Patterns of care and survival in cancer patients with brain metastases receiving immune checkpoint inhibitors

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Abstract

Introduction: Immune checkpoint inhibitors (ICI) have become a mainstay of treatment for different cancer types. The purpose of this study was to evaluate patterns of care and overall survival after diagnosis of brain metastases in patients managed with ICI as component of care.

Methods: Retrospective cohort study. Fifty patients were included (34 with brain metastases at first cancer diagnosis, 16 with metachronous spread).

Results: Depending on symptoms, lesion number and size, and other individualized criteria, multidisciplinary tumor board (MDT) discussion resulted in highly individualized treatment sequences. Selected patients received systemic treatment alone. Twenty-four patients (48%) had any stereotactic radiosurgery (SRS) or neurosurgical resection at some point in time (upfront/salvage). Only 7 patients (14%) were never treated with brain irradiation or neurosurgery. Median overall survival (OS) was 13.0 months. Better Karnofsky performance status (KPS), absence of extracranial metastases, and time interval between cancer diagnosis and brain metastases of 0-18 months predicted for improved survival. Treatment sequence was not associated with survival. Patients without extracranial metastases had median OS of 52.2 months.

Discussion/Conclusion: Long-term survival is possible in patients managed with ICI ± brain-directed treatment. This study did not identify a clear treatment sequence of choice. MDT assessment at diagnosis and each progression is recommended to ensure favorable outcomes.

Introduction

While local control of parenchymal brain metastases from common primary cancers such as lung or breast cancer is achievable with surgical resection, different radiotherapy approaches and combinations thereof, progressive and uncontrollable extracranial manifestations have long been a major challenge and leading cause of death [1, 2]. Several studies have demonstrated that patients receiving both brain-directed and systemic anticancer therapy survive longer than those receiving, e.g. radiotherapy of their brain metastases without further drug treatment [3-6]. Systemic therapy is now more efficacious than previously, and some of the newer drugs also contribute to disease control in the brain [7, 8]. Even drugs that cannot cross the blood-brain barrier may contribute to longer survival by preventing rapid extracranial progression, if combined with brain-directed approaches [9]. For many patient groups at high risk of brain metastases, e.g. those with lung cancer and malignant melanoma [10], systemic treatment now includes immune checkpoint inhibitors (ICI), e.g. atezolizumab, durvalumab, ipilimumab, nivolumab and pembrolizumab, representing a major transition from previous guideline-based regimens [11-14].

In our hospital's ICI-treated cancer patient population, a previous retrospective study focusing on those with short survival (maximum 3 months from start) has shown that presence of brain metastases was not among the factors explaining such unfavorable outcome, in contrast to reduced performance status (PS) or advanced age [15]. Given that patients with brain metastases represent a particular, potentially vulnerable subgroup (especially if suffering from reduced neurological or cognitive function), a detailed analysis of patterns of care and survival in an expanded database appeared warranted.

Patients and Methods

This was a retrospective single-institution quality-of-care analysis of a continuously updated database that includes all cancer patients managed with any ICI. The treatment period was 01.01.2017 – 30.06.2022. All patients who had a synchronous or metachronous diagnosis of brain metastases (not pure leptomeningeal dissemination) were included (Figure 1). Baseline parameters and survival were obtained from electronic health records. Magnetic resonance imaging was used to diagnose brain metastases, without histological confirmation except for few patients who underwent neurosurgery. Positron emission tomography (PET, tracer fluorodeoxyglucose) was routinely performed except in few patients with very disseminated disease on standard computed tomography (CT) imaging. Histological confirmation was obtained from the primary tumor or an easier accessible metastasis, including molecular markers/mutations triggering specific treatment algorithms such as tyrosine kinase inhibitors (TKI).

Management was discussed in diagnosis-specific multidisciplinary tumor boards (MDT). The MDT selected the type of systemic therapy according to national Norwegian guidelines. If indicated, maintenance treatment was administered. Upfront brain-directed treatment was also recommended by the MDT, depending on symptoms, lesion number and size, and other individualized criteria. There was no defined cut-off determining, e.g., indication for stereotactic radiosurgery (SRS). Selected patients received systemic treatment alone. Later during the course of the disease, further lines of systemic therapy and delayed (salvage) brain-directed treatments could be administered, as judged appropriate by the MDT. For example, patients who started with ICI monotherapy could afterwards receive chemotherapy, sequential courses of SRS and eventually whole-brain irradiation (WBRT).

Neurosurgical resection was usually followed by postoperative stereotactic radiotherapy. Overall, this strategy of highly personalized treatment resulted in a large number of different care pathways.

Actuarial survival from the day of treatment initiation (systemic or local) for brain metastases was calculated with the Kaplan-Meier method and compared between subgroups with the log-rank test. Thirty-two patients had died and 18 patients were censored at the time of their last follow-up (median 18 months). The validated prognostic score LabBM (serum hemoglobin, platelets, albumin, C-reactive protein, lactate dehydrogenase) was calculated as previously described [16]. The impact of continuous variables such as age and number of brain metastases on survival was examined in univariate Cox analyses. A multivariate forward conditional Cox analysis of prognostic factors for survival was then performed. A p-value <0.05 was considered statistically significant. Intra- and extracranial response rates, toxicity and patterns of progression were not evaluated. Separate analyses were performed for the largest subgroup, i.e. treatment-naïve patients (synchronous brain metastases). The database created for this quality-of-care analysis does not require approval by the local Ethics Committee (REK Nord).

Results

The majority of patients (34 of 50, 68%) presented with de novo, synchronous brain metastases at first cancer diagnosis. The median time interval was 14 months in those with metachronous presentation. Fifty percent each had clinical symptoms and staging-detected, asymptomatic brain metastases. Non-small cell lung cancer

(NSCLC) was the most common tumor type (66%). Table 1 shows additional patient characteristics.

All patients received ICI (combined with chemotherapy or alone), sometimes preceded by other systemic therapy until progression (chemotherapy in 4 patients, TKI in 3). Four patients developed brain metastases while on ICI. Also in first-line ICI patients, systemic treatment was not necessarily started before brain-directed measures were completed. The latter, so-called late ICI approach was utilized in 16 patients (32%), including those selected for neurosurgery and postoperative irradiation.

Twenty-four patients (48%) had any SRS or neurosurgical resection at some point in time. Only 7 patients (14%) were never treated with brain irradiation or surgery.

Median overall survival was 13.0 months and projected 2-year survival 39% (Figure 2).

Eleven of 12 patients alive 2 years after diagnosis of brain metastases had received some kind of brain-directed treatment. Nine of 12 had also received salvage brain-directed treatment (8 of 10 in the group with upfront brain-directed treatment and 1 of 2 in the group with upfront systemic therapy alone).

All baseline and treatment-related parameters displayed in Table 1 or mentioned in the text were tested for significant univariate association with survival. Primary tumor type, sex, synchronous presentation, staging-detected brain metastases and maximum size were not significant. As shown in Table 2, Karnofsky PS (KPS), extracranial metastases and other variables were significantly associated with survival. In the multivariate analysis, no treatment-related parameters remained significant. Better KPS, brain metastases only and time interval 0-18 months predicted for improved survival.

In the subgroup of patients with brain metastases detected at first cancer diagnosis slightly different prognostic factors were identified (Table 3). Brain metastases only and LabBM score 0-1 predicted for longer survival. Again, treatment-related parameters were not significant in multivariate analysis.

Among 32 patients who had died at the time of analysis, cause of death was brain metastases progression in 4 (Table 4), extracranial progression in 17 and unknown in 11 who died in distant hospitals or nursing homes without available information in our hospital's patient records. Table 5 shows detailed information about all 6 patients who died within 3 months from diagnosis of brain metastases. Such early death was always caused by extracranial disease progression.

Discussion

This study described patterns of care and survival in a real-world database of ICI treatment in patients with brain metastases. Our MDT-recommended treatment algorithms were highly individualized, both at diagnosis of brain metastases and progression. We did not identify a clear treatment sequence of choice, because multivariate analyses failed to confirm that, e.g., early SRS/surgery resulted in prolonged survival. Likely, the univariate result that suggested a benefit from SRS/surgery was confounded by imbalances in disease extent and/or KPS. Furthermore, progressive brain metastases were typically salvaged with brain-directed treatments such as SRS. Eventually, only 7 patients (14%) were never treated with brain irradiation or surgery. Survival was shortest in patients who developed brain metastases during ICI treatment and longest in those with so-called delayed ICI. In addition, brain metastases more than 18 months after cancer diagnosis were associated with shorter survival. The latter observation might reflect the fact that

patients who already have exhausted certain treatment options have limited options left in later lines. However, selection factors such as comorbidity or low-volume extracranial disease might have influenced the MDT decision to postpone ICI therapy in certain patients.

Interestingly, patients with brain-only metastases had median survival of 52.2 months, resembling survival data from previous studies of oligometastatic cancer [17-19]. In this context, one should note the impact of PET staging, which was widely used in our patients and contributes to better staging accuracy. Limitations of this study include the lack of histological confirmation of brain metastases and programmed death ligand 1 (PD-L1) score. It is possible, that higher PD-L1 expression might explain some of the survival differences. According to Sperduto et al., median survival of patients with lung adenocarcinoma and brain metastases with 0, 1% to 49%, and ≥50% PD-L1 expression was 17, 19, and 24 months, respectively ($p<0.01$), confirming PD-L1 is a prognostic factor [20]. Further limitations of this study include the retrospective design, cohort size and heterogeneity, and lack of statistical power to analyze small subgroups and treatment-related survival differences. We were not able to analyze quality of life data, treatment-free intervals, toxicity or other outcomes, which might impact on determining a treatment sequence of choice. Despite such limitations, the study showed low rates of death from uncontrolled brain metastases and suggested that early death typically resulted from rapid extracranial disease progression (Table 5). As also shown in Table 5, 30-day mortality was low (1 of 50), compared to the general brain metastases literature [21].

Historical studies already pointed to the fact that brain metastases with permeable blood-brain barrier may respond to systemic chemotherapy [22, 23]. Such data has stimulated researchers to pursue strategies of delayed or completely eliminated brain

irradiation, particularly after the advent of targeted TKIs for molecularly-defined types of NSCLC and in the current era of ICI therapy. However, this issue is not completely resolved yet [24-26]. The present results (11 of 12 patients alive 2 years after diagnosis of brain metastases had received some kind of brain-directed treatment) suggest that tailored strategies are needed to ensure optimum brain control. Given that extracranial progression was a common cause of death in the present and other studies, further improvement of extracranial disease control (especially widespread large-volume disease) and systemic treatment beyond first line is needed. Our treatment algorithms did not include extracranial consolidation radiotherapy to oligometastases after systemic treatment.

It is difficult to compare the present study to the literature, because of differences in design and patient characteristics. The initial discussion (present paragraph) relates to primary ICI treatment. A meta-analysis from 2021, which was not focused on survival outcomes, included 12 studies with a total of 566 NSCLC patients [13]. ICI treatment led to an intracranial response rate of 16% and a disease control rate of 45% (similar in patients with brain metastases who were treated with radiation before ICI start and those who were treated with ICI only). Goldberg et al. performed a phase 2 trial of pembrolizumab in patients with NSCLC (or melanoma) with untreated brain metastases (n=42) [11]. Some patients had brain metastases progressing after previous radiotherapy, but none had neurological symptoms or corticosteroid requirement. Patients were separated in two cohorts: cohort 1 had PD-L1 expression of at least 1% and cohort 2 had PD-L1 less than 1% or unevaluable. The primary endpoint of the study was the proportion of patients achieving a brain metastasis response. Eleven of 37 patients (30%) in cohort 1 had such a response. There were no responses in cohort 2. Overall, estimated survival at 2 years was 34% (39% in our

study). Descourt et al. performed a national, retrospective, multicenter study that consecutively included all French patients with PD-L1-positive (tumor proportion score ≥ 50%) advanced NSCLC who initiated first-line treatment with pembrolizumab as a single agent between 2017 and 2019 [27]. The study included 845 patients, of whom 176 had brain metastases at diagnosis. There were no significant differences in outcomes for patients with and without brain metastases: 9.2 and 8 months for median progression-free survival, and 29.5 and 22 months for median overall survival, respectively. Indirectly, these figures support previous notions of relatively long survival in subgroups with higher PD-L1 expression [20] (discussed earlier). In the French study, overall response rates were 47% and 45% in patients with and without cerebral metastases. In multivariate analysis, PS 2-4 vs. 0-1 and neutrophil-to-lymphocyte ratio ≥ 4 vs. < 4 were the main independent negative factors for survival, while presence of brain metastases was not predictive. Neutrophil-to-lymphocyte ratio was unknown in the present study and is not among traditional parameters included in the brain metastases literature. A pooled analysis of three KEYNOTE trials included 171 NSCLC patients with stable baseline brain metastases [12]. Their median overall survival was 18.8 months with pembrolizumab plus chemotherapy and 7.6 months with chemotherapy. Corresponding median PFS was 6.9 months and 4.1 months, respectively. Objective response rates were higher and duration of response longer with pembrolizumab plus chemotherapy versus chemotherapy.

Many institutions have adopted a strategy of combined treatment with ICI and SRS, postponing WBRT as long as possible also in patients with 5-10 initial lesions. The literature suggests that SRS-associated toxicity rates are fairly low after such combinations [28-30]. In a multicenter study of melanoma patients with previously untreated brain metastases, the addition of radiotherapy (SRS or other regimes)

resulted in a favorable overall survival on systemic therapy [31]. A German group retrospectively analyzed data of 93 patients with 319 distinct brain metastases from different cancer types (67% malignant melanoma) who received PD-1 inhibitors and radiotherapy between 2014 and 2020 [32]. Median overall survival was 12.2 months (13 months in the present study). Independent prognostic factors for survival were concurrent RT-ICI application (median 17.6 vs. 6.8 months), PS, cancer type favoring melanoma, and brain metastases volume favoring ≤3 cm^3. A recent meta-analysis limited to NSCLC also suggested that combined ICI and brain irradiation exhibited favorable efficacy and acceptable toxicity, and that concurrent administration might be the preferred option [33]. Despite considerable inter-study heterogeneity, long-term survival is possible in patients managed with ICI ± brain-directed treatment. The present, relatively small study did not identify a clear treatment sequence of choice. However, the observed median survival of 29 months in the subgroup whose treatment included SRS/surgery is in line with other studies discussed in this paragraph. MDT assessment at diagnosis and each progression is recommended to ensure timely access to all available treatment options and thus favorable outcomes.

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Figure 1.

Study diagram.

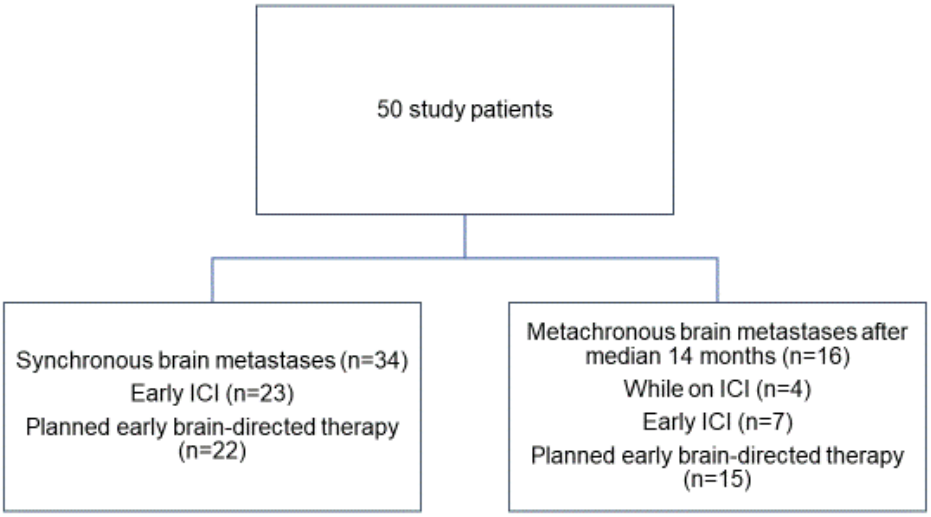

Figure 2.

Actuarial overall survival (Kaplan-Meier plot).

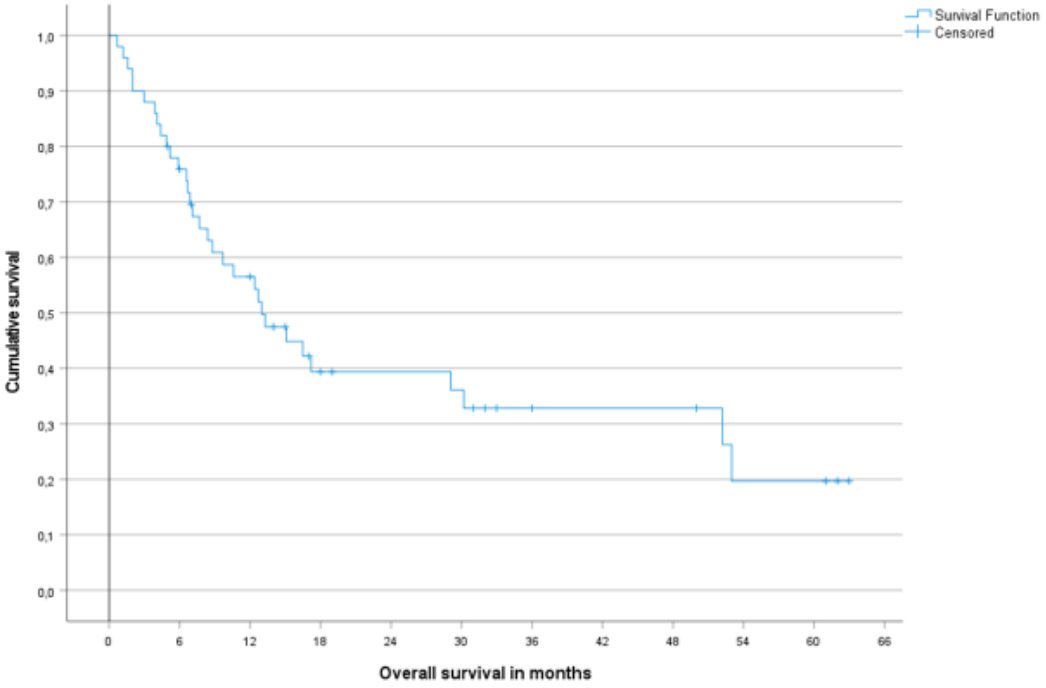

Table 1. Patient characteristics (n=50, time period 2017-2022)

Parameter	n	%
Sex		
Female	25	50
Male	25	50
Cancer type		
Non-small cell lung cancer	33	66
Small cell lung cancer	5	10
Malignant melanoma	6	12
Kidney cancer	3	6
Other tumors	3	6
Patterns of metastases		
No extracranial metastases	13	26
Liver metastases	10	20
Bone metastases	16	32
Only one extracranial distant site affected	18	36
Two or more organs affected	19	38
Karnofsky performance status		
90-100	21	42

70-80	26	52
<70	3	6
Treatment		
Primary systemic therapy	23	46
Delayed systemic therapy	27	54
Planned early SRS/OP	21	42
Planned early WBRT	16	32
Any SRS/OP irrespective of timing	24	48
Any OP irrespective of timing	6	12
Salvage WBRT	4	8
No RT/OP at all	7	14
Single brain metastasis	17	34
Median number of brain metastases, range	2.5	1-40
Median size of the largest lesion, range (mm)	17	2-54
Median age, range (years)	67	44-79
Median LabBM score, range (points)	1.0	0-3.0

SRS: stereotactic radiosurgery, OP: neurosurgery, WBRT: whole-brain radiotherapy

Table 2. Prognostic factors for survival (all 50 patients)

Parameter	Median survival (mo)	Univariate p-value	Multivariate p-value
Time interval		0.048	0.049
≤18 months	15.1		
>18 months	4.9		
Extracranial metastases		<0.001	0.001
Absent	52.2		
1 organ, e.g. lung(s)	10.6		
>1 organ, e.g. lung/bone	7.1		
KPS		0.005	0.003
90-100	29.1		
70-80	8.8		

<70	1.6		
Number of brain metast.		<0.001	>0.1
1-2	52.2		
>2	7.1		
Age (years)		0.030	>0.1
<74	15.1		
≥74	4.9		
LabBM score (points)		0.056	>0.1
0-1	16.5		
1.5-2	8.4		
2.5-3	2.0		
Initial brain treatment		0.035	>0.1

WBRT	4.9		
SRS/surgery	29.1		
Systemic only	8.8		
ICI setting		0.010	>0.1
On ICI	5.9		
Early ICI start	13.3		
Delayed ICI start	30.2		

KPS: Karnofsky performance status, WBRT: whole-brain radiotherapy, SRS: stereotactic radiosurgery, ICI: immune checkpoint inhibitor

Table 3. Prognostic factors for survival (34 patients who presented with synchronous brain metastases)

Parameter	Median survival (mo)	Univariate p-value	Multivariate p-value
Extracranial metastases		0.003	0.008
Absent	52.2		
Present	8.8		
KPS		0.003	>0.1
90-100	29.1		
70-80	8.8		
<70	1.6		
Number of brain metast.		0.005	>0.1
1-2	30.2		
>2	8.8		

LabBM score (points)		<0.001	0.003
0-1	17.2		
1.5-2	12.4		
2.5-3	1.6		
Initial brain treatment		0.009	>0.1
SRS/surgery	29.1		
No SRS/surgery	8.8		

KPS: Karnofsky performance status, SRS: stereotactic radiosurgery

Table 4. Detailed description of patients who died from uncontrolled brain metastases (n=4)

Time interval	Tumor characteristics	Treatment sequence	Survival*
0	Lung cancer, 40 BM	CTx, WBRT, later triple CTx/ICI	12.4
0	Lung cancer, 3 BM	Triple ICI and upfront SRS, later salvage SRS	7.7
48	Melanoma, 10 BM	WBRT followed by first-line nivolumab	4.1
11	Lung cancer, 3 BM	SRS, later salvage WBRT and triple CTx/ICI	10.6

BM: brain metastases, CTx: platinum-based chemotherapy, WBRT: whole-brain radiotherapy, ICI: immune checkpoint inhibitor, SRS: stereotactic radiosurgery

*months from diagnosis of brain metastases

Table 5. Detailed description of patients who died within 3 months from diagnosis (all from extracranial progression, n=6)

Time interval	Tumor characteristics	Treatment sequence	Survival*
0	Lung cancer, KPS 70, multiple extracranial organs, 3 BM	Primary atezolizumab	1.2
0	Lung cancer, KPS 30, multiple extracranial organs, 1 BM	Primary triple CTx/ICI	0.7
0	Lung cancer, KPS 60, 2 extracranial organs, 1 BM	Primary triple CTx/ICI	1.6
0	Lung cancer, KPS 70, bone metastases, 7 BM	WBRT and pembrolizumab	2.0
31	Melanoma, KPS 90, 2 extracranial organs, 8 BM	WBRT and nivolumab	3.0

16	Lung cancer, KPS 70, extracranial organs, 7 BM	2 WBRT and atezolizumab	2.0

KPS: Karnofsky performance status, BM: brain metastases, CTx: platinum-based chemotherapy, WBRT: whole-brain radiotherapy, ICI: immune checkpoint inhibitor

*months from diagnosis of brain metastases