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Research Article

Use of radiotherapy in breast cancer patients with brain metastases– a retrospective 11-year single center study

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ABSTRACT

Aim: To analyse the use of radiotherapy (RT) and factors affecting overall survival (OS) after RT in breast cancer patients with brain metastases.

Methods: Breast cancer patients treated from 2008 to 2018 with whole brain RT (WBRT) or stereotactic radiosurgery (SRS) at a large regional cancer referral center were identified from the hospital's RT register. Clinical variables were extracted from medical records. OS was calculated from date of first RT until death or last follow up. Potential factors affecting OS were analyzed.

Results: 255 females with WBRT (n = 206) or SRS (n = 49) as first RT were included. An increased use of initial SRS was observed in the second half of the study period. The most common WBRT fractionation regimen was 3 Gy × 10. SRS was most often single fractions; 18 or 25 Gy between 2009 and 2016, while fractionated SRS was mostly used in 2017 and 2018. Median OS in the WBRT group was 6 months (CI 1–73) relative to 23 (CI 0–78) in the SRS group. Age, performance status, initial RT technique, extracranial disease, brain metastasis surgery, number of brain metastases and DS-GPA score had significant impact on OS. Only ECOG 0 and brain metastasis surgery were associated with superior OS in multivariate analysis.

Conclusion: WBRT was the most frequent primary RT. An increased use of initial SRS was observed in the second half of the study period. Only ECOG 0 and brain metastasis surgery were associated with superior OS in multivariate analysis.

RÉSUMÉ

But : Analyser l'utilisation de la radiothérapie (RT) et les facteurs affectant la survie globale (SG) après la RT chez les patientes atteintes d'un cancer du sein avec métastases au cerveau.

Méthodologie : Les patientes atteintes d'un cancer du sein traitées de 2008 à 2018 par RT au cerveau entier (WBRT) ou par radiochirurgie stéréotaxique (SRS) dans un grand centre régional de référence pour le cancer ont été identifiées à partir du registre de RT de l'hôpital. Les variables cliniques ont été extraites des dossiers médicaux. Le taux de survie globale (SG) a été calculé à partir de la date de la première RT jusqu'au décès ou au dernier suivi. Les facteurs potentiels affectant la SG ont été analysés.

Résultats : 255 femmes dont la première RT était la WBRT (n = 206) ou la SRS (n = 49) ont été incluses. Une utilisation accrue du SRS initial a été observée dans la seconde moitié de la période d'étude. Le schéma de fractionnement du WBRT le plus courant était de 3 Gy × 10. Le SRS était le plus souvent des fractions simples; 18 ou 25 Gy entre 2009 et 2016, tandis que le SRS fractionné était surtout utilisé en 2017 et 2018. La SG médiane dans le groupe WBRT était de 6 mois (IC 1–73) par rapport à 23 (IC 0–78) dans le groupe SRS. L'âge, l'état de performance, la technique de

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RT initiale, la maladie extracrânienne, la chirurgie des métastases cérébrales, le nombre de métastases cérébrales et le score DS-GPA ont eu un impact significatif sur la SG. Seuls l'ECOG 0 et la chirurgie des métastases cérébrales ont été associés à une SG supérieure dans l'analyse multivariée.

Conclusion : La WBRT était la RT primaire la plus fréquente. Un recours accru à la RT initiale a été observé dans la seconde moitié de la période d'étude. Seuls l'ECOG 0 et la chirurgie des métastases cérébrales ont été associés à une SG supérieure dans l'analyse multivariée.

Keywords: Breast cancer; Brain metastases; Radiotherapy; Whole brain radiation therapy; Stereotactic radiosurgery; Overall survival; Fractionation

Introduction

Up to 30% of breast cancer patients are diagnosed with brain metastases, depending on tumor subtype and stage at diagnosis.[1–3] Overall, the incidence of brain metastases in breast cancer patients is increasing due to increasing incidence of breast cancer, improved precision and more frequent use of imaging, and better systemic control of extracranial disease leading to prolonged survival time.[4–6] Patient involvement, treatment guidelines and prognostic scoring systems may aid treatment decisions in order to choose the most appropriate brain metastasis treatment.[7,8] One of the most recognized prognostic scoring systems for brain metastasis treatment is Diagnosis Specific Graded Prognostic Assessment (DS-GPA).[9] The DS-GPA is based on well-known prognostic factors for the specific cancer diagnoses. This facilitates therapeutic decisions by classifying patients according to intermediate and least favorable prognosis. In breast cancer, prognostic factors are genetic subtype, age and performance status.[10] Other factors previously found to impact on OS in breast cancer patients with brain metastases are number of brain metastases,[11] extracranial disease activity, and factors related to the brain metastasis treatment.[9] Treatment options for brain metastases include corticosteroids, surgery, radiotherapy (RT), systemic treatments and best supportive care.[9] As systemic treatment of brain metastases is less effective[12] against intracranial metastases because of the blood-brain barrier, surgical resection and RT are the preferred treatment options.[4] In patients with poor prognosis, best supportive care is the recommended treatment.[7]

Whole brain radiotherapy (WBRT), given typically in 10 fractions, has been the most common method to treat patients with short expected survival and multiple brain metastases for decades.[13] Whereas the acute toxicities after WBRT are mostly mild and reversible, late effects such as progressive cognitive dysfunctions may profoundly impair the patients' quality of life and functions.[14,15]

Stereotactic radiosurgery (SRS) allows small intracranial lesions to be treated with high radiation doses in one or few fractions. SRS is most often used for patients with a limited number of brain metastases, typically 1–4, brain metastases with a diameter <4 cm, or after surgical resection,[15–18] increasingly used also in patients with ≥5 brain metastases.[19,20] This technique significantly increases local control and reduces radiation dose to healthy brain tissue compared to WBRT.[21] Hence, profound long-term side effects such as impaired cognitive function are less common than for WBRT.[15] However, subsequent development of brain tissue radionecrosis after SRS is a relatively rare, but clinically relevant with serious late side effect that increases with dose of RT, treated brain volume and previous RT to the same region.[22]

Although overall survival (OS) for breast cancer patients with brain metastases is considerably longer compared to other cancer diagnoses, such as lung and melanoma, the prognosis is generally poor.[23] Reported median OS after brain metastasis diagnosis in breast cancer patients varies from 7 to 15 months, although some patients live substantially longer.[6,9,11] Reported OS in breast cancer patients after treatment with either WBRT alone or SRS was 4–8 and 13–16 months, respectively.[9,10,24] Patients with poorly controlled extracranial disease and poor performance status are more often referred to WBRT[23] implying a generally shorter OS compared to patients referred to SRS. Further, studies on the effect of WBRT and SRS in combination versus SRS alone have not shown significant differences in OS. However, improved quality of life and cognitive function was found after 3–4 months in patients treated with SRS alone.[15,25] The use of SRS is increasing overall, including in breast cancer patients with brain metastases.[24,26] As length of survival after brain metastasis diagnosis is increasing,[8] prevention of late side effects becomes more important. Therefore, it is relevant to gain knowledge about clinical practice by studying changes over time in the use of RT and survival after RT for brain metastases in breast cancer patients. At Oslo University Hospital-Radiumhospitalet (OUH), use of SRS started in 2008, and the first breast cancer patient was treated in 2009. OUH is the only institution providing SRS in our health care region, covering approximately 3 million people (60% of the Norwegian population). This study aimed to investigate the use of RT and factors affecting OS in breast cancer patients treated for brain metastases at OUH during the period of 2008–2018.

Materials and methods

Patients

All breast cancer patients with brain metastases who received RT to the brain from January 2008 through December 2018 at OUH were identified from the hospital's RT register. Inclusion criteria were females who received and completed RT treatment for parenchymal brain

metastases, diagnosed by brain imaging. A total of 255 patients met the inclusion criteria.

Demographic patient data including age, date of brain metastasis diagnosis, number of brain metastasis lesions, Eastern Cooperative Oncology Group (ECOG)[27] performance status at time of initial RT, extracranial disease, histologic subgroup and data on brain metastasis treatment, both RT and surgery were collected from the electronic medical records. Histologic information and receptor status were collected from the primary tumor in most patients, and from brain metastases in patients who had had brain metastasis surgery (n = 41). In patients with no information on ECOG, performance-status at the time of initial RT was estimated based on the clinical information in the medical records. DS-GPA scores were calculated in patients with available data (236/255) on genetic subtype, Karnofsky's Performance Status (KPS) and age. DS-GPA incorporates KPS, therefore, ECOG status was converted to KPS: ECOG 0 = KPS 90–100, ECOG 1 = KPS 80 and ECOG ≥2 = KPS≤70.[28] Further, four DS-GPA groups were defined (Table 2) based on the sum of scores given by the following scores: Age ≥60 = 0, <60 = 0.5. KPS ≤50 = 0, 60 = 0.5, 70–80 = 1, 90–100 = 1.5. Genetic subtype Basal = 0, Luminal A = 1, HER2 = 1.5, Luminal B = 2.[29] Groups were created for scores 0–1.0, 1.5–2.0, 2.5–3.0 and 3.5–4.0.

Radiation treatment planning and delivery

Patients receiving WBRT were immobilized in thermoplastic masks and had a RT plan with two laterally opposed treatment fields created in Oncentra Masterplan v.4.5.3 (Elekta, Stockholm, Sweden) on the base of a RT planning CT. Treatment fields covered all brain tissue, treatment delivery was 5 fractions/week. The treatment planning and delivery of WBRT remained consistent throughout the study period.

Patients receiving SRS were immobilized in framed thermoplastic masks and treatment planning was performed in iPlan RT Dose v.4.5.5 (BrainLab, Munich, Germany) or Raystation v.9.a (Raysearch, Stockholm, Sweden) based on co-registered CT and Magnetic Resonance images.

Prescribed doses and fractionation were due to Radiation Therapy Oncology Group (RTOG) and European Association of Neuro-Oncology (EANO) guidelines, taking into account localization, size and number of brain metastasis lesions, dose to healthy brain tissue and prior WBRT or brain metastasis surgery. Fractionated SRS was delivered with at least one day between fractions to reduce the risk of brain edema. For SRS, a consistent treatment planning was employed during the study period. Moreover, SRS was delivered using a Varian Clinac linear accelerator with 5 mm multi leaf collimators (MLC) until 2013. From 2013, treatment was delivered by a Varian TrueBeam STx with 2.5 mm MLC.

Statistical analysis

Standard descriptive statistics were used for patient characteristics. OS was analyzed from date of the first RT treatment

Table 1
Patient characteristics.

	n (%)
Included patients	255 (100)
Median age in years at BM diagnosis [min, max]	58.8 [31.4, 89.4]
<65 years	178 (70)
≥65 years	76 (30)
Missing[a]	1 (0.4)
Median follow-up in months [min, max]	8.2 [0.1, 75.8]
Mean follow-up in months (SD)	13.2 (±14)
Median follow-up in months in patients alive [min, max]	21.1 [10.9, 67.2]
ECOG performance status at BM diagnosis	
0	102 (40)
1	90 (35)
2	48 (19)
3	14 (6)
Unknown	1 (0.4)
Histology	
IDC	240 (94)
ILC	9 (3)
Other	2 (1)
Unknown	4 (2)
Estrogen receptor status	
Positive	138 (54)
Negative	109 (43)
Unknown	8 (3)
Progesteron receptor status	
Positive	88 (35)
Negative	159 (62)
Unknown	8 (3)
HER2 status	
Positive	94 (37)
Negative	146 (57)
Unknown	15 (6)
Genetic subtype	
Basal	57 (22)
Luminal A	86 (34)
Luminal B	53 (21)
HER2	41 (16)
Unknown	18 (7)
Number of BM at time of BM diagnosis	
1	64 (25)
2-4	71 (28)
≥5	120 (47)
Extracranial disease	
Yes	191 (75)
No	62 (24)
Unknown	2 (1)
Alive at end of follow-up	
Yes	27 (11)
No	228 (89)
Radiation therapy[b]	
Initial WBRT	206 (81)
Initial SRS	49 (19)
BM surgery[b]	
Before initial RT	35 (14)
After initial RT	6 (2)

Abbreviations: BM = Brain Metastasis, SD = Standard Deviation, ECOG = Eastern Cooperative Oncology Group, IDC =Intraductal Carcinoma, ILC = Intralobular Carcinoma, HER2 = human epidermal growth factor 2, RT = Radiation Therapy, WBRT = Whole Brain Radiation Therapy, SRS = Stereotactic RadioSurgery.

[a] Date of BM diagnosis unknown.

[b] For details, see Fig. 1.

until death or date of final data collection (October 1, 2019), using the Kaplan–Meier method. Groups were compared based on clinical and treatment related factors by the log-rank test. All tests were two-sided, and a statistic level of significance was set to $p < 0.05$. Multivariate Cox regression analysis was performed using those covariates that were statistically significant in the univariate analysis, excluding DS-GPA, to calculate effect sizes given as hazard ratios. Statistical analyses were carried out using IBM SPSS Statistics for Windows, version 26.0. (IBM Corporation, Armonk, NY, USA).

Ethics

The Data Protection Officer at OUH approved the review of data included in this retrospective study (reference no. 17/17690). The Regional Committees for Medical and Health Research Ethics considered this as a quality assurance study, not requiring any formal approval (reference no. 2017/2535). As most patients had died at the time of data collection, informed consent was waived after consideration by the Norwegian Directorate of Health (reference no. 18/5770). Patients alive at the time of final data collection received written information about the study with opportunity to withdraw from participation, which no one did.

Results

Demographic characteristics for the 255 included patients are shown in Table 1. The mean follow-up time from diagnosis of brain metastases was 13.2 months. An overview of local brain metastasis treatment is illustrated in Fig. 1.

A total of 206 of 255 patients (81%) received initial WBRT (Table 2 and Fig. 1). Of these 206 patients, 178 (87%) received WBRT as the only RT treatment, while the remaining 28 also received salvage SRS after prior WBRT. Twenty-eight in this group had brain metastasis surgery before (n = 23) or after (n = 5) initial WBRT (Fig. 1).

Seventy-seven breast cancer patients were treated with SRS. Of these, 49 patients received SRS as initial RT as shown in Figs. 1 and 2 and Table 2. Of the 49 patients with SRS as initial RT, 36/49 (73%) were treated with SRS alone while 13 received salvage WBRT and 4 patients received SRS twice (Table 2, Fig. 1). The first SRS was given in 2009 with variations in use during the following years, and SRS as initial RT became more common in the second half of the study period as presented in Fig. 2. The only year more patients were treated with SRS (n = 17) compared to WBRT (n = 13) was 2018 (Fig. 2).

Fractionation in 94% of patients treated with WBRT was 3 Gy × 10. Single fraction was most often used in patients receiving SRS treatments in the period 2009–2016, frequently used doses were 18 Gy (39%) and 25 Gy (20%) (Table 2 and Fig. 3). Fractionated SRS was most common in 2017 and 2018 and was delivered with 3 fractions of 6–9 Gy per fraction (Figs. 2 and 3).

Of the patients receiving initial WBRT, 42% had ≤4 brain metastases, whereas all patients treated with SRS (both initial SRS and salvage SRS) had ≤ 4 brain metastases (Table 2). Fig. 2 demonstrates a reduction in the use of initial WBRT for patients with ≤4 brain metastases from 44% in 2008–2015 to 30% in 2016–2018.

Median OS for the 255 patients was 8.6 months (Table 2). Median OS was 5.6 and 23.3 months ($p < 0.001$) for patients treated with initial WBRT or initial SRS, respectively. For the total patient cohort, 12-months survival was 41%, with 15% alive after 24 months (Table 2, Fig. 4).

Median OS after initial RT for patients with DS-GPA 0–1.0, 1.5–2.0, 2.5–3.0 and 3.5–4.0 was 7.2, 6.6, 10.2 and 17.4 months, respectively. Furthermore, one year OS was 19%, 37%, 46% and 61%, respectively (Table 2, Fig. 4).

In addition to RT technique, other factors significantly associated with OS in the univariate analyses were age, performance status, extracranial disease, brain metastasis surgery

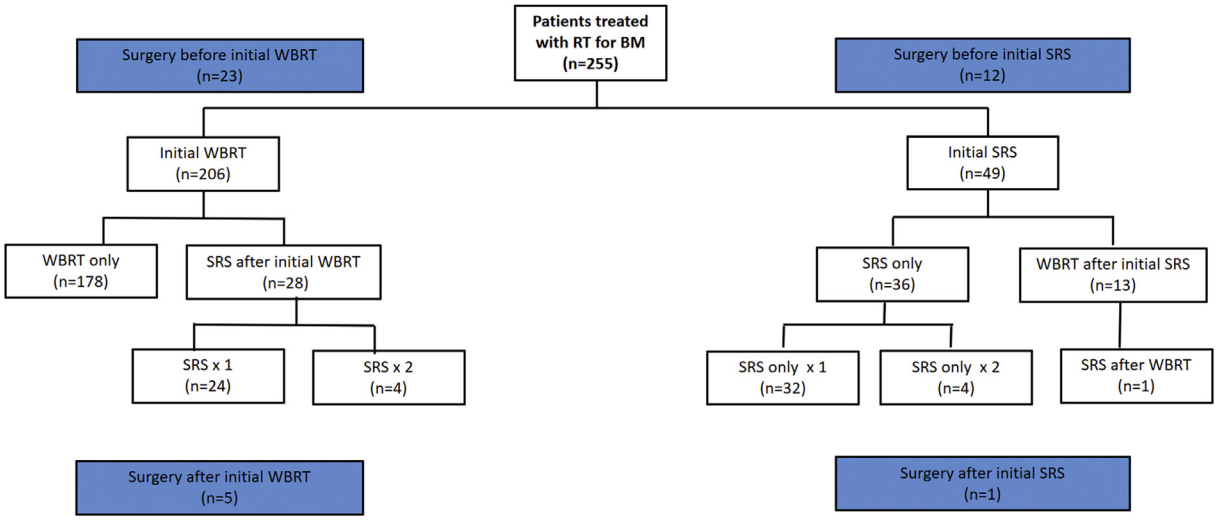

Fig. 1. An overview of local RT treatment of breast cancer patients after brain metastasis diagnosis.

Table 2
OS and factors associated with OS after BM radiation treatment.

Parameter	No of patients	Median overall survival months [min, max]	Univariate p-value (95% CI)	Multivariate		3 months survival n= (%)	6 months survival n= (%)	12 months survival n= (%)	24 months survival n=(%)
				HR (95% CI)	p-value				
Included patients	255	8.2 [0.1, 75.8]	(7.1–12.3)			190 (74.5)	156 (61.2)	100 (41.1	40 (15.7)
Age at BM diagnosis (years)			<.001						
<65	179	10.6 [0.3, 75.8]	(7.9–13.3)	Reference[a]		143 (79.9)	122 (68.2)	85 (47.4)	44 (21.0)
≥65	76	4.1 [0.1, 46.7]	(2.3–5.8)	1.3 (1.0–1.8)	.083	46 (60.5)	33 (43.4)	19 (25.0)	10 (14.1)
ECOG-status at BM diagnosis			<.001						
0	102	16.5 [0.1, 71.3]	(12.4–20.6)	Reference		90 (88.2)	81 (79.4)	58 (56.9)	23 (22.5)
1	90	8.1 [0.3, 75.8]	(6.6–9.5)	1.1 (0.8–1.4)	<.001	74 (82.2)	54 (60.0)	32 (35.6)	14 (15.6)
2	48	2.2 ([0.1, 66.0]	(1.6–2.8)	1.8 (1.2–2.7)	<.001	21 (43.8)	18 (37.5)	8 (16.7)	3 (6.3)
3	14	2.2 [0.6, 13.0]	(1.4–3.0)	3.2 (1.7–5.8)	.03	4 (28.6)	2 (14.3)	1 (7.1)	0 (0.0)
Extracranial disease present at BM diagnosis			.008						
Yes	191	6.4 [0.1, 71.3]	(5.0–20.8)	Reference		131 (68.6)	107 (56.0)	67 (35.1)	28 (14.7)
No	62	12.8 [0.4, 75.8]	(5.9–9.0)	0.8 (0.6–1.2)	.40	57 (91.9)	47 (75.8)	32 (51.6)	12 (19.4)
Initial type of RT			<.001						
SRS	49	23.3 [0.1, 49.1]	(15.6–31.0)	Reference		45 (91.8)	43 (87.8)	28 (57.1)	14 (28.8)
WBRT	206	5.6 [0.5, 71.3]	(3.9–7.4)	1.4 (0.9–2.0)	.11	145 (70.4)	113 (54.9)	72 (35.0)	26 (12.6)
BM surgery before or after initial RT			<.001						
Yes	41	23.2 [1.5, 75.8]	(17.2–29.2)	Reference		39 (95.1)	36 (87.8)	27 (65.8)	14 (34.1)
No	214	7.4 [0.1, 71.3]	(6.0–8.9)	1.9 (1.2–3.0)	.004	151 (70.6)	120 (56.1)	73 (34.1)	26 (12.1)
Number of BM lesions			<.001						
1	64	12.2 [0.3, 75.8]	(7.2–17.2)	Reference		56 (87.5)	52 (81.3)	33 (53.2)	14 (21.9)
2–4	71	9.0 [0.1, 67.2]	(5.8–12.1)	1.3 (1.0–1.6)	.74	50 (70.4)	42 (59.2)	29 (40.1)	15 (21.1)
≥5	120	6.2 [0.6, 71.3]	(2.4–8.0)	1.8 (1.3–2.3)	.67	84 (70.0)	62 (51.7)	38 (31.7)	11 (9.2)
No of BM lesions treated with initial WBRT			.16						
1	33	8.7 [0.9, 75.8]	(6.4–11.0)			30 (91.0)	25 (75.8)	13 (39.4)	7 (21.2)
2–4	53	4.5 [0.5, 67.2]	(0.0–9.2)			31 (58.0)	25 (47.2)	18 (34.0)	4 (7.5)
≥5	120	6.5 [0.6, 71.3]	(4.4–8.5)			82 (68.3)	61 (50.8)	41 (34.2)	14 (11.7)
No of BM lesions treated with initial SRS			.72						
1	31	22.5 [0.3, 49.1]	(8.1–37.0)			28 (90.3)	28 (90.3)	17 (54.8)	9 (29.0)
2–4	18	24.3 [0.1, 45.6]	(15.4–33.3)			15 (83.3)	15 (83.3	11 (61.1)	5 (27.8)
≥5	0	–	–	–	–	–	–	–	–
DS-GPA			.016						
0–1.0	21	7.2 [0.8, 15.2]	(2.1–12.4)			16 (76.2)	11 (52.4)	4 (19.0)	2 (9.5)
1.5–2.0	82	6.6 [0.1, 75.8]	(3.8–9.4)			53 (65.4)	43 (53.1)	28 (36.9)	10 (17.4)
2.5–3.0	88	10.2 [0.6, 71.3]	(6.2–14.2)			73 (82.0)	62 (69.7)	40 (46.0)	18 (23.0)
3.5–4.0	45	17.4 [0.6, 13.0]	(13.6–21.2)			37 (84.1)	33 (75.0)	25 (61.4)	9 (25.1)
Fractionation scheme WBRT			.98						
3Gy × 10	205	7.8 [0.5, 78.5]	(6.5–9.2)			147 (71.7)	117 (57.1)	72 (35.1)	30 (14.6)

(*continued on next page*)

Table 2 (*continued*)

Parameter	No of patients	Median overall survival months [min, max]	Univariate p-value (95% CI)	Multivariate HR (95% CI)	Multivariate p-value	3 months survival n= (%)	6 months survival n= (%)	12 months survival n= (%)	24 months survival n=(%)
Other	14	7.6 [1.2, 25.8]	(0.0–26.1)			11 (78.6)	10 (71.4)	7 (50.0)	1 (7.1)
Fractionation scheme SRS[b]									
18 Gy × 1	30	20.9 [0.3, 52.7]	(12.8–27.9)			28 (93.3)	26 (86.7)	21 (70.0)	10 (33.3)
25 Gy × 1	15	27.5 [0.1, 67.2]	(8.0–46.9)			13 (86.7)	9 (60.0)	7 (46.7)	7 (46.7)
Other	32	23.6 [2.1, 75.8]	(11.9–59.2)			31 (96.9)	29 (90.6)	23 (71.9)	10 (31.3)

Abbreviations: BM = Brain Metastasis, ECOG = Eastern Cooperative Oncology Group, RT = Radiation Therapy, WBRT = Whole Brain Radiation Therapy, SRS = Stereotactic RadioSurgery, Gy = Gray, CI = Confidence Interval, HR = Hazard Ratio, No = Number DS-GPA = Diagnosis Specific Graded Prognostic Assessment.

Only variables significant in univariate analysis were included in multivariate analysis.

[a] Reference is equal to HR of 1.00.

[b] If more than one fractionation scheme was used, the scheme with highest fraction dose was used to define groups.

before or after RT, number of brain metastasis lesions and DS-GPA group ($p < 0.05$, Table 2). However, in the multivariate regression analysis, ECOG ≥1 and no brain metastasis surgery remained associated with inferior OS as shown by the HR in Table 2. DS-GPA was left out of the multivariate analysis as it is a combination of factors included in the univariate analyses.

Discussion

In this study, the use of RT and factors affecting OS were investigated in 255 breast cancer patients receiving RT for brain metastases from 2008 to 2018 at OUH. The majority of the patients (81%) received initial WBRT. The use of SRS as initial RT was not common in the period from 2009 to 2014 but increased from 2015. Patients receiving initial SRS had longer OS than those treated with initial WBRT. Additional treatment with brain metastasis surgery and ECOG = 0 were significantly associated with longer OS in multivariate analyses.

WBRT is reported as the most common RT technique in treatment of brain metastases in breast cancer patients in the studies carried out by Znidaric et al.,[9] Pasquier et al.[24] and Kim et al.,[30] covering patients treated between 2000 and 2015. The results of the current study (Table 2) agree with these findings. Bentley and colleagues[31] found that SRS was the most frequently used local therapy in a retrospective audit from the UK for the years 2016–2017. In our study the use of SRS as initial RT peaked in 2018, also showing a greater number of patients treated with SRS compared to WBRT. Our results also show that during 2015–2018, the preferred choice of RT treatment in patients with ≤4 brain metastasis lesions was SRS, and this change in choice of RT might be associated with experience in using SRS, more specific guidelines and knowledge about the late side effects after WBRT. Still, about 42% of the patients with ≤4 brain metastases received initial WBRT in our study indicating that traditions may still play a role in clinical practice when deciding RT technique for brain metastases.

A Swedish cohort study by Frisk et al. (17) reported that fractionation schemes of 4 Gy × 5 and 3 Gy × 10 were used in 88% and 12% of 241 breast cancer patients treated with WBRT, respectively. Another study have reported a median total dose of 30 Gy and 3 Gy × 10 fractionation regime as the most employed fractionation in WBRT treatment of breast cancer patients.[9] Studies have shown that the use of 4 Gy × 5 or 3 Gy × 10 do not seem to have statistically significantly different impact on symptom relief or neurologic function and OS after WBRT is not affected by fractionation, as most patients do not decease from brain metastases.[7,32,33] In our study, 3 Gy × 10 was the most commonly used fractionation. This result reflects the fractionation recommendation of 3 Gy × 10 described in treatment guidelines by the Norwegian Breast Cancer Group.[34] When using SRS, a single fractionation of 18–20 Gy is most commonly reported,[9,35,36] corresponding with our finding with 18 Gy × 1 as the most

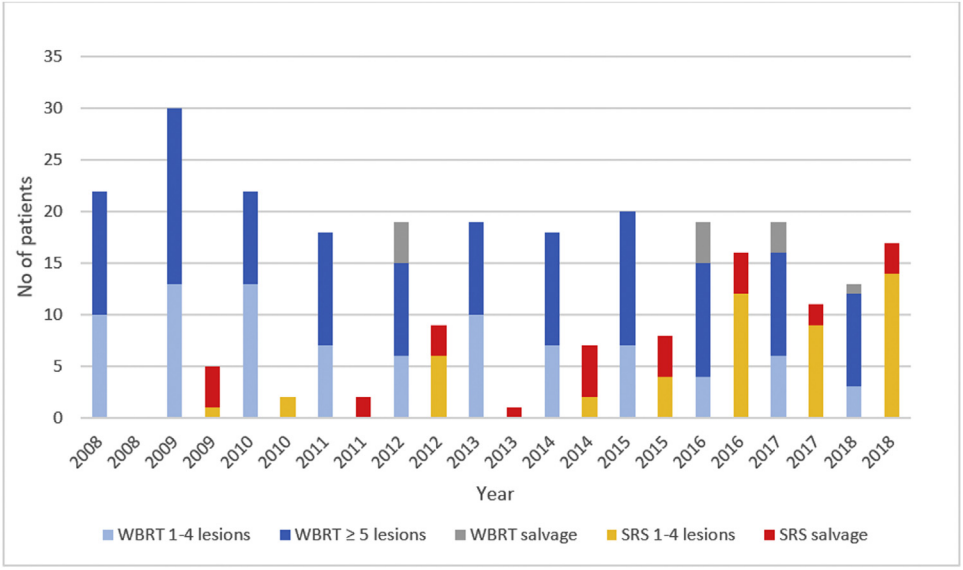

Fig. 2. Use of RT treatment in breast cancer patients with brain metastases during 2008–2018.

common fractionation. However, the results of our study show an increase of using fractionated SRS in the period 2016–2018. An increased awareness of the risk factors of radionecrosis following SRS, change of local treatment tradition and or the EANO guidelines[7] together might have contributed to make fractionated SRS more common.

The results of the current study show a median OS of 8.6 months corresponding with median OS from 7.6 months to 9.1 months as reported in other breast cancer studies.[9,11,24,37] Furthermore, our results along with the results of two earlier studies (10, 32) show a significant difference in OS in patients treated with initial WBRT versus those treated with initial SRS ($p < 0.001$). Most likely, this difference in OS is due to patient selection rather than the radiation technique itself, as initial RT technique was not associated with OS in the multivariate analyses. Furthermore, the initial SRS group ($n = 49$) in our cohort was much smaller compared to initial WBRT group ($n = 206$) and thirteen of the SRS patients had surgery before or after RT. This might have an impact on the estimated OS after initial SRS.

Our results show that 30% of the patients died within 3 months after start of WBRT. Moreover, 25% of the included patients had ECOG ≥2 at start of RT. This indicates that RT treatment was given to patients with a limited life expectancy,

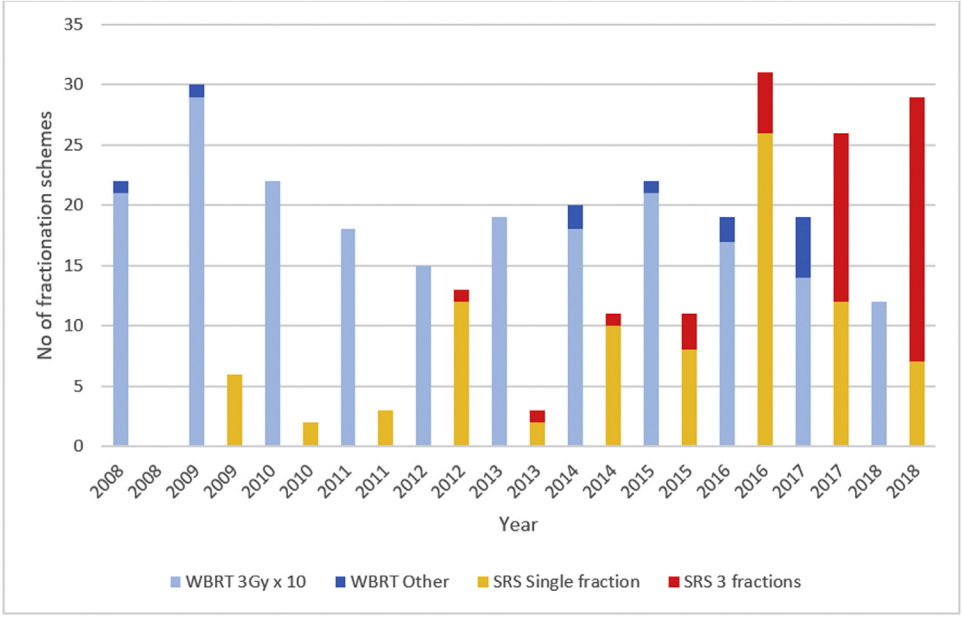

Fig. 3. Fractionation schemes using WBRT and SRS during 2008–2018.

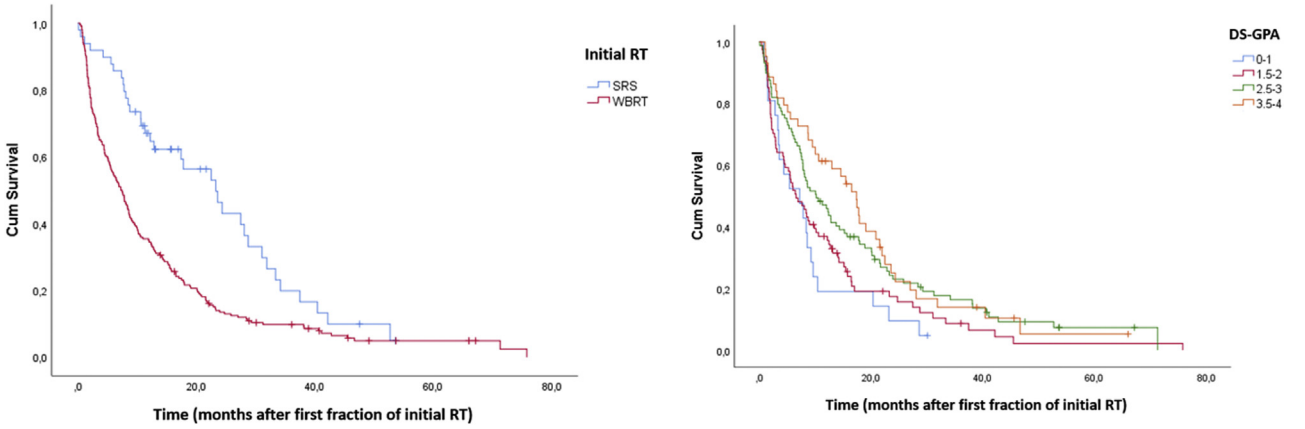

Fig. 4. Overall survival by initial RT and DS-GPA.

and a relatively poor performance status. Hence, there is reason to believe that a proportion of these patients had little benefit of the RT and might have been better off with best supportive or specialized palliative care. In this respect, assessment of patient preferences and patient-reported symptom burden should guide treatment decisions and must be part of all consultations prior to start of treatment. These factors are essential outcomes but there is a paucity of studies conducting longitudinal follow-up conducting longitudinal studies, resulting in a lack of data to support improved OS or quality of life in patients receiving WBRT over best supportive care.[38]

The DS-GPA is designed to aid in the treatment decisions by providing a prognostic score for OS based on age, performance status and here; subtype of breast cancer. In our study, median OS in the most favorable DS-GPA groups of 3.5–4 and 2.5–3 was 17 and 10 months, respectively. In the less favorable DS-GPA groups of 0–1 and 1.5–2 an inferior OS of approximately 7 months was observed. The OS in group 3.5–4 corresponds to findings by Znidaric et al.[9] and Sperduto et al.,[10] reporting median OS of 24 and 25 months, respectively, while group 0–1 had shortest OS of 3 months in both studies. The difference in OS in our study versus above mentioned studies might be due to the fact that our study had a cohort size of about 60% of the above-mentioned studies, and they also included patients with leptomeningeal disease.

The impact of other univariate individual factors such as age, performance status, surgery, extracranial disease and number of lesions on OS in our study is in agreement with the results of other relevant studies.[9–11,23,30,31,36,37] Furthermore, our results of the multivariate regression analysis indicating an inferior OS in patients with ECOG $\geq$1 and no brain metastasis surgery as shown by the HR in Table 2 correspond with the results of earlier studies.[9,10,24,37]

There are several limitations to this retrospective study. One of the limitations was the lack of information on systemic treatment which leaves the impact of systemic treatments on OS unknown, however, all patients received treatment according to standard guidelines. Additionally, the statistical analyses were not adjusted for the time factor showing improved OS over time.[8] Also, the number of patients in some groups (e.g. initial SRS, or patients treated with surgery) were small, and the estimates regarding OS in these groups must be interpreted with caution. Another limitation noted was the ECOG estimation in patients with lack of ECOG evaluation. Furthermore, the results of the multivariate analyses including brain metastasis surgery should be interpreted with caution due to the small number of this patient group. On the other hand, the population investigated covers more than half of Norway's population, and this gives detailed information on the clinical practice regarding use of RT in breast cancer patients with brain metastases for more than a decade.

Conclusion

WBRT was the most commonly used RT technique, but increased use of SRS was observed in the second half of the study period. The longest OS was observed in patients treated with initial SRS, but can probably be associated with patient selection. ECOG 0 and brain metastasis surgery were associated with superior OS in multivariate analysis. As 30% of patients died within 3 months after RT, this may indicate that the use of RT in brain metastasis patients with poor performance status may be of little benefit to the patients and must be seriously considered.

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