Paradigm shift in patients with multiple brain metastases from whole brain radiotherapy to high precision multimodality treatment including stereotactic radiotherapy

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RESEARCH

Paradigm shift in patients with multiple brain metastases from whole brain radiotherapy to high precision multimodality treatment including stereotactic radiotherapy

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Abstract

Background Whole brain radiotherapy (WBRT) is increasingly being replaced by high precision multimodality treatment including stereotactic radiotherapy (SRT) in patients with ≥4 brain metastases (BMs). The implications of this trend on survival rates are uncertain. Our study examines the time trends for survival rates of patients treated with radiotherapy for brain metastases during this era of shifting treatment paradigms.

Methods Patients with newly diagnosed BMs treated with SRT or WBRT between 2010 and 2023 were included, regardless of the number of brain metastases or the primary malignancy. Patients were excluded if they had previously undergone cranial radiotherapy. Differences in survival between treatment years were evaluated using Log-rank tests. A P value of ≤0.05 (two-sided) was considered statistically significant.

Results A total of 1106 patients were included for analysis. Of these, 832 (75%) were treated with SRT, while 274 (25%) were treated with WBRT. The median number of BMs was 2 (IQR 1–5), while 367 (33%) patients had≥4 BMs. The proportion of patients with ≥4 BMs who were treated with linear accelerator-based SRT instead of WBRT increased over time: 2010–2014: 9 (11%); 2015–2019: 52 (31%); 2020–2023: 80 (68%). An improvement in survival rates of patients with ≥4 BMs was observed over time (median survival 2010–2014: 5 months; 2015–2019: 6 months; 2020–2023: 7 months, $P<0.001$).

Conclusion In patients treated for multiple (≥4) BMs, survival increased when radiotherapy modality shifted from WBRT to high precision multimodality treatment including SRT, resection, and systemic therapy.

Keywords Brain metastases · Stereotactic radiotherapy · Whole brain radiotherapy · Survival

Introduction

In the past 15 years, there have been significant shifts in the radiation treatment of multiple brain metastases (BMs). Until 2020 the Dutch guideline advised SRT up to 3 BM and Whole Brain Radiotherapy (WBRT) for patients with 4 or more BM. From 2020 the Dutch guideline suggested SRT as an alternative treatment to WBRT also in selected patients with 4 or more BM. From then on WBRT has mostly been replaced by stereotactic radiotherapy (SRT) for multiple BMs to better preserve neurocognitive function and quality of life without negative impact on survival [1–5]. With technical advancements such as single-isocenter for multiple targets SRT, many of the previous disadvantages of linear

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accelerator (LINAC)-based SRT compared to WBRT have become less relevant [6, 7]. As a result, patients with ≥ 4 BMs can undergo SRT in a session of 30 min.

At the same time, systemic treatment options such as targeted therapy and immunotherapy for specific primary tumors have also become available [8–10]. These treatments have shown greater efficacy in treatment of BMs than most chemotherapeutical agents. In cases of small and asymptomatic BMs, radiotherapy can be delayed in favor of immunotherapy and/or targeted agents [11]. However, the majority of BMs are symptomatic and therefore do require local treatment such as surgery and SRT [12, 13].

Long-term survival trends in patients with BMs are unclear, with several large studies reporting conflicting results on whether rates are improving or remaining stable over time [13, 14]. In this report, we aim to evaluate the survival trends in patients with BMs over a 13 year period, with emphasis on patients with ≥ 4 BMs and radiotherapy treatments.

Methods & materials

Patient selection & ethics

Adult patients treated between 2010 and 2023 with either SRT or WBRT at the Haaglanden Medical Center for any number of BMs were retrospectively included, regardless of the number of brain metastases or the primary malignancy. Exclusion criteria were: patients who had previously received intracranial RT ($n=64$); patients with cytologically or histologically confirmed or radiologically evident leptomeningeal disease (LMD) prior to treatment. Patients with some localized contrast enhancement of the meninges potentially caused by other causes than LMD were not excluded. Prior neurosurgical resection was no exclusion criterion.

The Medical Ethics Committee Leiden The Hague Delft granted a waiver of informed consent for this study (reference number N24.102).

Treatment characteristics

Gross tumor volume (GTV) was determined for patients where this information was available, the majority of whom were treated with SRT for in situ BMs. Clinical target volume (CTV) was the same as GTV in patients with in situ BMs, but was defined as the resection cavity in patients where the resection cavity was irradiated postoperatively. The planning target volume (PTV) was defined as the CTV with an additional radial margin of 0 mm, 1 mm, or 2 mm. The CTV-PTV margin of 2 mm was used prior to 2015, while 1 mm margins have been utilized since 2017. No CTV-PTV margin was used between 2015 and 2016 or when the BM was located close to the brainstem.

Patients were treated with a Novalis Classic LINAC (Brainlab AG, Feldkirchen, Germany) for SRT and a Synergy LINAC (Elekta, Stockholm, Sweden) for WBRT from 2010 until 2016 and with a Versa HD LINAC (Elekta, Stockholm, Sweden) from 2016 onward. The SRT dose and fractionation schedule was usually 1 × 21 Gy or 1 × 18 Gy for smaller tumors and 3 × 8.5 Gy or 3 × 8 Gy for larger tumors or resection cavities. WBRT dose and fractionation schedule was most commonly 5 × 4 Gy or 10 × 3 Gy. Before 2020, WBRT was prescribed when the number of BMs was ≥ 4 or when the primary tumor was small cell lung cancer (SCLC). From 2020 onward, single-isocenter SRT became available meaning that SRT could be utilized in patients with more than 4 BMs [7] with a limited total tumor volume. WBRT was still occasionally prescribed in patients where the individual BM volume or cumulative BM volume was deemed too large for SRT.

The follow-up of patients was typically performed through MRI with gadolinium-enhanced T1-weighted images, T2-weighted images, diffusion weighted series, and a perfusion series (when indicated) every three to four months, combined with a visit at an outpatient clinic.

Definition of treatment outcomes

Survival time was calculated from the date of BM diagnosis until the date of death. Local recurrence (LR) was defined as new tumor growth within the area of the original BM according to the RANO-BM criteria (definition) [15]. Radionecrosis (RN) was defined as a contrast-enhancing lesion developing within the original PTV. Typical features included hypoperfusion, edema, and loss of volume following an initial increase. Contrast enhancement which was limited in size or which was seen shortly after SRT and did not change afterwards, was not defined as RN [16]. RN could be classified as asymptomatic (grade 1) or symptomatic (grade ≥ 2) according to CTCAE version 5.0. Histological evidence, when available, was also used in the evaluation, especially when distinguishing RN from LR. Regional recurrence (RR) was defined as new tumor growth in the brain or dura mater occurring outside of the original PTVs. Lastly, LMD was defined as tumor spread into the arachnoid, pia mater, or cerebrospinal fluid (CSF), typically diagnosed with MRI and/or CSF cytology.

Statistics

Overall survival was estimated using the Kaplan-Meier method. A log-rank test was used to assess statistically

significant difference in survival rates between groups with appropriate degrees of freedom. Univariable and multivariable Cox regression analyses were used to define the associations between independent variables and clinical outcomes (survival, LR, RN). When a significant difference was found for an independent variable in the univariable analysis, this variable was also included in the multivariable Cox regression analysis. These independent variables included sex, age, Karnofsky Performance Status (KPS), primary tumor, number of BMs, cumulative BM volume, largest individual BM volume, pre-RT resection, treatment period, RT modality (SRT or WBRT), and presence of extracranial metastases. For independent variables with more than two categories, one reference variable was chosen (i.e., largest group for primary tumor, score of 100 for Karnofsky Performance Status, 2010–2014 for treatment period). Separate analyses were performed to specifically compare patients with 1–3 versus ≥ 4 BMs, 1–10 versus > 10 BMs, and for patients with a cumulative BM volume of 0–30 cm^3 versus > 30 cm^3, because these are the cutoff points in the Dutch guideline where treatment with SRT over WBRT is currently advised [17]. Patients who were still alive at the time of analysis were censored at the date they were last known to be alive. A complete case analysis approach was used for the Cox regression analyses. A P value of ≤ 0.05 (two-sided) was considered statistically significant. All statistical analyses were performed using the software R version 4.3.1.

Results

Baseline characteristics

A total of 1106 patients with BMs were included. SRT was used in 832 (75%) patients, while 274 (25%) patients were treated with WBRT. The median number of BMs was 2 (IQR 1–5). The primary tumor was lung cancer in most patients (772/1106; 65%), most commonly NSCLC adenocarcinoma (455/1106; 41%), breast cancer (133; 12%), and NSCLC non-adenocarcinoma (93; 8%). Detailed patient data is shown in Table 1. The 832 patients treated with SRT had a combined total of 1896 treated BMs. Of these, 1724 (91%) were BMs in situ, while 172 (9%) were irradiated postoperatively. Detailed individual BM data can be found in Supplementary Tables 1 and Supplementary Table 2. Median survival over time for the most common primary tumors can be found in Supplementary Table 3.

Treatment shift from WBRT to SRT for ≥ 4 BMs

Median survival was 10 months in patients with 1–3 BMs and 6 months in patients with ≥4 BMs (P<0.001) (Fig. 1). The proportion of patients with ≥4 BMs increased over time: 123/375 (33%) in 2010–2014, 206/445 (46%) in 2015–2019, and 132/286 (46%) in 2020–2023. The proportion of patients with ≥4 BMs treated with SRT also increased over time: 9/86 (10%) in 2010–2014, 52/170 (31%) in 2015–2019, and 80/118 (68%) in 2020–2023 (Supplementary Fig. 1).

A significant increase in survival over time was found for patients with ≥4 BMs (Fig. 2A) and for patients with 1–3 BMs (Fig. 3A). For patients with ≥4 BMs, no increase in survival over time was seen when analyzing those treated with SRT (Fig. 2B) and WBRT (Fig. 2C) separately. For patients with 1–3 BMs, increased survival over time was seen in patients treated with SRT (Fig. 3B), but not in those treated with WBRT (Fig. 3C).

Prognostic factors for survival

Median survival in all patients was 8.5 months (Supplementary Fig. 2), while this was 10 months for those treated with SRT and 5 months for those treated with WBRT (P<0.001; Supplementary Fig. 3). The proportion of patients treated with SRT who first underwent a BM resection increased over time: 41/285 (14%) in 2010–2014, 61/306 (20%) in 2015–2019, and 88/244 (36%) in 2020–2023.

In the multivariable Cox regression analysis, factors independently and significantly associated with worse survival were: higher age, no pre-RT resection, higher cumulative volume, WBRT compared to SRT, KPS of 80 and lower, presence of extracranial metastases, treatment in 2010–2014 compared to 2020–2023, and several primary tumors including SCLC, melanoma and colorectal carcinoma (Table 2). A higher number of BMs was not associated with lower survival when corrected for factors such as cumulative BM volume.

SRT for ≥ 10 BMs or cumulative BM volume ≥ 30 cm^3

In patients treated with SRT with > 10 BMs (n=34), median survival was 7.5 months (38% after 12 months). In patients treated with SRT for 1–10 BMs (n=798), median survival was 10 months (44% after 12 months). There was no statistically significant difference in survival between patients with > 10 BMs and those with 1–10 BMs (P=0.418).

When dividing the cohort of patients treated with SRT based on cumulative BM volume, these differences were found: median survival of 10 months and 41% after 12 months (volume 0–15 cm^3), median survival of 7 months and 32% after 12 months (volume 15–30 cm^3), and median survival of 4 months and 17% after 12 months (> 30 cm^3). When divided as such, the difference in survival was not significant (P=0.078). When cumulative volume was analyzed

Table 1 Patient characteristics

	Total (*N* = 1106)	SRT			WBRT		
		2010–2014 (*N* = 282)	2015–2019 (*N* = 306)	2020–2023 (*N* = 244)	2010–2014 (*N* = 93)	2015–2019 (*N* = 139)	2020–2023 (*N* = 42)
Sex							
Male	508 (46%)	135 (48%)	144 (47%)	113 (46%)	36 (39%)	58 (42%)	22 (52%)
Female	598 (54%)	147 (52%)	162 (53%)	131 (54%)	57 (61%)	81 (58%)	20 (48%)
Age at diagnosis							
Mean (SD)	63.9 (10.8)	63.4 (11.6)	63.9 (10.6)	64.1 (10.6)	62.9 (11.1)	64.6 (10.3)	65.1 (9.90)
Total number of BMs**							
1	408 (37%)	150 (53%)	143 (47%)	99 (41%)	7 (8%)	8 (6%)	1 (2%)
2–3	324 (29%)	123 (44%)	111 (36%)	65 (27%)	9 (10%)	13 (9%)	3 (7%)
4–10	224 (20%)	9 (3%)	46 (15%)	52 (21%)	49 (53%)	57 (41%)	11 (26%)
> 10	150 (14%)	0 (0%)	6 (2%)	28 (11%)	28 (30%)	61 (44%)	27 (64%)
Number of irradiated BMs*							
1	429 (39%)	155 (55%)	151 (49%)	107 (44%)	7 (8%)	8 (6%)	1 (2%)
2–3	324 (29%)	121 (43%)	110 (36%)	68 (28%)	9 (10%)	13 (9%)	3 (7%)
4–10	214 (19%)	6 (2%)	40 (13%)	51 (21%)	49 (53%)	57 (41%)	11 (26%)
> 10	139 (13%)	0 (0%)	5 (2%)	18 (7%)	28 (30%)	61 (44%)	27 (64%)
Karnofsky Performance Status							
100	82 (7%)	31 (11%)	28 (9%)	14 (6%)	6 (6%)	2 (1%)	1 (2%)
90	348 (31%)	89 (32%)	105 (34%)	93 (38%)	24 (26%)	28 (20%)	9 (21%)
80	278 (25%)	84 (30%)	82 (27%)	54 (22%)	14 (15%)	35 (25%)	9 (21%)
70	241 (22%)	58 (21%)	56 (18%)	65 (27%)	21 (23%)	26 (19%)	15 (36%)
<=60	80 (7%)	8 (3%)	27 (9%)	14 (6%)	11 (12%)	16 (12%)	4 (10%)
Missing	77 (7%)	12 (4%)	8 (3%)	4 (2%)	17 (18%)	32 (23%)	4 (10%)
Symptomatic at baseline							
Yes	941 (85%)	237 (84%)	259 (85%)	195 (80%)	84 (90%)	128 (92%)	38 (90%)
No	148 (13%)	29 (10%)	47 (15%)	48 (20%)	9 (10%)	11 (8%)	4 (19%)
Missing	17 (2%)	16 (6%)	0 (0%)	1 (1%)	0 (0%)	0 (0%)	0 (0%)
Extracranial metastases							
Yes	655 (59%)	146 (52%)	149 (49%)	154 (63%)	67 (72%)	107 (77%)	32 (76%)
No	442 (40%)	127 (45%)	157 (51%)	90 (37%)	26 (28%)	32 (23%)	10 (24%)
Missing	9 (1%)	9 (3%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Postoperative							
Yes	206 (19%)	41 (15%)	61 (20%)	88 (36%)	6 (6%)	9 (6%)	1 (2%)
No	900 (81%)	241 (85%)	245 (80%)	156 (64%)	87 (94%)	130 (94%)	41 (98%)
Primary tumor							
NSCLC adenocarcinoma	455 (41%)	83 (29%)	158 (52%)	117 (48%)	31 (33%)	54 (39%)	12 (29%)
NSCLC non-adenocarcinoma	93 (8%)	26 (9%)	40 (13%)	16 (7%)	5 (5%)	5 (4%)	1 (2%)
NSCLC n.o.s.*	72 (7%)	37 (13%)	11 (4%)	7 (3%)	9 (10%)	7 (5%)	1 (2%)
SCLC	88 (8%)	0 (0%)	4 (1%)	26 (11%)	13 (14%)	31 (22%)	14 (33%)
Lung cancer n.o.s.*	14 (1%)	4 (1%)	5 (2%)	1 (1%)	3 (3%)	1 (1%)	0 (0%)
Breast cancer	133 (12%)	31 (11%)	27 (9%)	25 (10%)	19 (20%)	24 (17%)	7 (17%)
Melanoma	45 (4%)	28 (10%)	7 (2%)	2 (1%)	5 (5%)	3 (2%)	0 (0%)
Colorectal cancer	62 (6%)	19 (7%)	18 (6%)	18 (7%)	4 (4%)	3 (2%)	0 (0%)
Renal cell carcinoma	44 (4%)	19 (7%)	12 (4%)	11 (5%)	1 (1%)	0 (0%)	1 (2%)
Esophageal cancer	29 (3%)	11 (4%)	5 (2%)	8 (3%)	0 (0%)	3 (2%)	2 (5%)
Ovarian cancer	17 (2%)	8 (3%)	5 (2%)	1 (1%)	1 (1%)	2 (1%)	0 (0%)
Bladder cancer	15 (1%)	6 (2%)	5 (2%)	1 (1%)	1 (1%)	1 (1%)	1 (2%)
Unknown primary	12 (1%)	4 (1%)	3 (1%)	1 (1%)	0 (0%)	3 (2%)	1 (2%)
Other	27 (2%)	6 (2%)	6 (2%)	10 (4%)	1 (1%)	2 (1%)	2 (5%)

*In some patients with multiple BMs treated with SRT, not all BMs were irradiated (especially in cases of multiple smaller BMs)

n.o.s. = not otherwise specified

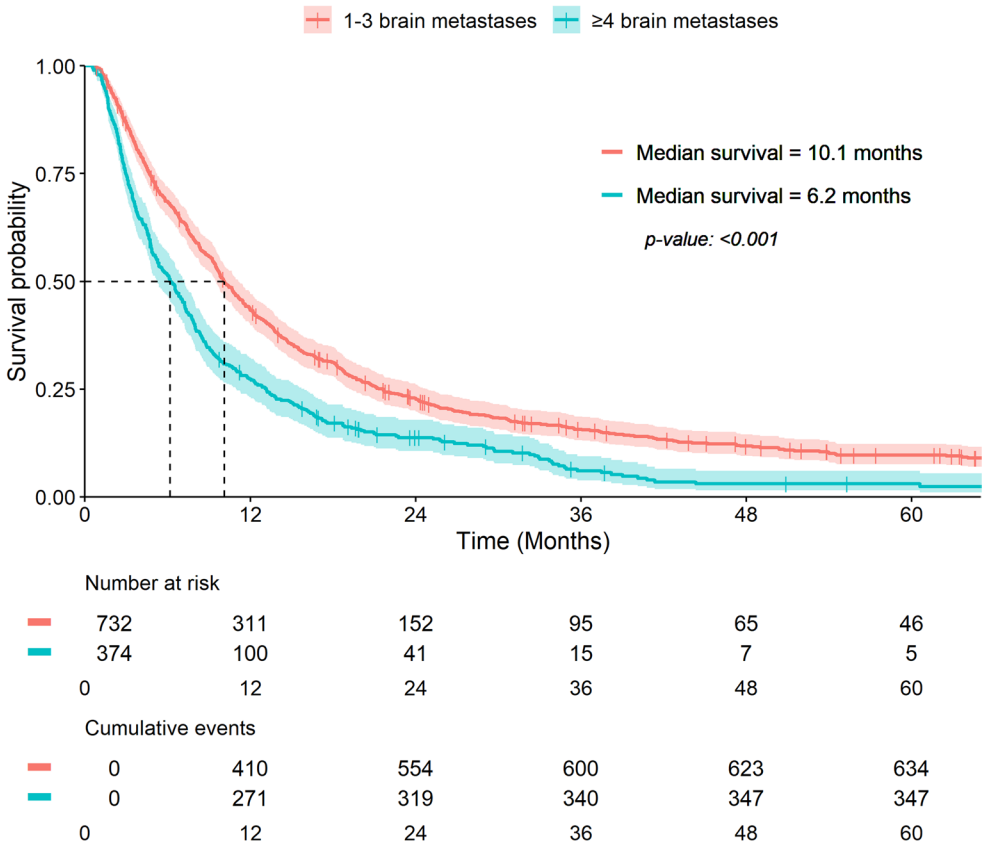

Fig. 1 Survival after diagnosis in patients with 1–3 BMs and with ≥4 BMs (2010–2023)

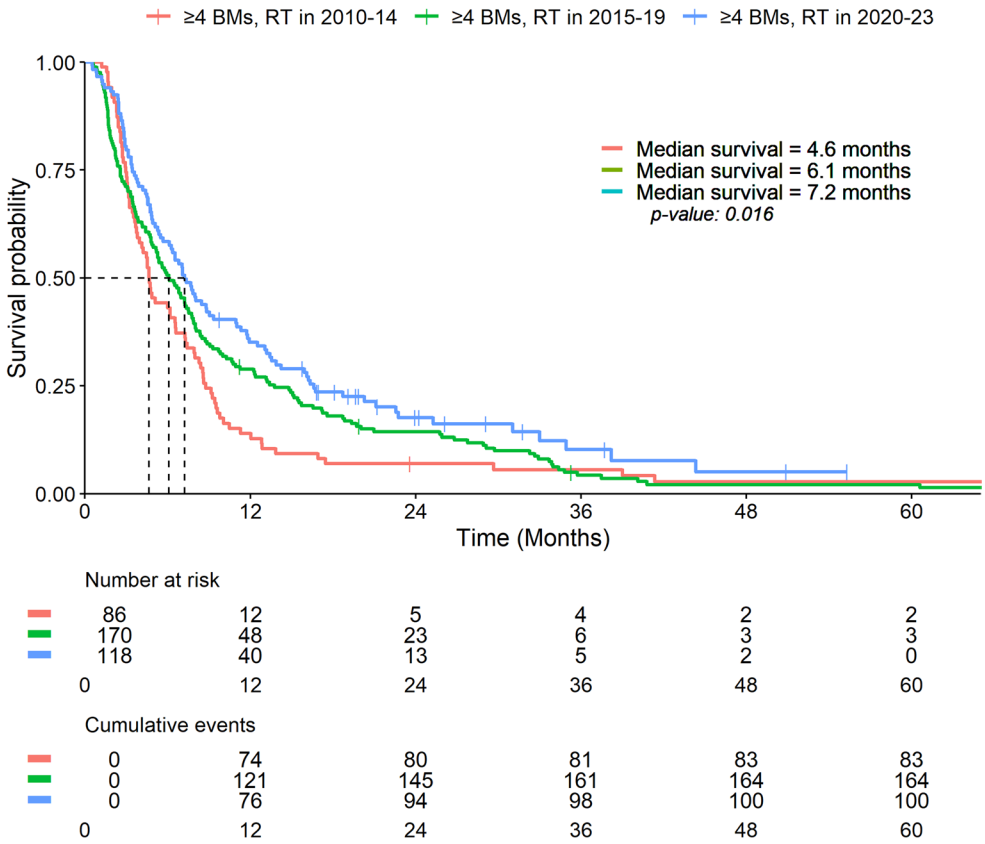

Fig. 2A Survival in patients with ≥4 BMs in three different treatment periods (2010–2014, 2015–2019, 2020–2023)

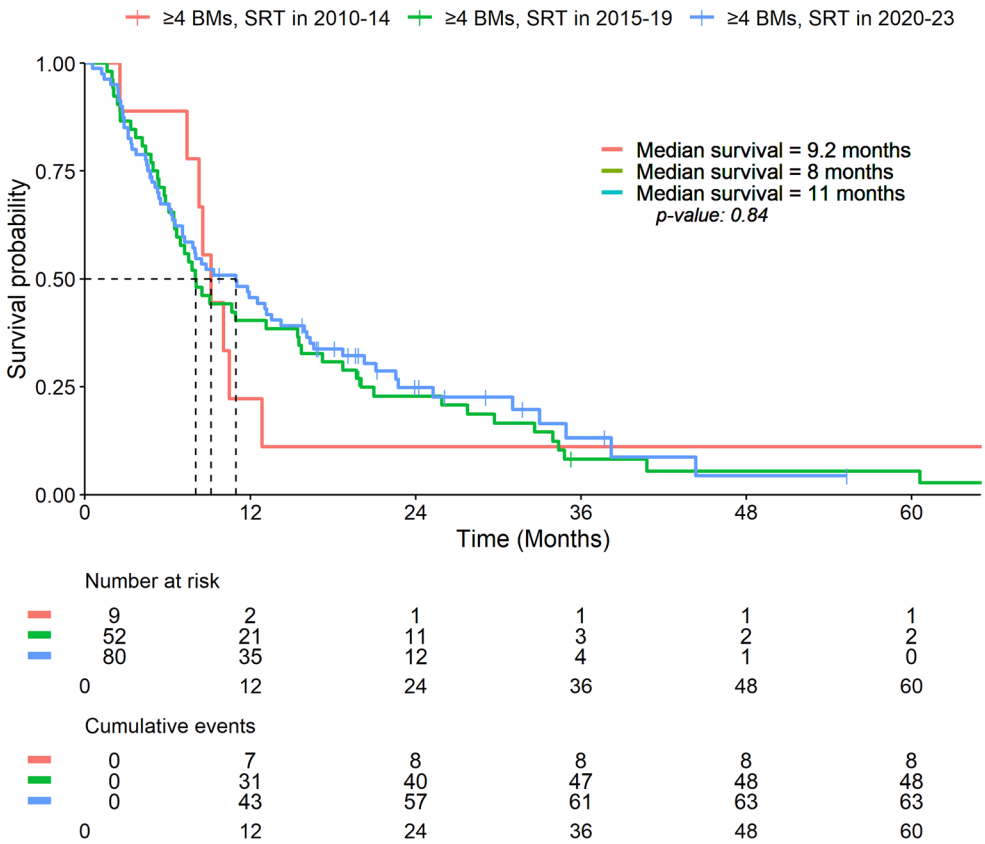

Fig. 2B Survival in patients with ≥4 BMs treated with SRT in three different treatment periods (2010–2014, 2015–2019, 2020–2023)

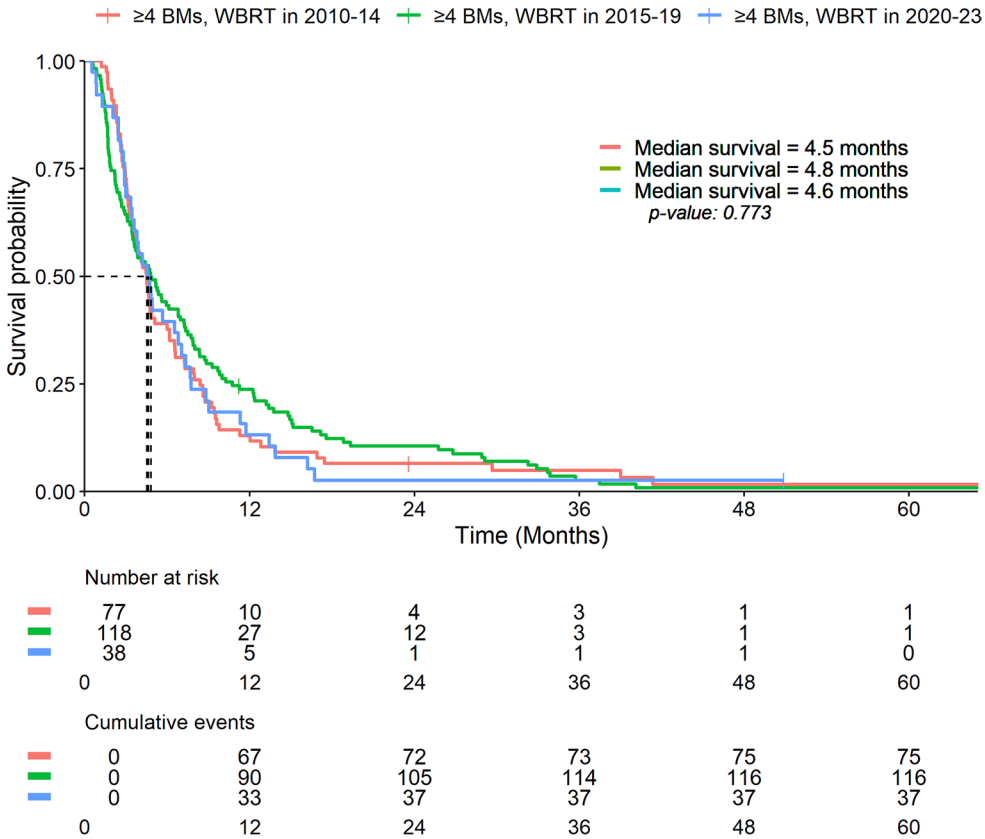

Fig. 2C Survival in patients with ≥4 BMs treated with WBRT in three different treatment periods (2010–2014, 2015–2019, 2020–2023)

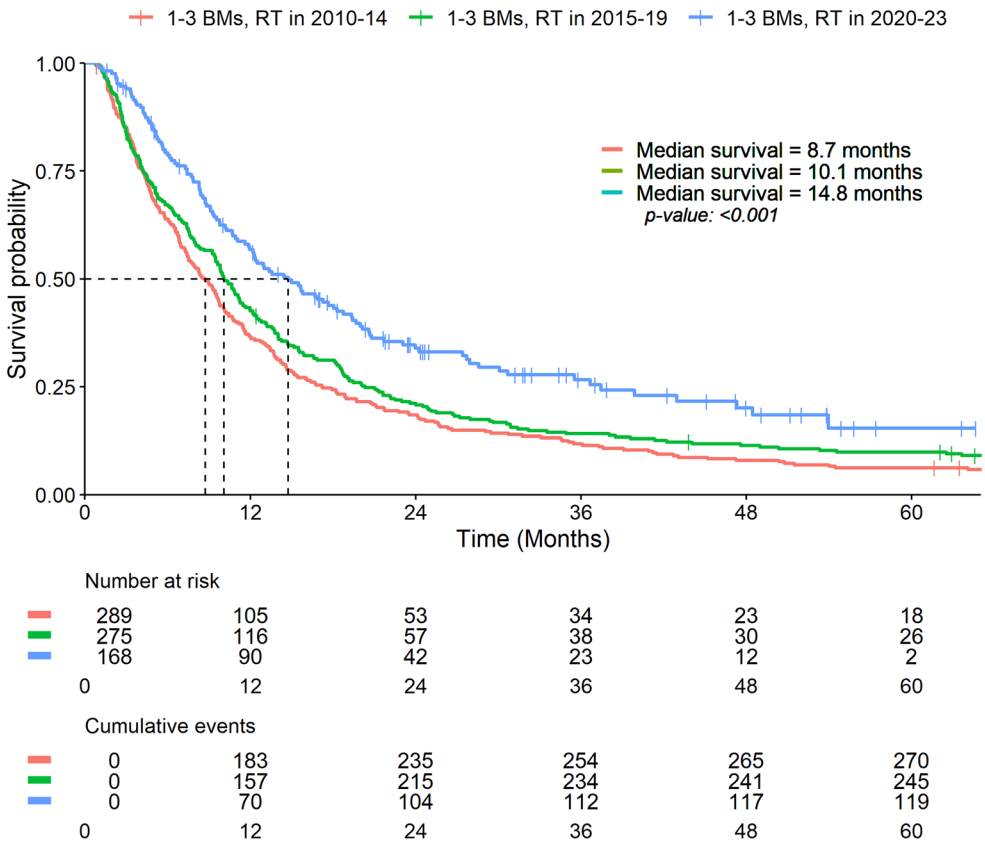

Fig. 3A Survival after diagnosis in patients with 1–3 BMs in three different treatment periods (2010–2014, 2015–2019, 2020–2023)

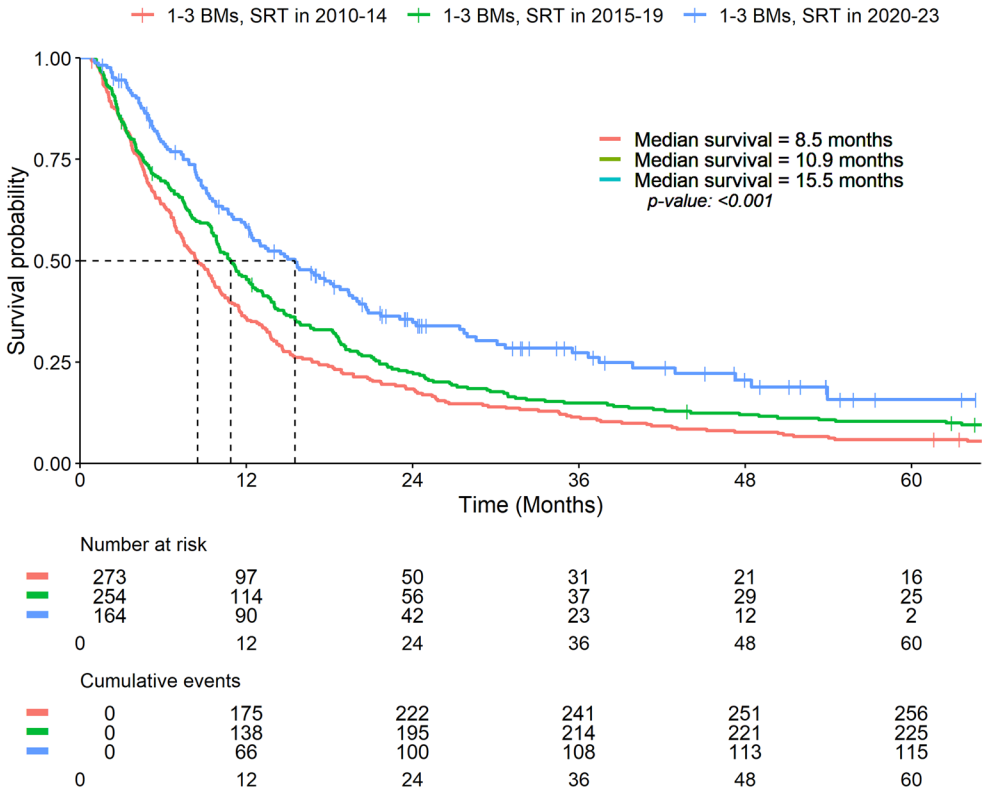

Fig. 3B Survival after diagnosis in patients with 1–3 BMs treated with SRT in three different treatment periods (2010–2014, 2015–2019, 2020–2023)

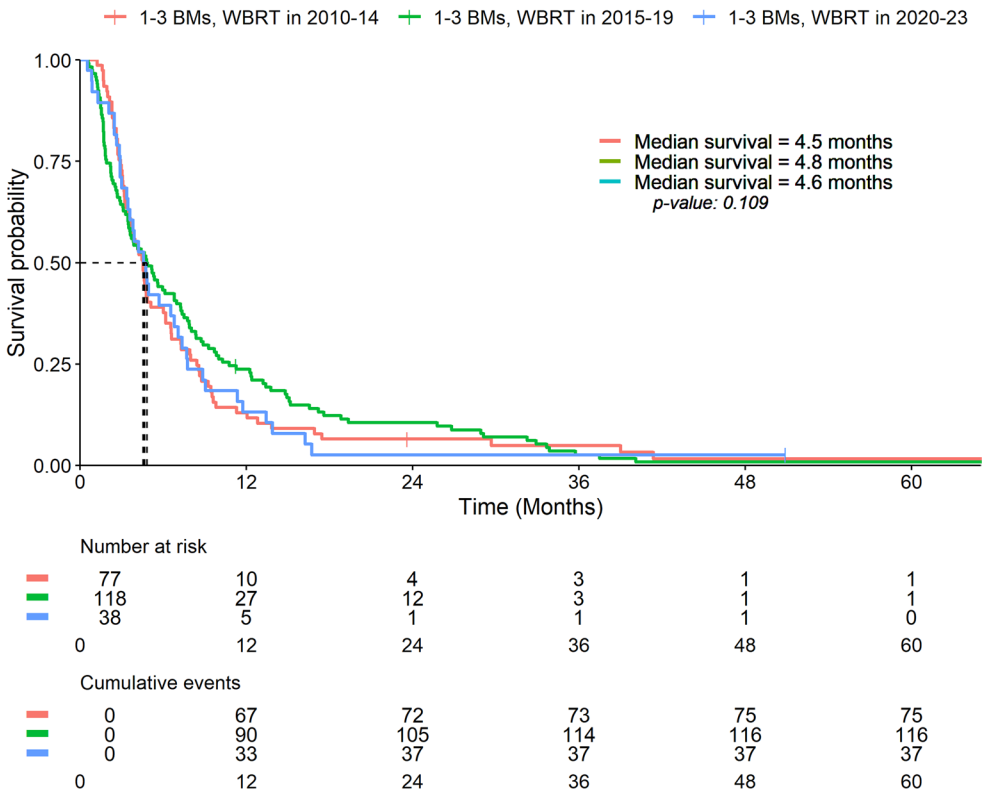

Fig. 3C Survival after diagnosis in patients with 1–3 BMs treated with WBRT in three different treatment periods (2010–2014, 2015–2019, 2020–2023)

as a continuous variable, however, it was significantly associated with survival ($P=0.008$).

Radionecrosis and recurrence after SRT

RN was found in 151 (8%) BMs after SRT, of which 42 were grade 1 (asymptomatic) and 109 (6%) BMs were grade≥2. Symptomatic RN-free survival was 93% after 12 months, and 84% after 5 years (Supplementary Fig. 4). Treatment consisted of dexamethasone, bevacizumab, and surgery (Supplementary Table 4). In 3 cases, RN was found in BMs after having been treated again with SRT after LR. In 6 cases, RN was found in BMs, which had been treated with salvage SRT after RR. No cases of RN were reported after WBRT.

LR occurred in 92 (5%) BMs in 75 (9%) patients treated with SRT, while it occurred in 25 (9%) patients treated with WBRT. LR-free survival after SRT were 94% after 1 year, 87 after 5 years (Supplementary Fig. 5). RR occurred in 329 (40%) patients treated with SRT, while it occurred in 29 (11%) patients treated with WBRT. Treatment for LR and RR included (re-)WBRT, (re-)SRT, and (re-)resection (Supplementary Table 4). LMD was found in 63 (8%) patients after treatment with SRT and in 11 (4%) patients after treatment with WBRT.

WBRT-free survival

The majority of patients treated with SRT did not receive WBRT at a later point. After SRT, 74 (9%) patients received WBRT for LR, RR, or LMD. WBRT-free survival after SRT was 94% after 6 months, 88% after 12 months, and 82% after 5 years (Supplementary Fig. 6). In patients treated in 2010–2014, WBRT-free survival was 84% after 12 months and 71% after 5 years. In patients treated in 2015–2019, WBRT-free survival was 87% after 12 months and 84% after 5 years. In patients treated in 2020–2023, WBRT-free survival was 92% after 12 months, and 91% after 3 years.

Discussion

This study shows a paradigm shift in the treatment of ≥ 4 BMs, with SRT use increasing from 10% to 68% between 2010 and 2023, largely replacing WBRT. Despite omitting elective irradiation of healthy brain tissue, survival improved over time supporting this treatment paradigm shift. SRS is used as part of a multimodality treatment with resection and systemic therapy in patients with multiple BMs. In this palliative setting, use of WBRT should be limited due to its detrimental effect on quality of life in accordance to the QUARTZ trial [2–4, 18]. With the availability of efficient LINAC-based single-isocenter for multiple targets techniques, patients can be treated within 30 min for multiple

Table 2 Univariable and multivariable Cox regression analysis of survival

	Univariable			Multivariable		
	HR	95% CI	*P*	HR	95% CI	*P*
Male	1.0 (reference)			1.0 (reference)		
Female	0.832	0.735–0.943	**0.004**	0.884	0.746–1.047	0.153
Age	1.016	1.01–1.022	**<0.001**	1.008	1.001–1.016	**0.036**
Post-resection	1.0 (reference)			1.0 (reference)		
No resection	2.006	1.692–2.377	**<0.001**	1.534	1.247–1.887	**<0.001**
Number of BMs	1.006	1.004–1.008	**<0.001**	1.004	0.999–1.008	0.054
RT in 2010–2014	1.0 (reference)			1.0 (reference)		
RT in 2015–2019	0.929	0.806–1.070	0.305	0.876	0.730–1.053	0.159
RT in 2020–2023	0.683	0.577–0.809	**<0.001**	0.624	0.500–0.778	**<0.001**
Cumulative BM volume (cm^3)*	1.014	1.008–1.020	**<0.001**	1.008	1.002–1.014	**0.008**
Largest individual BM volume (cm^3)**	1.011	1.004–1.019	**0.003**	1.004	0.996–1.013	0.341
SRT	1.0 (reference)			1.0 (reference)		
WBRT*	1.983	1.722–2.284	**<0.001**	1.603	1.342–1.914	**<0.001**
KPS 100	1.0 (reference)			1.0 (reference)		
KPS 90	1.418	1.085–1.852	**0.011**	1.275	0.948–1.714	0.108
KPS 80	2.216	1.689–2.907	**<0.001**	1.957	1.443–2.654	**<0.001**
KPS 70	2.940	2.229–3.879	**<0.001**	2.431	1.768–3.343	**<0.001**
KPS 60 or lower	3.798	2.730–5.285	**<0.001**	3.053	2.013–4.631	**<0.001**
ECM	1.0 (reference)			1.0 (reference)		
No ECM	0.638	0.561–0.726	**<0.001**	0.725	0.613–0.857	**<0.001**
NSCLC adenocarcinoma	1.0 (reference)			1.0 (reference)		
NSCLC non-adenocarcinoma	1.298	1.025–1.644	**0.030**	1.275	0.97–1.678	0.082
NSCLC n.o.s.	1.979	1.535–2.551	**<0.001**	1.474	1.061–2.049	**0.021**
SCLC	1.583	1.252–2.001	**<0.001**	1.591	1.057–2.395	**0.026**
Lung cancer n.o.s.	1.312	0.769–2.239	0.319	1.248	0.638–2.441	0.517
Breast cancer	0.999	0.814–1.225	0.991	1.005	0.755–1.337	0.974
Melanoma	1.529	1.111–2.105	**0.009**	1.980	1.351–2.901	**<0.001**
Colorectal cancer	2.080	1.584–2.731	**<0.001**	1.929	1.408–2.642	**<0.001**
Renal cell carcinoma	0.786	0.551–1.122	0.185	0.755	0.508–1.121	0.164
Esophageal cancer	1.301	0.881–1.921	0.186	1.336	0.852–2.095	0.206
Ovarian cancer	0.702	0.412–1.196	0.193	0.625	0.337–1.159	0.136
Bladder	1.305	0.779–2.186	0.312	1.071	0.573–2.002	0.830
Unknown	1.942	1.093–3.451	**0.024**	0.795	0.373–1.693	0.551
Other	1.234	0.803–1.896	0.338	1.194	0.725–1.964	0.486

*The cumulative BM volume was not known in patients treated with WBRT. For this reason, a separate multivariable Cox regression analysis was performed where the impact of WBRT on survival was separately analyzed, corrected for all other variables except cumulative BM volume. No changes in significance occurred in the other variables, except that number of BMs became significant ($P=0.004$), when cumulative BM volume was left out

**The individual BM volume was tested separately from the cumulative BM volume in the multivariable analysis to avoid multicollinearity. As explained above*, the impact of WBRT and BM volume could not be tested in the same multivariable analysis

ECM = extracranial metastases; KPS = Karnofsky Performance Status; n.o.s. = not otherwise specified

BMs with high treatment plan quality and favorable clinical outcomes [6, 7, 19–21]. This makes SRT for multiple BMs feasible in routine clinical practice.

This study has some limitations, which should be considered when analyzing the results. The retrospective design limits the ability to make definitive conclusions, but is rather hypothesis generating for design of prospective trials. Differences between subgroups, such as SRT and WBRT treatment, in factors such as Karnofsky Performance Status, number of BMs, and primary tumor can be found between the SRT/WBRT groups in Table 1. Furthermore, with current imaging techniques it is often not possible to accurately distinguish between RN and LR. As a result, the diagnosis relies on a combination of clinical factors and radiological evidence over time with a level of diagnostic uncertainty. Despite these limitations, the study describes a large patient cohort ($n=1106$) including all patients treated with radiotherapy for BMs in the period 2010–2023 at our department, which makes it representative of the patient population at other departments. This large number of patients enabled multivariable analyses of survival rates, thereby allowing for the adjustment of confounding factors.

Survival improved over time for the entire cohort despite the fact that the proportion of patients with ≥ 4 BMs also increased over time (46% in 2020–2023 compared to 33% in 2010–2014). Survival also improved both for patients with ≥ 4 BMs (Fig. 2A) and for those with 1–3 BMs (Fig. 3A). The increased survival in patients with ≥ 4 BMs is likely multifactorial. Reasons for this improvement may be increased availability of systemic treatment options capable of penetrating the blood-brain barrier and targeting BMs from specific primary tumors. Recent evidence has indeed indicated improved survival rates in patients treated with immunotherapy [22, 23]. These treatment options were not widely available during the earlier time cohorts, which can explain the increased survival in the most recent time cohorts. Another explanation can be earlier detection of BMs through improved and more widely available imaging techniques. The increasing use of surgical resection for BMs, including in patients with multiple MBs as a multimodality treatment, may also be a contributing factor.

Our data showed that the shift away from WBRT in favor of high precision multimodality treatment (SRT, resection, and systemic therapies) increased survival rates in patients with ≥ 4 BMs. When analyzing survival in either the WBRT or SRT cohort separately, survival remained stable over time (Fig. 2B and C) with better survival rates in the SRT group compared to the WBRT group. In the last years, there was an increasing proportion of patients being treated with SRT compared to WBRT, especially in patients with multiple BM. When analyzing all patients together, there was an improved survival over time (Fig. 2A). This implies that, as survival rates for SRT and WBRT stayed stable in patients with ≥ 4 BMs, the shift from WBRT to SRT contributed to improved survival rates. The results also suggest that SRT is non-inferior to WBRT in patients with ≥ 4 BMs, which is consistent with recent literature [24–26].

The number of BMs did not independently impact survival rates when corrected for factors such as cumulative BM volume (Table 2). This suggests that cumulative BM volume is more relevant than the number of BMs. Therefore, when estimating life expectancy and making clinical decisions, factors such as cumulative BM volume should be prioritized over the number of BMs. Our results support alterations to existing prognostic tools that use the number of BMs rather than volume, such as the current Graded Prognostic Assessment [13].

In the majority of patients, WBRT could be omitted for multiple years. WBRT-free survival was high in our cohort at 82% after 5 years. This also increased over time (92% after 1 year in 2020–2023), which may be partly due to increased reluctance from radiation oncologists to prescribe WBRT since the publication of the QUARTZ trial [18]. This randomized study showed no improvement in survival from WBRT compared to optimal supportive care. Our results show that after SRT, WBRT can usually be avoided in clinical practice, which may benefit quality of life.

Several guidelines, including the Dutch guideline for BMs, recommend SRT for patients with up to 10 BMs and a limited cumulative BM volume < 30 cm^3 [17]. A limited number of patients with more than 10 BMs or a larger cumulative BM volume were treated with SRT in our cohort. Survival rates in these patients appeared relatively adequate with 1 year survival rate of 38% in patients with > 10 BMs. The survival rates of patients with a cumulative BM volume of > 30 cm^3 was not negligible at 17% after 12 months and a median survival of 4 months. The question then becomes if SRT should be preferred over WBRT in patients with a high cumulative BM volume, because outcomes after WBRT are generally poor with median survival of 2–4 months in frail patients [27].

Future research will further clarify the optimal treatment strategy of large volume BM, such as staged SRT, pre-operative SRT, and hypofractionated SRT. Also, the interaction of radiotherapy with immunotherapy and other modern systemic therapies needs further investigation.

Conclusion

In the period from 2010 to 2023, the treatment modality for the majority of patients with ≥4 BMs shifted from WBRT to SRT, resection, and systemic therapies. Despite omission of elective irradiation of the brain, survival increased during this period, supporting the treatment paradigm shift in this palliative setting.

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Declarations

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