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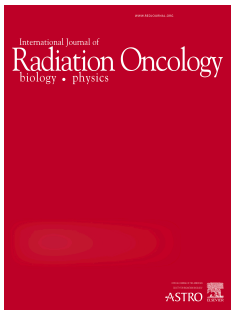

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Single-fraction versus multi-fraction (3 x 9 Gy) stereotactic radiosurgery for large (> 2 cm) brain metastases: a comparative analysis of local control and risk of radiation-induced brain necrosis

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Key words: brain metastases, stereotactic radiosurgery, survival, radiation-induced complications, brain necrosis.

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Disclosure of interest

The authors have no conflicts of interest to declare.

Summary

Stereotactic radiosurgery (SRS) is an effective treatment in patients with brain metastases, although a worse local control and higher risk of radiation-induced brain necrosis have been observed in patients with large lesions. For patients with brain matastases >2 cm in size, our study shows that multi-fraction SRS at doses of 27 Gy in three daily fractions is associated with better local control and a reduced risk of brain necrosis as compared with single-fraction SRS.

Single-fraction versus multi-fraction (3 x 9 Gy) stereotactic radiosurgery for large (> 2 cm) brain metastases: a comparative analysis of local control and risk of radiation-induced brain necrosis

Abstract

Purpose: to investigate the factors affecting local control and radiation-induced brain necrosis in patients with brain metastases >2 cm in size who received single-fraction or multi-fraction stereotactic radiosurgery (SRS). Factors associated with the clinical outcomes and the development of brain radionecrosis have been assessed.

Patients and Methods: Two hundred and eighty-nine consecutive patients with brain metastases >2.0 cm who received SRS as primary treatment at XXXX were analyzed. Cumulative incidence analysis was used to compare local control and radiation-induced brain necrosis between groups from the time of SRS. To achieve a balanced distribution of baseline covariates between treatment groups, a propensity score analysis were used.

Results: The 1-year cumulative local control rates were 77% in single-fraction SRS (SF-SRS) group and 91% in multi-fraction SRS (MF-SRS) group (p=0.01). Recurrences occurred in 25 and 11 patients who received SF-SRS or MF-SRS (p=0.03), respectively. Thirty-one (20%) patients undergoing SF-SRS and 11 (8%) subjected to MF-SRS experienced brain radionecrosis (p=0.004); the 1-year cumulative incidence rates of radionecrosis were 18% and 9% (p=0.01), respectively. Significant differences between the two groups in terms of local control and risk of radionecrosis were maintained after propensity score adjustment.

Conclusions: In conclusion, MF-SRS at doses of 27 Gy in three daily fractions appears to be an effective treatment modality for large brain metastases

associated with better local control and a reduced risk of radiation-induced radionecrosis as compared with SF-SRS.

Introduction

Stereotactic radiosurgery (SRS) alone has become an increasingly treatment option in the initial management of patients with brain metastases. Its efficacy has been demonstrated in randomized trials that report a local control (LC) of approximately 75% at 1 year and survival benefit similar to that observed with the use of SRS plus whole-brain radiation therapy (WBRT) (1-3).

The most common late-delayed radiation effect of SRS is the development of brain radionecrosis (RN), which is associated with the presence of different degrees of neurological deficits in up to one third of patients (4-6). Factors correlated with the development of RN are the radiation dose, the tumor volume, the use of chemotherapy, and the volume of normal brain irradiated at specific doses (5-10). Using the normal brain volume exposed to 12 Gy ($V_{12\text{-}Gy}$) during SRS to predict the risk of developing RN, a few studies have observed an occurrence of necrosis up to 60% for $V_{12\text{-}Gy}$>10 cm^3 (4-7), and this is likely to happen when treating large lesions.

Multi-fraction SRS (MF-SRS, 2-5 fractions) has been employed as an alternative to single-fraction SRS (SF-SRS) with the aim to reduce the incidence of late radiation-induced toxicity while maintaining high local control rates. Using doses

of 24-35 Gy given in 3-5 fractions, a few retrospective studies have reported a local control from 70% to 90% at 1 year, with a variable risk of RN in the range of 2-15% (11-14).

In the present study we have evaluated the LC and incidence of RN in patients who received SF-SRS or MF-SRS (3x9 Gy) for brain metastases >2 cm in size. Related factors associated with the clinical outcomes and the development of RN have been assessed.

Patients and Methods

Between September 2008 and October 2014, 354 consecutive patients ≥18 years old with cerebral metastases >2 cm in size on contrast-enhanced magnetic resonance imaging (MRI) derived from an histologically confirmed systemic cancer, and who received SF-SRS or MF-SRS (3x9 Gy), were retrospectively evaluated. All radiographic, surgical, and pathologic information were drawn from a prospectively maintained database of patients with brain tumors treated at XXXXXX. Sixty-five patients were excluded due to insufficient clinical information (n=14), prior WBRT (n=18), different radiation schedules used to treat brainstem metastases (3x7 Gy;n=11), or skull base metastases involving the optic pathway (5x5 Gy;n= 22). Finally, a total of 289 patients remained in the final analysis. The Institutional Review Board approved the study.

All metastatic tumors were treated with LINAC-based SRS using a commercial

stereotactic mask fixation system in conjunction with the IPlan treatment planning system (BrainLab). In each patient, the gross tumor volume (GTV) was delineated using postcontrast thin-slice (1-mm) gadolinium-enhanced T1-weighted axial MRI sequences fused with planning computed tomography (CT) scans. The clinical tumor volume (CTV) was a zero-margin-expansion of the GTV. A 2-mm margin was geometrically added to GTV/CTV to generate the planning target volume (PTV) in 165 metastases (2008-2011; SF-SRS, 88; MF-SRS, 77); subsequently, the margin was reduced to 1 mm (SF-SRS, 96; MF-SRS, 84). For patients who received SF-SRS, doses were 18 Gy for metastases of 2-3 cm and 15-16 Gy for metastases ≥3 cm in size. MF-SRS was most commonly used to treat brain metastases ≥3 cm in size or located in close proximity to critical areas. Using the linear quadratic model for the estimation of dose-effect relationship adjusted for high doses (15), the biological effective dose (BED) of multi-fraction SRS at doses of 27 Gy in 3 fractions was 40 Gy assuming an α/β of 12 Gy for brain metastases (BED_{12}), corresponding to a single dose of about 22 Gy. Doses were prescribed to the 80-90% isodose line to achieve a minimum 95% target coverage of the prescribed dose. Treatment volumes were achieved with 6-15 noncoplanar dynamic arcs or fixed beams. CT imaging and the ExacTrac® image-guided system (from 2012) were used for setup verification before each fraction.

Patients were examined clinically one month after SRS and then every 2 months. MRI was made every 2 months in the first year after the treatment, and then every 3-4 months or as appropriate. Complete and partial responses were

defined as total radiographic disappearance of lesion or decrease in tumor volume >50%. At each visit, the neurological status and the severity of complications were rated according to Radiation Therapy Oncology Group (RTOG) central nervous system (CNS) toxicity criteria.

Diagnoses of tumor progression or RN were determined on the basis of histologic findings (in patients who underwent surgical resection) or by imaging using MRI and 3,4-dihydroxy-6-(18)F-fluoro-l-phenylalanine (F-DOPA) PET-CT, with a sensitivity of 86.7% and 90% and a specificity of 92.3% and 68.2%, respectively (16). In summary, tumor progression was defined as any increase of tumor on contrast-enhanced T1-weighted images in at least two subsequent MRI studies associated with: - a cerebral blood volume ratio (rCBV) >2.0 at dynamic susceptibility-weighted contrast-enhanced perfusion images (calculated for each lesion by dividing the tumor CBV by the mean CBV value of normal white matter), and – a maximum lesion to maximum background uptake ratio ($SUVL_{max}/Bkgr_{max}$) >1.59 at F-DOPA PET-CT. Stable or shrinking lesions over a 6-month period associated with: - a rCBV <2.0 and – a $SUVL_{max}/Bkgr_{max}$ <1.59 were diagnosed as RN. Distant failure was defined by the presence of new brain metastases or leptomeningeal enhancement outside the PTV.

Data analysis

Overall survival (OS) was estimated using the Kaplan-Meier method from the date of SRS to the date of death from any cause, or censored at the date of last

follow-up for survivors. As censoring patients at time of death with Kaplan-Meier method would lead to biased probability of LC and occurrence of RN given the high rate of death in patient population, cumulative incidence curves and Gray's test (17) were used to compare - the distant brain control rates accounting for death as competing risk, and – LC and RN rates accounting for either death or distant brain progression treated with WBRT as salvage therapy or local relapse (RN analysis) as competing risks. Patients who did not experience an event were censored at the time of the last follow-up. Chi-Square and non-parametric Mann-Whitney tests were used to examine between-group covariate differences, and the Cox proportional hazards model was employed for univariate and multivariate analysis to assess the effects of clinical/treatment variables on clinical outcomes. Variables at significance levels of $p<0.1$ were included in multivariate analysis. According to previous published risk prediction models of RN (5,6,14), we have analyzed the correlation between $V_{12\text{-Gy}}$ (SF-SRS) or $V_{18\text{-Gy}}$ (MF-SRS) and the risk of RN.

To avoid the effects of confounding variables on LC and risk of RN due to the non-randomized comparisons of groups, a propensity score matching was used to achieve a balanced distribution of baseline covariates (18). Using SRS as dependent variable (control condition, SF-SRS), patients and controls were matched one-to-one by nearest-neighbor method, using a caliper distance of width equal to 0.2 of the standard deviation of the pooled propensity scores. Covariates presumed to influence LC and development of RN from univariate analysis were included in a propensity score-matched analysis as independent

variables to allow more patients to be compared. The adjusted treatment groups were assessed for balance, using the overall Chi-Square balance test and the relative multivariate imbalance measure (L1) (19,20). In addition, significant differences in treatment characteristics were adjusted using the inverse-probability-of-treatment weighting (IPTW) propensity score method (21). Independent covariates included age at diagnosis, gender, histology, number of metastases, extracranial disease, and irradiated volumes. The discrimination and calibration abilities of each propensity score model were assessed using the C statistic and the Hosmer-Lemeshow statistic. The Cox proportional hazards model was applied using PS-based matching for estimating treatment effects. Gray's test was used to test for differences in the cumulative incidence of LC and RN between groups. Standard softwares were used for statistical analysis (SAS software, version 9.3; XLSTAT).

Results

Patient characteristics and survivals

A total of 289 consecutive patients with 343 metastases >2 cm in size were analyzed. Patient characteristics are shown in Table 1. One hundred and fifty-one patients received SF-SRS and 138 patients received MF-SRS. Two hundred and sixty-one received one or two lines of therapy prior to SRS. There were no statistically significant differences between groups in terms of gender, age, histology, KPS scores, the diagnosis-specific graded prognostic assessment

score (DS-GPA) (22), site of tumor, and conformity index (as defined by the prescribed isodose volume/tumor volume encompassed by the prescription isodose volume). However, patients given SF-SRS were more likely to have smaller GTV and PTV. At the time of analysis (May 2015), 47 patients were still alive (single-fraction SRS, 16; multi-fraction SRS, 31).

At a median follow-up study of 29 months, median and 1-year OS were 13.4 months and 54% (95%CI, 45-62%), respectively (Figure 1). The cumulative incidence rates of distant brain failure at one year was 40% (95%CI, 34-46%) (Figure 2). One-year OS and distant brain failure did not differ significantly by groups: SF-SRS, 53% (95%CI, 36-70%) and 41% (95%CI, 34-49%); MF-SRS, 56% (95%CI, 39-74%) and 39% (95%CI, 31-48%).

A clinical neurological improvement of pre-SRS existing symptoms was recorded in 47 out of 78 patients (60%), being similar between groups (p=0.15). One hundred and ninety-one patients succumbed to their extracranial disease and 51 patients died of progressive intracranial disease. Salvage therapies for intracranial progression included surgery (21), WBRT (57), and SRS (68) given alone or in combination. For progressive disease, 178 patients received chemotherapy (104) and/or molecular targeted agents (74), including erlotinib (n=28), trastuzumab (n=6), bevacizumab (n=8), sunitinib (n=5), everolimus (n=7), lapatinib (n=6), ipilimumab (n=4), vemurafenib (n=2), pembrolizumab (n=3), or other agents (n=11).

In the multivariate analysis, stable extracranial disease, breast cancer histology and KPS >70 emerged as significant indices of prolonged OS. According to the DS-GPA score, median survival times were 7.6, 14 and 22.5 months in patients with scores of 0-1, 1-2.5, and 3-4 (p=0.001), respectively. The presence of multiple metastases (p=0.04) and melanoma histology (p=0.03) were associated with an increased risk of distant failure.

Local control

After a median radiological follow-up of 10 months, 25 lesions in SF-SRS group and 11 lesions in MF-SRS group recurred (p=0.03), as suggested by imaging; median times to progression were 10 months (range, 6–42 months) and 12 months (range, 6–27 months), respectively. Diagnosis of recurrence/progression was made by imaging in 21 patients (multi-fraction SRS, 6/11; single-fraction SRS, 14/25) and by histology in 15 patients (MF-SRS, 5/11; SF-SRS, 11/25) who underwent surgery. Other local salvage treatments included repeated SRS (n=16) or WBRT (n=5). Cumulative LC rates were 97% and 94% at 6 months, 92% and 85% at 9 months, and 90% and 77% at 12 months (p=0.01) for MF-SRS and SF-SRS groups, respectively (Figure 3); for lesions ≥3cm, 6-month and 12-month, LC rates were 62% and 54% after SF-SRS and 81% and 73% after MF-SRS (p=0.03), respectively. Complete and partial response occurred in 18 and 47 lesions after SF-SRS and 28 and 64 lesions after MF-SRS, respectively.

Analysis of factors predictive of local failure showed that melanoma histology

was associated with worse LC as compared with other histologies. Specifically, the 1-year local failure rates for melanoma metastases were 45% and 33% in single-fraction and multi-fraction SRS groups (p=0.1), respectively. No other factors were predictive of local failure, although tumor size ≥3 cm was of borderline significance in patients receiving SF-SRS (p=0.07).

Analysis of complications

Thirty-one (20%) patients undergoing SF-SRS and 11 (8%) subjected to MF-SRS group experienced RN (p=0.004), as suggested by MRI and PET-CT imaging; in 17 out of 18 patients who underwent surgery, imaging results were confirmed by histology. Diagnosis of RN was made by imaging in 25 patients (MF-SRS, 7/11; SF-SRS, 18/31) and by histology in 17 patients (MF-SRS, 4/11; SF-SRS, 13/31) who underwent surgery. Median volumes of radionecrotic lesions were 12.7 cm^3 in SF-SRS group and 18.0 cm^3 in SF-SRS group (p=0.04), with respective median times to RN of 10 months (range 4-32 months) and 12 months (6-24 months). The cumulative 1-year incidence of RN was 18% after SF-SRS and 9% after MF-SRS (p=0.01) (Figure 4); for lesions ≥3 cm, respective incidence rates of RN were 33% and 14% (p=0.01). RN was syntomatic in 13/151 and 4/138 patients after SF-SRS and SF-SRS, respectively (p=0.04), requiring surgery or medical treatment. RTOG grade 2 or 3 neurological deficits included seizure (n=5), motor deficits (n=10), cognitive deficits (n=3), and speech deficits (n=3).

In SF-SRS group, univariate analysis showed that the tumor size, the GTV and the volumes of normal brain that received doses of 12-16 Gy were predictive of

brain necrosis. The $V_{12\text{-}Gy}$ was the most significant variable associated with the development of RN; at a median radiological follow-up of 10 months, the incidence of RN was 13% for $V_{12\text{-}Gy}$ ≤13.2 cm^3 and 28% for $V_{12\text{-}Gy}$ >13.2 cm^3 (p=0.02). Based on $V_{12\text{-}Gy}$ quartiles (Q1-Q4) distribution, the 1-year risk of developing RN was 15%, 21%, 33%, and 49% for $V_{12\text{-}Gy}$ <10.5 cm^3 (Q1), 10.5-13.2 cm^3 (Q2), 13.3-18.2 cm^3 (Q3), and >18.2 cm^3 (Q4), respectively.

In multi-fraction SRS group, the GTV and the volumes of normal brain receiving doses of 15-24 Gy were predictive of RN. The brain volume receiving 18 Gy ($V_{18\text{-}Gy}$) was the most significant prognostic factor for RN; the incidence of RN was 5% for $V_{18\text{-}Gy}$ ≤30.2 cm^3 and 14% for $V_{18\text{-}Gy}$ >30.2 cm^3 (p=0.04). According to quartiles distribution, the 1-year risk of developing RN was 0%, 6%, 13%, and 24% for volumes <22.8 cm^3, 22.8-30.2 cm^3, 30.3-41.2 cm^3, and >41.2 cm^3, respectively. No other factors emerged as predictors of RN in both groups.

Propensity score-matching analysis

Propensity score matching resulted in 102 matched pairs, for a total of 208patients. Matched-pairs were constructed for evaluation of LC and RN by matching by age, sex, histology, tumor size, and irradiated volumes (but not the presence of extranial disease, number of metastases or KPS, which did not appear to affect LC or RN to allow more patients included in the analysis). The overall Chi-Square test for balance (p=0.996) and the L1 index (0.84) suggested that the treatment groups were well-balanced across all covariates. The 1-year cumulative LC rates were 91% and 76% (p=0.01) (Figure 1S), respectively, and

cumulative incidence rates of RN were 8% and 20% (p=0.01) (Figure 2S), respectively. In Table 2, results of pair-matched and IPTW propensity score analyses are shown. The adjusted Cox regression models confirmed significantly better LC and lower risk of RN in MF-SRS group as compared with SF-SRS group.

Discussion

Results of this study, where either SF-SRS or MF-SRS was delivered to patients with brain metastases >2 cm in diameter, indicate that MF-SRS is superior in terms of LC and risk of RN. Above findings are strengthened by propensity score analyses, which address potential bias when retrospective data of two non-randomized groups are compared.

A worse LC has been seen in patients with large lesions after SF-SRS (23-26). Using the RTOG recommended dose of 15 Gy for lesions >3 cm in diameter, Vogelbaum et al. (24) reported 12-month LC rate of 45% as compared with 85% for lesions ≤2 cm that received 24 Gy. In 153 brain metastases treated with SF-SRS, Chang et al. (23) reported a 12-month LC rates of 86% in tumors ≤1 cm in size and 56% in tumors >1 cm, and similar results have been observed in other few studies (25,26). In our study, the most significant difference in LC between groups was observed for lesions ≥3 cm in size, being 52% and 71% at 1 year after single-fraction and multi-fraction SRS (p=0.02), respectively. Using the linear-quadratic model adjusted for high doses, Wiggenraad et al. (27) have

compared the BED_{12} of different radiation schedules for the treatment of brain metastases. Analysis of published studies showed that a BED_{12} of at least 40 Gy, corresponding to 3x8.5 Gy or 20 Gy in single fraction, was necessary to achieve a 1-year local control ≥70%. Different BED_{12} values may explain, at least in part, the better LC reported in our series with 3x9 Gy as compared with single doses of 16-18 Gy, suggesting that MF-SRS may represent a better treatment option for large metastases.

RN represents the most important late toxicity reported after SRS. In the current study, the development of radiological changes suggestive of RN was significantly higher in patients who received single-fraction SRS as compared with those receiving multi-fraction SRS, and this was associated with an increased risk of neurological deficits. The $V_{12\text{-}Gy}$ and $V_{18\text{-}Gy}$ were the most significant predictors of RN for lesions treated with SF-SRS or MF-SRS, respectively; the 1-year risk of RN was up to 49% for $V_{12\text{-}Gy}$>13.2 cm^3 and up to 24% for $V_{18\text{-}Gy}$>30.2 cm^3, being consistent with previous published studies (5,6,10).

Using the $V_{12\text{-}Gy}$ as predictors of RN in 63 patients with a total of 173 brain metastases who received single-fraction SRS, Blonigen et al. (5) have reported a risk of RN up to 69% for volumes larger than 10.8 cm^3. In another series of 198 intracranial tumors treated with Gamma Knife SRS, Korytko et al. (10) confirmed the significant correlation between the $V_{12\text{-}Gy}$ and the risk of symptomatic RN; the risk was 55.3% for $V_{12\text{-}Gy}$>10 cm^3 versus 22.5% for $V_{12\text{-}Gy}$<10 cm^3. A lower risk of

RN has been reported after fractionated SRS (11-14,32). In a series of 98 patients treated with either SRS or hypofractionated radiotherapy for brain metastases, Kim et al (28) observed a lower risk of toxicity in patients who received 6x6 Gy as compared with those who were given 20 Gy in single fraction (5% and 17%, respectively; $p<0.05$). Similarly, Fokas et al. (13) found that the use of 5x5 Gy or 10x4 Gy schedules was associated with a lower rate of toxicity than SF-SRS in 260 patients with 1-3 brain metastases. In general, according to the linear-quadratic model, a risk of RN of 2-15% has been reported for BED values of 90-127 Gy3 ($\alpha/\beta=3$ Gy) for late effects, corresponding to a radiation dose of 24-35 Gy given in 3-5 fractions (11,12,14). Overall, our data support the use of MF-SRS as an alternative to SF-SRS for large lesions especially when located close to critical structures to minimize the risk of long-term neurological toxicity.

The major weakness of the present study are the retrospective nature of the analysis and the clinical eterogeneity of patients with brain metastases. Moreover, the presence of unobserved confounding covariates may contribute to the observed differences in local control and risk of RN between groups, even when sophisticated statistical analysis are applied to reduce the impact of selection bias on outcomes. A randomized trial would be the ideal way to compare the two regimen used.

In conclusion, multi-fraction SRS at doses of 27 Gy in three consecutive fractions appears to be an effective treatment modality for brain metastases >2 cm in size

associated with improved LC and reduced risk of RN as compared with SF-SRS. The optimal dose/fractionation radiosurgical schedules need to be determined in future studies.

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Figure legends

Figure 1. Overall survival time for all patients after stereotactic radiosurgery.

Figure 2. **Cumulative incidence of** time to progression at distant brain sites for all patients after stereotactic radiosurgery.

Figure 3. **Cumulative incidence of local control** after single-fraction and multi-fraction stereotactic radiosurgery (SRS). Local control was significantly higher in multi-fraction SRS group (p=0.01).

Figure 4. **Cumulative incidence of brain radionecrosis** after stereotactic radiosurgery (SRS). The difference between the single-fraction and the multi-fraction SRS groups was significant (p=0.01).

Table 1. Summary of patient characteristics and treatment parameters

Variable	Patients who received single-fraction SRS N = 151	Patients who received multi-fraction SRS N = 138	P
Sex (F/M)	77/74	69/69	0.9
Age (years)			
median	64	62	0.9
range	30-80	28-82	
Histology			0.6
NSCLC	62 (41%)	58 (42%)	
breast carcinoma	25 (17%)	24 (17%)	
colon carcinoma	20 (13%)	22 (16%)	
melanoma	22 (15%)	18 (13%)	
renal cell carcinoma	11 (7%)	9 (7%)	
others*	11 (7%)	7 (5%)	
KPS			0.6
median	80	80	
60-70	54 (36%)	44 (32%)	
80-100	97 (64%)	94 (68%)	
Extracranial diseae			0.5
present	113 (75%)	99 (72%)	
absent	38 (25%)	39 (28%)	
Number of metastases			0.3
single	86 (48%)	81(49%)	
multiple (2-4)	93 (52%)	83 (51%)	
DS-GPA score			
≤ 1.0	35 (23%)	31(22%)	0.6
1.5 -2.5	76 (50%)	71 (51%)	
≥ 3	40 (37%)	36 (27%)	
Size of metastases			0.15
2-3 cm	99 (55%)	78 (47%)	
> 3 cm	80 (45%)	86 (53%)	
GTV (cm^3)			0.005
median	8.8	12.5	
range	3.1 - 24.1	4.1 - 47.9	
PTV (cm^3)			0.001
median	12.2	17.9	
range	4.4 - 32	5.6 - 54	
Conformity index*			0.2
median	1.62	1.69	
range	1.31-2.1	1.38-2.2	

KPS, Karnofsky Performance Status; RPA, Recursive Partitioning Analysis
DS-GPA, Diagnosis-Specific Graded Prognostic Factors; GTV, Gross Target Volume; PTV, Planning Target Volume; *Others histologies included 6 rectal, 2 sarcomas, 2 bladder, 4 ovarian, 2 esophageal, and 2 gastric carcinomas;
*calculated as prescribed isodose volume/tumor volume encompassed by the prescription isodose volume

T**able 2**. Effect of single-fraction SRS and multi-fraction SRS on LC and RN risk [a,b]

Outcome	HR*	95% CI	p
Local control			
Unadjusted cohort	0.43	0.21 to 0.9	0.03
Propensity score matching	0.35	0.13 to 0.76	0.01
IPTW propensity score	0.33	0.16 to 0.68	0.007
RN risk			
No adjustment	0.42	0.21 to 0.83	0.03
Propensity score matching	0.22	0.14 to 0.73	0.005
IPTW propensity score	0.23	0.18 to 0.66	0.001

Abbreviations: SRS, stereotactic radiosurgery; LC, local control; RN,radiation-induced brain necrosis; HR, hazard ratio; CI, confidence interval; * Single-fraction SRS is the reference group;

a Propensity score-matching and inverse-probability-of-treatment weighting (IPTW) propensity score

b age at diagnosis, gender, histology, number of metastases, extracranial disease, and tumor volumes.

Figure 1

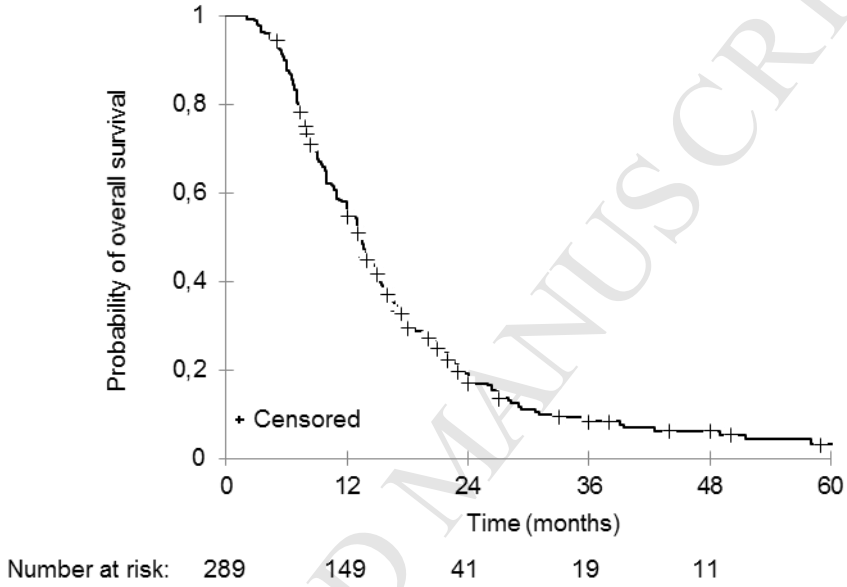


Figure 2

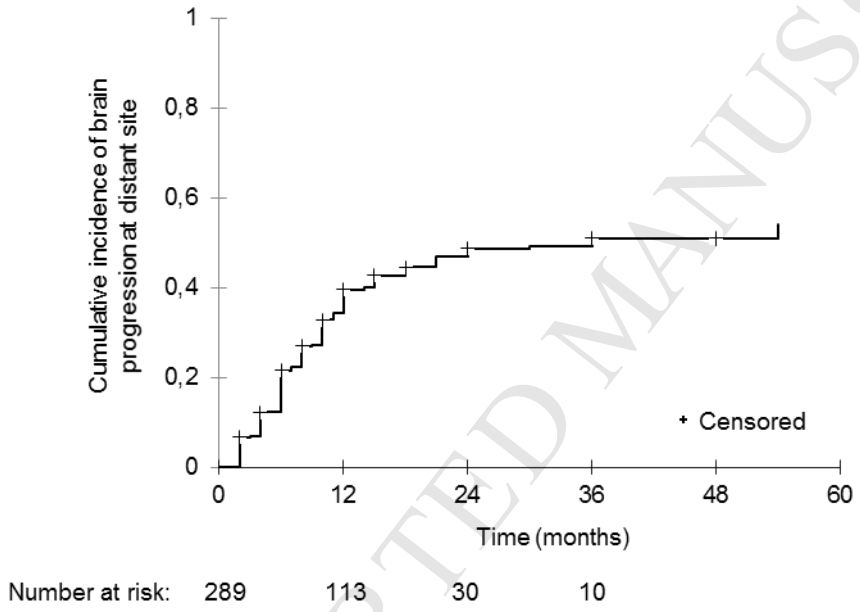
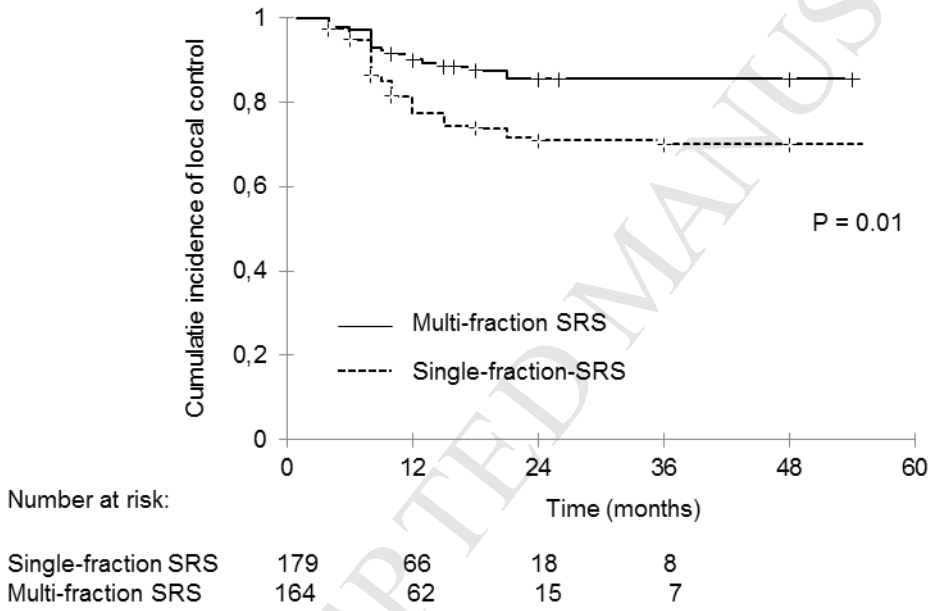


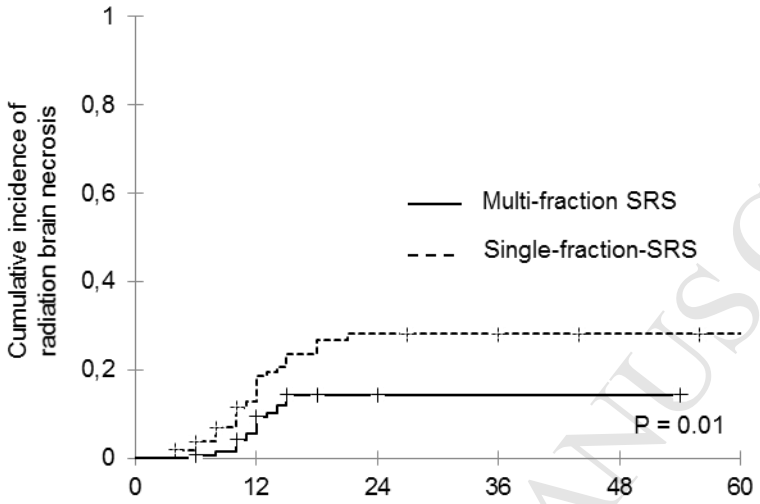
Figure 3



Number at risk:

Single-fraction SRS	179	66	18	8
Multi-fraction SRS	164	62	15	7

Figure 4



Number at risk:

Single-fraction SRS	179	64	17	6
Multi-fraction SRS	164	60	14	5