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Can vascular risk factors influence number and size of cerebral metastases? A 3D-MRI study in patients with different tumor entities

Sandra Nagel[a,1], Benjamin-Andreas Berk[a,c,1], Rolf-Dieter Kortmann[a], Karl-Titus Hoffmann[b], Clemens Seidel[a,*]

[a] Klinik für Radioonkologie und Strahlentherapie, Universitätsklinikum Leipzig, Germany
[b] Abteilung für Neuroradiologie, Universitätsklinikum Leipzig, Germany
[c] Department of Clinical Sciences and Services, Royal Veterinary College, Hawkshead Lane, Hatfield, United Kingdom

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ABSTRACT

Objective: There is increasing evidence that cerebral microangiopathy reduces number of brain metastases. Aim of this study was to analyse if vascular risk factors (arterial hypertension, diabetes mellitus, smoking, and hypercholesterolemia) or the presence of peripheral arterial occlusive disease (PAOD) can have an impact on number or size of brain metastases.

Patients and Methods: 200 patients with pre-therapeutic 3D-brain MRI and available clinical data were analyzed retrospectively. Mean number of metastases (NoM) and mean diameter of metastases (mDM) were compared between patients with/without vascular risk factors (vasRF).

Results: No general correlation of vascular risk factors with brain metastases was found in this monocentric analysis of a patient cohort with several tumor types. Arterial hypertension, diabetes mellitus, hypercholesterolemia and smoking did not show an effect in uni- and multivariate analysis. In patients with PAOD the number of BM was lower than without PAOD. This was the case independent from cerebral microangiopathy but did not persist in multivariate analysis.

Conclusion: From this first screening approach vascular risk factors do not appear to strongly influence brain metastasation. However, larger prospective multi-centric studies with better characterized severity of vascular risk are needed to more accurately detect effects of individual factors.

1. Introduction

Brain metastases (BM) are a frequent complication of cancer. Up to 30–40% of patients with solid tumors develop brain metastases during course of disease [1]. The number of brain metastases has prognostic impact in several tumors (melanoma, lung cancer, renal cell cancer) [2] and is of major importance for decision on local treatment (surgery/local radiotherapy) or whole brain radiotherapy [1,3,4].

There is increasing evidence that in addition to tumor biology the vascular compartment plays a significant role in brain metastasation [5]. Highly vascularized parts of the brain at the junction between white and gray matter are predilection sites for brain metastases [6,7] compared to less perfused deep white matter [8,9]. In addition, small vessel disease of the brain (also called cerebral microangiopathy) is associated with less brain metastases in patients with NSCLC [10,11] and other tumors [12]. Predisposing factors for cerebral microangiopathy are vascular risk factors, i.e. arterial hypertension, diabetes mellitus, smoking and hypercholesterolemia. Peripheral arterial occlusive disease (PAOD) is - as a systemic vascular disease - often associated with cerebral microangiopathy. Aim of this study was to evaluate if the presence of vascular risk factors or of PAOD influences the number and size of brain metastases.

2. Materials and methods

The selection process of patients for is displayed in Fig. 1.Firstly, the charts of all patients that presented at the radiotherapy department of the University Hospital Leipzig from October 2004 to January 2015 with the diagnosis "brain metastasis or brain metastases" were screened (identification). In total 501 patients have been identified. To be included in the analysis the following two criteria (screening 1, 2) needed to be fulfilled:

1) Pre-Therapeutic 3 T MRI with 3D T1-weighted sequence after

* Corresponding author at: Klinik für Strahlentherapie und Radioonkologie, Universitätsklinikum Leipzig, Stephanstr. 9a, 04103 Leipzig, Germany.
E-mail address: clemens.seidel@medizin.uni-leipzig.de (C. Seidel).
[1] These authors contributed equally to this work.

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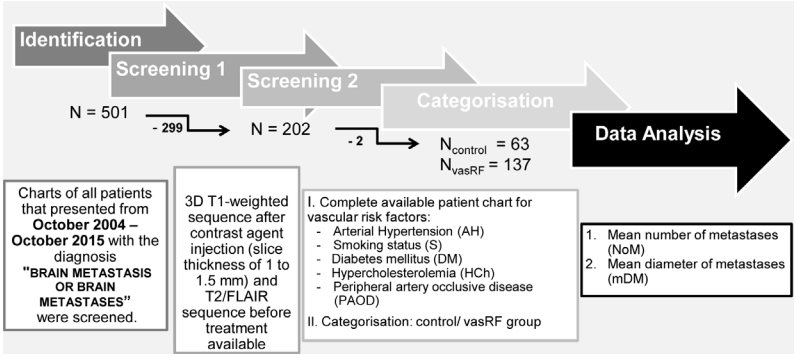

Fig. 1. Selection process. Charts of all patients that presented from October 2004 to January 2015 with the diagnosis "brain metastasis or brain metastases" were screened. In total 200 of 501 patients fulfilled the criteria for this study. These 200 patients were categorized into a control group (N = 63) and test group (N = 137). All patients within the test group were at least positive for one vascular risk factor.

contrast agent injection (slice thickness of 1–1.5 mm) and T2/FLAIR sequence

2) Complete available patient chart including vascular risk factors (vasRF): arterial hypertension (AH), smoking status (S), diabetes mellitus (SM), hypercholesterolemia (HCh) and peripheral arterial occlusive disease and respective medication

The study design has been evaluated and officially accepted by the local ethics committee. Written informed consent regarding scientific use of anonymized medical data was received from all patients at initial presentation in our department.

2.1. Analysis of MRI and patient charts

Pre-treatment MR axial 3D T1-weighted images of the brain of the included patients were retrospectively analyzed by SN and BAB under the supervision of CS (with more than 7 years experience in clinical neuroradiology). Number and diameter of all metastases were determined blinded for presence of vascular risk factors. In addition, presence of cerebral microangopathy (also called white matter lesions (WML) was determined according to the Fazekas score [13]. Vascular risk factors at time of presentation were retrospectively compiled on basis of medical files. All patients with the diagnosis of AH received anti-hypertensive medication at time of documentation for > 5 years. Patients with DM or hypercholesterolemia (duration > 5 years) could be with or without pharmacological treatment. Smokers (duration > 5 years) and Ex-smokers that stopped smoking ≤5 years before presentation were defined as smokers.

2.2. Statistical analysis

Statistical analysis was performed with IBM SPSS V22.0. Mean number (NoM) and mean diameter (mDM) of brain metastases were calculated per patient. Initially, the Kolmogorov–Smirnov test was used to determine whether or not the sample of values follows a normal distribution [14]. NoM and mDM did not follow a normal distribution ($p = 0.001$), thus statistical evaluation were conducted with Mann-Whitney-*U* test ($N_{group} = 2$) or multiple Independent-Samples Kruskal-Wallis-Test ($N_{group} > 2$). Statistical significance was accepted at $p < 0.05$. Univariate (UVA) and multivariate data analyses were carried out. Figures were generated with IBM SPSS V22.0 and Microsoft Office Version 2015.

Mean number (NoM) and mean diameter (mDM) of the brain metastases were compared between control and vasRF group using Mann-Whitney *U* test. Secondly, single vasRF were compared against the control and corresponding vasRF negative subgroup. Furthermore, the different vasRF subgroups and tumor types were compared using Independent-Samples Kruskal-Wallis-Test. In case of significant effects of single vasRF it was examined if effects were independent from presence of WML. Different multivariate analyses were conducted (variable combination of vasRF, accumulation 1–4 vasRF, ± PAOD, tumor entity ± vasRF). SN, BAB and CS performed analysis and wrote the article with valuable input of, KTH, RDK (radiology).

3. Results

3.1. Patient characteristics

200 patients fulfilled the inclusion criteria. 63 patients (31.5%) had no vascular risk factor (control group). The rest of 137 (68.5%) patients had at least one vascular risk factor recorded (vasRF group). 121 patients were male (60.5%)/79 female (39.5%), median age: 65 years [range: 32–91 years].

3.2. Tumor characteristics and vascular risk factors

The population consisted of patients with non-small-cell lung cancer (NSCLC) (n = 89), small-cell lung cancer (SCLC) (n = 14), breast cancer (BC) (n = 20), malignant melanoma (MM) (n = 30), renal cell carcinoma (RC) (n = 17), colorectal cancer (CRC) (n = 10) and other tumors (OT) (n = 20). 31 patients (15.5%) had a singular brain metastasis, 42 patients (21%) had 2 metastases, 91 patients (45.5%) had 3–9 metastases and 36 patients had > 9 metastases. Within the vascular risk factor group 99 patients (72.3%) had arterial hypertension, 37 patients (27%) were diabetics, 68 patients (49.6%) were smokers and 8 patients (6%) had high blood cholesterol level (Fig. 2b). 23 patients (11.5%) had developed a PAOD (Fig. 2a). Most of the patients in the vasRF group had only one vascular risk factor (n = 77, 56.2%), 46 patients (33.6%) had two risk factors, 13 patients (9.5%) had three risk factors and only one patient (0.7%) had four risk factors. 70% (16/23) of the patients with PAOD had additional vascular risk factors (Fig. 2a and c).

3.3. Effects of vascular risk factors on NoM and mDM

Number of metastases of patients with and without vasRF were not significantly different (Mean: 6.07 vs. 5.32, $p = 0.34$, Median: 4.00 vs. 3.00). Same applied to diameter of metastases of patients with and without vasRF (Mean: 12.63 mm vs. 14.37 mm, $p = 0.15$, Median: 9.70 vs. 11.00; (Fig. 3a and b). Patients with PAOD had significant less brain metastases than patients without PAOD (Mean: 4.43 vs. 6.02, $p = 0.043$, Median 3.00 vs. 4.00); (Fig. 3a). In case of presence of WML no difference of NoM with/without PAOD was found (Mean: 4.9 vs. 5.1, Median: 3.00 vs. 3.00), while there was a significant difference dependent on PAOD-status in patients without WML (Mean: 1.30 vs. 7.30, $p = 0.01$, Median: 1.00 vs. 5.00) (Fig. 4). There were no other relevant differences of NoM or mDM between patients with or without arterial hypertension, diabetes mellitus, hypercholesterolemia and smoking.

3.4. Effects of tumor entities on NoM and mDM

Significant less brain metastases were found for CRC compared to