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ORIGINAL ARTICLE

Volume specific response criteria for brain metastases following salvage stereotactic radiosurgery and associated predictors of response

MATTHEW J. FOLLWELL[1], KATHLEEN J. KHU[2], LU CHENG[3], WEI XU[3], DAVID J. MIKULIS[4], BARBARA-ANN MILLAR[1], MAY N. TSAO[1], NORMAND J. LAPERRIERE[1], MARK BERNSTEIN[2] & ARJUN SAHGAL[1,5]

[1]*Department of Radiation Oncology, Princess Margaret Hospital, University of Toronto, Toronto, Ontario, Canada,* [2]*Division of Neurosurgery, Toronto Western Hospital, University of Toronto, Toronto, Ontario, Canada,* [3]*Department of Biostatistics, Princess Margaret Hospital, University of Toronto, Toronto, Ontario, Canada,* [4]*Department of Medical Imaging, Toronto Western Hospital, University of Toronto, Toronto, Ontario, Canada and* [5]*Department of Radiation Oncology, Sunnybrook Health Sciences Centre, University of Toronto, Toronto, Ontario, Canada*

Abstract

Background. We aimed to derive three-dimensional volume-based (V_{3D}) response criteria that approximate those based on Response Evaluation Criteria in Solid Tumours (RECIST) in patients with brain metastases (BM) treated with salvage stereotactic radiosurgery (SRS). *Material and methods.* Seventy patients with 178 BM were treated with SRS. Each BM was characterised at baseline and at each follow-up MRI according to its widest diameter and V_{3D} using ITK-SNAP image segmentation software. *Results.* The median tumour diameter was 1.2 cm (range, 0.2–4.5 cm) and V_{3D} was 0.73 cm^3 (range, 0.01–22.7 cm^3). The V_{3D} percent changes that best matched RECIST response criteria were: an increase of $\geq$71.5% for progressive disease, a $\geq$58.5% decrease for partial response and a $<$58.5% decrease or increase of $<$71.5% for stable disease (k = 0.85). A baseline diameter $>$3.0 cm (p = 0.006) and a $V_{3D} > 6.0$ cm^3 (p = 0.043) predicted for local failure, and a baseline cumulative V_{3D} of $>$3.0 cm^3 (p = 0.02) was adversely prognostic for survival. *Conclusions.* We define 3D volume specific criteria to base response upon for brain metastases treated with salvage SRS. Tumours with a V_{3D} of greater than 6 cm^3 are at a higher risk of local failure.

Response criteria for tumours in general have been traditionally based on changes in linear dimensions and not true three-dimensional (3D) volume based assessments [1]. Specific to the reported clinical trials literature for brain metastases, there have been no consistent criteria for response determination, and some have used Response Evaluation Criteria In Solid Tumours (RECIST) guidelines [1–3], some have used World Health Organization (WHO) based criteria [4,5] and others have applied locally derived criteria [6]. This heterogeneity in response classification is hazardous when comparing outcomes, and RECIST was in fact developed to overcome this barrier [1]. However, when considering how to categorise tumour response in a cohort of patients with brain metastases treated with stereotactic radiosurgery (SRS), we found the current gold standard RECIST [1] to be lacking.

The limitations of RECIST [1], and any linear dimension based criteria for that matter, include generalising the complexity of tumour geometry to a linear dimension, the difficulty in estimating the maximum tumour diameter for irregular or confluent lesions [7], discrepancies in scan planes and patient positioning can result in erroneous measurements, the number of tumours within an organ are limited to no more than five, the smallest tumour permitted to be tracked is 1 cm in maximal diameter [1], and in cases of multiple tumours the dimensions of the individual tumours are summed to yield an overall response classification [1] rather than considering each tumour independently.

Correspondence: A. Sahgal, Department of Radiation Oncology, Princess Margaret Hospital, 610 University Avenue, Toronto M5G 2M9, Ontario, Canada. Tel: +1 416 946 2000/+1 416 946 2111. E-mail: arjun.sahgal@rmp.uhn.on.ca

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With modern technology allowing for segmentation of individual tumours on diagnostic magnetic resonance (MR) images, we are now able to obtain accurate 3D volume measurements of individual lesions with relative ease. 3D volumes will undoubtedly replace the more crude and imprecise linear measurement approach, and should yield more accurate subsequent response assessments. This is particularly relevant for brain metastases, as we often treat multiple tumours, small sub-centimetre tumours, and each treated metastases should be considered biologically independent given that growth of any one lesion has a clinical impact on the patient's treatment course. However, one barrier to adopting 3D volume-based measurements has been the lack of formally recognised percent volume change criteria to base response upon. The aim of this study was to derive 3D volume-based criteria for response that best approximate RECIST classifications, and specific to brain metastases treated with SRS.

Material and methods

All patients with brain metastases treated with Gamma Knife SRS [8] between December 2005 and May 2008 were retrospectively reviewed. One hundred and nineteen patients with 287 brain metastases were identified. Patients were excluded if metastases were located within the brainstem, had been treated with the intent of boost SRS (pre- or post-WBRT within eight weeks of SRS) or if no follow-up imaging was performed. The final cohort consisted of 70 patients with 178 treated metastases (Table I).

Our first task was to classify the response of each treated brain metastases according to the RECIST [1] classifications (Table II) of partial response (PR, $>30\%$ decrease in maximum diameter), stable disease (SD $<30\%$ decrease and $<20\%$ increase in maximum diameter), and progressive disease (PD $>20\%$ increase in maximum diameter). Complete response (CR) was defined as the complete disappearance of the tumour.

The primary objective of this study was to then derive those 3D volume (V_{3D}), and calculated sphere volume (Vc), percent volume change criteria that would best approximate the response classifications defined by RECIST. Importantly, we determined response for each lesion independently, and did not sum diameters or volumes nor consider grouping targets into a single metric when multiple lesions were treated in the same patient. New metastases were not considered unless they were treated with SRS and followed, as our intent was focussed on local control of only those radiosurgerised metastases.

In our cohort, 95% of patients had been treated with salvage intent in patients previously irradiated with whole brain radiotherapy (WBRT). Therefore, our secondary objective was to determine those predictive and prognostic factors in the salvage SRS setting that can help identify patients best suited for this therapy, given that these factors are not well described in the literature.

Table I. Baseline patient and tumour characteristics (n = 70 patients, 178 metastases).

Characteristics	No.	%
Median age (range)	56 years (25–79)	
Female	39	56
Male	31	44
Performance status		
• KPS < 70	5	7
• KPS 70–80	17	25
• KPS 90–100	48	69
Primary histology		
• Lung primary	33	47
• Breast primary	9	13
• Renal cell or melanoma primary	13	19
• Other or unknown primary	15	21
Systemic disease status		
• No evidence of systemic disease	1	1
• Stable systemic disease	24	36
• Progressive systemic disease	22	30
• Synchronous systemic disease	23	33
Targets treated per patient: median (range)	1 (1–18)	
Median individual target V_{3D} (range)	0.7 cm^3 (0.01–22.7)	
Median cumulative target V_{3D} (range)	3.6 cm^3 (0.1–39.1)	
WBRT prior to SRS	161	95
No prior WBRT	17	5
Median survival (range)	15.3 months (4.6–23.3)	

KPS, karnofsky performance status; SRS, stereotactic radiosurgery, supratentorial deep lesions where those located within the basal ganglia, thalamus, or hypothalamus; V_{3D}, segmented volume; WBRT, whole brain radiotherapy.

Treatment

All patients were treated with the Gamma Knife 4C (Elekta Instruments, Atlanta, GA, USA) unit [8]. Briefly, the treatment process consists of applying a Leksell invasive stereotactic head frame for rigid head fixation on the day of SRS. Then T1-post gadolinium MRI axial images and axial T2-fluid attenuation inverse recovery images were obtained with the frame in place for subsequent treatment planning. All patients were treated with single fraction SRS. The dose guidelines were based on RTOG criteria [9]; however, modified according to the calculated volume of a sphere. Our guidelines suggest doses of 24 Gy, 21–24 Gy, 18 Gy, and 15 Gy or less for tumour volumes of <4 cm^3, 4–8 cm^3, 8–14 cm^3, and 14–30 cm^3, respectively, and typically prescribed to the 50% isodose. The doses in this study ranged from 12–24

Table II. RECIST response criteria according to Therasse et al. [1] and the derived percent volume changes that co-relate with RECIST for Vc and V_{3D} based on the present analysis.

Response	RECIST†	Vc	V_{3D}
Complete response (CR)	100% decrease	100% decrease	100% decrease
Partial response (PR)	≥30% decrease	≥65% decrease	≥58.5% decrease
Stable disease (SD)	<30% decrease or <20% increase	<65% decrease or <75% increase	<58.5% decrease or <71.5% increase
Progressive disease (PD)	≥20% increase	≥75% increase	≥71.5% increase

†RECIST definitions are based on the described established criteria according to percent change in maximum diameter [1]. The V_{3D} (segmented volume) and V_c (calculated volume) response definitions are those derived experimentally by our analyses using RECIST as the reference.

Gy (median, 24 Gy), and the prescription isodose ranged from 40–95% (median, 50%). Lower doses, and a higher prescription isodose, than those recommended were generally prescribed for lesions located near critical structures or for very large tumours.

Follow-up and treatment response

Patients were followed with gadolinium contrast-enhanced brain MRIs every 2–5 months (median, 3 months) following SRS. Using ITK-SNAP 1.8.0 image segmentation software [10] we recorded individual tumour measurements that included the true 3D segmented volume (V_{3D}), and the maximal x, y and z linear dimensions, at baseline (day of SRS) and at each subsequent follow-up image. All image segmentations were performed by a single investigator (KK) for consistency. We used the maximum linear diameter in any plane for subsequent RECIST response evaluation [1], and to determine the Vc according to $Vc = 4/3\pi r^3$ (r is the radius and determined by dividing the maximum diameter by 2). We first determined the response of each treated metastases according to RECIST, and if PD was determined (or if further intervention with surgery or whole brain radiotherapy occurred), then the tumour was censored at that time.

Statistical analysis

The primary objective of this study was to derive the V_{3D} and Vc percent volume changes for PD, SD, PR and CR, that would best approximate tumour response as classified first by RECIST criteria. The weighted Kappa co-efficient was used to evaluate the agreement using RECIST as the reference standard.

Descriptive statistics were reported with median and range for continuous variables, and frequencies and proportions for categorical variables. Association was analysed between the predictors and clinic outcomes such as local control and overall survival. Overall survival and time to PD were calculated using the Kaplan-Meier method. The Cox-proportional hazard regression model was applied to estimate the hazard ratio (HR) and 95% confidence interval (CI).

Factors analysed for predictors of local tumour control included primary cancer type, metastasis location (supratentorial, infratentorial), prescribed dose (12–15 Gy, 18–21 Gy, 24 Gy), baseline metastasis diameter (<1.0 cm, 1.0–3.0 cm, >3.0 cm) and baseline segmented volume (>6.0 cm^3 vs. ≤6.0 cm^3). Factors analysed as potential predictors of overall survival included primary cancer type, patient age (<60 years, ≥60 years), Karnofsky Performance Status (KPS) (<70, 70–80, 90–100), Recursive Partitioning Analysis [11] (RPA) category, Graded Prognostic Index [12] (GPA) score (≤2.5, >2.5), number of treated metastases (1–4, ≥4), SRS intent (salvage or primary), baseline metastasis diameter (<3.0 cm, ≥3.0 cm) and baseline cumulative total segmented volume (<3.0 cm^3, 3.0–6.0 cm^3, 6.0–10.0 cm^3, and >10.0 cm^3). Based on those significant factors ($p \leq 0.05$) identified from the univariate analyses, a multivariate analysis was performed. Two-sided tests were applied. Results were considered significant if the p-value was ≤0.05. Statistical analyses were performed using Version 9.2 of the SAS system and user's Guide (SAS Institute, Cary, NC, USA).

Results

Patient, metastasis, and treatment characteristics

Patient characteristics are reported in Table I. Thirty-seven patients (51%) were treated for a solitary brain metastasis, otherwise the number of brain metastases treated ranged from 2 to 18. The median maximum linear diameter was 1.2 cm (range, 0.2–4.5 cm), V_{3D} was 0.73 cm^3 (range, 0.01–22.7 cm^3) and Vc was 0.7 cm^3 (range, 0.004–47.1 cm^3). The most common indication for SRS was to salvage metastases in patients treated with previous WBRT (95%). The median follow-up post-SRS was 18.3 months.

Target response and concordance of Vs, Vc and RECIST

Based on RECIST criteria [1], we classified the response of each tumour treated at 3, 6, 9, 12, 18 and 24 months post-SRS with respect to CR, PR, SD and PD (Table III). We then derived the optimal percent volume changes for both V_{3D} and Vc that would yield the highest concordance with those RECIST response classifications determined at each follow-up time-point. We clearly observe in Table III the consistency in the rates of CR, PR, SD and PD at each follow-up time point according to RECIST, V_{3D}, and Vc. Based on the last follow-up assessment, the weighted kappa correlation statistic (k) for V_{3D} and RECIST was 0.85 ($p < 0.0001$), and for Vc and RECIST was 0.95 ($p < 0.0001$). Furthermore, consistency was observed when considering the median time to progression according to RECIST, V_{3D} and Vc (14, 13, and 13 months, respectively), and according to the 1 and 2 year accumulative PD rates (0.41, 0.46, and 0.45 and 0.74, 0.76 and 0.76, respectively). Those experimentally derived percent volume change criteria for V_{3D} and Vc that yielded this high level of agreement to RECIST are summarised in Table II.

Predictors and prognostic factors

We performed a univariate analyses to determine factors predictive of local control (Table IV) according to each criteria. For maximum linear diameter tumour measurements RECIST criteria apply, and we observe metastases with a baseline diameter > 3.0 cm to be at higher risk of PD (Table IV). According to V_{3D} tumour measurements, we observe a significant relationship between those tumours with a V_{3D} of ≥ 6.0 cm^3 ($p = 0.043$, Table IV, Figure 1) and a greater risk of PD. At the time of our analysis, 26 patients had died, the median survival time was 15.3 months (95% CI 8.3–20.7), and the 1- and 2-year survival probabilities were 0.54 and 0.10, respectively. Univariate analyses were performed to assess prognostic factors (Table V), and a baseline cumulative V_{3D} of < 3.0 cm^3 ($p = 0.02$) was the only factor associated with greater overall survival (Figure 2).

Discussion

The major challenge in adopting 3D volume based measurements to determine tumour response has been the lack of formalised response criteria. Several investigators have reported concordance in response categorisation when comparing uni- and bi-dimensional measurements; however, discordance when compared to 3D volumetric assessments [13,14]. The discordance is likely based on the incorrect assumption that percent volume changes extrapolated from RECIST to determine PD, SD, and PR based on a sphere volume would be valid for true 3D volume assessments. Our aim was to derive the percent volume change criteria that apply to 3D segmented tumour volume measurements, for radiosurgerised brain metastases, indexed to RECIST response criteria as the reference standard.

We first report RECIST based CR, PR, SD and PD responses for brain metastases treated with SRS. We then derived the optimal percent volume change criteria for Vc and V_{3D} measurements that best matched those RECIST-based response classifications at each follow-up time point. The consistencies in the response rates at each follow-up assessment based on RECIST, Vc and V_{3D} are clearly observed in Table III, and compare well to the published SRS literature [15]. We then summarise those derived Vc and V_{3D} percent volume change criteria for each response classification (CR, PR, SD and PD) in Table II that yielded this high level of agreement.

We first report an almost perfect concordance in Vc response classifications with RECIST ($k = 0.95$). We don't expect to see perfect agreement, i.e. a $k = 1$, as Vc is not a perfect linear function of RECIST, and the k value here is to evaluate the agreement between two response criteria that are based on corresponding

Table III. Target response rates according to RECIST, Vc and V_{3D} at each specified follow-up.

Time point (months)	RECIST (%)				Vc (%)				V_{3D} (%)			
	CR	PR	SD	PD	CR	PR	SD	PD	CR	PR	SD	PD
3	8	22	61	8	8	22	60	9	8	17	64	10
6	14	23	50	13	14	23	47	15	14	22	52	12
9	14	24	47	15	14	24	44	18	14	23	47	16
12	14	22	47	18	14	23	43	20	14	23	44	19
18	13	22	47	19	13	22	44	22	13	22	44	20
24	13	22	47	19	13	22	44	22	13	22	44	21

CR, complete response; PD, progressive disease; PR, partial response; SD, stable disease; V_c, calculated volume; V_{3D}, segmented volume. Note the derived criteria in percent volume change that yielded the consistency in the responses observed in this table at each follow-up are summarised in Table II.

Table IV. Predictors of progressive local disease.

Factor	Local control %	RECIST Global *p*-value	Vc Global *p*-value	V_{3D} Global *p*-value
Primary cancer				
• Breast	75	0.599	0.408	0.91
• RCC or melanoma	91			
• Lung	82			
• Other or unknown	75			
Location				
• Supratentorial	83	0.405	0.77	0.477
• Infratentorial	75			
Dose (cGy)				
• 1200–1500	87	0.15	0.217	0.078
• 1800–2100	78			
• 2400	79			
Metastasis diameter (cm)				
• <3.0	86	0.006	N/A	N/A
• >3.0	57			
Metastasis volume (cm^3)				
• ≤ 6	86	N/A	0.088	0.043
• >6	50			
Cumulative volume (cm^3)				
• <3.0	83	N/A	0.716	0.618
• 3.0–6.0	66			
• 6.0–10.0	44			
• >10.0	56			

N/A, not applicable; RCC, renal cell carcinoma; Vc, calculated volume; V_{3D}, segmented volume.

percentage changes. We also observe that the percent volume changes according to Vc were not the same as those we derived according to V_{3D} measurements (Table II). This reflects that true segmented 3D volume measurements (V_{3D}) are independent of those simply calculated. Our analysis supports an increase

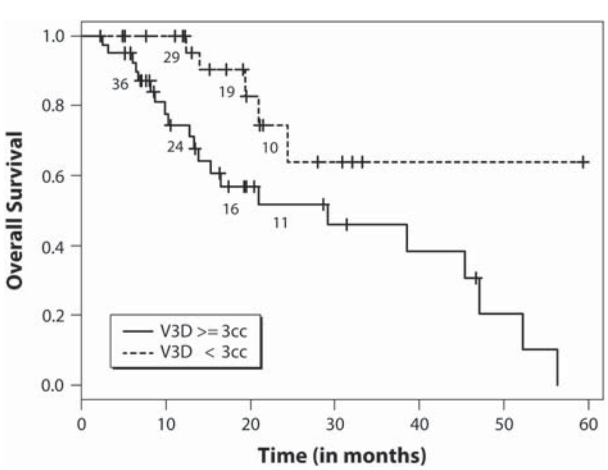

Figure 1. Intracranial progressive disease rates according to baseline segmented contrast volume (V_{3D}) >6 cm^3 vs. ≤ 6 cm^3.

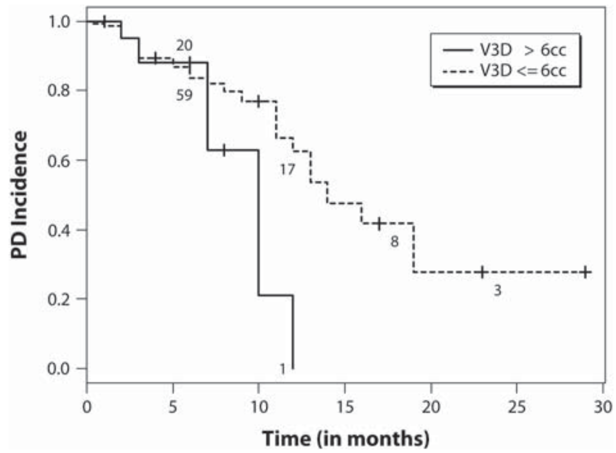

Figure 2. Overall survival distribution based on cumulative tumour baseline segmented contrast volume (V_{3D}) ≥ 3 cm^3 vs. <3 cm^3.

of at least 71.5% in V_{3D} to classify PD, a reduction in V_{3D} by at least 58.5% to classify a PR and SD classified by a reduction of less than 58.5% and an increase no more than 71.5% in V_{3D} (with RECIST

Table V. Prognostic factors for overall survival.

Factor	% alive	Global *p*-value
Primary cancer		
• Breast	73	0.423
• RCC or melanoma	71	
• Lung	70	
• Other or unknown	67	
Age		
• <60 years	63	0.634
• ≥ 60 years	64	
KPS (baseline)		
• <70	60	0.246
• 70–80	71	
• 90–100	60	
RPA (baseline)		
• 1	64	0.422
• 2	64	
• 3	50	
GPA (baseline)		
• ≤ 2.5	60	0.236
• >2.5	67	
Number of targets		
• 1–3	65	0.099
• ≥ 4	54	
Previous WBRT		
• No	67	0.896
• Yes	62	
Maximum diameter (cm)		
• <3.0	66	0.126
• ≥ 3.0	0	
Cumulative V_{3D} (cm^3)		
• <3.0	83	0.02
• ≥ 3.0	49	

GPA, graded prognostic index; KPS, karnofsky performance score; RCC, renal cell carcinoma; RPA, recursive prognostic analysis index; V_{3D}, segmented volume; WBRT, whole brain radiotherapy.

as the reference standard). Based on these derived response criteria for V_{3D} we observe a high level of agreement with RECIST as the k = 0.85.

Our secondary endpoints were to determine prognostic and predictive factors specific to salvage SRS given that 95% of our patients had been treated with prior WBRT. There is limited literature specific to this population. We observed using linear dimensions and RECIST criteria that tumours greater than 3 cm are at greater risk of PD. The relationship to increasing tumour diameter and increasing risk of PD has been well described and; therefore, our results consistent [16–20]. Based on V_{3D}, we determined a volume of 6 cm^3 as a predictive factor for PD, and this outcome is valuable given the lack of true 3D volume analysis in the literature post-SRS. A volume of 6 cm^3 roughly translates to a maximum linear diameter of 2 cm. Therefore, we are again consistent with the literature [20,21]; however, specific to V_{3D}. With respect to cumulative volume, we did not observe any relationship with individual tumour local control. This implies that each tumour should be considered independently rather than a single measure based on a sum of individual tumour dimensions. With respect to survival, we observed a cumulative V_{3D} of >3 cm^3 as a significant prognostic factor. We did not observe those traditional factors associated with survival and brain metastases as prognostic which include RPA class and GPA score. This may be a function of the patient population under study, as these well known prognostic factors were determined for patients treated upfront for brain metastases with radiation and not in patients treated with SRS as salvage post-WBRT. Within the limited literature reporting outcomes for this patient cohort, similar observations have been made [21–23].

Although the population under study is the one of the largest to be analysed with the intent of determining V_{3D} response thresholds, these criteria need to be tested in a larger population and validated. However, the statistical significance is strong and compelling such that use of these criteria is justified. Other limitations include the population under study, where 95% of patients had previous WBRT and treated with SRS as salvage. We were unable to judge with certainty whether tumours were treated for progression despite WBRT or due to new tumours developing in the previously radiated brain. This was due to the predominant use of CT at the time of WBRT, lack of imaging-based follow-up post-initial WBRT, and MR imaging only performed at the time of referral for salvage SRS. However, there are no compelling data to suggest that there is a differential response according to these two clinical scenarios. We also did not compare bi-dimensional measurements as per WHO response criteria [5]. Given that other investigators have shown concordance between determined response categories when using either RECIST or WHO [13,14], we did not feel this to be necessary and limited our analysis to RECIST. With respect to possibility of radiation necrosis resulting in a sufficient increase in tumour dimension to score PD as opposed to true PD, this is a limitation of the study. We censored treated tumours once the criteria had been met for PD, and did not bias the analysis by then retrospectively scoring those PD cases that could have been necrosis according to further imaging analysis. There are major challenges in diagnosing radiation necrosis from true PD and a definitive diagnosis can only be made upon surgical resection and pathological evaluation. Moreover, radiation necrosis is not common (~2% [6]), and we felt that it was not a factor in our patient population upon review of the imaging. Similarly, there may be some treated lesions that transiently increase in size and then stabilise or regress analogous to pseudoprogression in glioma [24]. This potential treatment effect is not well described and in our analysis occurred in only 2% of cases (data not shown). Lastly, whether these criteria are generalisable to other treatments for brain metastases (studies evaluating the response of brain metastases to chemotherapy, whole brain radiotherapy, ultrasound), or to any tumour for that matter is unknown and a subject of further study.

In conclusion, we define 3D tumour volume response criteria in a population of patients treated with SRS for brain metastases based on RECIST criteria as the reference standard. These criteria are a step forward in formalising 3D volume based tumour measurements as a future standard to replace linear-based measurements. We also observe that in the salvage setting, individual metastases with a baseline 3D volume of greater than 6 cm^3 are at higher risk of local failure, and a baseline cumulative 3D tumour volume of >3.0 cm^3 ($p = 0.020$) was adversely prognostic for survival.

Declaration of interest: None of the authors have any actual or potential conflicts of interest.

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