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ORIGINAL ARTICLE

Overall survival after initial radiotherapy for brain metastases; a population based study of 2140 patients with non-small cell lung cancer

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ABSTRACT

Background: Brain metastases (BM) occur in about 30% of all patients with non-small cell lung cancer (NSCLC). BM treatment guidelines recommend more frequent use of stereotactic radiotherapy (SRT). Overall, studies report no difference in overall survival (OS) comparing SRT to whole-brain radiotherapy (WBRT). We examined survival after radiotherapy for BM in a population-based sample from the South-Eastern Norway Regional Health Authority treated 2006-2018.

Methods: We reviewed electronic medical records of 2140 NSCLC patients treated with SRT or WBRT for BM from 2006–2018. Overall survival (OS) was compared to predicted survival according to the prognostic systems DS-GPA and Lung-molGPA.

Results: Use of SRT increased during the period, from 19% (2006–2014) to 45% (2015–2018). Median OS for all patients was 3.0 months, increasing from 2.0 (2006) to 4.0 (2018). Median OS after SRT was 7.0 months ($n = 435$) and 3.0 months after WBRT ($n = 1705$). Twenty-seven percent of SRT patients and 50% of WBRT patients died within 90 days after start of RT. Age $\geq$70, male sex, KPS $\leq$70, non-adenocarcinoma histology, ECM present, multiple BM, and WBRT were associated with shorter survival ($p < .001$). Actual mOS corresponded best with predicted mOS by DS-GPA and Lung-molGPA for the SRT group.

Conclusion: Overall survival after radiotherapy (RT) for BM improved during the study period, but only for patients treated with SRT. Survival after WBRT remains poor; its use should be questioned. DS-GPA and Lung-molGPA seem most useful in predicting prognosis considered for SRT.

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Introduction

The overall number of cancer patients diagnosed with brain metastases (BM) is ascending, corresponding to increased cancer incidence, more frequent imaging with improved diagnostics and better systemic control of the primary tumor prolonging survival [1,2]. About 30% of all non-small cell lung cancer (NSCLC) patients are diagnosed with BM during the disease trajectory depending on their mutational status [3,4]. Without treatment, overall survival (OS) in lung cancer patients after BM diagnosis ranges from 2 to 6 months [5,6].

Treatment options for BM include surgery, stereotactic radiotherapy (SRT), whole-brain radiotherapy (WBRT), systemic tumor directed treatment and corticosteroids together with best supportive care. According to the most recent European Association of Neuro-Oncology (EANO) [7] and American Society of Radiation Oncology (ASTRO) guidelines [8], SRT is the preferred treatment in patients with 1–4 BM, while WBRT is recommended for patients with multiple (>4) or non-resectable BM >3–4 cm when SRT is not feasible. Guidelines recommend best and palliative care over RT to patients with poor performance status and/or expected survival <3 months. NSCLC- patients with molecular drivers, e.g., epidermal growth factor receptor (EGFR) and anaplastic lymphoma kinase translocation (*ALK*), are candidates for targeted therapy (TT) as initial treatment, also for BM. Thus, the prognostic scoring system diagnosis specific Graded Prognostic Assessment (DS-GPA), was recently updated to Lung-molGPA including molecular markers as one of the prognostic criteria [9,10]. Data on the immunotherapy (IT) effect on BM in NSCLC-patients are still limited but promising [11,12].

There has been a gradual shift from a predominant use of WBRT toward more use of SRT over the last 10 years [13]. With the increased awareness of potential long-term cognitive deficits, WBRT is today more used as salvage therapy for

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intracranial relapse or progression if other therapeutic options are not possible [14]. SRT is easy to deliver with high precision while sparing the surrounding normal tissue to preserve cognitive function. Randomized clinical trials (RCT) have found no difference in OS after treatment with SRT compared to WBRT [15–17]. The QUARTZ-RCT found that WBRT provided little or no additional clinical benefit in NSCLC-patients not candidates for surgery or SRT [18].

However, BM patients included in clinical studies are highly selected; more often in generally better health condition than patients seen in daily clinical practice and asymptomatic from their BM [19,20]. Only 27% to 45% of advanced NSCLC-patients meet the eligibility criteria for clinical studies [19]. As study samples often differ from real-world patients, it is not known whether outcomes in clinical studies are applicable to daily clinical practice and if the prognostic systems are useful [19].

In the part of Norway covered by the South-Eastern Norway Regional Health Authority (HSØ), covering approximately 57% (3 million) of the Norwegian population, three centers provide radiotherapy. Oslo University Hospital (OUH) is the only center providing SRT (introduced in 2006). We examined the use of SRT and WBRT in all 2140 NSCLC-patients who received RT for BM in our health care region from the introduction of SRT in 2006 through 2018.

Primary study objective was to examine OS after initial RT for BM in NSCLC-patients. Secondly we examined how actual OS compares to OS predicted by the DS-GPA and Lung-molGPA.

Whereas clinical studies have found no difference in OS after SRT or WBRT for BM, it may be questioned whether this also apply to real-world patients. Our hypothesis was that the use of SRT increased from 2006 to 2018 with no improvement in OS and that OS estimates using DS-GPA and LungmolGPA would correspond to actual OS.

Material and methods

Identification

All NSCLC-patients with BM treated with RT from 2006 to 2018 in the HSØ region were identified from RT registries at Oslo University Hospital (OUH), the regional referral center, and the other two smaller radiotherapy centers in the region. Patients were grouped as WBRT and SRT according to initial RT modality, Supplementary Figure 1.

The following inclusion criteria applied: Histologically, clinically and/or radio logically confirmed NSCLC, age >18 and BM diagnosed by cerebral CT and/or MRI. Patients were either diagnosed with BM when presenting with clinical symptoms or regular during follow-up by a brain CT or MRI taken at the discretion of the treating physician. In patients with multiple cancers, lung cancer had to be identified and documented as the most likely source of BM. Primary BM surgery and systemic therapy were accepted. The only exclusion criteria were prior BM diagnosis and/or radiotherapy to the brain of any modality including Gamma Knife.

Patient characteristics

Patient and disease characteristics were extracted from the electronic medical records according to a predefined checklist of relevant variables defined by consensus discussion among experienced oncologists and researchers in the project. Number of BM was based on the brain MRI or CT decisive for the choice of RT modality. ECM at BM diagnosis was categorized as present (≥N3 or M1 according to TNM8) or not [21]. Complete follow-up data were confined to documentation in the electronic medical records available at our center only (OUH).

Treatment

Date and fractionation of RT were collected from the radiotherapy registry. All WBRT and SRT were performed on a linear accelerator (LINAC) based system; no patients were treated with gamma-knife. WBRT was categorized as 1–5 or > 5 fractions. SRT was given as 1–5 fractions with 7–25 Gy per fraction.

DS-GPA and lung-molGPA

The predefined checklist included all necessary data for calculations of the DS-GPA and for the Lung-molGPA (age, Karnofsky performance status (KPS), number of BM, ECM present or not, histology, status of EGFR mutation and *ALK* translocation) [9,10]. Eastern Cooperative Oncology Group Performance Status (ECOG status) was estimated from nurses' and doctors' notes if missing in the electronic medical records. As ECOG was often used in the medical records, ECOG status was converted to KPS as follows: ECOG 0 = KPS 90-100, ECOG 1 = KPS 80 and ECOG ≥2 = KPS ≤ 70 [22]. In both GPA indices, a score for each prognostic factor (0, 0.5 or 1.0) is summarized to categorize patients into four prognostic groups (0–1.0, 1.5–2.0, 2.5–3.0 and 3.5–4.0), predicting a median OS for each group [9,10]. GPA was not calculated for 644 patients missing exact data on ECM, number of BM or histology, Supplementary Figure 1.

Statistical analysis

Descriptive statistics were used for patient characteristics using the chi-square test to compare categorical variables between RT groups. All 2140 patients were used in the calculations of OS based on start of RT to death of any cause. Overall survival was analyzed by the Kaplan-Meier estimator supplemented by the log-rank test. Univariate and multivariate analyses were performed in the proportion of patients with available data using the Cox proportional hazards model to determine the clinical factors associated with longer survival. The assumption of proportional hazards was checked by visual inspection of log - log plots. DS-GPA and Lung-molGPA were calculated only for patients with sufficient data, Supplementary Figure 1. As a sensitivity analysis we estimated propensity scores (PS) for WBRT by logistic regression including age, sex, KPS ≤70, non-adenocarcinoma

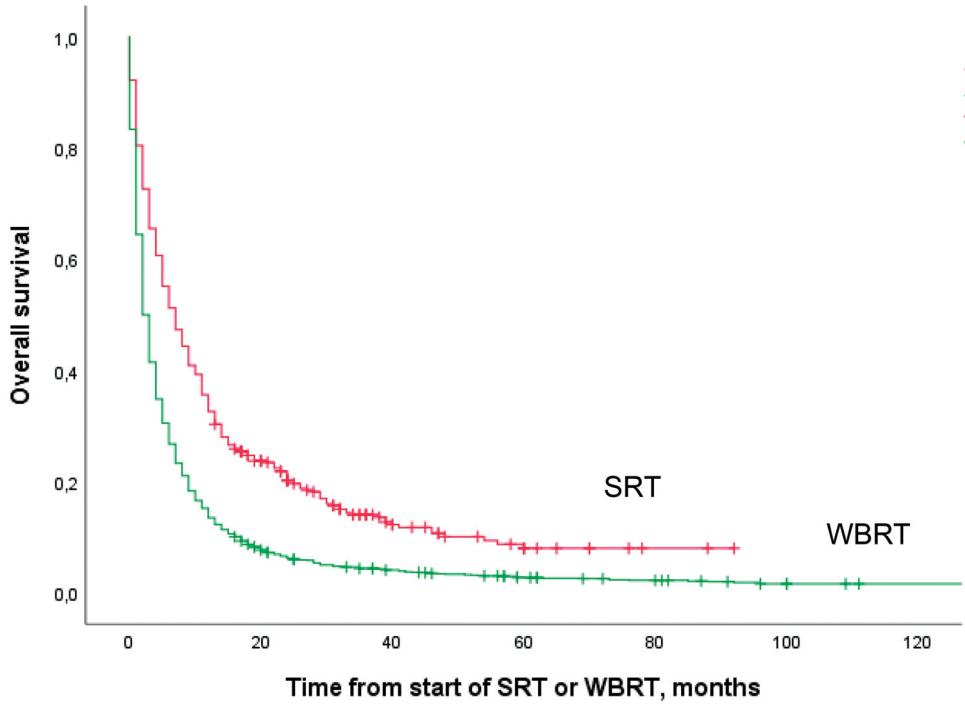

Figure 1. Overall survival after start of initial RT, SRT group ($N = 435$) and WBRT group ($N = 1705$).

histology, ECM present, number of BM, synchronous diagnosis of BM, primary cancer and year as covariates. We compared the distribution of propensity scores between RT groups and performed a PS stratified analysis using nine strata plus separate analyses in each stratum to assess different associations across strata.

All analyses were performed by SPSS Statistics 25 (IBM Corp. Armonk, NY). Non-overlapping 95%CI represents a *p*-value of $<.05$ [23].

Ethical considerations

This study was considered a quality improvement project by the Norwegian Regional Committees for Medical and Health Research Ethics (reference no. 2017/2535). The Data Protection Agency at Oslo University Hospital approved the study (reference no 17/17690). The Norwegian Directorate of Health issued a waiver of patient consent for inclusion (reference no. 18/5770), and most eligible patients (95%) were dead at the time of the study. Patients still alive received written information about the project. All data are stored and handled according to General Data Protection Regulation (GDPR).

Results

Overall, 2140 patients were identified and included in the OS analysis. The BM diagnosis was confirmed by MRI in 35% and CT scans in the remaining 65%. Median age was 65 years (range 29–101), the majority (67%) was <70 and 51% were women. At last follow-up (June 2020), 95 (4%) patients were still alive with a median follow-up time of 49 months (range 13–167). Median OS in the entire study population was 3.0 months, 7.0 in the SRT-group, and 3.0 in the WBRT-group, Figure 1. Median OS in the entire study population increased significantly from 2.0 months in 2006 (when SRT was introduced) to 4.0 months in 2018, Table 1. Overall, 15% of the patients had died within 30 days after start of RT, 45% within 90 days. The 1-year survival rate was 20% with a trend toward longer survival time at the end of the study period, Table 1. Corresponding values for survival data in the SRT- and WBRT-groups, respectively, are shown in Table 1. Patients in the WBRT-group lived shorter compared to the SRT-patients (30-days mortality 17% versus 8%, 90-days mortality 50% versus 27%). 1-year survival rate was 15% in the WBRT-group compared to 35% in the SRT-group.

Treatment patterns

Detailed information about the administered RT is illustrated in Supplementary Figure 1. Of the entire study population (2140 patients), 1705 (80%) patients received WBRT as initial treatment. The annual number of patients given RT for BM and the proportion of patients treated with SRT as initial treatment increased during the study period, Supplementary Figure 2. The majority of the WBRT-patients received 30 Gy (68%), but the use of 20 Gy increased during the period from 32% in 2014 to 43% in 2018.

Univariate and multivariate analysis

Complete medical data were available for the 1496 patients treated at OUH, Table 2, who were included in the uni- and multivariate analyses, Table 3. Age >70, male sex, KPS ≤ 70, histology other than adenocarcinoma, ECM present, multiple BM and WBRT were associated with shorter OS both in univariate and multivariate analyses ($p < .001$), Table 3. In the SRT group, patients had a significantly higher proportion of

Table 1. Overall survival (OS) after initial RT ($N = 2140$).

	Entire group N 2140(%)	All patients 2006 (before SRT) N 133 (%)	All patients 2018 (routine SRT) N 163 (%)	SRT group N 435 (%)	WBRT group N 1705 (%)
Median OS (95% CI), months	3.0 (2.8–3.2)	2.0 (1.6–2.4)[a]	4.0 (2.2–5.8)[a]	7.0 (5.7–8.3)	3.0 (2.8–3.2)
Died within 30 days	323 (15)	21 (16)	16 (10)	34 (8)	287 (17)
Died within 90 days	973 (45)	75 (56)	70 (43)	119 (27)	854 (50)
Alive > 1 year	409 (19)	19 (14)[b]	47 (29)[b]	153 (35)	256 (15)

95% confidence interval (95% CI).
[a] $p < .001$
[b] $p = .002$.

Table 2. Characteristics of patients with complete medical data ($N = 1496$).

	SRT[a] and WBRT[b] N 1496 (%)	SRT[a] N 423 (%)	WBRT[b] N 1073 (%)	*p*-value[e]
ECOG / KPS				
ECOG 0-1 / KPS > 70	842 (56)	304 (72)	538 (50)	<.001
ECOG ≥ 2 / KPS ≤ 70	654 (44)	119 (28)	535 (50)	
Histology				
Adenocarcinoma	987 (66)	309 (73)	678 (63)	<.001
Squamous cell carcinoma	201 (13)	65 (15)	136 (13)	
Large cell carcinoma	53 (4)	15 (4)	38 (3)	
Non-small cell	232 (15)	29 (7)	203 (19)	
Other	23 (2)	5 (1)	18 (2)	
EGFR mutation				
Yes	78 (5)	28 (7)	50 (5)	<.001
No/unknown[c]	1418 (95)	395 (93)	1023 (95)	
ALK translocation				
Yes	24 (2)	10 (2)	14 (1)	<.001
No/unknown[c]	1472 (98)	413 (98)	1059 (99)	
Extracranial metastases[d]				
Present	964 (64)	218 (52)	746 (70)	<.001
Not present	532 (36)	205 (48)	327 (30)	
Number of BM				
1	502 (34)	233 (55)	269 (25)	<.001
2	247 (16)	110 (26)	137 (13)	
3	156 (10)	51 (12)	105 (10)	
4	73 (5)	14 (3)	59 (5)	
≥ 5	518 (35)	15 (4)	503 (47)	<.001

[a] SRT – patients with clinical data given SRT as initial RT
[b] WBRT – patients with clinical data given WBRT as initial RT
[c] testing of EGFR mutation and ALK translocation routine from 2011/2013 and prevalence after that found to be like estimated; EGFR 7,5% and ALK 2,5%
[d] ≥N3 according to TNM8
[e] chi-squared test was used to compare *p*-values for SRT and WBRT.

Table 3. Overall survival (OS) after start of initial RT in patientswith complete medical data ($N = 1496$).

	Univariate analysis		Multivariate analysis	
Factor	HR (95% CI)	*p*-value	HR (95% CI)	*p*-value
Age > 70				
< 70 ($n = 1035$)	1		1	
≥70 ($n = 529$)	1.3 (1.1–1.4)	<.001	1.3 (1.1–1.4)	<.001
Gender				
Male ($n = 753$)	1		1	
Female ($n = 811$)	0.9 (0.8–0.9)	.002	0.9 (0.8–1.0)	.009
Histology				
Adenocarcinoma ($n = 1005$)	1		1	
Non-adenocarcinoma ($n = 515$)	1.4 (1.3–1.6)	<.001	1.3 (1.2–1.5)	<.001
Extracranial metastases present				
No ($n = 550$)	1		1	
Present ($n = 996$)	1.6 (1.5–1.8)	<.001	1.1 (1.0–1.1)	.002
Number of BM				
1 ($n = 521$)	1		1	
2-4 ($n = 486$)	1.3 (1.2–1.5)	<.001	1.4 (1.2–1.5)	<.001
≥ 5 ($n = 533$)	1.6 (1.4–1.8)	<.001	1.5 (1.3–1.7)	<.001
KPS				
> 70 ($n = 858$)	1		1	
≤ 70 ($n = 706$)	1.8 (1.6–2.0)	<.001	1.6 (1.4–1.7)	<.001
RT				
SRT ($n = 423$)	1		1	
WBRT ($n = 1073$)	1.7 (1.5–1.9)	<.001	1.4 (1.2–1.6)	<.001

KPS >70, single BM and adenocarcinomas, $p < .001$. Extracranial disease and ≥ 5 BM were significantly more frequent in the WBRT group, $p < .001$. The estimated HR for WBRT vs SRT in the PS stratified sensitivity analysis was very similar to the estimate from the multivariable model (HR = 1.3 95% CI 1.2 to 1.6 and HR = 1.4 95% CI 1.2 to 1.6).

These 1496 patients were included in the analysis of DS-GPA and Lung-molGPA. According to the calculated DS-GPA scores, 50% (745) had low score (0–1) indicating poor prognosis and predicted median survival of 3.0 months. In our population however, the actual mOS was shorter, only 2.0 months, Supplementary Table 1(a). For the remaining patients, actual mOS were within the predicted interquartile range (IQR), Supplementary Table 1(a). For WBRT-patients with score of 0–1 and 1.5–2.0, mOS were shorter than predicted by DS-GPA, Supplementary Table 1(a). For SRT-patients, actual values for mOS and/or IQR overlapped with the predicted values, Supplementary Table 1(a).

In the Lung-molGPA calculations, there were 987 patients with adenocarcinomas and 509 with non-adenocarcinomas, Supplementary Table 1(b). For 1229 patients with Lung-molGPA score 0–2 in both groups, actual mOS were shorter than predicted, Supplementary Table 1(b). However, for patients in the SRT-group, actual mOS corresponded to the predicted time in all groups except for the 25 patients with a non-adenocarcinomas with score of 0–1 (actual mOS vs. predicted: 1 vs. 5.3 months, respectively), Supplementary Table 1(b).

Discussion

In our historic cohort of 2140 NSCLC-patients, we found that the median OS (mOS) after radiotherapy for BM improved from 2006 to 2018, contrasting to our hypothesis. However, an extended mOS was found in the SRT-group only, and not in the WBRT-group. mOS was longer in the SRT-group compared to the WBRT-group. Fifty percent of the WBRT-patients died within 90 days after start of RT. In the multivariate analysis, we confirmed that age, histology, KPS, number of BM and ECM were associated with OS, however, the RT modality remained associated with OS.

Improved mOS in the study period is in line with a retrospective study of 6001 patients with BM (50% with lung

cancer) presented at ESMO 2020, that also found improved overall mOS from 1986 to 2020 after RT treatment (ESMO 2020, Proffered Paper no 3630 Steindl *et al*). Improved OS after SRT alone is in line with a study on BM from small-cell lung cancer published 2018 [24]. However, superior mOS after SRT compared to WBRT contrasts results from randomized clinical trials (RCTs) that have not found improved survival after SRT compared to WBRT [15,16]. Also, a matched-pair study by Rades [17] found similar mOS (10 months) comparing WBRT to SRT in patients with 1–3 BM (50% with lung cancer). We believe that the prolonged OS after SRT in our study cannot be attributed to the RT modality only. Patient-related and medical factors such as neurological symptom burden [25], potential side effects of different RT modalities, comorbidity, provision of systemic treatment, life-time expectancy, patients' preferences and quality of life (QoL) not included in our study or prognostic systems are important in treatment decisions, and probably explain the difference in survival after SRT and WBRT. More patients in the SRT-than in the WBRT-group had KPS $>$ 70 and adenocarcinomas. Rades [17] included mainly patients with KPS $\geq$80 (68%) relative to 72% and 50% in the SRT- and WBRT-groups in our study. In our opinion, this probably explains the superior mOS in the Rades study compared to ours and can be attributed to the fact that patients in better general health condition are more likely to be offered and benefit from systemic treatment and inclusion in RCTs. As only one hospital in our health care region provides SRT, patients are referred for such treatment. A possible bias in our study may be that only the fittest patients are referred to SRT. Together with increased imaging in asymptomatic patients, the superior sensitivity of MRI versus CT has probably resulted in more patients being diagnosed with smaller, single BM. These patients in turn may be in better health condition and are offered SRT. Consequently, MRI diagnostics and imaging in asymptomatic patients may augment the difference in mOS between the SRT- and WBRT-groups. In sum, superior survival after SRT is probably multifactorial.

mOS after WBRT remained poor throughout the study period. This is also in line with a German retrospective study reporting a mOS of 2.5 months after WBRT and a Swedish study reporting that 55% of the patients died within 3 months [26,27]. As 50% of patients in the WBRT-group died within 90 days after the start of RT, many patients probably had little benefit of the RT, as they died before symptom relief occurred, and on the contrary, were at risk of adverse side-effects and having less time at home near end-of-life. It is important to question whether this group of patients should be offered RT at all in line with the EANO guidelines [7]. This is in line with the QUARTZ-study, which revealed that WBRT provides little additional survival and/or quality of life benefit in patients who are not candidates for surgery or SRT [18]. One argument for WBRT has been to control microscopic intracranial disease. This indication for WBRT may now be questioned as multiple studies have demonstrated intracranial activity of targeted agents [28,29] that could be used in conjunction to SRT, at least in patients with oncogenic driven tumors.

We found that more patients received WBRT in five fractions at the end of the study period. As WBRT fractionation has no impact on survival [30] there might be an increasing eagerness to continue systemic treatment, explaining the wish to shorten treatment-time. Additionally, in patients with poor performance status, clinicians may find it difficult to stop tumor-directed therapy instead of focusing on symptomatic palliative care.

The proportion of patients treated with SRT as initial RT increased during the study period. With less acute side effects and lower impact on cognitive function and QoL compared to WBRT [15,31], especially with less than five BM [7,8], this is in line with current guidelines [7,8], and with results from the retrospective Austrian study (presented at ESMO 2020, Proffered Paper no 3630, Steindl *et al.*).

Predicting length of survival is difficult in clinical practice, especially in lung cancer patients who often have respiratory diseases and other comorbidities associated with shorter OS [19]. Our historic real-world study found that the prognostic tools DS-GPA and Lung-molGPA were reliable instruments to categorize survival in the SRT-patients, but not in the WBRT patients, in contrast to our hypothesis that OS estimates would correspond to actual OS regardless of RT modality. Real-world patients differ from patients who are eligible for studies, so prognostic tools based on data from RCTs should be used with caution. The database that served as a basis for the DS-GPA [9] included patients in good general condition (85% KPS $>$ 70, 75% $<$3 BM and 67% with no ECM), quite similar to our SRT-group, whereas the corresponding numbers for all these three factors accounted for about 50% in our WBRT-group. Secondly, 50% of the patients in the analysis for the Lung-molGPA [10] were treated with SRT alone versus 22% WBRT alone, which probably explains why this tool was most reliable in the SRT-group. In line with this, a retrospective study by Nagtegaal *et al.* also found Lung-molGPA to be a reliable tool to classify BM patients treated with SRT [32]. However, studies including other clinical and patient-related factors are warranted [33]. Hence, we are now running a prospective study following patients from the diagnosis of BM until death or for 2 years, including clinical data on comorbidities, treatments and diverse patient-reported outcomes (ClinicalTrials NCT03346655).

Limitations and strengths

Retrospective studies are essential to evaluate and improve daily clinical practice and to evaluate whether clinical study results are applicable to real-world patients. Strengths of our study include the large sample size and a multi-institutional database representing daily clinical practice at three academic hospitals performing RT to BM patients in the largest part of our country, thereby reducing selection bias.

ECOG/KPS was inconsistently reported in the electronic medical records during the period, though more frequently documented at the end of the period. If performance status was missing, this was estimated from nurses' and doctors' notes by the first author, a highly experienced lung oncologist, but some misclassification cannot be ruled out.

Improved molecular pathology and imaging diagnostics with more exact diagnostics have led to a potential group-shift in the GPA systems. Additionally, Lung-molGPA could be calculated even with missing data on biomarkers (EGFR etc.) as the 'unknown' marker status is included in the scoring system [10]. This means that all patients get a score, regardless of missing or present biomarker. A misclassification due to this was less likely at the end of the period as testing became routine from 2011 (EGFR) and 2013 (*ALK*).

The retrospective design and missing data in the electronic medical records give a lack of information about novel biomarkers of tumor aggressiveness, size and location of the BMs, extracranial disease control and systemic therapies.

Conclusion

Overall survival after RT for BM in NSCLC patients improved during the study period, but only for patients treated with SRT. This is probably due to other factors than SRT itself. As survival after WBRT remains poor the use of WBRT should be questioned. DS-GPA and Lung-molGPA seem to be most useful in predicting prognosis in NSLCL patients considered for SRT.

Disclosure statement

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