Christ *et al. Radiation Oncology* (2024) 19:148
https://doi.org/10.1186/s13014-024-02542-2

Radiation Oncology

RESEARCH Open Access

Influence of brain metastases on the classification, treatment, and outcome of patients with extracranial oligometastasis: a single-center cross-sectional analysis

Sebastian M. Christ[1*], Gabriel W. Thiel[2], Philip Heesen[2], Siyer Roohani[3], Michael Mayinger[1], Jonas Willmann[1], Maiwand Ahmadsei[1], Urs J. Muehlematter[4], Alexander Maurer[4], Josef A. Buchner[5], Jan C. Peeken[5], Rifaquat Rahman[6], Ayal Aizer[6], Emilie Le Rhun[7,8], Nicolaus Andratschke[1], Michael Weller[7], Martin Huellner[4] and Matthias Guckenberger[1]

Abstract

Background and introduction Increasing evidence suggests that a subgroup of patients with oligometastatic cancer might achieve a prolonged disease-free survival through local therapy for all active cancer lesions. Our aims are to investigate the impact of brain metastases on the classification, treatment, and outcome in these patients.

Materials and methods We analyzed a total of 7,000 oncological positron emission tomography scans to identify patients with extracranial oligometastatic disease (defined as ≤ 5 intra- or extra-cranial metastases). Concurrent magnetic resonance imaging brain was assessed to quantify intracranial tumor burden. We investigated the impact of brain metastases on oligometastatic disease state, therapeutic approaches, and outcome. Predictors for transitioning from oligo- to polymetastatic states were evaluated using regression analysis.

Results A total of 106 patients with extracranial oligometastases and simultaneous brain metastases were identified, primarily originating from skin or lung/pleura cancers (90%, $n=96$). Brain metastases caused a transition from an extracranial oligometastatic to a whole-body polymetastatic state in 45% ($n=48$) of patients. While oligometastatic patients received systemic therapy (55% vs. 35%) more frequently and radiotherapy for brain metastases was more often prescribed to polymetastatic patients (44% vs. 26%), the therapeutic approach did not differ systematically between both sub-groups. The oligometastatic sub-group had a median overall survival of 28 months compared to 10 months in the polymetastatic sub-group ($p<0.01$).

Conclusion In patients with brain metastases, a low total tumor burden with an oligometastatic disease state remained a significant prognostic factor for overall survival. Presence of brain metastases should therefore not serve as exclusion criterion for clinical trials in the field of oligometastatic disease. Moreover, it underscores the importance of considering a multimodality treatment strategy in oligometastatic cancer patients.

Keywords Oligometastasis, Brain metastasis, Treatment paradigms

*Correspondence:
Sebastian M. Christ
sebastian.christ@usz.ch

Full list of author information is available at the end of the article

Introduction and background

Brain metastases (BMs) represent a prevalent type of metastases in adults, affecting up to 40% of cancer patients. The primary tumors most frequently metastasizing to the brain include those lung cancer (>50%), breast cancer (15–25%), and malignant melanoma (5–20%) [1–3]. Overall survival (OS) for patients with BMs remains dismal; with only 8.1% surviving at two years, and up to 52% succumbing to neurological complications during the course of their disease [4, 5].

Several studies have shown that the intracranial tumor burden represents a prognostic and predictive factor for OS. *Nieder et al. (2020)* found that patients with 1–2 BMs have longer long-term OS rates compared to those with 3–5 BMs [6]. Similarly, studies by *Niibe et al. (2016)* and *Bai et al. (2016)* found that non-small-cell lung cancer (NSCLC) patients with BMs have significantly longer OS when they have a smaller number of BMs (1–2) compared to those with a larger number of lesions (3–5) [7, 8]. Several trials have provided evidence that patients with intracranial lesions achieve better quality-of-life, potentially even a survival benefit if treated with stereotactic radiosurgery (SRS) instead of low-dose whole brain radiation therapy (WBRT) [9–12]. In parallel, the oligometastatic disease (OMD) hypothesis has been developed [13, 14], indicating that patients with a (mostly extracranial) low metastatic tumor burden may achieve long-term disease control or even oncological cure by the integration of local treatment to all cancerous sites in addition to standard-of-care systemic therapy [15–17].

As of now, it remains uncertain whether the progression of disease in patients with BMs is intricately linked to the distinction between an OMD and a polymetastatic disease (PMD) state. It thus remains to be seen whether the extracranial disease state – OMD vs. PMD – indeed holds prognostic value for patients with a limited number of BMs, given the presence of BMs itself is being a strong prognostic factor, linked to very poor prognosis.

Given this context, our retrospective, single-center, cross-sectional study analyzed patients with an extracranial OMD burden and the presence of BMs. The primary objective was to investigate whether tumor burden (OMD vs. PMD) retains significance as prognostic factor in patients with BMs. Secondary objectives were to investigate the therapeutic variances between OMD and PMD patients and to identifying risk factors associated with transitioning from an OMD to a PMD state following the additional diagnosis of BM.

Materials and methods

OMD patients

All fluorodeoxyglucose (FDG) and prostate-specific membrane antigen (PSMA) positron emission tomography (PET) scans and concurrent brain magnetic resonance imaging (MRI) scans that were conducted of oncological patients at the Comprehensive Cancer Center Zurich (CCCZ) in the year 2020 were screened. For patients to be included in this study, the following requirements needed to be met: (1) Evidence of solid organ malignancy; (2) Evidence of metastasis on imaging; and (3) Extracranial tumor burden limited to a maximum of five distant metastases. Furthermore, a brain scan conducted within 30 days of the index PET scan needed to display evidence of BMs. Patients were excluded there were manifestations of malignant pleural effusion, pleural carcinomatosis, peritoneal carcinomatosis, or lymphangitic carcinomatosis as per PET imaging.

OMD definition

OMD typically denotes a state in which a solid malignancy has manifested in the form of a limited number of distant metastases [18]. At present, no consensus has been reached regarding the precise number of distant metastases, which clearly distinguish OMD from PMD, yet most studies adopt ranges of 1–3 or 1–5 distant metastases [19]. Since most most research groups work with the 1–5 definition, we also chose to employ a threshold of five distant metastases, including both extra- and intracranial lesions, for characterizing OMD within this study. In this study, we did not differentiate between the different sub-categories of oligometastatic diseases (genuine', 'induced', 'de-novo' or 'repeat') as outlined in the 2020 consensus recommendation of the "European Society for Radiotherapy and Oncology and European Organisation for Research and Treatment of Cancer" [20]. Furthermore, we assessed the current metastatic disease status, accounting for the total numbers of intra- and extracranial distant metastases visible on imaging, irrespective of whether they have been previously treated or not (active or recurrent lesions).

Data collection

All data was collected in Microsoft® Excel® (Version 16.0). One author (GWT) recorded and at least one other author (SMC or PH) reviewed PET and brain scan imaging data. For every OMD case, pertinent data was gathered: Date of birth, sex, date of primary diagnosis, age at primary diagnosis, synchronous or metachronous state, time between primary diagnosis and PET scan date, initial diagnosis (ICD-10), date of PET scan, date of brain scan, number of extracranial metastases, number of BMs, primary treatment modality targeting BMs (radiotherapy, surgery, systemic therapy, watch & wait, best supportive care (BSC)) survival status, and date of death or last contact. Patients in the radiotherapy, BSC, surgical intervention, and combined therapy groups may have received adjunctive systemic therapy but were not included in the 'systemic therapy only' category. Irradiated patients

received either SRS with 1×20 Gy @ 80% or stereotactic radiotherapy (SRT) with 6×5 Gy @ 80%; no patients received WBRT; for statistical analysis purposes, SRT/SRT was subsumed under "radiotherapy."

Statistical methods

Descriptive statistics were calculated for all variables under study. Patient data was presented as medians with ranges for continuous variables, and as absolute and percentage numbers for categorical variables. Analysis aimed to discern differences between patients whose extracranial OMD remained OMD after the inclusion of BMs and patients whose extracranial OMD transitioned to PMD following the inclusion of BMs. The significance of frequency disparities between the two groups was calculated using a two-proportion z-test.

To evaluate possible predictors for the re-classification from OMD to PMD, after adjusting for the presence of BMs, we performed uni- and multivariable logistic regression analysis (UVA, MVA). Independent variables were transformed using dummy coding, following commonly accepted definitions and frequently chosen thresholds including sex (female vs. male), age (<65 vs. ≥65 years), OMD state (synchronous vs. metachronous), primary malignancy (lung and pleura vs. all others; skin vs. all others) and number of extracranial metastases (>1 vs. 1).

OS was analyzed using a Kaplan-Meier estimator. OS was calculated from the date of the diagnostic brain scan. For patients lost-to-follow-up within the subsequent 36 months, the date of their last documented hospital contact served as the censoring point. The statistical significance of disparities in median OS probabilities was determined via a log-rank test, while the difference in the total number of patients alive at the cut-off date was assessed using a chi-squared test. All statistical analysis was performed using the statistical computing program R (Version 2023.03.01+446).

Ethical approval

Approval from the Cantonal Ethics Committee was obtained prior to the initiation or the study (BASEC ID# 2018−01794). The hospital's internal data governance board (DGB) also signed off on the project. The project was conducted in accordance with the Declaration of Helsinki, and all patients provided general informed consent prior to study inclusion. The PET and brain scan imaging database builds the backbone for several other projects exploring questions around the OMD and PMD states.

Results

A total of 106 patients with a maximum 5 extracranial metastases in PET imaging and BMs in MRI imaging were included into this analysis (see Fig. 1). The median age at OMD diagnosis was 61 years (interquartile range (IQR): 52–70), with females constituting 37% (n=39) of the sample. The primary malignancies were predominantly skin or lung/pleural cancer (each 45%, n=48), followed by breast cancer (5.6%, n=6), genitourinary cancer (1.9%, n=2), and cancers of unknown origin (1.9%, n=2). According to PET imaging reports and diagnostic history, 14% (n=15) had synchronous OMD, while 86% (n=91) had a metachronous OMD. On average, patients had 2 extracranial metastases (SD: 1.2), with the distribution as follows: 41% (n=44) had one, 25% (n=26) had two, 18% (n=19) had three, 11% (n=12) had four, and 4.7% (n=5) had five. Brain scans revealed one BM in 27% (n=29) of patients, two in 18% (n=19), three in 16% (n=17), four in 1.9% (n=2), five in 4.7% (n=5), and more than five in 32% (n=34). Following the brain scan analysis, 45% (n=48) of patients transitioned from an extracranial OMD to a total-body PMD (see Table 1). The relationship between the number of BMs and the number of extracranial metastases is shown in Fig. 2.

Treatment of BMs employed various therapeutic approaches: Systemic therapy alone was the most frequent treatment, administered to 46% (n=49) of patients. This was followed by radiotherapy in 34% (n=36), BSC in 9.4% (n=10), "watch & wait" in 6.6% (n=7), and neurosurgery alone or combined with radiotherapy in 3.8% of patients (n=4). Radiotherapy was administered 1.7 times more frequently in the PMD compared to the OMD group (44% vs. 26%). This difference did not reach significance, with a p-value of 0.084 (Table 2).

We investigated multiple potential predictors associated with the transitioning from extra-cranial OMD to total-body PMD using both univariate and multivariate logistic regression analyses. None of the predictors examined showed a significant association with the transitioning in either analytical approach. For a detailed summary of the findings, please refer to Table 3.

Median OS for all patients included was 17.2 months (IQR: 6.59–29.2) from the time of their initial brain scan. As of the study's cut-off date on March 5th, 2023, 31% (n=33) of patients were alive. Of these surviving patients, the median OS, calculated based on the last recorded contact with the hospital, was 28.0 months (IQR: 26.3–31.5).

From the time of undergoing the index brain scan, patients which remained oligometastatic had a significantly longer median OS compared to their polymetastatic counterparts. The median OS probability for the OMD group was 28.2 months (IQR: 23.3–32.0), whereas for the PMD group it was 10.0 months only (IQR:

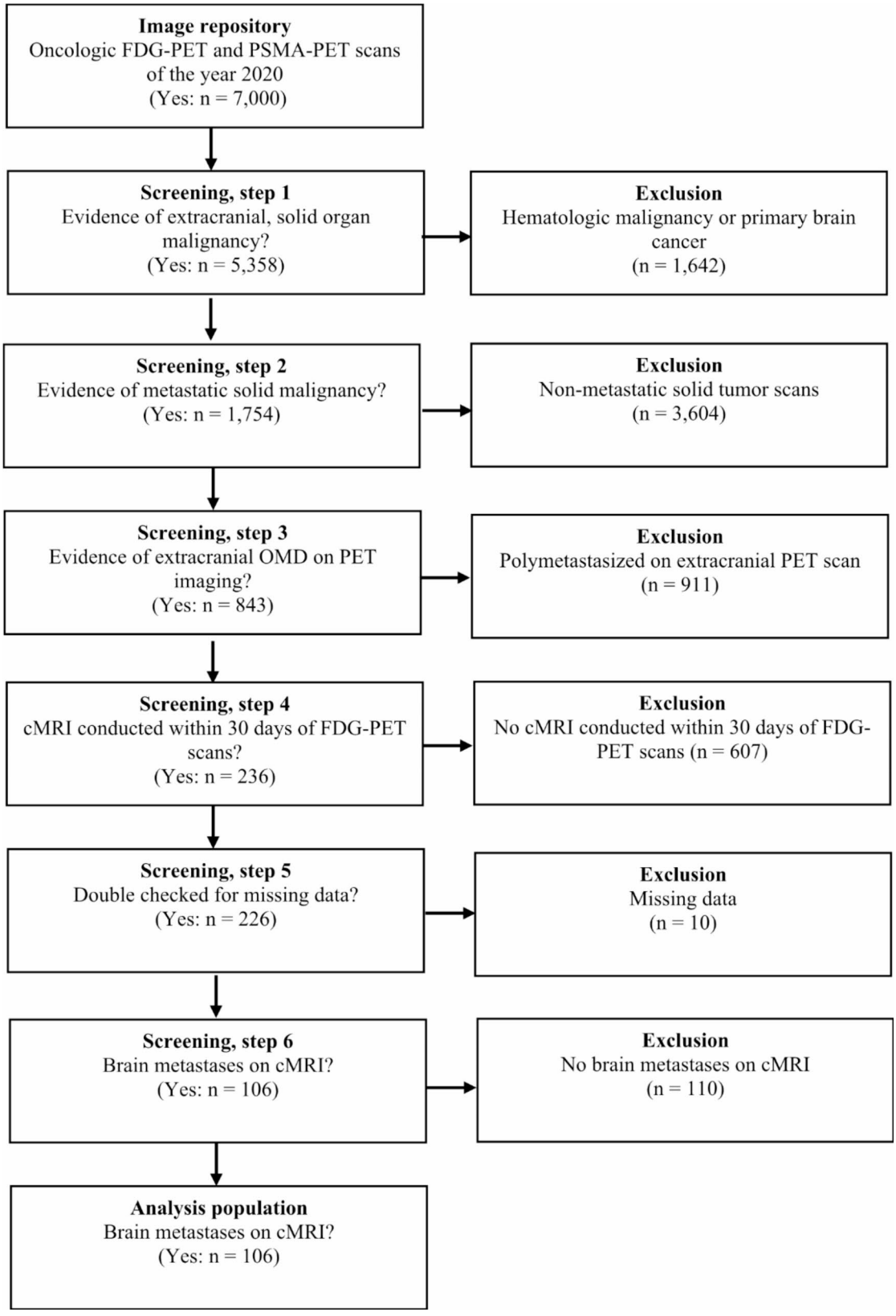

Fig. 1 CONSORT diagram

Table 1 Demographic data for the sample patient population

Parameters	Data (*n* = 106 patients)
Age at OMD diagnosis, years (IQR)	61 (52–70)
Female gender, n (%)	39 (37)
Primary cancer, n (%)	
• Skin[1]	48 (45)
• Lung[2] and pleura	48 (45)
• Breast	6 (5.6)
• Genitourinary	2 (1.9)
• Cancer of unknown origin	2 (1.9)
Oligometastatic state, n (%)	
• Synchronous presentation	15 14)
• Metachronous presentation	91 (86)
Number of distant metastases at OMD diagnosis, median (IQR)	2 (1–3)
Number of brain metastases on imaging, median (IQR)	3 (1–6)
Number of patients alive at time of analysis, n (%)	33 (31)
Median OS from imaging OMD diagnosis, months (IQR)[3]	17.2 (6.59–29.2)
Median survival time for patients alive at cut-off date, months (IQR)	28.0 (26.3–31.5)
Frequency of number of distant metastases, n (%)	
• 1 distant metastasis	44 (41)
• 2 distant metastases	26 (25)
• 3 distant metastases	19 (18)
• 4 distant metastases	12 (11)
• 5 distant metastases	5 (4.7)
Frequency of number of brain metastases, n (%)	
• 1 brain metastasis	28 (26)
• 2 brain metastases	19 (18)
• 3 brain metastases	17 (16)
• 4 brain metastases	2 (2.0)
• 5 brain metastases	5 (4.7)
• > 5 brain metastases	34 (32)
Number of patients that underwent a switch from OMD to PMD after brain scan review, n (%)	48 (45)

Notes: IQR = Interquartile range; OMD = Oligometastatic disease (≤ 5 distant metastases); PMD = Polymetastatic disease (> 5 distant metastases); SD = Standard deviation; OS = Overall survival

[1]Skin includes malignant melanoma and squamous cell carcinoma; [2]Lung includes non-small cell and small cell carcinoma; [3]The cut-off date is the 05.03.2023

7.29–15.1). A log-rank test revealed a highly significant difference in OS probabilities between the two groups ($p < 0.01$). As of the study's cut-off date, 41% ($n = 24$) of patients in the OMD category were still alive, compared to only 19% ($n = 9$) in the PMD category, a significant disparity substantiated by a Chi-square test ($p = 0.03$) (see Fig. 3 and Fig. 4).

Discussion

In this single-center, cross-sectional retrospective study, we analyzed 106 patients with extracranial OMD who were initially identified using PET imaging and screened for the presence of BMs using concurrent brain MRI scans. The primary cancers predominantly originated either from skin or lung and pleura, each accounting for 45% of patients, respectively. In 45% of patients, the disease state transitioned from OMD to PMD upon accounting for BMs, illustrating the dynamic nature of metastatic progression in this patient cohort. In this cohort of patients with a low extra-cranial tumor burden and presence of brain metastases, the oligometastatic state remained significantly associated with OS, with a median OS of 28 months compared to 10 months in the OMD vs. PMD group. These results indicate that the total number of metastases and total-body OMD status remains an important prognostic factor in patients with BMs.

In the landscape of phase II OMD trials, the inclusion or exclusion of patients with BMs has varied, leading to a nuanced evaluation of the prognostic significance of BMs in OMD patients. Notably, the NSCLC phase II trial by *De Ruysscher et al. (2012)* and the study by *Gomez et al. (2016)* allowed OMD patients with BMs, yet the percentages of such cases in the two studies varied, with 43.9% and 27% of patients exhibiting BMs, respectively [21, 22]. Interestingly, despite the prevalence of OMD patients with BMs in both studies, neither trial could establish prognostic significance for OS or PFS. Similarly, the NSCLC phase II trial by *Iyengar et al. (2018)* included patients with treated BMs, but the presence of BMs did not achieve statistical significance for OS or PFS either [17]. In contrast, while the SABR-COMET trial by *Palma et al. (2019)* allowed for the presence of BMs, patients with one to three BMs or a dominant BM requiring surgical decompression was excluded, resulting in only 4% of patients exhibiting BMs [15]. The trial by *Wang et al. (2022)* with EGFR-mutated OMD NSCLC patients deliberately excluded patients with BMs, highlighting the different approaches in study design [23]. Furthermore, the NRG-BR001 phase I and II/III trials on OMD breast cancer patients by *Chmura et al. (2021 and 2022)* also strictly excluded patients with evidence of BMs [24, 25]. The variability in the inclusion and exclusion criteria across these OMD studies underscores the challenges in assessing the prognostic significance of BMs in OMD patients, as the limited number of cases in some trials precludes a robust analysis of this important factor.

The inconsistency in BMs as an important factor in OMD trials persists in ongoing research efforts. Despite the significance of the OMD status with BMs as a potentially important prognostic factor for OS, the exclusion of BMs remains a notable practice in numerous ongoing clinical trials targeting OMD patients. A snapshot of the current landscape, as of February 2024, gleaned from *ClinicalTrials.gov*, reveals a lack of uniformity in trial design [26]. Out of 41 RCTs focusing on OMD across

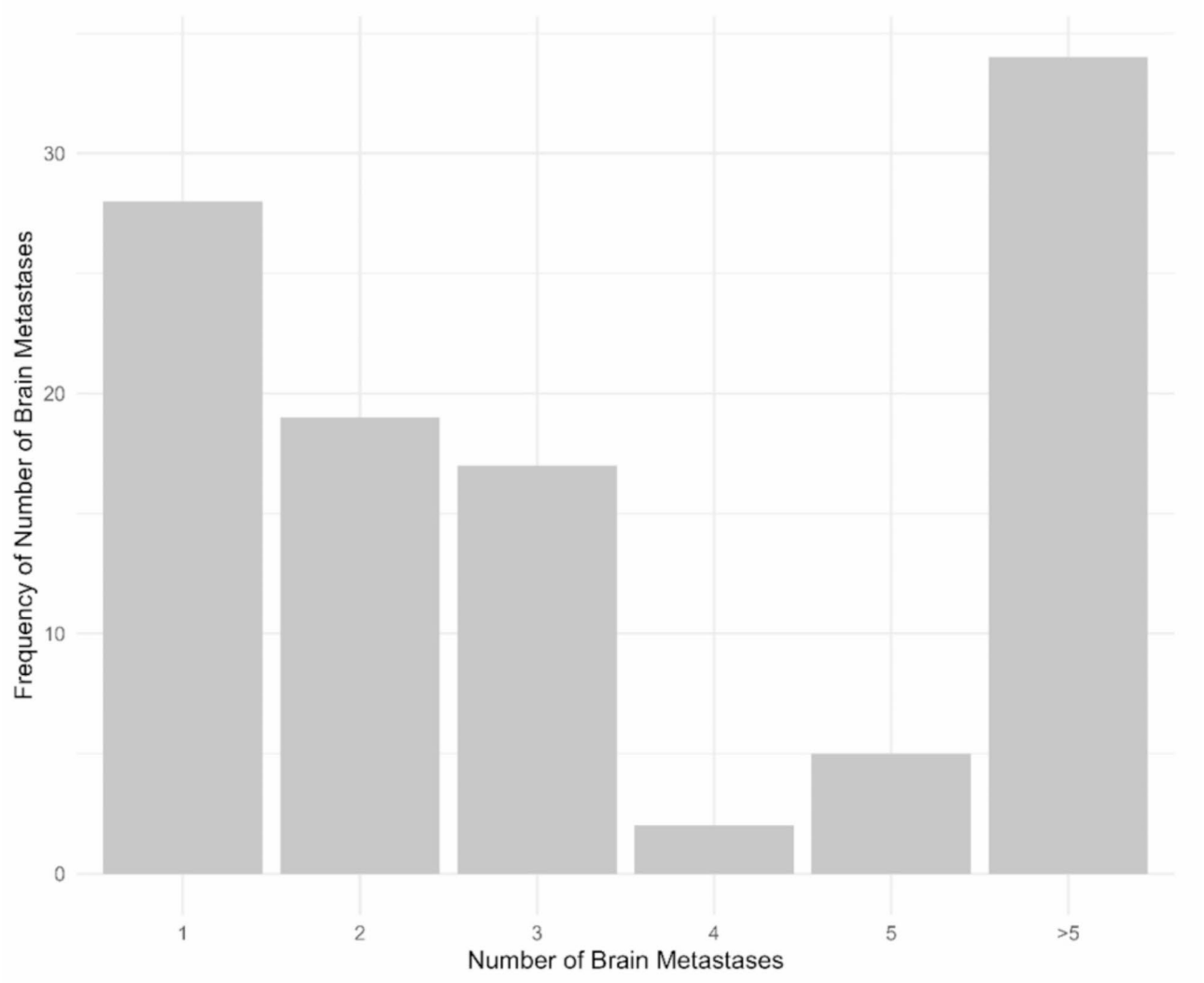

Fig. 2 Frequency distribution of brain metastases

Table 2 Overview of the treatment of brain metastases, broken down by oligometastatic and polymetastatic patients

Treatment of brain mets	Data			*p*-value
Groups	All patients	Total-body OMD status	Total-body PMD status	
n (%)	106 (100)	58 (100)	48 (100)	
Systemic therapy only	49 (46)	32 (55)	17 (35)	0.067
Radiotherapy (SRS or SRT)	36 (34)	15 (26)	21 (44)	0.084
Best supportive care	10 (9.4)	3 (5.2)	7 (15)	0.188
Watch & wait	7 (6.6)	4 (6.9)	3 (6.3)	1.00
Neurosurgery alone	2 (1.9)	2 (3.4)	0 (0)	0.561
Neurosurgery and postoperative radiotherapy	2 (1.9)	2 (34)	0 (0)	0.561

Notes: OMD = Oligometastatic disease (≤ 5 distant metastases); PMD: Polymetastatic disease (> 5 distant metastases); SRS = Stereotactic radiosurgery; SRT = Stereotactic radiotherapy; *p*-values were calculated with a two-proportion z-test

diverse primary tumors, only 20 (48.8%) trials allowed the inclusion of patients with BMs, while seven (17.0%) trials explicitly excluded them. Adding to the complexity, 14 (34.1%) studies implemented precise criteria for distant metastases, such as permitting only those exclusively located in regional lymph nodes, for instance. This disparity in the approach to tackling BMs in ongoing OMD trials mirrors the inconsistency observed in previously conducted studies, further underscoring the challenge

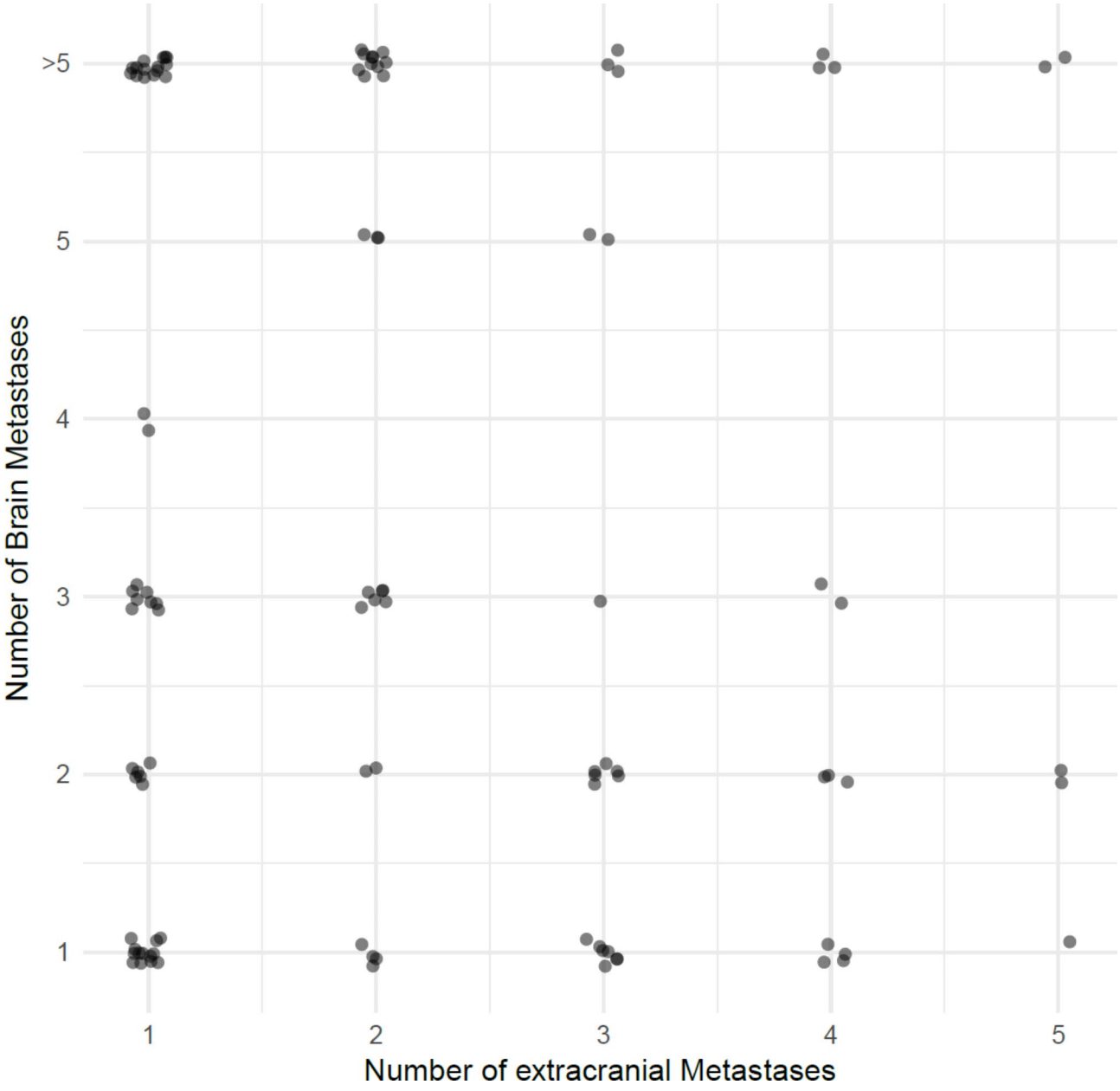

Fig. 3 Jitter plot[1] depicting the relationship between the number of brain metastases and the number of extracranial metastases

[1] Jitter plots function like scatter plots, with each dot representing a patient. The difference lies in the "jittering" (or small random displacement) of the dots to help visualize the distribution and density of data points if multiple data points are located at the exact same position and, therefore, would cover each other. The jittering itself is random and does not convey any information

Notes: Pearson's correlation of the number of brain metastases and the number of extracranial metastases: t = -1.795; degrees of freedom: 103; *p*-value: 0.283

of establishing a cohesive understanding of the impact of BMs on OMD patient outcomes.

Exploring the distribution of BMs within the context of OMD reveals interesting patterns that could potentially impact their prognostic significance. Our study suggests that, similar to the bimodal distribution observed in extracranial OMD and as recently published by our research group [27], the distribution of BMs in OMD patients may also demonstrate a bimodal pattern. In our study, nearly 50% of OMD patients with BMs presented with either one or two intracranial lesions, while roughly 30% exhibited more than five BMs. The observation that many OMD patients have one of two BMs resonates with findings from the study by *De Ruysscher et al. (2012)*, where the brain emerged as the most common distant metastasis site, with a notable majority of

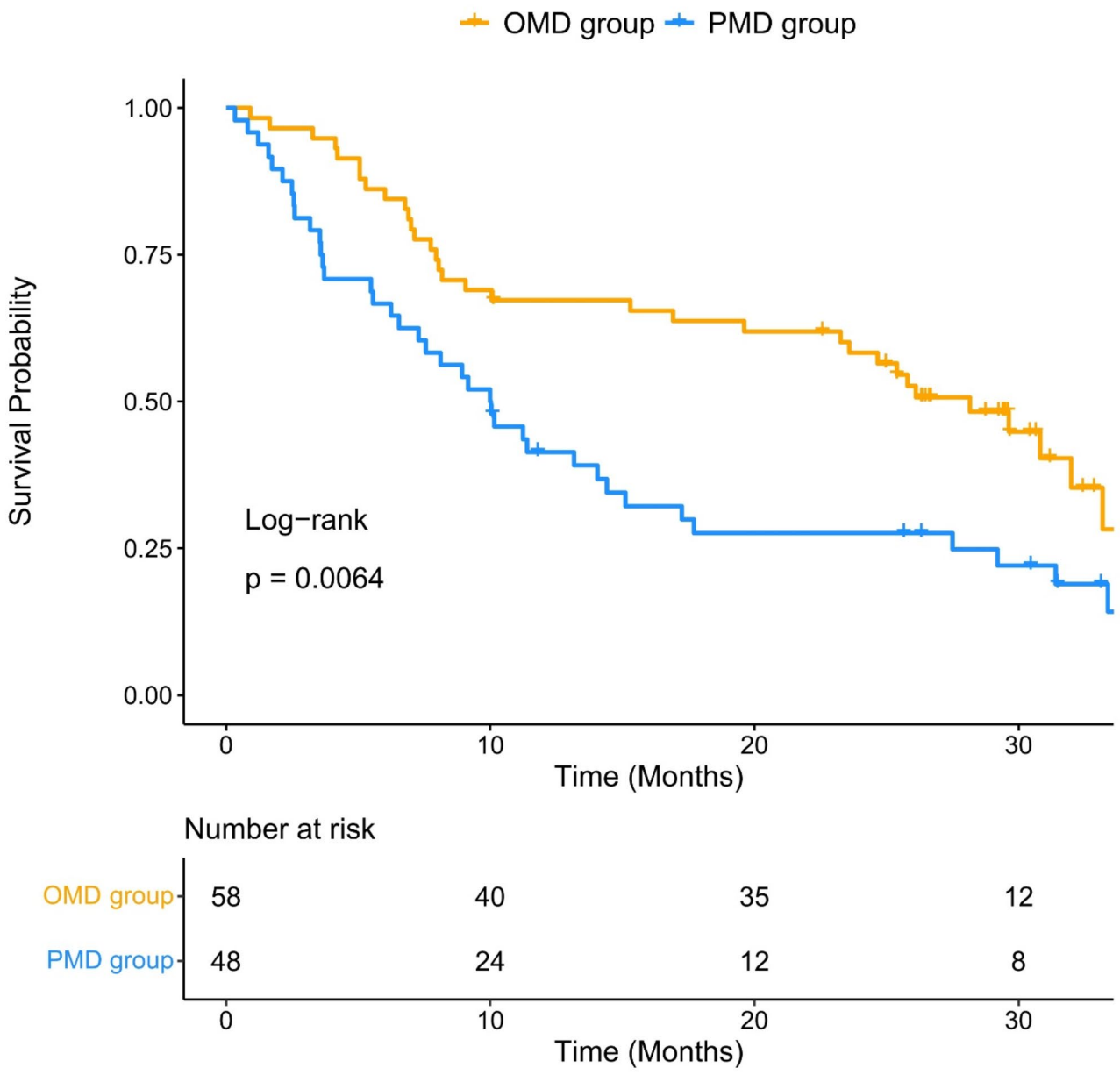

Fig. 4 Kaplan Meier-curve of OMD and PMD patients
Notes: cMRI = cranial magnetic resonance imaging; OMD = oligometastatic disease (≤ 5 distant metastases); PMD = polymetastatic disease (> 5 distant metastases); The starting point is the date of the cMRI

patients harboring only a single BM [21]. This bimodal distribution prompts consideration of potential implications for prognostic assessments in OMD patients with BMs. The distinctive patterns in the number of intracranial lesions may contribute to the heterogeneity observed in patient outcomes, suggesting that identifying the presence of BMs as a crucial prognostic factor in OMD could be influenced by the specific distribution and number of brain lesions. Further investigation into these nuanced aspects may enhance our understanding of the prognostic power of BMs in OMD, refining strategies for patient risk stratification and tailored therapeutic interventions.

Is it a strength of our study to be grounded in a large initial dataset of 7,000 oncological PET scans, However, our study's single-center and retrospective design introduced potential bias and limited the generalizability of our findings to more diverse populations. While the initial dataset was extensive, our study's final inclusion criteria narrowed it down to only 106 patients. This reduction significantly impacted our study's statistical

Table 3 Univariable analysis and multivariable analysis of predictors for the OMD-to-PMD transition

Predictors	Univariable analysis		Multivariable analysis	
	OR (95% CI)	*p*-value	OR (95% CI)	*p*-value
Sex • Female vs. male	1.73 (0.782–3.87)	0.178	1.57 (0.632–3.94)	0.331
Age (years) • < 65 vs. ≥65	1.87 (0.853–4.18)	0.122	2.11 (0.932–4.94)	0.0775
OMD state • Synchronous vs. metachronous	1.46 (0.484–4.48)	0.501	1.29 (0.381–4.37)	0.683
Primary histology				
• Lung and pleura vs. all other	1.21 (0.563–2.63)	0.620	1.37 (0.318–6.11)	0.668
• Skin vs. all other	0.820 (0.337–1.77)	0.614	1.21 (0.285–5.38)	0.793
Number of distant metastases • > 1 vs. 1	1.87 (0.853–4.18)	0.122	1.82 (0.760–4.46)	0.184

Notes: CI = Confidence interval; OMD = Oligometastatic disease (≤6 metastases); OR = Odds ratio. Odds ratios and *p*-values were calculated with logistic regressions

power. Additionally, the diagnostic tools used – namely PET and brain MRIs – although currently the best available options, are not infallible in terms of sensitivity and specificity for detecting metastases. This inherent limitation introduced a measure of error into our data, which must be considered when interpreting the results. This was further magnified by the fact that the constrained sample size prevented differentiation between patients with or without prior intracranial cancer treatment, including radiotherapy. Consequently, this led to the presence of ablated BMs alongside active ones, making them difficult to distinguish on MRI.

In conclusion, almost half of extracranial OMD patients were re-classified to PMD when BMs were considered. Our study confirmed that BMs in OMD patients with a low total tumor burden remained a significant prognostic factor for OS. However, no significant correlation between treatment types for the two groups and risk factors for transitioning from OMD to PMD states were found. To expand on this research, future studies should leverage multi-center, longitudinal data spanning multiple years, allowing for more nuanced differentiation between patients and exploration of the behavior of BMs from various primary cancers.

Abbreviations

BASEC	Business Administration System for Ethics Committees
BSC	Best supportive care
CCCZ	Comprehensive Cancer Center Zurich
CI	Confidence interval
CT	Computed tomography
FDG	Fluorodeoxyglucose
MRI	Magnetic resonance imaging
IQR	Interquartile range
NSCLC	Non-small-cell lung cancer
OMD	Oligometastatic disease
OR	Odds ratio
PET	Positron emission tomography
PMD	Polymetastatic disease
PSMA	Prostate-specific membrane antigen
SD	Standard deviation
SRS	Stereotactic radiosurgery
SRT	Stereotactic radiotherapy
USZ	University Hospital Zurich
UZH	University of Zurich
WBRT	Whole brain radiation therapy

Acknowledgements

The project was also supported through the C3Z Precision Oncology Funding Program 2022/2023 as part of "The CCCZ oligometastatic disease program – OMD^{ZH}".

Author contributions

All authors made significant contributions to this project. The idea and conceptualization of the project were developed by MG and SMC. SC obtained the ethical approval for the project. UJM and AM extracted all imaging scans and reports. GWT reviewed all PET and brain scan reports. SMC and/or PH reviewed and quality checked all data entries. GWT conducted all data analysis. GWT, SMC and MG prepared the manuscript. The manuscript was critically reviewed by all co-authors (GWT, PH, SR, MM, JW, MA, UJM, AM, JAB, JCP, RR, AA, ELR, NA, MW, MH, MG). The final version of the manuscript was approved by all authors.

Funding

Sebastian M. Christ received support through the "Young Talents in Clinical Research" Beginner's Grant from the Swiss Academy of Medical Sciences (SAMW) and the Bangerter-Rhyner Foundation.

Data availability

No datasets were generated or analysed during the current study.

Code availability

Not applicable for this publication.

Declarations

Ethics approval

This study was approved by the Swiss Cantonal Ethics Committee before the initiation of the project (BASEC ID# 2018 – 01794).

Competing interests

The authors declare no competing interests.

Presentations

The abstract of this manuscript was presented as a Poster at the 2024 ESTRO congress in Glasgow, Scotland.

Clinical trial number
Not applicable.

Author details
[1]Department of Radiation Oncology, University Hospital Zurich, University of Zurich, Rämistrasse 100, Zurich 8091, Switzerland
[2]University of Zurich, Zurich, Switzerland
[3]Department of Radiation Oncology, Charité - Universitätsmedizin Berlin, Corporate Member of Freie Universität Berlin and Humboldt-Universität zu Berlin, Augustenburger Platz 1, 13353 Berlin, Germany
[4]Department of Nuclear Medicine, University Hospital Zurich, University of Zurich, Zurich, Switzerland
[5]Department of Radiation Oncology, Klinikum rechts der Isar, Technical University of Munich, Munich, Germany
[6]Department of Radiation Oncology, Dana-Farber Cancer Institute, Brigham & Women's Hospital, Boston, MA, USA
[7]Department of Neurology, University Hospital Zurich, University of Zurich, Zurich, Switzerland
[8]Department of Neurosurgery, University Hospital Zurich, University of Zurich, Zurich, Switzerland

Received: 10 June 2024 / Accepted: 16 October 2024
Published online: 27 October 2024

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