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Survival patterns of 5750 SRS-treated brain metastasis patients as a function of the number of lesions

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Abstract

Background—The number of brain metastases (BM) plays an important role in the decision between stereotactic radiosurgery (SRS) and whole brain radiation therapy (WBRT).

Methods—We analyzed the survival of 5750 SRS-treated BM patients as a function of BM number. Survival analyses were performed using Kaplan-Meier analysis as well as univariate and multivariate Cox proportional hazards models.

Results—BM patients were first categorized as those with 1, 2–4, and 5–10 BM based on the scheme proposed by Yamamoto et al (Lancet Oncology 2014). Median overall survival for patients with 1 BM was superior to those with 2–4 BMs (7.1 mo v. 6.4 mo, p=0.009), and survival of patients with 2–4 BMs did not differ from those with 5–10 BMs (6.4 mo v. 6.3 mo, p=0.170). The median survival of patients with >10 BMs was lower than those with 2–10 BMs (6.3 mo v. 5.5 mo, p=0.025). In a multivariate model that accounted for age, Karnofsky Performance Score (KPS), systemic disease status, tumor histology, and cumulative intracranial tumor volume (CITV), we

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observed a ~10% increase in hazard of death when comparing patients with 1 versus 2–10 BM ($p<0.001$) or 10 versus >10 BM ($p<0.001$). When BM number was modeled as a continuous variable rather than using the Yamamoto classification, we observed a step-wise 5% increase in the hazard of death for every increment of 5–6 BM ($p<0.001$).

Conclusions—The contribution of BM number to overall survival is modest, and should be considered as one of the many variables considered in the decision between SRS and WBRT.

Keywords

Stereotactic radiosurgery; brain metastasis; radiation; survival; prognostication

INTRODUCTION

An estimated 25–45% of all cancer patients develop brain metastases (BM), which is uniformly fatal if left untreated[1]. Because of the blood-brain barrier, most chemotherapy agents fail to achieve therapeutic concentration in the central nervous system. Thus, radiation remains the mainstay for BM patients who are poor surgical candidates[1,2]. Radiation can be given as whole brain radiation therapy (WBRT), where cumulative dose is fractionated in time, or stereotactic radiosurgery (SRS), where cumulative dose is fractionated in space[3]. Generally speaking, both modalities are effective in controlling tumor growth.[4] The available data suggests that the radiation modality does not significantly impact survival of BM patients[5–7], as systemic disease control remains the major determinant of overall survival[8–10]. However, with increased recognition of the deleterious neuro-cognitive effects of WBRT[11,12], increased utilization of SRS has been noted in recent studies[13,14].

One important criterion in the deliberation between WBRT and SRS involves the number of metastases[15]. WBRT is generally used as treatment for patients with a high number of BM, while SRS is typically considered for patients with a limited number of BM[16,17]. The threshold for this determination remains an area of active research. The early randomized controlled studies of SRS were designed to test efficacy in patients with <4 BM[4,5], with the implication that WBRT should be considered for patients with >4 BM. This framework was challenged by the landmark study by Yamamoto et al.[18], demonstrating similar survival patterns for SRS-treated BM patients with 2–4 versus 5–10 BM. Despite these studies, the published literature addressing this matter remains limited. Here, we examined the issue using a collated database of 5750 consecutive BM patients. Our results indicate that the contribution of BM number to survival is modest and should be considered as one of the many variables in the decision between SRS and WBRT.

METHODS

Study Cohort

All data was collected under Institutional Review Board (IRB) approved retrospective reviews at all involved institutions. Data was compiled by the four co-senior authors (AH, RS, MY, and CCC) and represents consecutive BM patients treated with SRS from 1994–2014. Each patient had confirmed histologic diagnosis and underwent SRS without surgical

resection based on the recommendation of a multidisciplinary brain tumor board. Patients who underwent surgical resection of BM were not included in this study. In total, 124 patients were collected by AH (Melanoma Institute of Australia, Wollstonecraft, Australia), 3067 patients by TS (Tsukiji Neurological Clinic, Tokyo, Japan), 2504 by MY (Katsuta Hospital Mito GammaHouse, Hitachinaka, Japan), and 1180 by CCC (University of California, San Diego, USA).

All patients in our retrospective study were deceased at the time of data compilation. Follow-up on vital status in the US cohort was performed using the social security death index. Only patients with cancer of the breast, gastrointestional tract (GI), lung, kidney, and melanoma were included in the study. The compiled dataset includes a total of 5750 patients. Missing information was found in 408 patients (7% of the studied population).

Radiosurgery Technique

Radiosurgery was performed as previously described[19,20]. In brief, patients underwent Magnetic Resonance Imaging (MRI) of the brain with either the Toshiba America Medical Systems MRI machine (Tustin, California) at 2 mm slices or the GE Healthcare MRI machine (Milwaukee, Wisconsin) using 1 mm slices in conjunction with the Leksell stereotactic head frame. MRI was performed using axial and coronal T1-weighted pre- and post-contrast sequences. Following the initial MR radiography, cases underwent review by a team consisting of at least one of each of the following specialists: neurosurgeon, radiation oncologist, and medical physicist. Planning of the radiation dose for each of the metastases was performed using the Elekta Gamma Plan software. The calculated dose was given to the 50% isodose line in all patients. Generally speaking, dosing was in line with the RTOG 95-08 clinical trial[4]. Patients' clinical presentation/status, number of metastases, tumor volume, and prior or planned WBRT were all weighed prior to the final determination of dosage. Doses to particularly sensitive areas of the brain such as the optic nerve and brainstem were limited to 10 Gy and 18 Gy respectively with no single dose of radiation exceeding 24 Gy.

Clinical parameters and modeling

Patient and BM characteristics (age, Karnofsky Performance status [KPS], systemic disease status, tumor histology, cumulative intracranial tumor volume [CITV], and number of metastasis) were collected at the time of presentation for the initial radiosurgery. Overall survival was determined from the time of the initial SRS to the time of death. Based on the classification scheme utilized by the previous prospective study by Yamamoto et al.[18], patients were initially stratified as presenting with 1, 2–4, 5–10, or >10 BM. For each cohort, Kaplan-Meier survival plots were created and median overall survival times were calculated. Univariate Cox proportional hazards models were then created to examine the influence of age, KPS, CITV, systemic disease control, tumor histology, and number of metastases (1, 2–4, 5–10, >10) on survival. Because overall survival did not significantly differ between patients who presented with 2–4 and 5–10 BM, these categories were ultimately collapsed into a single category of 2–10 BM. A multivariate cox proportional hazards model was then used to test whether the risk of death differed between patients who presented with 1, 2–10,

and >10 BM after accounting for age, KPS, CITV, systemic disease control, and tumor histology.

Statistical analysis

All statistical analyses and figure generation were performed using R version 3.3.1 with all p-values < 0.05 considered significant. The R package “Survival” was used in order to create Kaplan-Meier (KM) plots, as well as to perform the corresponding multivariate Cox proportional hazards (CPH) model regression. The R package “tableone” was used to create the demographics table.

RESULTS

Patient demographics and tumor characteristics

Patient characteristics stratified by primary tumor histology are provided in Table 1. The predominant cancer type in this study was lung (n=3746), followed by breast (n=710), GI (n=692), renal cell carcinoma (n=321), and melanoma (n=282). There were 1753 patients with 1 BM, 1872 patients with 2–4 BM, 1144 patients with 5–10 BM, and 981 patients with >10 BM. Of the four centers participating in this study, we found that patients treated in the U.S. center were more likely to harbor single BM relative to the Japanese and Australian Centers (Supplemental Table 1). The distribution of age ($p=0.138$) and KPS ($p=0.130$) were similar across BM number categories. Gender, systemic disease status, and primary tumor pathology differed between each of the metastasis groupings ($p<0.001$). Lastly, CITV increased with the number of BM ($p<0.001$).

Median survival of SRS-treated patients

The median follow-up of the cohort was 6.4 months. Kaplan-Meier (KM) plots were generated for patients with 1, 2–4, 5–10, and >10 BM (Figure 1). Median overall survival for patients with 1 BM was superior to those with 2–4 BMs (7.1 mo v. 6.4 mo, respectively, $p=0.009$) (Table 2). The median survival of patients with 2–4 BMs did not significantly differ from those with 5–10 BMs (6.4 mo v. 6.3 mo, respectively, $p=0.170$), while the median survival of patients with >10 BMs was lower than that of patients with either 2–4 or 5–10 BMs (6.3 mo v. 5.5 mo, respectively, $p=0.025$). Based on these initial observations, we performed all subsequent analyses with both the original groupings and the new groupings combining the 2–4 and 5–10 categories. A similar set of KM plots was created for the new metastasis groupings (Figure 2).

We next imposed the selection criteria previously imposed by Yamamoto et al in the landmark prospective study[18] and repeated our analysis after excluding patients that did not fulfill these criteria. This repeat analysis revealed survival estimates whose confidence intervals overlap those reported by Yamamoto et al. (Table 3).

Univariate survival analysis

In a univariate Cox proportional hazards model (Table 4), we found that patient age, KPS, systemic disease status, CITV, and tumor histology were each independently associated with overall survival. In terms of BM, the hazard ratio (HR) of death for patients with 1 BM

significantly differed from those with 2–4 BM (*p=0.010)*. When comparing patients with 2–4 and 5–10 BM, the risk of death was similar (*p=0.170*). Finally, the HR of death was lower in patients who presented with 5–10 BM relative to those with >10 BM (*p=0.025*).

Multivariate survival analysis

We next created a multivariate Cox proportional hazards model to determine whether BM-number category remains a significant predictor of survival after accounting for patient age, KPS, systemic disease status, CITV, and tumor histology. Given that the median overall survival analysis and univariate Cox models both suggested no significant difference between patients who presented with 2–4 and 5–10 BM, these two categories were combined in the multivariate analysis (right columns of Table 5). As shown in Table 5, all variables that were significant in univariate analysis remain statistically significant in the multivariate model. We found that the hazard of death for patients with 2–10 BM was increased by 11% relative to those with 1 BM (*p<0.001*). The hazard of death for patients with 2–10 BM was increased by 14% relative to those with >10 BM (*p<0.001*).

Model comparison

We wished to use an established statistical metric to assess how collapsing the 2–4 and 5–10 groupings into a single category would impact the prognostic utility of our model. Akaike Information Criteria (AIC) is a commonly used metric in this regard. It determines how well a model explains the data, while penalizing incorporation of variables that do not contribute to this process. Typically, an AIC difference of ≥2 between models implies that the model with the lower AIC is superior with statistical significance[21]. As shown in Table 5, the model with the old groupings had an AIC of 80238 and the new grouping model had an AIC of 80203, with a difference of 35. As the only change performed was the grouping of the middle two categories, we can attribute the improvement directly to the combination of BM categories.

Analysis by primary cancer histology

We wished to determine whether the survival association with BM number remains robust after stratification by the primary cancer histology. Kaplan-Meier survival analysis was separately performed for SRS-treated BM patients suffering from lung, melanoma, renal cell, GI, and breast cancer (Fig 3). In lung, melanoma, renal cell, and GI patients, the survival association with BM number (classified based on the Yamamoto scheme) remained robust. However, no significant survival difference was observed between breast cancer patients suffering from 1, 2–10, and > 10 BM.

Analysis of hazard ratio as a function of BM number

We next examined the HR of death as a function of BM number treated as a continuous variable rather than based on the Yamamoto scheme[18]. We performed a multivariate Cox proportional hazards model to determine the risk of death by increasing BM after accounting for patient age, KPS, systemic disease status, CITV, and tumor histology. Since we did not find robust association between BM number and overall survival in breast cancer patients, we excluded the breast cancer patient cohort in this analysis. In Figure 4, we plotted the

increase in HR for the number of BM relative to the previous number of BM. For instance, the HR indicated by two on the abscissa is the relative risk of death for patients with 2 or fewer BM relative to those suffering from 3 or greater BM. In this analysis, we did not observe a continuous increase in the hazard of death for every increment of one BM. Instead, we observed a step-wise increase in the hazard of death, with an ~4% increase for every increment of 6–7 BM ($p<0.001$).

DISCUSSION

In clinical practice, the number of metastases plays a key role in the determination of optimal radiation modality for an individual BM patient. Here, using rigorous statistical methodologies, we show that the contribution of BM number to survival is relatively modest and constitutes only one of the many variables that should be considered in the decision between SRS and WBRT. In our collated dataset of 5750 SRS-treated BM patients, we observed an approximate ~10% increase in hazard of death when comparing patients with 1 versus 2–10 BM ($p<0.001$) or 2–10 versus >10 BM ($p<0.001$). When BM number is modeled as a continuous variable rather than based on the Yamamoto classification of 1, 2–10, and >10, we observed stepwise 4% increase in the hazard of death for every increment of 6–7 BM ($p<0.001$). Importantly, these survival effects were rigorously calculated after controlling for key clinical variables previously shown to influence survival, including age, KPS, systemic disease status, and CITV. Since the contribution of BM number to survival is modest, it should be considered in the greater clinical context in the decision between SRS and WBRT. The considerations for an 80-year-old lung cancer patient with 10 BM, KPS <50, uncontrolled systemic disease, and a CITV of 20cc who has exhausted all medical options are different relative to another patient with 10 BM who is a 40-year-old afflicted with HER2+ breast cancer with KPS of 100, CITV of <4cc, and systemically controlled cancer.

Consistent with results reported by Yamamoto et al.[18], we found that the relative survival pattern of patients afflicted with a single metastasis is more favorable than those afflicted with 2–4, 5–10, and >10 metastases. Also consistent was our finding that the survival patterns of SRS-treated patients with 2–4 and 5–10 metastases were comparable. While the absolute survival interval differed between our study and the Yamamoto study, these differences were entirely due to patient selection. Our study examined the outcome of all patients treated by the authors during the study period, while the Yamamoto study[18] prospectively enrolled patients with, for instance, KPS>70, CITV<15cc, and a reasonable survival expectation. When we repeated analysis of our data after imposing the criteria of the Yamamoto study, the median overall survivals obtained were comparable (Table 3). The apparent difference in the survival intervals between these two studies highlights the challenges in generalizing data from trials involving selected cohorts to the general patient population that clinicians treat on a daily basis[22,23].

In order to address the interaction between the number of metastases and CITV, we employed a statistical model that examined both variables and found that both independently contribute to survival. In broad strokes, this finding translates into the following. In terms of tumor volume, a SRS-treated patient with 10 “small” BM is expected to exhibit better

survival than a SRS-treated patient with 10 “big” BM. In terms of tumor number, a SRS-treated patient with two BM is expected to exhibit improved survival relative to a SRS-treated patients with six BM. Most interestingly, the number of BM continues to be an important prognosticator after controlling for CITV. This finding implies that given two patients with the same CITV, a patient with 2 BM is expected to survive longer than another patient with 10 BM. The biologic basis for this finding remains unclear.

In our study, we did not observe a robust association between the number of BM and survival in breast cancer patients. This finding is consistent with the published disease-specific graded prognostic scale (ds-GPA) for SRS-treated breast cancer patients, where the number of BM was not a prognostic variable.[9] In contrast, the number of BM was a prognostic variable for SRS-treated BM patients suffering from lung cancer, melanoma, and renal cell cancer in ds-GPA. Robust association between BM number and survival were observed in our study as well (Figure 2, Tables 4 and 5).

Significant survival gains have been made in recent years for a small subset of patients because of targeted therapy[24] or immunotherapy[25,26]. In non-small cell lung cancer, for instance, it is estimated that <25 % of all patients derive genuine benefit from these therapies[27–29]. While there is significant interest in studying the impact of SRS in these patients, we should not lose sight of the clinical need to study the population who does not derive benefit from targeted or immunotherapy. Our study is important in this regard. Only the tail end of our study period overlaps with the routine use of targeted or immunotherapy[30,31], and nearly all of our study population was not exposed to these therapies. As such, this study provides insights into the survival prognostication for majority of the BM patients who are not treated with targeted therapy or immunotherapy.

There are several inherent limitations to a retrospective multinational cohort study involving patients treated by different practitioners. The remarkable agreement between our results and those observed in a prospective observation study[18], however, supports the robustness of the reported findings. It is likely that pooling cohorts from multiple institutions and practitioners minimizes the impact of the inter-institutional variation in criteria of patient selection. The large sample size of this study should also mitigate the impact of patient specific variables on the reported results[32,33]. The lack of neuro-cognitive[11] and quality of life measures[34] in our study represents another limitation. While overall survival is an important outcome measure, considerations should also be given to the anticipated neuro-cognitive and quality of life deficits, as well as the risk for the development of distant metastasis[12,14,35]. Finally, though our study provides useful information for the majority of SRS-treated BM patients who are not treated with targeted or immunotherapy, there is a critical need to study the interaction between SRS and these agents. Unfortunately, our dataset provides little insight in this regard.

CONCLUSION

In our analysis of 5750 SRS-treated BM patients, we found a step-wise 4% increase in the hazard of death for every increment of 6–7 BM ($p<0.001$). This quantitative survival

association should be considered in the broader clinical context to personalize radiosurgery care for BM patients.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Abbreviation list in order of appearance

SRS	stereotactic radiosurgery
BM	brain metastasis(es)
WBRT	whole brain radiation therapy
RCC	renal cell carcinoma
KPS	Karnofsky Performance Score
CITV	cumulative intracranial volume
IRB	institutional review board
MRI	magnetic resonance imaging
RTOG	Radiation Therapy Oncology Group
Gy	Gray
KM	Kaplan-Meier
AIC	Akaike Information Criteria

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Highlights

- Here we present an analysis of a multi-institutional international cohort (n=5750) consisting of patients undergoing SRS for one or more brain metastases.
- The survival analyses performed include: Kaplan-Meier analysis, univariable and multivariable Cox proportional hazards, and Akaike Information Criteria comparison.
- There are different survival patterns for SRS-treated patients afflicted with 1, 2–10, and >10 BM, with an approximate 10% increment in the hazard ratios of death between these BM categories.
- On continuous analysis, our findings demonstrate a 4% increase in hazard of death for every increase of 6–7 metastases.

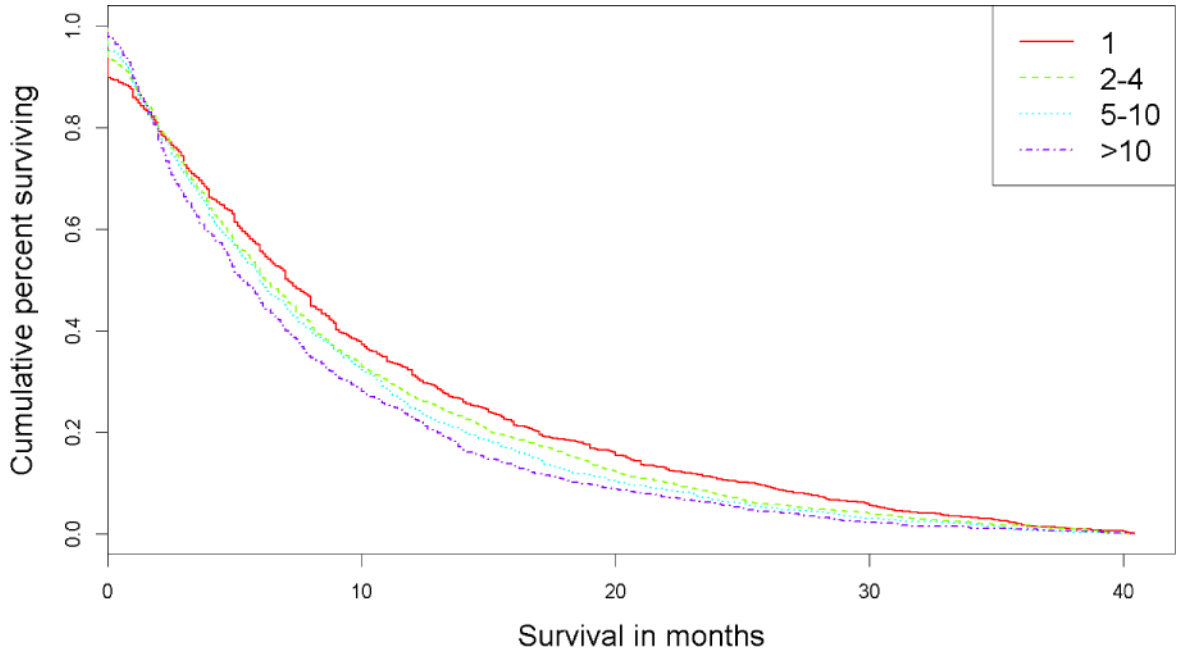

Figure 1.
Kaplan-Meier survival plot for original groupings

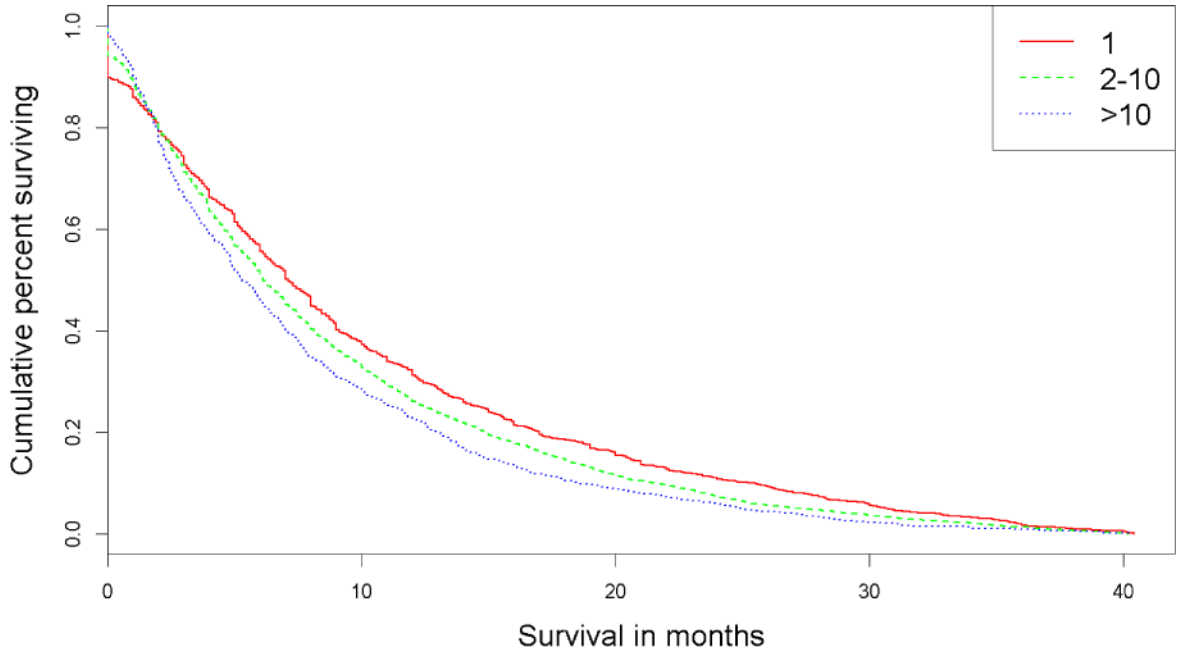

Figure 2.
Kaplan-Meier survival plot for condensed groupings

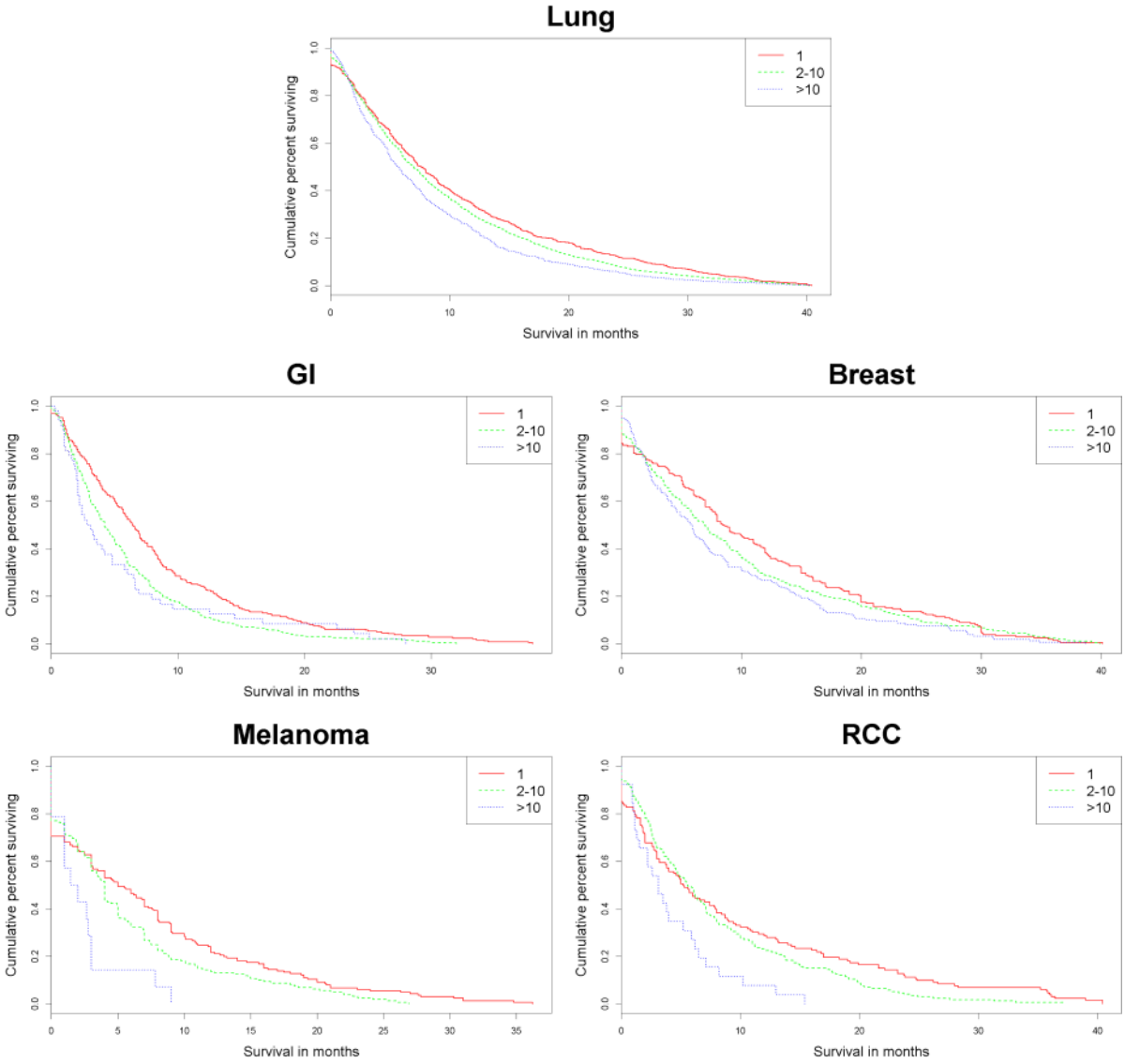

Figure 3.
Histology specific Kaplan-Meier survival plots

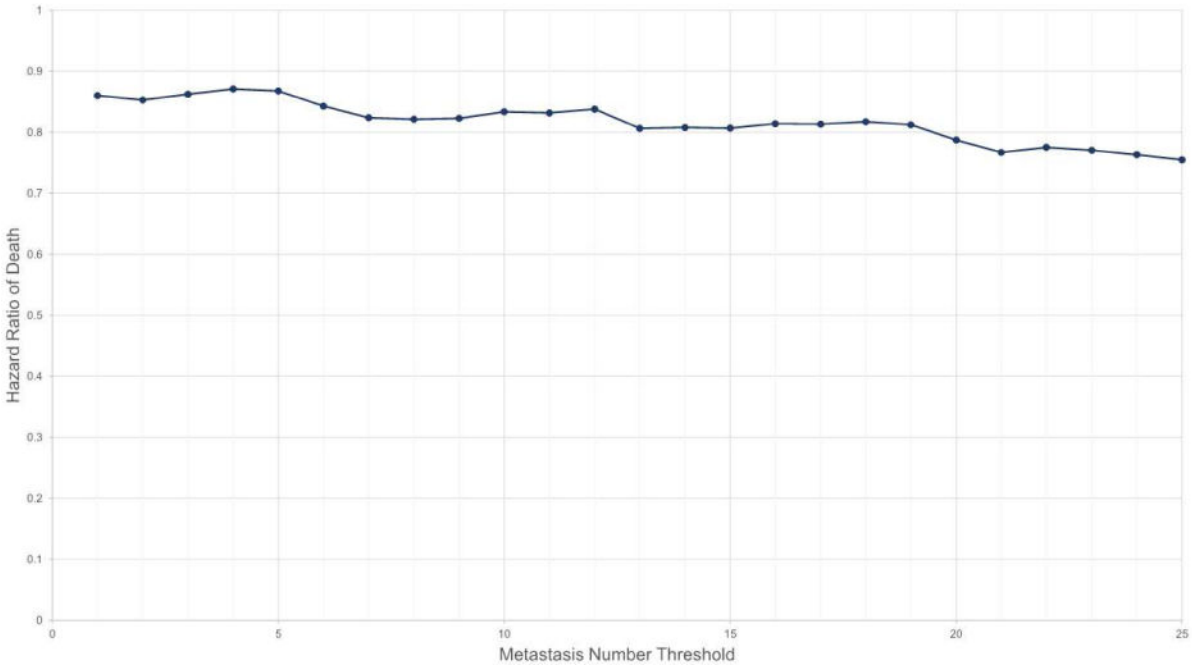

Figure 4.
Cox proportional hazards analysis by stepwise increments of metastasis number

Table 1

Demographics by primary tumor histology

	Breast	GI	Lung	Melanoma	RCC	p
n	710	692	3745	282	321	
Sex = M (%)	5 (0.7)	464 (67.1)	2556 68.3)	186 (66.0)	199 (62.0)	<0.001
Age (mean (sd))	55.72 (11.79)	65.89 (10.09)	65.29 (10.66)	57.95 (15.34)	62.40 (12.24)	<0.001
KPS (%)						<0.001
<70	81 (11.7)	135 (19.6)	289 (7.8)	36 (14.4)	58 (18.5)	
70–80	257 (37.1)	313 (45.4)	1092 (29.5)	122 (48.8)	121 (38.5)	
90–100	355 (51.2)	242 (35.1)	2324 (62.7)	92 (36.8)	135 (43.0)	
Systemic disease control (%)	166 (27.6)	47 (7.3)	352 (9.8)	16 (5.7)	24 (7.9)	<0.001
CITV (median [IQR])	6.90 [2.50, 16.45]	9.17 [4.40, 16.44]	3.75 [1.27, 9.58]	1.99 [0.65, 5.52]	5.35 [2.20, 10.30]	<0.001
Number of metastases (%)						<0.001
1	201 (28.3)	263 (38.0)	1003 (26.8)	155 (55.0)	131 (40.8)	
2–4	202 (28.5)	262 (37.9)	1200 (32.0)	96 (34.0)	112 (34.9)	
5–10	156 (22.0)	119 (17.2)	792 (21.1)	24 (8.5)	53 (16.5)	
10+	151 (21.3)	48 (6.9)	750 (20.0)	7 (2.5)	25 (7.8)	

Note: Percentages refer to percent of individual strata e.g. 0.7% of breast cancer patients were male.

Table 2

Median overall survival time by metastasis grouping

Original number of metastasis groupings	**1**	**2–4**	**5–10**	**>10**
Median Survival in Months	7.1	6.4	6.3	5.5
Collapsed number of metastasis groupings	**1**	**2–10**		**>10**
Median Survival in Months	7.1	6.4		5.5

Table 3

Median overall survival of patients who satisfy inclusion criteria by Yamamoto et al.[18]

Number of Brain metastases	Current cohort	Yamamoto et al 2014[18]
1	11.5 (10.5–12.2)	13.9 (12.0–15.6)
2–4	10.7 (10.0–11.4)	10.8 (9.4–12.4)
5–10	10.5 (9.9–11.4)	10.8 (9.1–12.7)

Median overall survival shown with 95% confidence interval in parentheses

Table 4

Univariate Cox proportional hazards model for both metastasis groupings

Original Groupings				**New groupings**		
	Reference	**Hazard Ratio**	**P value**	**Reference**	**Hazard Ratio**	**P value**
Number of Metastases	**1** vs 2–4	1.090	0.010	**1** vs 2–10	1.111	<.001
	2–4 vs 5–10	1.053		**2–10** vs >10	1.139	<.001
	5–10 vs >10	1.102	0.025			
Age (years)		1.005	<.001		1.005	<.001
KPS (points)		0.977	<.001		0.977	<.001
CITV (cc)		1.015	<.001		1.015	<.001
Systemic disease status	uncontrolled	0.511	<.001	uncontrolled	0.511	<.001
Breast vs. other histology	Other histology	0.885	0.002	Other histology	0.885	0.002

Note: Categories with no reference group were continuous variables, and their corresponding hazard ratios refer to an increment of 1 of their respective units.

Table 5

Multivariate Cox proportional hazards model for both metastasis groupings

Original Groupings				**New groupings**		
	Reference	**Hazard Ratio**	**P value**	**Reference**	**Hazard Ratio**	**P value**
Number of Metastases	**1** vs 2–4	1.103	0.005	**1** vs 2–10	1.110	0.001
	2–4 vs 5–10	1.015		**2–10** vs >10	1.128	0.002
	5–10 vs >10	1.117	0.014			
Age (years)		1.003	0.015		1.003	0.015
KPS (points)		0.979	<.001		0.979	<.001
CITV (cc)		1.007	<.001		1.007	<.001
Systemic disease Status	uncontrolled	0.582	<.001	uncontrolled	0.582	<.001
Breast vs other histology	Other histology	0.838	0.000	Other histology	0.839	<.001
AIC	80238			80203		

Note: Categories with no reference group were continuous variables, and their corresponding hazard ratios refer to an increment of 1 of their respective units.