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Descriptive statistical analysis of a real life cohort of 2419 patients with brain metastases of solid cancers

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ABSTRACT

Aim: We provide a descriptive statistical analysis of baseline characteristics and the clinical course of a large real-life cohort of brain metastases (BM) patients.

Methods: We performed a retrospective chart review for patients treated for BM of solid cancers at the Medical University of Vienna between 1990 and 2011.

Results: We identified a total of 2419 BM patients (50.5% male, 49.5% female, median age 59 years). The primary tumour was lung cancer in 43.2%, breast cancer in 15.7%, melanoma in 16.4%, renal cell carcinoma in 9.1%, colorectal cancer in 9.3% and unknown in 1.4% of cases. Rare tumour types associated with BM included genitourinary cancers (4.1%), sarcomas (0.7%). gastro-oesophageal cancer (0.6%) and head and neck cancers (0.2%). 48.7% of patients presented with a singular BM, 27.7% with 2–3 and 23.5% with >3 BM. Time from primary tumour to BM diagnosis was shortest in lung cancer (median 11 months; range 1–162) and longest in breast cancer (median 44 months; 1–443; p<0.001). Multiple BM were most frequent in breast cancer (30.6%) and least frequent in colorectal cancer (8.5%; p<0.001). Patients with breast cancer had the longest median overall survival times (8 months), followed by patients with lung cancer (7 months), renal cell carcinoma (7 months), melanoma (5 months) and colorectal cancer (4 months; p<0.001; log rank test). Recursive partitioning analysis and graded prognostic assessment scores showed significant correlation with overall survival (both p<0.001, log rank test). Evaluation of the disease status in the past 2 months prior to patient death showed intracranial progression in 35.9%, extracranial progression in 27.5% and combined extracranial and intracranial progression in 36.6% of patients.

Conclusions: Our data highlight the heterogeneity in presentation and clinical course of BM patients in the everyday clinical setting and may be useful for rational planning of clinical studies.

Key questions

What is already known about this subject?

- Brain metastases (BM) are an increasing challenge in modern oncology.
- Conduction of BM specific trials is challenging.

What does this study add?

- We describe the clinical characteristics of a large real-life cohort of 2419 BM patients and highlight the heterogeneity in presentation and clinical course.
- Disease status in the past 2 months prior to patient death showed intracranial progression in 35.9%, extracranial progression in 27.5% and combined extracranial and intracranial progression in 36.6% of patients.

How might this impact on clinical practice?

- Our data provide important information for clinical trial planning in BM specific trials, which in the future will translate to the improvement of treatment in BM patients.

INTRODUCTION

Brain metastases (BM) are a common challenge in oncology and have a devastating impact on the quality of life and the survival prognosis of patients.[1 2] Incidence of BM differs between tumour entities with lung cancer being the most frequent primary tumour causing BM, followed by breast cancer, melanoma, renal cell carcinoma and colorectal cancer.[3] Treatment strategies include neurosurgical resection, stereotactic radiosurgery and whole brain radiotherapy, depending on the number, size and localisation of BM. Systemic therapies may achieve intracranial responses, however, high-level evidence is lacking, as patients with BM have routinely been excluded from phase III trials of new systemic treatment strategies.[4–6]

BM specific trials are urgently needed in order to improve treatment strategies and BM are an area of high medical need. However, the design of BM specific trials is challenging due to the heterogeneity of clinical presentations and the multitude of

factors influencing the clinical course and patient outcomes.[7 8] Unfortunately, there is a lack of systematically collected data on baseline characteristics and clinical course of real-life BM patients. The available data are mainly based on small retrospective patient cohorts and few clinical trial populations that were selected based on specific inclusion criteria and thus do thus not represent everyday clinical reality.[9–13] However, a profound knowledge on the natural clinical course of BM patients is necessary for rational planning of clinical trials, particularly for patient selection and definition of appropriate study end points.[7] Therefore, we collected data on a large unselected cohort of BM patients managed at our institution over a time period of more than 20 years and performed descriptive statistical analyses to provide historical benchmarks as a basis for rational design of clinical studies on BM.

METHODS

Patients

Patients aged over 18 years and treated for BM from solid cancer at the Medical University of Vienna between 1990 and 2011 were identified from the clinical files of our institution. Clinical Data on the course of disease were obtained by chart review. Prognostic scores including recursive portioning analysis (retrisive partioning analysis (RPA)) and graded prognostic assessment (Graded Prognostic assesment (GPA)) were calculated as published previously based on clinical characteristics.[8 11 13–15] Disease status in the end of life period was evaluated by last available restaging including extracranial and intracranial disease within the past 60 days of life. If applicable, radiological screening procedure used MRI and secondary CT scan. Patient data were collected in a password secured database and handled anonymously.

Statistics

Differences according to histology of primary tumour were analysed for patients diagnosed with lung cancer, breast cancer, melanoma, renal cell carcinoma and colorectal cancer. Synchronous diagnosis was defined as diagnosis of primary tumour and/or new extracranial metastases and BM within 30 days. Analysis of pattern over time were conducted in patients diagnosed between 1994 and 2010, as during for this time period all patients treated either with neurosurgical resection, stereotactic radiosurgery or whole brain radiotherapy were identified. Overall survival time from primary tumour diagnosis was defined as time from radiological diagnosis of primary tumour to death or last follow-up. Overall survival from BM was defined as time from radiological diagnosis of BM to death or last follow-up.

Descriptive analysis of clinical characteristics was performed. For correlation of two parameters the χ^2 test, the Kruskal Wallis test and the spearman correlation were used as appropriate. For estimation survival analysis the Kaplan-Meier product limit method was used. Survival times were analysed in months. To test differences between groups respective to survival, the log-rank test was used. p Values ≤ 0.05 were considered to indicate statistical significance. Due to the hypothesis generating and exploratory approach of the present study the Bonferroini method as wells as no other adjustment for multiple testing was applied.[16]

RESULTS

Patients' characteristics

2419 (1222/2419 (50.5%) male; 1197/2419 (49.5%) female) patients (median age 59 years; range 23–91) with complete clinical follow-up including survival time were available for further analysis. Table 1 summarises patients characteristics. First-line treatment for newly

Table 1 Patients characteristics

	Entire population (n=2419)		
	n	% total	% group
Primary tumour type			
Lung cancer	1048	43.3	
NSCLC	696	28.8	66.4
SCLC	351	14.5	33.5
Not other specified	1	<0.1	0.1
Breast cancer	379	15.7	
HER2 positive	143	5.9	46.9
ER positive	155	6.4	40.8
Luminal A (ER positive, HER2 negative)	84	3.5	27.5
Luminal B (ER positive, HER2 positive)	57	2.4	15.0
Triple negative	78	3.2	25.6
Not other specified	74	3.1	19.5
Melanoma	397	16.4	
Renal cell carcinoma	221	9.1	
Colorectal cancer	224	9.3	
Cancer of unknown primary	34	1.4	
Others	116	4.8	
Oesophageal cancer	5	0.2	4.3
Stomach cancer	9	0.4	7.8
Ovary cancer	35	1.4	30.2
Head and neck cancer	5	0.2	4.3
Testis cancer	3	0.1	2.6
Haemangiopericytoma	1	<0.1	0.9
Bladder cancer	6	0.2	5.2
Parotid gland cancer	1	<0.1	0.9
Cervical cancer	12	0.5	10.3
Vaginal cancer	4	0.2	3.4
Tongue cancer	1	<0.1	0.9
Thyroid cancer	1	<0.1	0.9
Endometrial cancer	13	0.5	11.2
Sarcoma	17	0.7	14.7
Pancreatic cancer	1	<0.1	0.9
Mesothelioma	1	<0.1	0.9
Chorion cancer	1	<0.1	0.9

ER, estrogen receptor; HER, human epidermal growth factor receptor; NSCLC, non small cell lung cancer; SCLC, small cell lung cancer.

diagnosed BM was neurosurgical resection in 852/2418 (35.2%), SRS in 1017/2418 (42.0%), whole brain radiotherapy in 495/2418 (20.5%), chemotherapy in 20/2418 (0.8%) and best supportive care in 35/2418 (1.4%) patients (see online supplementary table S1).

Time from diagnosis of primary tumour to diagnosis of BM

649/2419 (26.8%) patients presented with synchronous diagnosis of BM and primary tumour. Patients with lung cancer (501/1048 (47.8%)) presented most frequently, while patients with breast cancer (13/366 (3.4%) presented least frequently with synchronous diagnosis of BM and primary tumour (p<0.001; χ^2 test; see online supplementary table S2; figure 1A). Importantly, BM were detected through routinely performed radiological staging procedures in 130/649 (20.0%) patients with synchronous diagnosis of primary tumour and BM, indicating that these patients presented with asymptomatic BM at diagnosis of the primary tumour (figure 1B). Median time to diagnosis of BM in patients with subsequent diagnosis of BM after diagnosis of primary tumour was 24 months (range 1–502). Patients with breast cancer (median 44 months; 1–443) presented with the longest time to diagnosis of BM, while patients with lung cancer (median 11 months; range 1–162) presented with the shortest time between diagnosis of primary tumour and development of BM (p<0.001;log rank test; figure 1C).

Clinical characteristics at diagnosis of BM

Extracranial involvement

1564/2419 (64.7%) patients presented with extracranial metastases at diagnosis of BM. BM as the only site of metastatic disease was most frequently observed among patients with lung cancer (535/1048 (51.0%)) and least frequently among patients with melanoma (72/397 (18.1%); p<0.001; χ^2 test; see online supplementary table S2; figure 2A).

1231/2419 (50.9%) patients presented with visceral metastases, while 60/2419 (2.5%) presented with only with osseous metastases and 188/2419 (7.8%) only lymph node metastases. Lung metastases were present in 1545/2419 (36.1%) and liver metastases in 490/2419 (20.3%) patients.

727/2419 (30.1%) patients presented with progressive extracranial disease at diagnosis of BM. Further, 671/2419 (27.7%) patients presented with synchronous new metastatic sites simultaneously with the diagnosis of BM. Patients with melanoma presented most frequently 204/397 (51.4%)), while patients with lung cancer (180/1048 (17.2%) presented least frequently with progressive extracranial disease at diagnosis of BM (p<0.001; χ^2 test; see online supplementary table S2; figure 2B).

421/2419 (17.4%) patients had no evidence of extracranial disease at diagnosis of BM. 136/421 (32.3%) of these patients develop systemic progression after diagnosis of BM. 627/2419 (25.9%) patients presented with brain only metastatic behaviour without any extracranial metastases during their course of disease. The brain only metastatic behaviour was most frequently observed among patients with lung cancer (349/1048 (33.3%) and least frequently among patients with melanoma (37/397 (9.3%); p<0.001; χ^2 test; see online supplementary table S2; figure 2C).

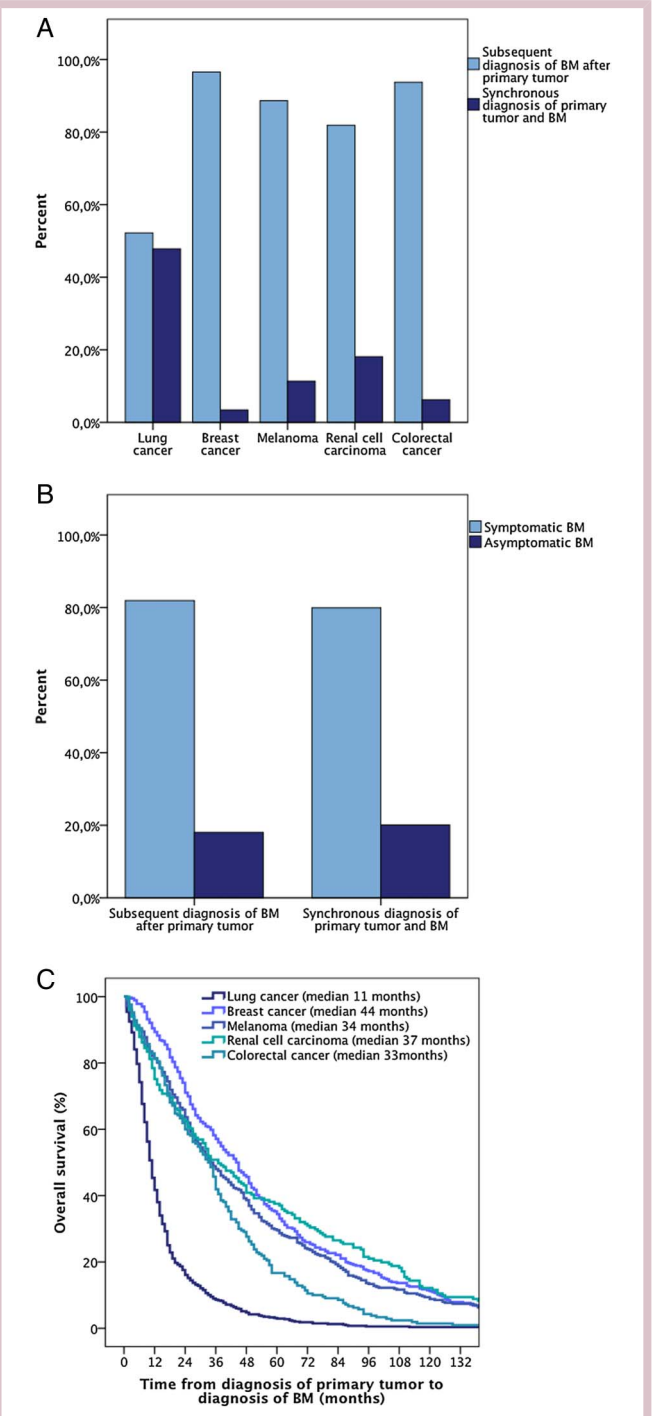

Figure 1 (A) Frequency of synchronous diagnosis of primary tumour and BM according to primary tumour type (B) Frequency of patients with asymptomatic BM at first diagnosis of primary tumour (C) Time from diagnosis to BM according to primary tumour type.

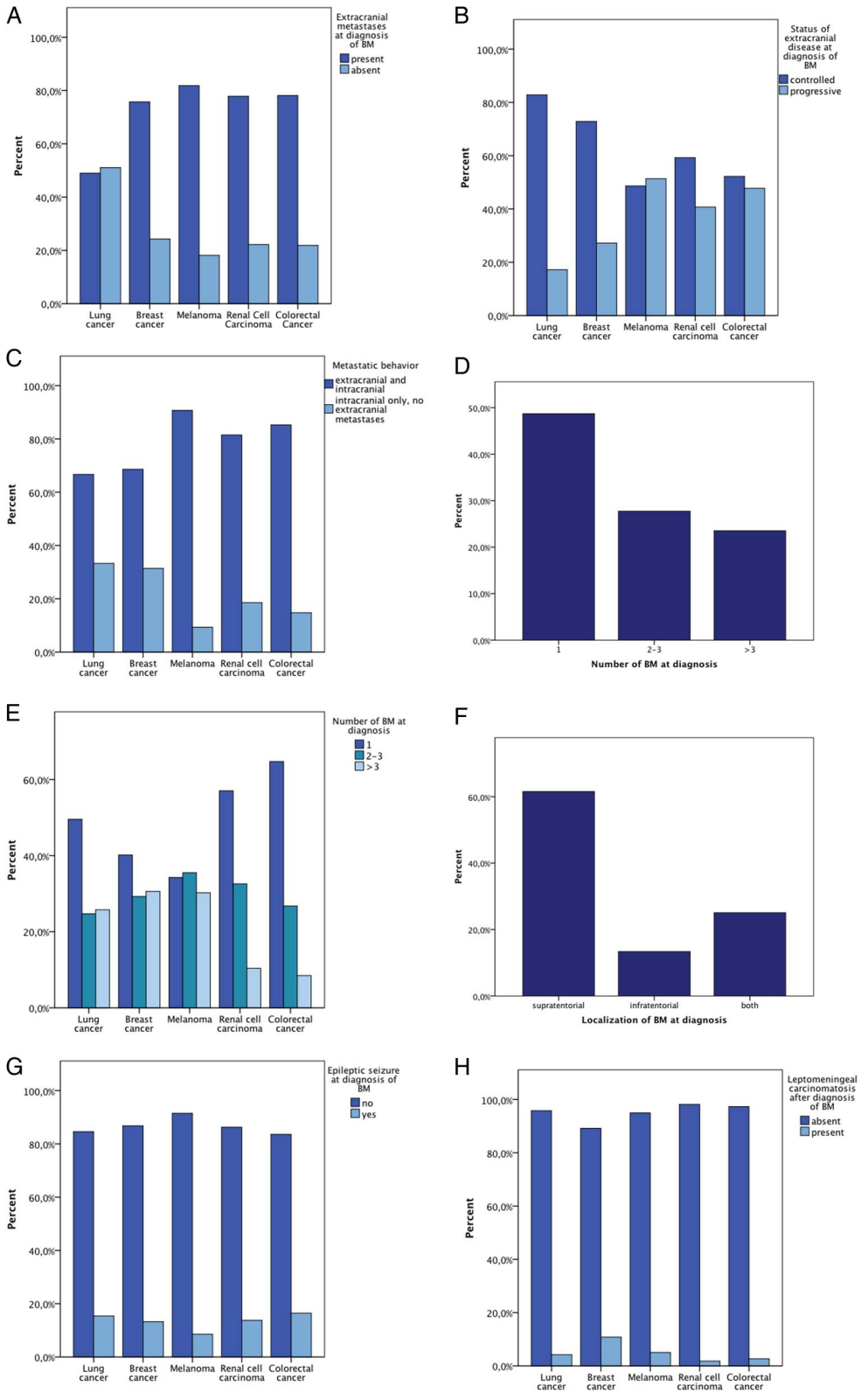

Figure 2 Clinical characteristics at diagnosis of brain metastases. (A) Extracranial involvement at diagnosis of BM according to primary tumour type (B) Frequency of progressive extracranial disease at diagnosis of BM according to primary tumour type (C) Frequency of brain only metastatic behaviour according to primary tumour type (D) Number of BM at first diagnosis of BM (E) Number of BM according to primary tumour type (F) Localisation of BM at diagnosis (G) Frequency of epileptic seizures at diagnosis of BM according to primary tumour type (H) Occurrence of additional leptomeningeal carcinomatosis after diagnosis of BM according to primary tumour type.

Number of BM

1177/2419 (48.7%) patients presented with a singular BM, 670/2419 (27.7%) with 2–3 and 569/2419 (23.5%) with >3 BM (see online supplementary table S2 and figure 2C). Patients with colorectal cancer presented most frequently (145/224 (64.7%)), while patients with melanoma presented least frequently with singular BM (136/397 (34.3%)). Multiple BM were most frequently observed among patients with breast cancer (115/376 (30.6%)) and least frequently among patients with colorectal cancer (19/224 (8.5%); p<0.001; χ^2 test; see online supplementary table S2; figure 2E).

Symptoms

445/2419 (18.6%) patients presented with asymptomatic BM, that were detected trough staging. 340/2419 (14.1%) patients presented with epileptic seizures, 768/2419 (31.7%) with signs of increased intracranial pressure and 1698/2419 (70.2%) with neurological symptoms.

Leptomeningeal carcinomatosis

54/2419 (2.2%) patients presented with leptomeningeal involvement at diagnosis of BM and 120/2419 (5.0%) patients developed leptomeningeal involvement within the course of disease. Patient with breast cancer presented most frequently with additional leptomeningeal carcinomatosis (41/379 (10.8%) and patients with renal cell carcinoma least frequently (4/221 (1.8%; p<0.001; χ^2 test; see online supplementary table S2; figure 2H).

Recurrence pattern after initial treatment of BM

980/2419 (40.5%) patients experienced extracranial progression after diagnosis of BM (see online supplementary table S3). Median time to extracranial progression was 3 months (range 0–207). Patients with melanoma presented most frequently with extracranial progression (189/397 (47.6%)) and patients with colorectal cancer least frequently (66/224 (29.5%); p<0.001; χ^2 test; see online supplementary table S3; figure 3A). Patients with colorectal cancer and melanoma presented with fastest extracranial progression (median 2 months), while extracranial progression was observed later in patients with breast cancer (median 5 months; p<0.001; log rank test; see online supplementary table S3).

1057/2419 (43.7%) patients presented with intracranial progression, 381/2419 (20.4%) at the local site after

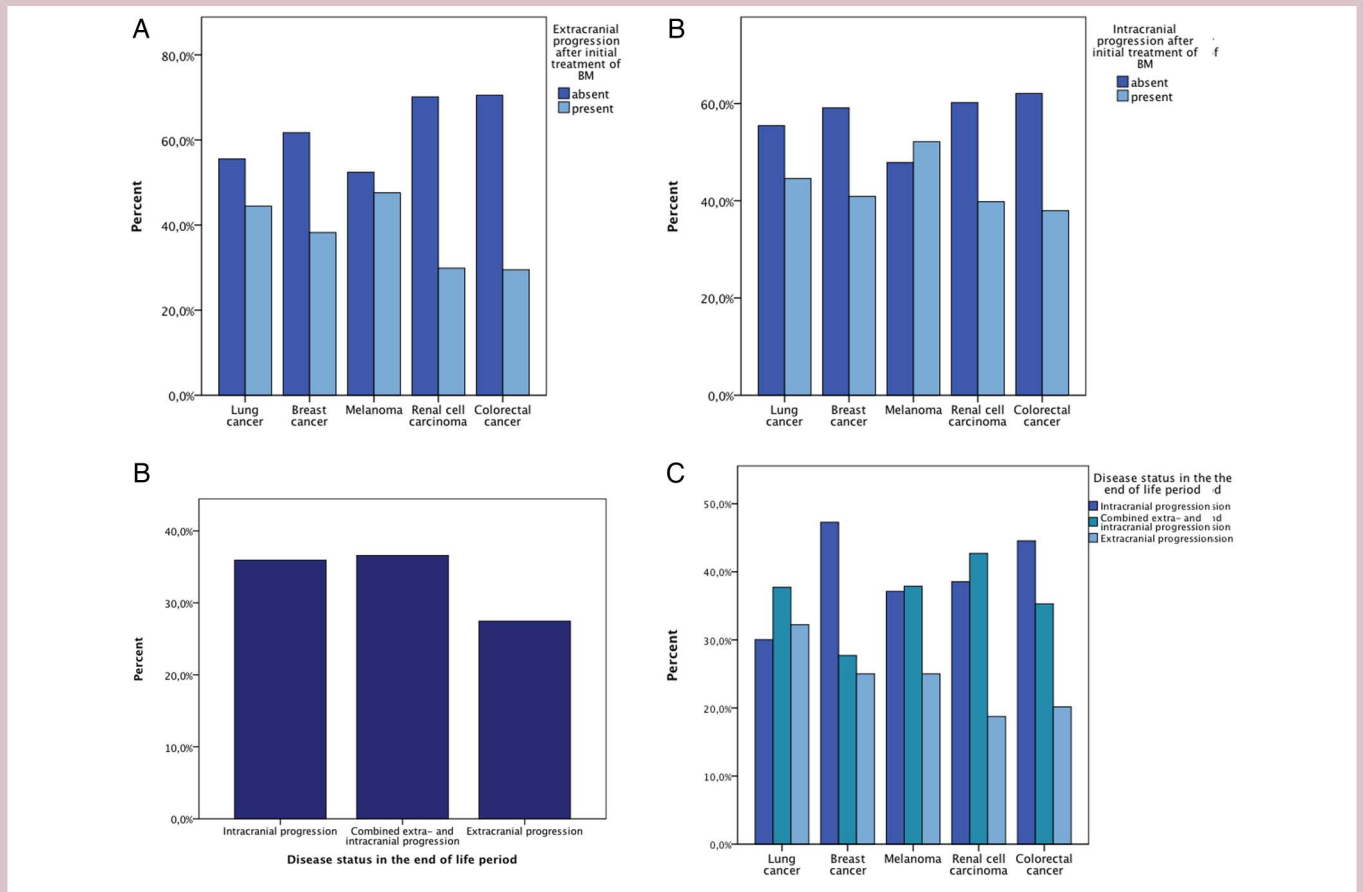

Figure 3 Recurrence pattern after initial treatment of brain metastases and cause of death. (A) Frequency of extracranial progression after initial treatment of BM according to primary tumour type (B) Frequency of intracranial progression after initial treatment of BM according to primary tumour type (C) Disease status in the end of life period (D) Disease status in the end of life period according to primary tumour type.

surgery or stereotactic radiosurgery (see online supplementary table S3). Patients with melanoma presented with the highest risk to experience intracranial progression (207/397 (52.1%), while patients with colorectal cancer presented less frequently with intracranial progression (85/224 (37.9%); p=0.002; χ^2 test; see online supplementary table S3; figure 3B). No difference in likelihood of intracranial progression was observed in patients with lung cancer according to histological subtype. 311/696 (44.7%) non small cell lung cancer BM patients experienced intracranial progression compared to 155/351 (44.2%) small cell lung cancer BM patients (p=0.872; χ^2 test). Median time to intracranial progression was 5 months (range 0–100). Patients with melanoma presented with shortest time to intracranial progression (median 3 months; p<0.001; log rank test; see online supplementary table S3).

Disease status in the end of life period

Evaluation of the disease status in the past 2 months prior to patient death showed intracranial progression in 35.9%, extracranial progression in 27.5% and combined extracranial and intracranial progression in 36.6% of patients (see online supplementary table S3; figure 3C). In the end of life period, combined extracranial and intracranial progression was most frequent in patients with lung cancer (226/599 (37.7%), intracranial progression was most common in patients with breast cancer (87/184 (47.3%)), combined extracranial and intracranial progression was most common in patients with melanoma (103/272 (37.9%)), extracranial and intracranial progression was most frequent in patients with renal cell carcinoma (41/96 (42.7%)) and intracranial progression was most frequent in patients with colorectal cancer (53/119 (44.5%); see online supplementary table S3; figure 3D).

Intracranial progression in the end of life period was most frequently observed among patients with breast cancer (87/184 (47.3%)) and least frequently among patients with lung cancer (180/599 (30.1%); p<0.001; χ^2 test; see online supplementary table S3; figure 3D). Extracranial progression in the end of life period was most frequently evident in patients with lung cancer (193/599 (32.2%)) and least frequently in patients with renal cell carcinoma (18/96 (18.8%); p<0.001; χ^2 test; see online supplementary table S3; figure 3D). Online supplementary table S4 lists disease status in the end of life period in specific BM subgroups.

SURVIVAL ANALYSIS

Prognostic scores

RPA

Patients in RPA class I presented with a median overall survival of 12 months, compared to 7 months in RPA class II and 2 months in RPA class III (p<0.001; log rank test; see online supplementary figure S2B).

GPA

Patients in GPA class I presented with a median overall survival of 15 months, compared to 11 months in class II, 7 months in class III and 3 months in class IV (p<0.001; log rank test; see online supplementary figure S2C).

Treatment modality

Survival time from diagnosis of BM differed significantly according to applied first-line treatment approach. Median overall survival was longest in patients treated with chemotherapy (median 10 months), followed by neurosurgical resection (median OS 8 months), SRS (median 6 months), whole brain radiotherapy (median 5 months) and best supportive care (median 0 months; p<0.001; log rank test). Patients treated with chemotherapy after diagnosis of BM presented with an improved overall survival of median 11 months, compared to patients not treated with chemotherapy after diagnosis of BM (median 4 months; p<0.001; log rank test).

Frequency patterns of BM over time

The frequency of patients treated for BM at our institution increased numerically in the past two decades (Spearman correlation coefficient 0.598; p=0.011; figure 4A). Further, a trend towards an increased frequency in lung cancer BM could be observed (Spearman correlation coefficient 0.621; p<0.001; figure 4B). Increase in lung cancer BM differed according to gender, as female patients presented with stronger increase (Spearman correlation coefficient 0.798; p<0.001) as compared to male patients (Spearman correlation coefficient 0.558; p=0.020; figure 4C). No increased frequency was observed for breast cancer BM (Spearman correlation coefficient 0.479; p=0.052), melanoma BM (Spearman correlation coefficient 0.371; p=0.142), renal cell carcinoma BM (Spearman correlation coefficient 0.730; p=0.780) or colorectal cancer BM (Spearman correlation coefficient −0.145; p=0.578; figure 4B).

The survival prognosis increased over the past two decades as patients diagnosed before 2000 presented with a median overall survival of 5 months compared to 7 months in patients diagnosed and treated after 2000 (p=0.005; log rank test; figure 4D).

DISCUSSION

BM patients are a heterogeneous patient population. Prognosis as well as clinical course varies significantly according to clinical factors like histology of the primary tumour, number of BM and status of the extracranial disease.[8 15 14] Definition of appropriate patient cohorts for clinical trials is challenging, as investigated cohorts should resemble prognostically comparable patient populations.[7] In the current study, we investigated a unique, large real-life cohort of BM patients and provide

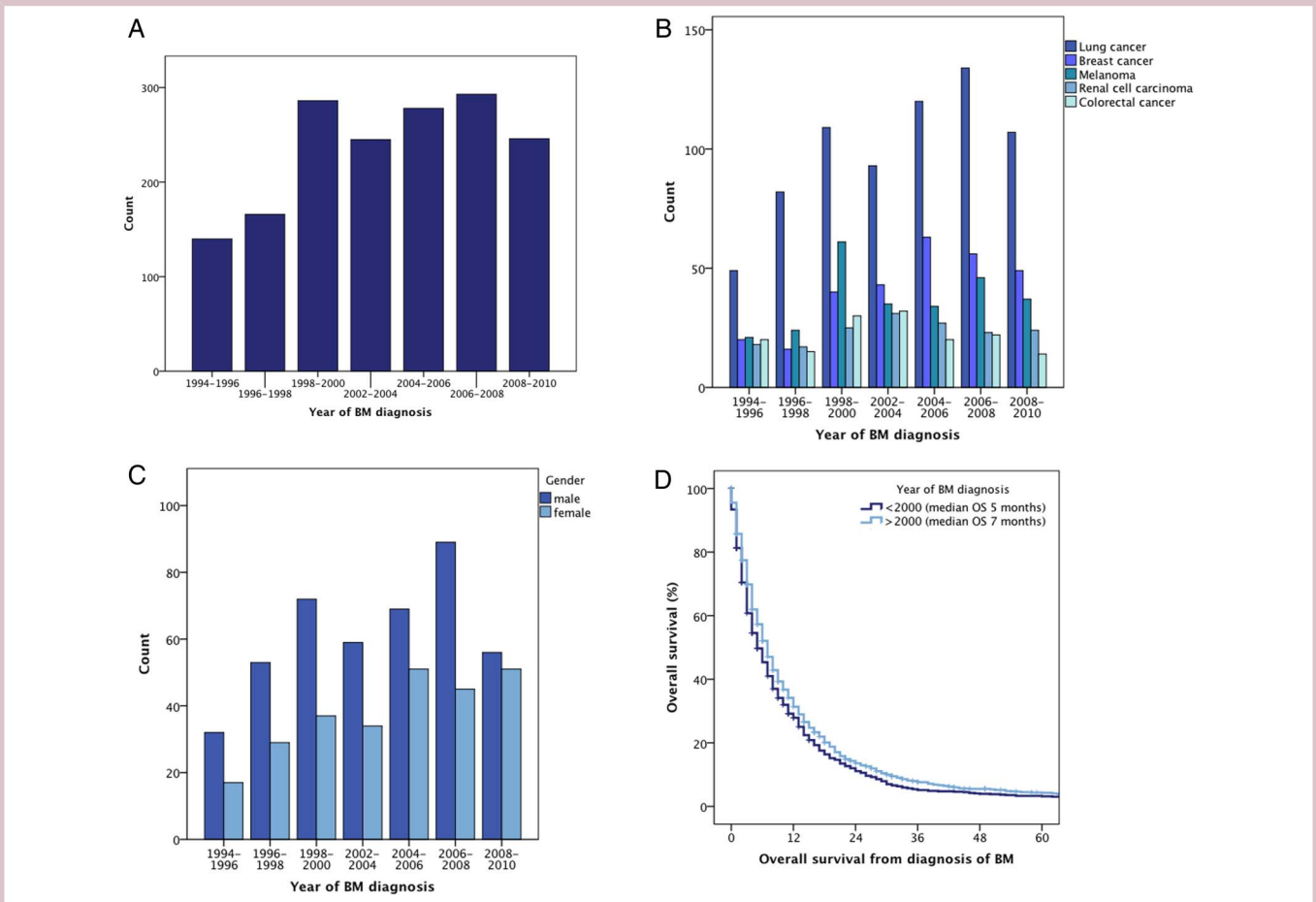

Figure 4 Frequency patterns of brain metastases over time. (A) Frequency of BM diagnosed between 1994 and 2010 (B) Frequency of BM according to primary tumour between 1994 and 2010 (C) Frequency of lung cancer BM in female and male patients between 1994 and 2010 (D) Overall survival from diagnosis of BM according to year of diagnosis.

information on baseline characteristics and the clinical course of BM patients.

Expectedly and in line with prior epidemiological studies, the majority of BM cases in our cohort were from lung cancer, breast cancer, melanoma, renal cell cancer and colorectal cancers.[9] However, our cohort also included some cases of tumour types that rarely lead to BM such gastro-oesophageal cancers, genitourinary cancers, head and neck cancers and sarcomas. Our data clearly show considerable differences in BM frequency, clinical presentation and clinical course between patients with different tumour types. For example, we detected significant differences in symptoms at BM diagnosis, time from primary tumour to BM diagnosis, rate of synchronous BM and primary tumour diagnoses, number of BM at presentation, and median overall survival times between tumour types. The reasons for these differences need to be elucidated in further studies, but are likely related to molecular factors and the interaction of metastatic tumour cells with the specific microenvironment of the central nervous system.[17–19] In any case, these findings highlight the profound heterogeneity of BM patients and the need for informed patient selection and stratification for conduction of meaningful clinical trials in this patient population. Importantly, pooling of BM patients of different primary tumour types in clinical studies seems unadvisable and focused enrolment of BM patients with specific tumour types is likely to produce more robust clinical trial data.[7]

Several prognostic scores based on clinical parameters have been developed for BM patients. The RPA and GPA scores, which take into account age, status of the extracranial disease, number of BM and the Karnofsky performance score are most commonly used and we confirm the strong statistical correlation of these scores with median overall survival times in our cohort.[11 13] The use of these scores as inclusion criterion or as stratification factor in BM-specific trials can help to design clinical studies based on rational and robust statistical assumptions. It must be noted, however, that prediction of individual patient survival time in the clinical setting based on these clinical appears not to be accurately possible.[20] Refinement of prognostic scores by inclusion of additional parameters, for example, of laboratory, tissue-based, imaging-based factors, may help to increase their prognostic accuracy.[21–24]

Response assessment is particularly challenging in BM patients, as intracranial and extracranial disease status has to be considered. Recently, the Response Assessment in Neuro-Oncology (RANO) group has proposed an algorithm that integrates response assessment in the intracranial and extracranial compartment for use and standardised reporting in clinical trials.[25 26] Our data support this concept, as 43.7% of patients showed intracranial and 40.5% of cases showed extracranial disease progression during the clinical course after initial BM-directed treatment. Moreover, radiological evaluation of the disease status in the end-of life period (ie, the past 2 months prior to patient death) showed intracranial progression in 35.9%, extracranial progression in 27.5% and combined extracranial and intracranial progression in 36.6% of patients in our series. Our data thus are in line with some smaller and older studies that indicated that at least half of the patients die with progression of their extracranial disease.[27–29] Cumulatively, the available data show that in a considerable fraction of patients systemic disease contributes significantly to the poor outcome of patients with BM and therefore there is a strong need and rationale to perform studies with novel systemic agents in BM patients.[7] Unfortunately, so far BM patients have been systematically excluded from most clinical trials evaluating systemic drugs in patients with cancer. Recently however, some studies have shown clinically meaningful activity of systemic agents such as immunotherapies and tyrosine-kinase inhibitors in BM patient populations of melanoma, breast cancer and lung cancer, thus providing proof of concept for the efficacy of such approaches.[30–33]

Analysing changes over time in our cohort of BM patients treated at our institution in a period spanning more than 20 years, we noted some interesting findings. First, we found a modest increase of BM treated for BM at our institution over time. This finding may be explained by improvements and increased accessibility of diagnostic methods such as cranial CT and MRI, but could also be explained by a higher number of long-term surviving patients with cancer with novel therapeutic regimens. Also, changes in referral patterns with increased patient concentration due to the specific expertise in our tertiary care centre may have played a role. Second, a disproportionate and gender-specific increase in lung cancer BM cases was evident with women showing a significantly steeper increase than males. This finding is probably related to the increasing percentage of smokers among women and reflects the general increase of lung cancer cases in females.[34] Third, we found a statistically significant, albeit very modest, increase in median overall survival times of BM patients over time. Again, this finding may relate to recent advances in oncological care. However, overall the poor prognosis of most BM patients documented also in our study shows that this patient population represents a significant unmet clinical need that should be met with adequate research efforts. However, the poor prognosis of most BM patients as documented also in our study shows that this patient population has a significant unmet clinical need that should be met with adequate research efforts.

In summary, we present here a detailed clinical characterisation of the largest unselected real-life cohort of BM patients published to date. Our data highlight the heterogeneity in presentation and clinical course of BM patients in the everyday clinical setting and may be useful for rational planning of clinical studies.

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