Original Research

Diagnostic value of ^{18}F-fluordesoxyglucose positron emission tomography for patients with brain metastasis from unknown primary site

Fabian Wolpert [a,*], Michael Weller [a], Anna Sophie Berghoff [b], Elisabeth Rushing [c], Lisa Michaela Füreder [b], Gregory Petyt [d], Henning Leske [c], Nicolaus Andratschke [e], Luca Regli [f], Marian Christoph Neidert [f], Roger Stupp [g], Rolf Stahel [g], Reinhard Dummer [h], Thomas Frauenfelder [i], Patrick Roth [a], Nicolas Reyns [j], Philipp Antonio Kaufmann [k], Matthias Preusser [b], Emilie Le Rhun [a,l,m,n]

[a] *Department of Neurology and Brain Tumor Center, University Hospital and University of Zurich, Frauenklinikstrasse 26, CH-8091, Zurich, Switzerland*
[b] *Department of Medicine I, Clinical Division of Oncology, Comprehensive Cancer Center-CNS Tumours Unit (CCC-CNS), Medical University of Vienna, 18-20 Waehringer Guertel, AT-1090, Vienna, Austria*
[c] *Department of Neuropathology, University Hospital Zurich, Schmelzbergstrasse 12, CH-8091, Zurich, Switzerland*
[d] *Department of Nuclear Medicine, Lille University, CHU Lille, 59000, Lille, France*
[e] *Department of Radiation Oncology, University Hospital Zurich, Rämistrasse 100, CH-8091, Zurich, Switzerland*
[f] *Department of Neurosurgery, University Hospital Zurich, Frauenklinikstrasse 10, CH-8091, Zurich, Switzerland*
[g] *Department of Oncology, University Hospital Zurich, Rämistrasse 100, CH-8091, Zurich, Switzerland*
[h] *Department of Dermatology, University Hospital Zurich, Gloriastrasse 31, CH-8091, Zurich, Switzerland*
[i] *Institute of Diagnostic and Interventional Radiology, University Hospital Zurich, Rämistrasse 100, CH-8091, Zurich, Switzerland*
[j] *Department of Neurosurgery, Lille University, Inserm, CHU Lille, U1189 - ONCO THAI - Image Assisted Laser Therapy for Oncology, 59000, Lille, France*
[k] *Department of Nuclear Medicine, University Hospital Zurich, Rämistrasse 100, CH-8091, Zurich, Switzerland*
[l] *Neuro-oncology, Department of Neurosurgery, University Hospital Lille, Salengro Hospital, Rue Emile Laine, FR-59037, Lille, France*
[m] *Neurology, Department of Medical Oncology, Oscar Lambret Center, FR-59020, Lille, France*
[n] *Inserm U-1192, Villeneuve d'Ascq, France*

* *Corresponding author*: Fax: +41 44 255 45 07.
  E-mail address: fabian.wolpert@usz.ch (F. Wolpert).

Abstract   ***Background:*** In 30% of patients with brain metastasis (BM), neurological symptoms are the first clinical manifestation of systemic malignancy, referred to as BM from cancer of unknown primary site (BM-CUPS). Here, we define the diagnostic value of ^{18}F-fluordesoxyglucose positron emission tomography (FDG-PET/CT) in the workup of BM-CUPS.

Methods: We screened 565 patients operated for BM at the University Hospital Zurich and identified 64 patients with BM-CUPS with data on both FDG-PET/CT and contrast-enhanced chest/abdomen computed tomography (CT) available at BM diagnosis. A cohort of 125 patients with BM-CUPS from Lille and Vienna was used for validation.

Results: FDG-PET/CT was not superior to chest/abdomen CT in localising the primary lesion in the discovery cohort, presumably because most primary tumours were lung cancers. However, FDG-PET/CT identified additional lesions suspicious of extracranial metastases in 27 of 64 patients (42%). The inclusion of FDG-PET/CT findings shifted the graded prognostic assessment (GPA) score from 3 with CT alone to 2.5 for PET/CT (p = 3.8×10^{-5}, Wilcoxon's test), resulting in a predicted survival of 5.3 versus 3.8 months (p = 6.1×10^{-5}; Wilcoxon's test). All observations were confirmed in the validation cohort.

Conclusions: Lung cancers are the most common primary tumour in BM-CUPS; accordingly, CT alone shows similar overall sensitivity for detecting the primary tumour as FDG-PET/CT. Yet, FDG-PET/CT improves the accuracy of staging by detecting more metastases, reflected by decreased GPA scores and decreased predicted survival. Therefore, randomised trials on patients with BM should standardise methods of staging, notably when stratifying for GPA.
© 2018 Elsevier Ltd. All rights reserved.

1. Introduction

In a third of patients with the diagnosis of brain metastasis (BM), neurological symptoms are the first clinical manifestation of systemic malignancy: BM from cancer of unknown primary site (BM-CUPS) [1,2]. In 10% of patients with BM-CUPS, a primary tumour is never identified [1,3].

Young age, high Karnofsky performance score (KPS), low number of BM, absence of extracranial metastases and controlled primary tumour are predictors of favourable outcomes in patients with BM in general. The first four criteria are used to determine the graded prognostic assessment (GPA) score [3,4].

Targeted therapies and immunotherapy may improve overall survival in subgroups of patients with BM selected for molecular characteristics of the primary tumours [5−8]. Therefore, identifying the primary lesion and further extracranial metastases are a major clinical need in patients with BM-CUPS to define prognosis and treatment [4,9]. Chest/abdomen CT has commonly been considered the most valuable diagnostic test in patients with BM-CUPS, detecting the primary tumour in more than 80% of patients, largely because lung cancer is the most prevalent primary tumour among patients with BM-CUPS [1,2]. ^{18}F-Fluordesoxyglucose position emission tomography (FDG-PET/CT) has been established as a routine method in the diagnostic workup and follow-up of patients with cancer [10,11]. Here, we evaluated the role of FDG-PET/CT compared with chest/abdomen CT in localising the primary lesion and for staging in patients with BM-CUPS.

2. Patients and methods

2.1. Patients

We screened the archives of the University Hospital Zurich for patients who were operated for BM between January 2004 and December 2014: Of 565 patients identified, 126 were diagnosed with metastasis from a solid extracranial tumour as the first manifestation of disease, further referred to as patients with BM-CUPS. Data on both FDG-PET/CT and contrast-enhanced chest/abdomen CT were available at BM diagnosis for 64 patients (Fig. 1). A validation cohort of 125 patients with BM-CUPS was derived from a cohort of 220 patients followed up at the Medical University of Vienna, Austria (*n* = 100) and the University Hospital Lille, France (*n* = 120) (Fig. A.1). The study was approved by the Cantonal Ethics Committee Zurich.

2.2. Assessments

Only patients who had both FDG-PET/CT and contrast-enhanced chest/abdomen CT were considered. The primary tumour was considered identified if a lesion suspicious of tumour and matching histology of BM were reported. For determination of staging capabilities, reports of radiologists (CT) and nuclear medicine specialists (FDG-PET/CT) were compared. Lesions suspicious of extracranial metastasis were considered as true positive based on the judgement of the treating oncologist under consideration of all histological and imaging
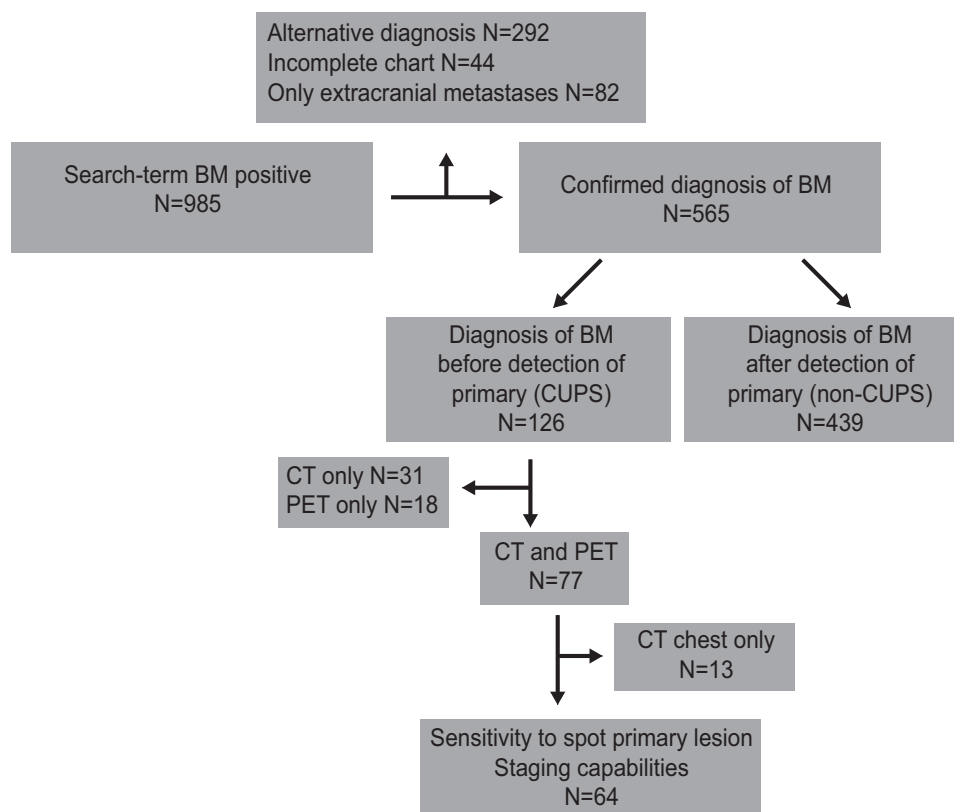
Fig. 1. **Consort chart.** The consort chart shows the selection path for patients to be included this study in the discovery (Zurich) cohort. The upper part documents the preselection process to identify all patients with BM, the middle part shows separation of patients with and without BM-CUPS, and the lower part shows selection of patients for evaluation of properties of primary tumour detection and staging. BM, brain metastasis; BM-CUPS, brain metastasis from cancer of unknown primary site; CT, computed tomography; PET, positron emission tomography.

data, response to tumour-specific treatment and other clinical aspects during the course of disease.

2.3. GPA, predicted survival and survival analysis

We determined general GPA scores [12], diagnosis-specific (DS) GPA scores [4] and molecular GPA (molGPA) scores [9] as indicated and calculated deduced predicted survival based on the respective score results. For the subgroup of non−small cell lung cancer (NSCLC), the molGPA [9] was also calculated. Information on anaplastic lymphoma kinase and epidermal growth factor receptor mutation status was obtained from the pathology report. Information on age, KPS and number of BM was obtained from the electronic charts. Presence or absence of extracranial metastases was determined based on information from chest/abdomen CT and FDG-PET/CT reports. Median survival from the diagnosis of BM-CUPS was calculated using the Kaplan−Meier method.

2.4. Statistical methods

The primary goal was to explore whether the inclusion of PET in the workup of patients with BM-CUPS

facilitates detection of the primary tumour. Furthermore, we sought to explore how the use of PET impacts the allocation of patients to prognostic subgroups, e.g. as defined by the GPA scoring system, and may alter management and outcome. The primary variables of interest were thus the rates of primary tumours diagnosed by FDG-PET/CT versus chest/abdomen CT and the contribution of FDG-PET to staging. Statistical analysis was performed by IBM SPSS statistics ®, version 23 (IBM Co., Armonk, NY, USA) and Graph-Pad Prism software, version 7.0 (La Jolla, CA, USA). Significant differences of paired nominal data were assessed using McNemar's test. Differences between ordinally coded data in paired samples were assessed by Wilcoxon's signed-rank test. Significance levels for two-sided p-values were set at $p < 0.05$ for significant and $p < 0.01$ for highly significant.

3. Results

3.1. Patient database screening

The overall distribution of primary tumours, BM-CUPS patient characteristics and the relative frequency of patients with BM-CUPS per entity in the discovery cohort
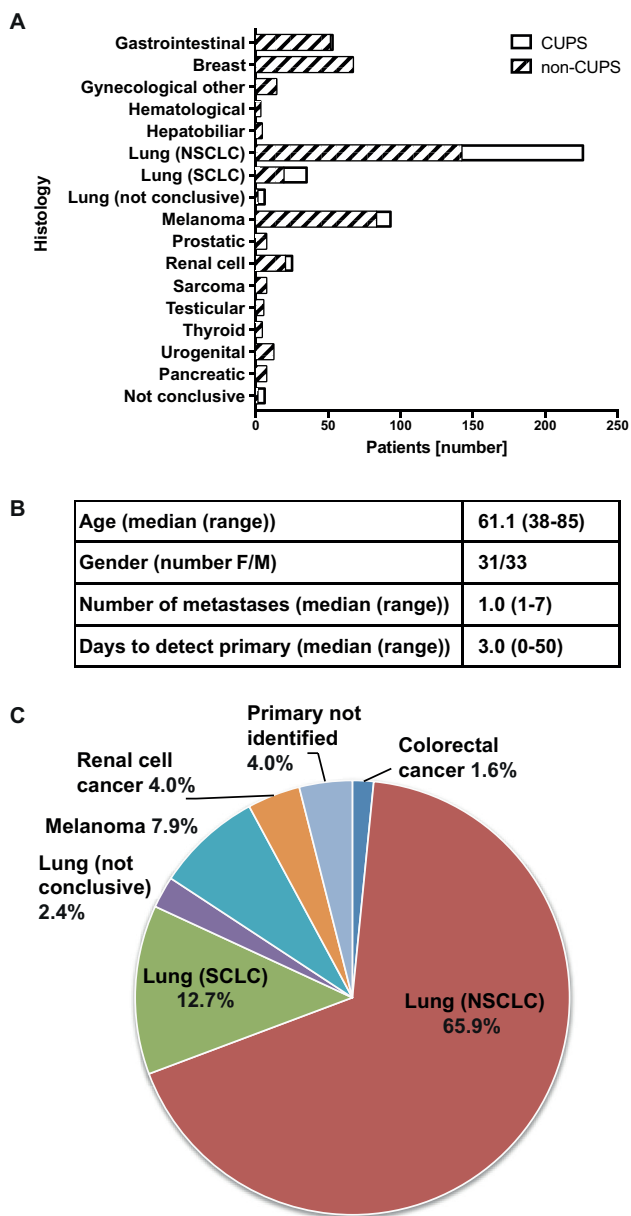
A

B

Age (median (range))	61.1 (38-85)
Gender (number F/M)	31/33
Number of metastases (median (range))	1.0 (1-7)
Days to detect primary (median (range))	3.0 (0-50)

C

Fig. 2. **Characteristics of patients with BM-CUPS.** A. Primary tumours in 565 patients with BM including 126 patients with BM-CUPS later assigned to the respective primaries shown as stacked columns. Patients without BM-CUPS are represented by the cross-hatched area of each bar and patients with BM-CUPS are represented by the open area. B. Characteristics of patients with BM-CUPS (n = 126). C. BM-CUPS diagnoses shown as a circular chart, with tumour entity and percentage of all patients with BM-CUPS annotated (n = 126). BM, brain metastasis; BM-CUPS, brain metastasis from cancer of unknown primary site; NSCLC, non−small cell lung cancer; SCLC, small cell lung cancer.

are shown in Fig. 2. Lung cancer was highly represented, mostly NSCLC (n = 85, 67.5% of all BM-CUPS patients), but also SCLC (n = 16, 12.7%). The primary lesion could not be classified histologically in five patients (3.9%). Median follow-up was 11.2 months (95% confidence interval [CI] 9.2−13.7), and median survival

was 12.5 months (95% CI 10.1−14.9). A total of 102 patients had died. Characteristics of the 64 patients investigated with both chest/abdomen CT and PET were similar to those of the 62 patients in whom studies were incomplete (Table A.1). Median survival was 12.9 months (95% CI 9.8−15.7); 52 of these 64 patients (81.3%) had died, and 12 patients (18.8%) were followed up for a median of 34.9 months (95% CI 9.6−95.1). A validation cohort of 125 patients from Lille and Vienna with available chest/abdomen CT and FDG-PET/CT was also established (Fig. A.1). Median survival was 12.99 months (95% CI 9−15.7); 102 of these patients were followed up until death (81.6%), and 23 patients (18.4%) were followed up for a median of 26.1 months (CI 15.6−36.7). Further patient characteristics were similar to the discovery cohort (Fig. A.1, A.B).

3.2. Sensitivity of diagnostic methods to detect the primary tumour

We first assessed which method led to the identification of the primary tumour, irrespective of additional tests in the further disease course. Primary lesions were identified most frequently by chest/abdomen CT (n = 35 of 64, 54.7%) and FDG-PET/CT (n = 8 of 64, 12.5%) in the discovery (Fig. 3A; see also Appendix A and Table A.2) and the validation cohort (chest/abdomen CT [73/125, 58.4%], followed by FDG-PET/CT [25/125, 20.0%]) (Fig. 3D). This reflected the sequence of diagnostic methods used: FDG-PET CT was more often performed after CT than vice versa in both cohorts (Fig. 3B,E). The sensitivity to localise the primary lesion did not differ in the discovery (CT: n = 56/64; 87.5%; FDG-PET/CT: n = 59/64; 92.2%; p = 0.25, McNemar's test) (Fig. 3C) or in the validation cohort (CT: n = 101/125, 80.8%; FDG-PET/CT: n = 107/125, 85.6%, p = 0.18, McNemar's test) (Fig. 3F). In a corresponding subanalysis of patients with lung cancer only, there was also no difference in the rate of primary tumour detection in the discovery cohort (CT: n = 50/54; 92.6%; FDG-PET/CT: n = 53/54; 98.1%; p = 0.25, McNemar's test) or the validation cohort (CT: n = 89/98; 90.1%; FDG-PET/CT: n = 93/98; 94.9%; p = 0.29, McNemar's test). In three patients of the discovery cohort, FDG-PET/CT but not chest/abdomen CT disclosed the primary tumour. In two of these patients, FDG-PET CT detected also additional extracranial lesions. As a consequence, the therapeutic strategy was moved towards radio/chemotherapy without resection of the primary tumour. In patients with tumour types other than lung cancer, chest/abdomen CT and FDG-PET/CT detected the primary lesion in six of 10 patients in the discovery cohort. In the validation cohort, the primary tumour from non-lung cancer was detected in 12 of 27 patients by chest/abdomen CT and in 13 or of 27 patients by FDG-PET/CT.
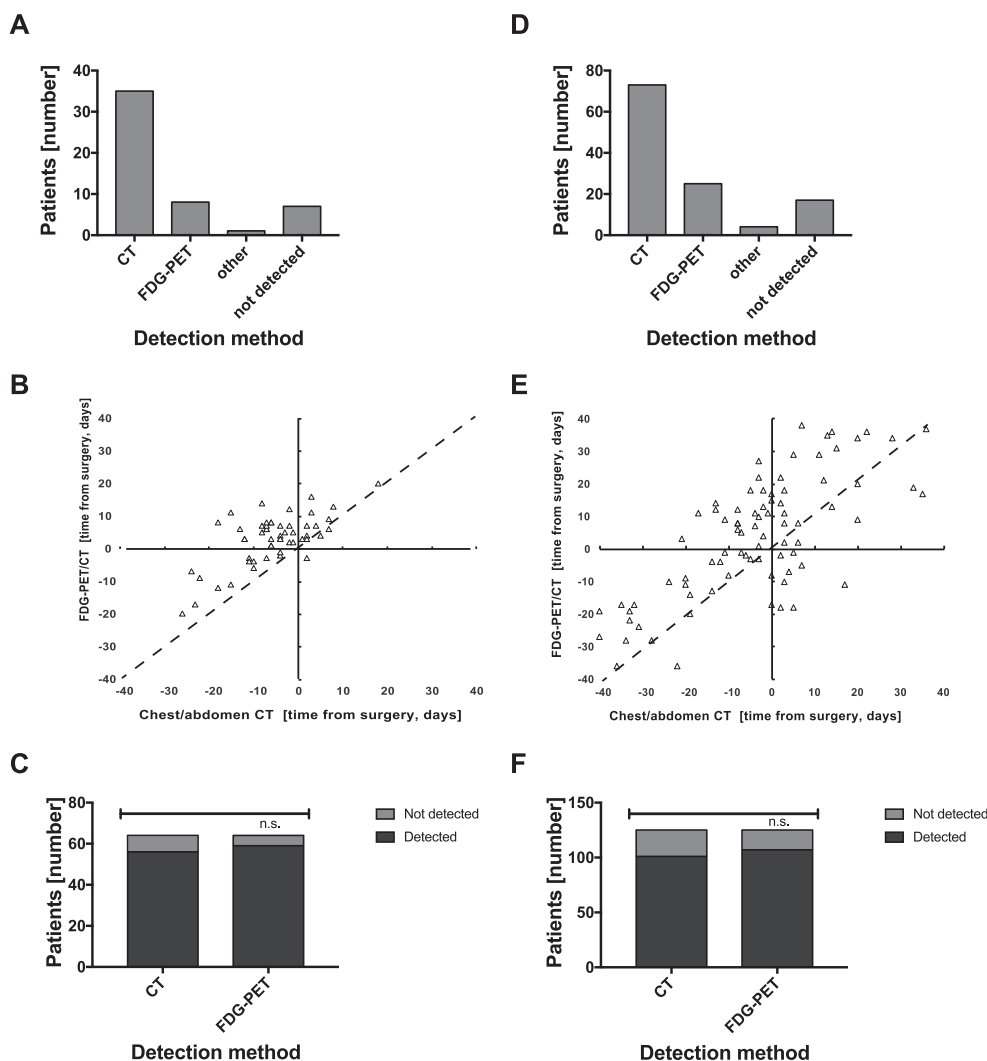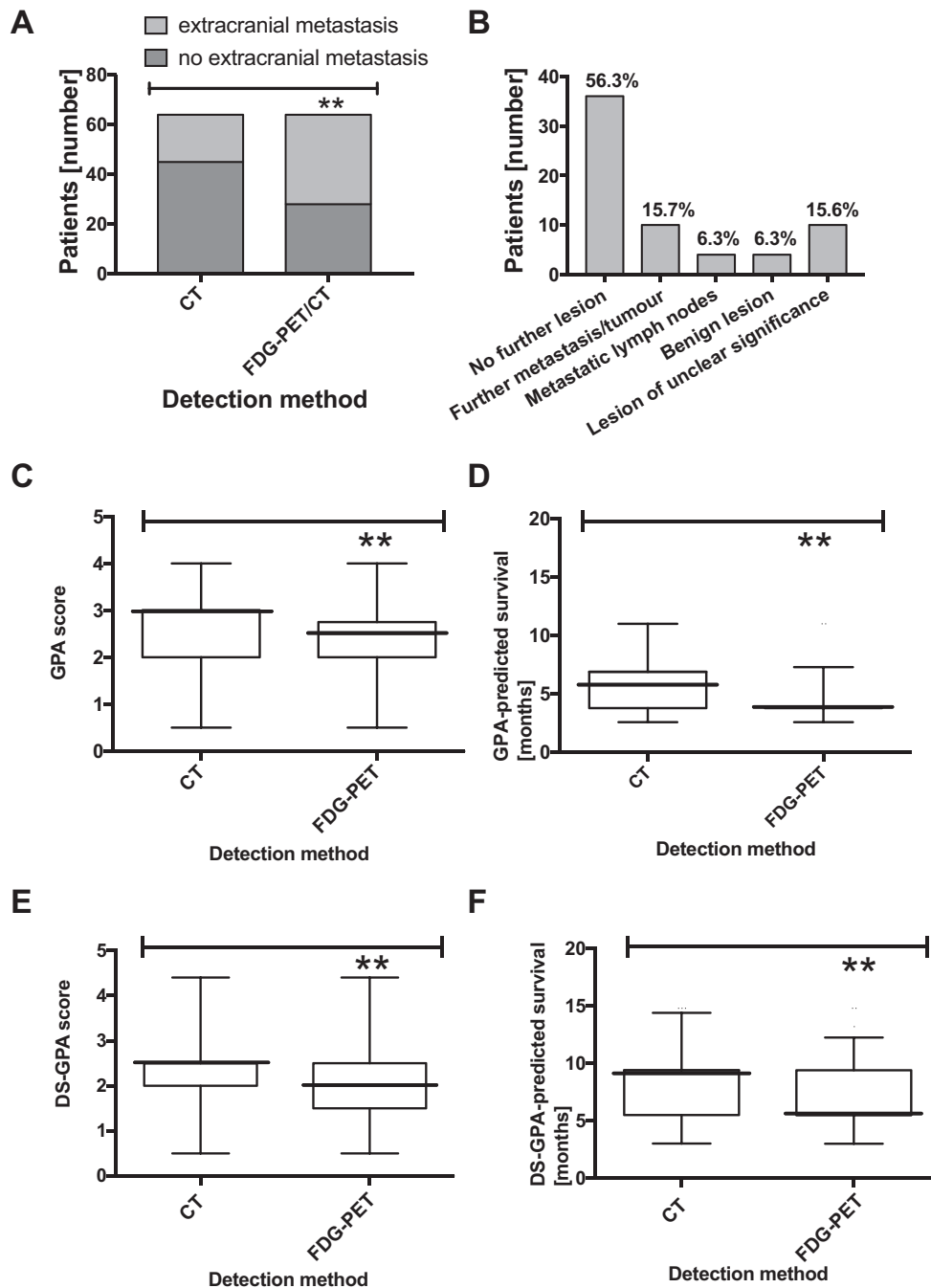
Fig. 3. **Diagnostic methods used to identify the primary tumour.** A, D. The respective methods that first identified the primary lesion and number of corresponding patients are shown as bar plots for the discovery (A, n = 64) and the validation cohort (D, n = 125). B, E. The sequence of diagnostic methods is shown as a scatter plot. The time from surgery in days is shown for chest-abdomen CT (x-axis) and FDG-PET/CT (y-axis). Each triangle represents a single patient, including a dashed line with a slope value of 1. Triangles on this line indicate that chest-abdomen CT (x-axis) and FDG-PET/CT (y-axis) were performed on the same day and triangles over the line indicate that chest-abdomen CT was performed before FDG-PET/CT and *vice versa*. C, F. Overall sensitivities of diagnostic methods are shown by stacked columns, showing the respective method and number of patients in which the primary tumour was detected (dark grey) or not detected (light grey) for the discovery (C) and validation cohort (F). CT, computed tomography; FDG-PET/CT, ^{18}F-fluordesoxyglucose positron emission tomography.

3.3. Staging by CT alone versus CT plus PET and impact on GPA

We then compared the staging properties of chest/abdomen CT versus FDG-PET/CT with regards to the identification of extracranial metastases. Based on the findings from chest/abdomen CT, 45 of 64 patients (70.3%) would have been declared as free from extra-cranial metastases in the discovery cohort, as opposed to only 28 patients (43.8%) based on FDG-PET/CT ($p = 1 \times 10^{-4}$, McNemar's test) (Fig. 4A). FDG-PET/CT detected additional lesions suspicious of malignancy compared with chest/abdomen CT in 28 of 64 patients (43.8%), whereas no lesions were disclosed by CT only, but not by PET. Eighteen of these 28 patients (64.3%) were further evaluated by biopsy (Fig. A.2): in 10 patients (15.7%), further metastatic lesions (n = 9) or another tumour entity (n = 1) confirmed by histology were found. Of these, two bone metastases of humerus and thigh were not located in the region examined by chest/abdomen CT. In four of the remaining eight patients (6.3%), pathologic lymph nodes were spotted and in four patients (6.3%), the additional lesion was benign. In 10 of 64 patients (15.6%), the additional lesion was not

Fig. 4. **Impact of FDG-PET/CT on GPA and DS-GPA scores and predicted survival.** A. Stacked columns show the fraction of patients with detection of extracranial metastases (light grey) compared with patients with no detection of extracranial metastases (dark grey) by either chest/abdomen CT or FDG-PET. B. The detailed results of FDG-PET/CT are shown as bar plots. Additional findings (x-axis) and number of patients (y-axis) are demonstrated, and percentage values are annotated at the top of each bar. C, D. Median GPA scores and GPA-predicted survival based on information from chest/abdomen CT and FDG-PET/CT are shown as whisker box plots. E, F, Median DS-GPA scores and DS-GPA−predicted survival based on information from chest/abdomen CT and FDG-PET/CT from patients with lung cancer are shown as whisker box plots. In C−F, boxes represent the interquartile range and Whiskers 95% CI, and medians are shown as broad, bold lines. Wilcoxon rank-sum test was used for statistical evaluation (**$p < 0.01$). CI, confidence interval; CT, computed tomography; FDG-PET/CT, ^{18}F-fluordesoxyglucose positron emission tomography; GPA, graded prognostic assessment.

biopsied (Fig. 4B and Fig. A.2). In the validation cohort, CT and FDG-PET/CT delivered the same result to localise lesions suspicious of extracranial metastases in 86 of 125 patients (68.8%). In the remaining 39 patients,

FDG-PET/CT detected further suspicious lesions compared with chest/abdomen CT (Fig. A.3A).

The detection of additional extracranial metastases by FDG-PET/CT had significant impact on GPA scores

and on predicted survival in the discovery cohort (GPA-CT = 3 versus GPA-PET/CT = 2.5, $p = 3.8 \times \times 10^{-5}$; GPA-predicted survival CT = 5.3 months, FDG-PET/CT = 3.8 months, $p = 6.1 \times \times 10^{-5}$; Wilcoxon's signed-rank test) (Fig. 4C and D). The GPA score has been refined to account for the primary tumour, referred to as diagnosis-specific (DS) GPA. For lung cancer, GPA and DS-GPA are identical. When the GPA score was applied to patients with lung cancer only ($n = 54$), there was again a difference in both score results and deduced survival (DS-GPA-CT = 2.5 versus DS-GPA-PET = 2.0, $p = 0.002$; DS-GPA-predicted survival CT = 9.4 months, FDG-PET/CT = 5.5 months, $p = 0.003$; Wilcoxon's signed-rank test) (Fig. 4E and F) (see also Appendix B for consideration of molecular markers).

Because of additional PET findings, 16 patients of the overall cohort experienced a GPA change: from 3.5 to 2.5 (n = 1), 3 to 2 (n = 5), 2.5 to 1.5 (n = 6), 2 to 1 (n = 3) or 1.5 to 0.5 (n = 1). Survival was 11.8 months (95% CI 4.8–14.4 months) in the 16 patients who experienced a GPA change because of PET findings as opposed to 12.8 months (95% CI 9.6–15.8 months) in 48 patients with unaltered GPA score and thus not significantly shorter (p = 0.80) (see also Appendix C for data in the validation cohort).

4. Discussion

Early identification of primary tumour and further metastatic lesions is crucial for selecting appropriate treatment and for prognostic assessment in patients with BM-CUPS. Previous studies on FDG-PET indicated a sensitivity of 96% for metastases from lung cancer [13], of 74% for renal cell cancer [14] and of 95% for colorectal cancer [15]. The sensitivity for melanoma was lower; however, FDG-PET was superior to CT (PET/CT 42%, CT only 25%) [16]. Conversely, a detection rate for the primary tumour of 40% was reported for patients with CUPS with extracranial metastases as first evidence of disease [17]. The availability of such data for patients with BM-CUPS is limited. There is only one retrospective study of 16 patients that indicated a high capability of FDG-PET to localise the primary lesion in patients with BM-CUPS [18]. Here, we compared the diagnostic value of FDG-PET/CT and chest/abdomen CT for the identification of primary tumour and for staging in patients with BM-CUPS.

BM-CUPS patient characteristics were comparable in the discovery and validation cohorts (Fig. 2A–C, Fig. A.1, AB) and were in line with previous reports [1,2,18]. Chest/abdomen CT and FDG-PET/CT were highly and comparably sensitive in the detection of the primary lesion (Fig. 3C). In eight of 64 patients from the discovery cohort, the primary tumour was not detected by chest/abdomen CT; however, in three of these patients, the primary tumour was spotted by FDG-PET/CT, all originating from the lung. Simultaneous detection of extracranial metastases in two of these patients resulted in adjustment of the therapeutic strategy towards systemic therapy without resection of the primary tumour. There was no case with a primary lesion visible on CT, but not FDG-PET/CT. The validation cohort essentially confirmed these findings (Fig. 3F).

The superiority of FDG-PET/CT over CT in terms of staging properties has been demonstrated for different tumour entities in controlled, prospective trials [10,11]. However, these studies focused on patients with known systemic malignancies and provided no specific information on patients with BM, CUPS or BM-CUPS. The spectrum of primary tumours differs between patients with BM-CUPS and those with BM during the later clinical course [1,2]. Therefore, general data on FDG-PET imaging in cancer might not allow to draw conclusions on patients with BM-CUPS, and the optimal workup remains to be defined. We found FDG-PET/CT to disclose further metastases (Fig. 4A and B), other tumourous lesions or metastatic lymph nodes compared with chest/abdomen CT in 14 of 64 patients with BM-CUPS (22%), with similar results in the validation cohort (Fig. A.3, A). Owing to the retrospective design of our study, it was difficult to assess the relevance of these findings for the further course of disease. Yet, the number of patients classified as free from extracerebral metastases was significantly lower if information from FDG-PET/CT was used (Fig. 4A).

Survival estimation and risk stratification are crucial in the planning of therapy and clinical studies and therefore one of the main goals of staging. Therefore, we assessed the impact of divergent information from chest/abdomen CT and FDG-PET/CT on the GPA score, the most commonly used prognostic score for estimation of survival and standard tool for clinical decision-making in patients with BM [19]. If calculated based on the detection of extracranial metastases by FDG-PET/CT compared with chest/abdomen CT, median GPA score and predicted survival were significantly lower (Fig. 4C and D). This difference in predicted survival was even more prominent when we applied the DS-GPA for patients with lung cancer (Fig. 4E and F). This indicates that refined staging by FDG-PET/CT compared with chest/abdomen CT leads to an adjustment of prognosis as baseline for clinical decision-making. A survival analysis of the small group of patients who had their GPA decreased based on PET findings did not reveal an inferior outcome, but there is insufficient power to derive meaningful conclusions from such post-hoc analyses. Furthermore, the detection of additional lesions by FDG-PET/CT may also result in an increase of futile biopsies and expose patients to the risk of additional interventions, without improvement of the outcome.

The retrospective design and restricted number of patients are limitations of this study. Imaging reports

could possibly be biased because information from prior CT chest/abdomen or FDG-PET may have been available to the respective radiologist or nuclear medicine specialist, respectively. The predominant diagnostic sequence was chest/abdomen CT first followed by FDG-PET/CT. Furthermore, we included only patients undergoing BM biopsy or resection, which biased our cohort towards selection of patients with better overall clinical condition and limited disease. This explains also why the survival observed in our patient cohorts greatly exceeds the survival predicted by the GPA scores which were not derived from surgical BM patient cohorts. Final conclusions on the practical clinical utility and consequences of additional findings from FDG-PET/CT should be drawn based on prospective trials. Such prospective analyses should include not only risk benefit but also a cost-effectiveness analysis because PET is roughly three times as expensive as CT and additional cost may emerge because of workup for new lesions detected by PET. Altogether, our data show that both FDG-PET/CT and chest/abdomen CT are powerful tools for identifying the primary tumour in patients with BM-CUPS, with superior staging properties of FDG-PET/CT compared with those of chest/abdomen CT. As a consequence of our findings, FDG-PET/CT might be the preferred imaging modality for all patients with BM-CUPS. This is desirable because repeated non-conclusive diagnostic procedures bear potential risks of adverse effects, are expensive too and may delay the start of urgently needed therapies. The diverging number of patients with BM-CUPS investigated by FDG-PET/CT, e.g. in the centres from our validation cohort, indicates that this technique might not be broadly applied presently.

There are recognised limitations in the accuracy of prognostic scores [20]. Although prognostic scores were not the primary objective of this study, our data indicate that discrepancies might be partially explained by insufficient standardisation of staging methods. These were not specified in the publications on the DS-GPA score [4,12]. We suggest that future controlled prospective trials on clinical prognostic scores should be standardised or at least stratify for staging methods.

Conflict of interest statement

FW has received travel support from Roche. MW has received research grants from Acceleron, Actelion, Bayer, Isarna, MSD, Merck EMD, Novocure, Piqur and Roche and honoraria for lectures or advisory board participation or consultation from Celldex, Immunocellular Therapeutics, Isarna, Magforce, MSD, Merck EMD, Novocure, Pfizer, Roche and Teva. ASB has received travel support from Amgen, Roche and Bristol-Myers Squibb and honoraria for lectures or advisory board participation from Roche. RS has served on advisory boards and institution received honoraria from Celgene, Ipsen, Merck KGaA, MSD/Merck & Co, Novartis, Pfizer and Roche. RD receives research funding from Astra Zeneca, Novartis, Merck Sharp & Dhome, Bristol-Myers Squibb, Roche, GlaxoSmithKline and Bayer and has a consultant or advisory board relationship with Astra Zeneca, Novartis, Merck Sharp & Dhome, Bayer, Roche, Bristol-Myers Squibb, GlaxoSmithKline, Amgen and Takeda. TF has received honoraria for lectures from Bayer and for speakers' bureau from GE. PR has received honoraria for advisory board participation and lectures from Bristol-Myers Squibb, Molecular Partners, MSD, Novartis and Roche. MP has received research support from Böhringer-Ingelheim, GlaxoSmithKline, Merck Sharp & Dome and Roche and honoraria for lectures, consultation or advisory board participation from Bristol-Myers Squibb, Novartis, CMC Contrast, GlaxoSmithKline, Mundipharma and Roche. ELR has received research support from Mundipharma and Amgen and travel support or honoraria from Mundipharma and Novartis. The rest of the authors have no conflicts of interest to declare.

Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.ejca.2018.03.010.

References

[1] Agazzi S, Pampallona S, Pica A, Vernet O, Regli L, Porchet F, et al. The origin of brain metastases in patients with an undiagnosed primary tumour. Acta Neurochir 2004;146(2):153–7.

[2] Mavrakis AN, Halpern EF, Barker 2nd FG, Gonzalez RG, Henson JW. Diagnostic evaluation of patients with a brain mass as the presenting manifestation of cancer. Neurology 2005;65(6):908–11.

[3] Gavrilovic IT, Posner JB. Brain metastases: epidemiology and pathophysiology. J Neuro Oncol 2005;75(1):5–14.

[4] Sperduto PW, Kased N, Roberge D, Xu Z, Shanley R, Luo X, et al. Summary report on the graded prognostic assessment: an accurate and facile diagnosis-specific tool to estimate survival for patients with brain metastases. J Clin Oncol 2012;30(4):419–25.

[5] Gore ME, Szczylik C, Porta C, Bracarda S, Bjarnason GA, Oudard S, et al. Safety and efficacy of sunitinib for metastatic renal-cell carcinoma: an expanded-access trial. Lancet Oncol 2009;10(8):757–63.

[6] Robinson SD, O'Shaughnessy JA, Lance Cowey C, Konduri K. BRAF V600E-mutated lung adenocarcinoma with metastases to the brain responding to treatment with vemurafenib. Lung Cancer 2014 Aug;85(2):326–30.

[7] Bachelot T, Romieu G, Campone M, Dieras V, Cropet C, Dalenc F, et al. Lapatinib plus capecitabine in patients with previously untreated brain metastases from HER2-positive metastatic breast cancer (LANDSCAPE): a single-group phase 2 study. Lancet Oncol 2013;14(1):64–71.

[8] Margolin K, Ernstoff MS, Hamid O, Lawrence D, McDermott D, Puzanov I, et al. Ipilimumab in patients with melanoma and brain metastases: an open-label, phase 2 trial. Lancet Oncol 2012;13(5): 459–65.

[9] Sperduto PW, Yang TJ, Beal K, Pan H, Brown PD, Bangdiwala A, et al. Estimating survival in patients with lung cancer and brain metastases: an update of the graded prognostic assessment for lung cancer using molecular markers (Lung-molGPA). JAMA Oncol 2017 Jun 1;3(6):827–31.

[10] Reinhardt MJ, Joe AY, Jaeger U, Huber A, Matthies A, Bucerius J, et al. Diagnostic performance of whole body dual modality 18F-FDG PET/CT imaging for N- and M-staging of malignant melanoma: experience with 250 consecutive patients. J Clin Oncol 2006;24(7):1178–87.

[11] Fischer B, Lassen U, Mortensen J, Larsen S, Loft A, Bertelsen A, et al. Preoperative staging of lung cancer with combined PET-CT. N Engl J Med 2009;361(1):32–9.

[12] Sperduto PW, Berkey B, Gaspar LE, Mehta M, Curran W. A new prognostic index and comparison to three other indices for patients with brain metastases: an analysis of 1,960 patients in the RTOG database. Int J Radiat Oncol Biol Phys 2008;70(2):510–4.

[13] Fischer BM, Mortensen J, Hojgaard L. Positron emission tomography in the diagnosis and staging of lung cancer: a systematic, quantitative review. Lancet Oncol 2001;2(11):659–66.

[14] Alongi P, Picchio M, Zattoni F, Spallino M, Gianolli L, Saladini G, et al. Recurrent renal cell carcinoma: clinical and prognostic value of FDG PET/CT. Eur J Nucl Med Mol Imag 2016;43(3):464–73.

[15] Ye Y, Liu T, Lu L, Wang G, Wang M, Li J, et al. Pre-operative TNM staging of primary colorectal cancer by (18)F-FDG PET-CT or PET: a meta-analysis including 2283 patients. Int J Clin Exp Med 2015;8(11):21773–85.

[16] Veit-Haibach P, Vogt FM, Jablonka R, Kuehl H, Bockisch A, Beyer T, et al. Diagnostic accuracy of contrast-enhanced FDG-PET/CT in primary staging of cutaneous malignant melanoma. Eur J Nucl Med Mol Imag 2009;36(6):910–8.

[17] Burglin SA, Hess S, Hoilund-Carlsen PF, Gerke O. 18F-FDG PET/CT for detection of the primary tumor in adults with extracervical metastases from cancer of unknown primary: a systematic review and meta-analysis. Medicine (Baltim) 2017; 96(16):e6713.

[18] Klee B, Law I, Hojgaard L, Kosteljanetz M. Detection of unknown primary tumours in patients with cerebral metastases using whole-body 18F-flouorodeoxyglucose positron emission tomography. Eur J Neurol 2002;9(6):657–62.

[19] Sperduto PW, Kased N, Roberge D, Xu Z, Shanley R, Luo X, et al. Effect of tumor subtype on survival and the graded prognostic assessment for patients with breast cancer and brain metastases. Int J Radiat Oncol Biol Phys 2012;82(5):2111–7.

[20] Kondziolka D, Parry PV, Lunsford LD, Kano H, Flickinger JC, Rakfal S, et al. The accuracy of predicting survival in individual patients with cancer. J Neurosurg 2014;120(1):24–30.