analysis. Larger, prospective, multi-institutional patient cohorts with unified techniques or quality, longer follow-up periods, and detailed patient and dosimetry information are needed in order to validate our hypotheses further.

## Conclusions

Overall, robotic real-time breathing-motion-compensated SBRT can be an effective and safe treatment modality for solid tumors in moving organs allowing for high local tumor control rates with minimal toxicities. To reach sufficient local control rates (>90%), high mean GTV doses (>151.2 Gy<sub>10</sub>, >90 Gy<sub>15/21</sub>, and >90 Gy<sub>27</sub> for lung and liver lesions, respectively) appear to be necessary. On the other hand, if the standard practice PTV prescription dose of 3 × 15 Gy cannot be reached due to critical organ limitations, the prescription dose may be reduced to certain dose levels below the current standard with only minimal reduction in tumor control probability if a high mean GTV dose is maintained. Further studies regarding this topic are highly warranted.

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## Compliance with ethical guidelines

**Conflict of interest** S. Stera, P. Balermipas, M.K.H. Chan, S. Huttenlocher, S. Wurster, C. Keller, D. Imhoff, D. Rades, J. Dunst, C. Rödel, G. Hildebrandt and O. Blanck declare that they have no competing interests.

**Ethical standards** This retrospective analysis was approved by the local ethics committee of the medical faculty of the university Frankfurt (477/15), Rostock (A2016-0008) and Lübeck (13–218 A).

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