Recursive partitioning analysis of systemic therapy after radiotherapy in patients with brain metastases

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Abstract

Purpose: The purpose of this study was to identify factors associated with initiation or continuation of systemic treatment after brain irradiation. The outcome of interest was a utilization rate of at least 75%, given that active extracranial disease is common in patients with brain metastases. If left untreated, extracranial disease limits survival, regardless of successful local treatment of the brain metastases. In this context, systemic therapy has been shown to improve survival, e.g. after whole-brain radiotherapy.

Patients and Methods: The study included 185 patients with active extracranial disease, 60% of whom received systemic therapy.

Results: Survival from start of brain irradiation was longest in patients who received additional immune checkpoint inhibitors, endocrine treatment or anti-HER-2 drugs. After uni- and multivariate analyses, Eastern Cooperative Oncology Group performance status (PS) was selected as the first prediction criterion in the recursive partitioning analysis (RPA) decision tree analysis. RPA was successful for patients with PS 0-1, whereas patients with PS 2 had lower treatment utilization rates (maximum 60-70%, with disease-dependent impact of age and LabBM score (blood test results)). The highest utilization rates were observed in 1) patients with PS 0 and 2) those with breast cancer, small cell lung cancer or lung adenocarcinoma with PS 1.

Conclusions: These results inform multidisciplinary discussion and treatment planning in the common scenario of simultaneous intra- and extracranial metastases.

Introduction

From a historical perspective, survival after radiotherapy for brain metastases was disappointing and often compromised due to progression of extracranial disease, which is present in more than 50% of the patients [1, 2]. Such progression was difficult to avoid in the era of limited systemic treatment options. With introduction of targeted agents and immune checkpoint inhibitors, e.g. for kidney cancer, malignant melanoma, HER-2 positive breast cancer and subsets of non-small cell lung cancer, selected patients can now undergo up-front systemic therapy of their brain metastases [3-9]. However, sequential radiotherapy and systemic therapy continues to play a role in the interdisciplinary management of patients with brain metastases [10-14]. Achievement of both, brain and extracranial disease control is a pre-requisite for prolonged survival. If a patient is unlikely to receive systemic treatment after brain irradiation, the probability of long-term survival diminishes, as demonstrated in a previous study by our group [15]. The latter included patient cohorts treated with or without systemic treatment after completion of whole-brain radiotherapy (WBRT). Two landmark analyses requiring minimum survival of 1 or 2 months from start of WBRT were performed. Age and performance status (PS) requirements were also applied in order to resemble a prospective trial that would limit inclusion to patients with defined baseline characteristics, such as adequate PS. Irrespective of these different statistical scenarios, systemic treatment significantly improved survival. At present, many patients receive other types of brain irradiation, such as stereotactic radiosurgery (SRS), which may provide a better therapeutic ratio [16-18]. However, sophisticated local treatment is less appealing if followed by best supportive care (BSC) rather than systemic therapy. Given these considerations, it would be helpful if one could predict a patient's likelihood of receiving sequential systemic treatment at the time of radiation treatment referral. If additional systemic therapy is highly likely, one may

also opt for highly efficacious radiotherapy in order to provide optimum local control to all sites of disease. The purpose of this study was to identify factors associated with initiation or continuation of systemic treatment after brain irradiation.

Materials and Methods

A previously utilized [15], continuously maintained single-institution database that includes all patients with unresected parenchymal brain metastases from histologically verified extracranial primary tumors managed with first-line radiotherapy (WBRT, SRS or other fractionated focal radiotherapy; both, completed and interrupted treatment courses according to the intention-to-treat principle; no previous brain irradiation) was analyzed. In this real-world cohort, radiotherapy prescription was individualized, and so was further treatment for new or recurrent brain metastases, and systemic progression. The strategies consisted of salvage surgery, SRS, WBRT, systemic therapy or BSC. Systemic treatment was usually prescribed as judged appropriate by the patients' medical oncologists. The patients were treated between January 01, 2012 and December 31, 2019. Extracranial staging consisted of computed tomography (CT). If clinically relevant, other modalities were added to clarify CT findings, e.g., isotope bone scan, ultrasound, positron emission tomography etc. In addition to established baseline parameters such as age, disease extent and Eastern Cooperative Oncology Group (ECOG) PS, the validated LabBM score (blood test results) was included [19, 20]. All blood tests needed to calculate the LabBM score were routinely assessed approximately one week before radiotherapy (normal values: hemoglobin 11.7-15.3 g/dl (females) and 13.4-17.0 g/dl (males); platelets 130-400 $x10^9$; albumin 34-45 g/l; lactate dehydrogenase (LDH) <255 U/l; C-reactive protein (CRP) <5 mg/l). The LabBM score was calculated as described in the original study [19]. Briefly, one point was given for LDH and CRP measurement above

the upper limit of normal and 0.5 points for hemoglobin, platelets and albumin below the lower limit of normal. A point sum of 0 indicates a favorable prognosis. The maximum point sum is 3.5. After exclusion of 27 patients in the database who did not have active extracranial disease and thus were unlikely to be candidates for systemic treatment, the remaining 185 patients were included. Overall survival (time to death) from the first day of radiotherapy was calculated employing the Kaplan–Meier method, and different groups were compared using the log-rank test (SPSS 25, IBM Corp., Armonk, NY, USA). Eight of 185 patients were censored after median 9.5 months of follow-up (minimum 3 months). Date of death was known in all other patients. A forward stepwise Cox regression analysis was also performed (multivariate analysis of parameters predicting overall survival). The Chi-square test was used to identify factors associated with systemic treatment after brain irradiation. If a significant association was found ($p<0.05$), the respective parameter was included in a multi-nominal logistic regression analysis. Finally, recursive partitioning analysis (RPA), a well-established method in brain metastases research (a technique of building decision trees) [21], which previously was utilized by our group [22], was employed. A treatment utilization rate of 75% was defined as outcome of interest (an arbitrary, percentile-based decision).

Results

The study included mainly patients with extracranial metastases (90%) and multiple brain metastases (84%), often from lung cancer, as shown in Table 1. Most patients received palliative WBRT (59%), the others SRS, WBRT with boost and other approaches with high doses of radiation, which are more likely to provide local control. Overall, 111 patients (60%) received systemic treatment after radiotherapy (continuation of an ongoing or start of a new line). Compared to patients without systemic therapy (median survival

2.0 months), all groups treated with anti-cancer drugs survived significantly longer. The largest group received chemotherapy (n=76, median survival 6.0 months). Those treated with tyrosine kinase inhibitors (n=12) survived for a median of 4.4 months. Immune checkpoint inhibitors (n=13) resulted in a median survival of 8.7 months, endocrine treatment (n=5) in 13.6 months and anti-HER-2 drugs in 16.4 months. One patient received a tyrosine kinase and an immune checkpoint inhibitor. In the multivariate Cox regression analysis, systemic therapy (dichotomized yes/no; p=0.0001) and ECOG PS (four strata 0/1/2/3; p=0.006) were significantly associated with overall survival, in contrast to age (continuous variable, p=0.9) and primary tumor type (breast, small cell and adenocarcinoma lung cancer versus all others combined (Figure 1), p=0.5).

Univariate analysis (Chi-square test) indicated that primary tumor type, ECOG PS, symptoms from brain metastases, age and LabBM score were significantly associated with receipt of systemic treatment (Table 2). Except for symptoms from brain metastases, all parameters remained significantly associated with receipt of systemic treatment in multi-nominal regression analysis. The latter included primary tumor type as dichotomized variable (high utilization of systemic treatment in three tumor types versus low utilization in all others). Breast cancer, small cell lung cancer and adenocarcinoma of the lung were the tumor types associated with high utilization of systemic treatment (74-77%). However, the multi-nominal regression analysis identified ECOG PS as the single most important predictor (91, 67, 29, 0% in PS 0-3, respectively; Chi-square 20.2 as compared to 14.2 for tumor type and maximum 7 for other parameters). Therefore, ECOG PS was selected as the first prediction criterion in the RPA decision tree analysis. As displayed in Figure 2, RPA was successful for patients with PS 0-1, whereas patients with

PS 2 had lower treatment utilization rates (maximum 60-70%, with disease-dependent impact of age and LabBM score).

Discussion

The management of patients with brain metastases has never been more complex than in the present era of improved systemic treatment. Given that more than 50% of the patients harbor extracranial metastases, one cannot overstate the need for multidisciplinary assessment and decision-making, e.g. before proceeding to surgical resection [23]. Even if the medical specialist who has diagnosed the brain metastases and/or a tumor board recommend a sequence of brain irradiation (often SRS, sometimes fractionated radiotherapy, with or without preceding surgical resection) and systemic therapy, not all patients will still be eligible for systemic therapy after completion of brain-directed measures. Also in the present study, 5% of the patients failed to complete radiotherapy and none of these received systemic treatment. In other words, a discrepancy between planned and actual treatment may occur. It would be reassuring if one could assess the likelihood of systemic therapy when making treatment recommendations, parallel to looking at the patient's prognostic factors for survival. The latter assessment is often based on well-established prognostic models such as scores and nomograms [2, 24-27]. One of the aims of careful evaluation is to avoid unnecessarily complicated treatment in the final stage of disease [28-30].

The present study, which excluded patients with brain-only disease, has shown that a majority of patients received systemic treatment after brain irradiation and that survival varied with treatment approach. The latter fact reflects the underlying tumor biology, because for example endocrine treatment and HER-2-directed treatment are tailored to

the presence of certain receptors on the breast cancer cells. All drugs administered to the study patients were given after their approval in Norway, outside of clinical studies and financed by the public healthcare system that covers the whole population, i.e. without financial barriers. Patients with ECOG PS 3 did not receive systemic therapy. Those with staging-detected brain metastases were more likely to receive systemic treatment than their counterparts with symptomatic brain metastases. Age was also a strong predictor, but tumor type and ECOG PS outperformed all other parameters assessed in this study. It was possible to develop the RPA model presented above (Figure 1), however without succeeding in the identification of those PS 2 patients who are highly likely to receive systemic therapy. Given that three subgroups of PS 2 patients came close to the pre-specified 75% target, larger studies appear warranted.

Limitations

The present study with overall 185 patients resulted in very small subgroups and consequently considerable uncertainty regarding the PS 2 results. Patients with lung cancer were overrepresented (less than 30 patients in all other tumor groups). Potentially relevant parameters such as comorbidity and organ function were not available in our database. The validated LabBM score, which was available, is truly a surrogate of organ function, inflammation and cachexia [19], albeit not a sufficient reflection of a patient's eligibility for systemic therapy (lack of kidney, cardiac and complete bone marrow function). Uncertainty exists regarding the 75% utilization rate selected for this study. Both, higher and lower thresholds may be considered for future research that will involve larger databases.

Conclusions

As suggested by the multivariate results of this study and evident from daily clinical practice, a complex interplay of patient- and tumor-related factors, as well as previous exposure to anti-cancer drugs, determines the eligibility for additional systemic therapy. Prediction of eligibility by a validated model may enhance the quality of decision-making. Therefore, the present work should be regarded a first step towards a wider assessment of predictive models by the international oncology community, even in an era where not all patients should undergo upfront radiotherapy anymore.

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Figure 1.

Actuarial overall survival stratified by primary tumor type (breast, small cell and adenocarcinoma lung cancer versus all others combined; log-rank test p=0.002; median 5.7 versus 3.0 months). In the multivariate analysis, this parameter lost its statistical significance.

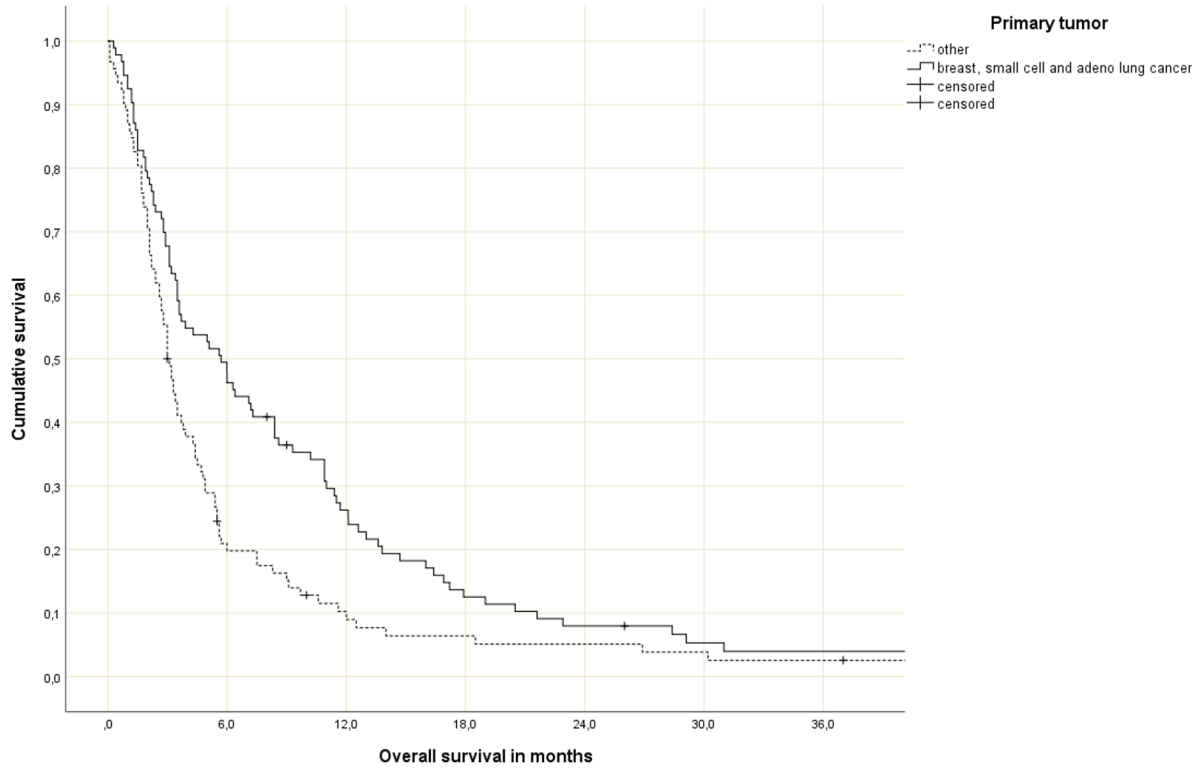
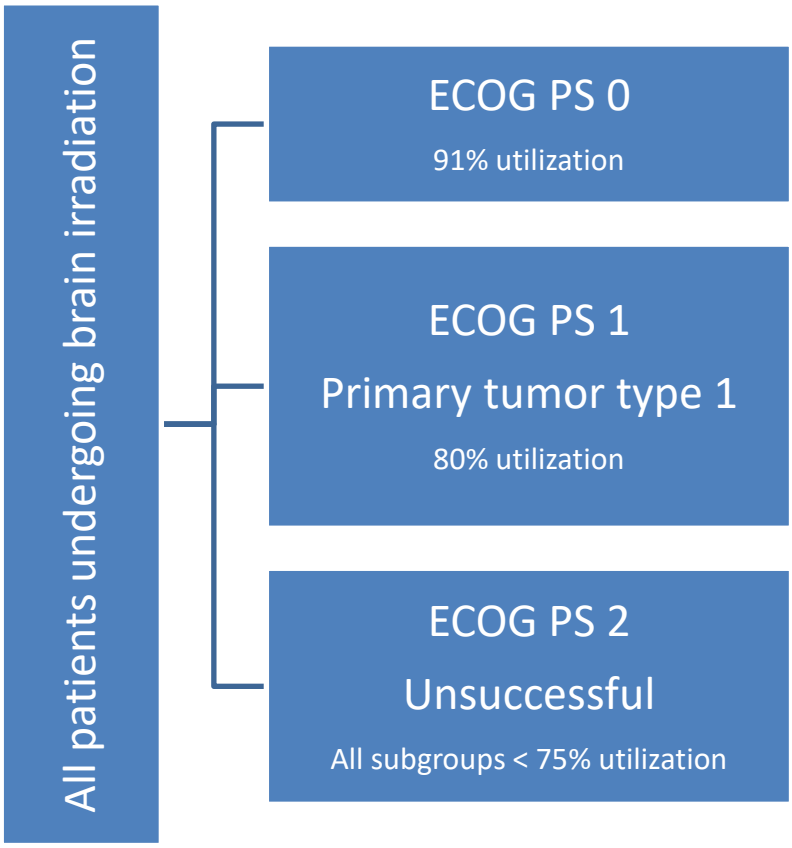


Figure 2.

Recursive partitioning analysis (RPA) with endpoint “utilization of systemic therapy in at least 75% of patients”



ECOG PS: Eastern Cooperative Oncology Group performance status

Primary tumor type 1: breast cancer, small cell lung cancer, lung adenocarcinoma

ECOG PS 2: highest utilization (60-70%) in patients with small cell lung cancer, kidney cancer if age younger than 75 years, and breast cancer if LabBM score 0-1.5

Table 1.

Patient characteristics.

Baseline parameter	Number	Percent
Female sex	94	51
Male sex	91	49
Non-small cell lung cancer, adenocarcinoma	53	29
Non-small cell lung cancer, squamous cell carcinoma	19	10
Non-small cell lung cancer, unspecified/mixed	9	5
Breast cancer	27	15
Malignant melanoma	20	11
Small cell lung cancer	13	7
Renal cell cancer	16	9
Colorectal cancer	15	8
Other primary tumors	13	7
No extracranial metastases	18	10
Extracranial metastases	167	90
Controlled primary tumor	106	57
Uncontrolled primary tumor	79	43
Single brain metastasis	30	16
Two, three or four brain metastases	74	40
Five or more brain metastases	81	44

Synchronous brain metastases	63	34
Metachronous brain metastases	122	66
Symptomatic brain metastases	160	87
Staging-detected brain metastases	25	14
Performance status 0	32	17
Performance status 1	102	55
Performance status 2	48	26
Performance status 3-4	3	2
Incomplete radiotherapy	10	5
Mean age, SD, range (years)	65, ±10, 24-93	
Age younger than 75 years	160	86
Age 75 years or older	25	14
LabBM score 0-1.0 (favorable)	117	63
LabBM score 1.5-2.5	63	34
LabBM score 3.0-3.5	5	3

Table 2.

Systemic treatment after brain irradiation.

Baseline parameter	Proceeded with systemic therapy (%)	Significance level Chi-square test	Significance level multi-nominal regression
Female sex	60	n.s.	
Male sex	60		
Non-small cell lung cancer, adenocarcinoma	75	0.03	0.001 (2 strata*)
Non-small cell lung cancer, squamous cell carcinoma	53		
Non-small cell lung cancer, unspecified/mixed	33		
Breast cancer	74		
Malignant melanoma	50		
Small cell lung cancer	77		
Renal cell cancer	56		
Colorectal cancer	40		
Other primary tumors	25		
No extracranial metastases	76	n.s.	
Extracranial metastases	59		
Controlled primary tumor	57	n.s.	
Uncontrolled primary tumor	64		
Single brain metastasis	67	n.s.	
Two, three or four brain metastases	59		
Five or more brain metastases	58		

Synchronous brain metastases	57	n.s.	
Metachronous brain metastases	67		
Symptomatic brain metastases	56	0.01	0.27
Staging-detected brain metastases	83		
Performance status 0	91	0.0001	0.0001
Performance status 1	67		
Performance status 2	29		
Performance status 3-4	0		
Age younger than 75 years	64	0.004	0.02
Age 75 years or older	32		
LabBM score 0-1.0 (favorable)	68	0.001	0.03
LabBM score 1.5-2.5	49		
LabBM score 3.0-3.5	0		

* group 1: non-small cell lung cancer (adenocarcinoma) + small cell lung cancer + breast cancer; group 2: others
n.s. not significant, p>0.05