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Estimation of intracranial failure risk following hippocampal-sparing whole brain radiotherapy

Saskia Harth [a,1], Yasser Abo-Madyan [a,c,1], Lei Zheng [b], Kerstin Siebenlist [a], Carsten Herskind [a], Frederik Wenz [a], Frank A. Giordano [a,*]

[a] Department of Radiation Oncology; [b] Experimental Radiation Oncology, Department of Radiation Oncology, Universitätsmedizin Mannheim (UMM), Medical Faculty Mannheim, Heidelberg University, Germany; [c] Department of Clinical Oncology and Nuclear Medicine (NEMROCK), Faculty of Medicine, Cairo University, Egypt

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ABSTRACT

Purpose: To estimate the risk of undertreatment in hippocampal-sparing whole brain radiotherapy (HS-WBRT).
Methods: Eight hundred and fifty six metastases were contoured together with the hippocampi in cranial MRIs of 100 patients. For each metastasis, the distance to the closest hippocampus was calculated. Treatment plans for 10 patients were calculated and linear dose profiles were established. For SCLC and NSCLC, dose–response curves were created based on data from studies on prophylactic cranial irradiation, allowing estimating the risk for intracranial failure.
Results: Only 0.4% of metastases were located inside a hippocampus in 3% of all patients. SCLC showed a relatively high rate of hippocampal metastasis (18.2% of all SCLC patients) and HS-WBRT in a commonly applied fractionation scheme would increase the risk for brain relapse by ~4% compared to conventional WBRT. NSCLC showed a lower rate of brain metastasis in the hippocampi (2.8%) and HS-WBRT would account for a slightly increased absolute risk of 0.2%.
Conclusions: Prophylactic or therapeutic HS-WBRT is expected to be associated with a low risk of undertreatment. For SCLC, it bears a minimally elevated risk of failure compared to standard WBRT. In NSCLC, HS-WBRT is most likely not associated with a clinically relevant increase in risk of failure.
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Brain metastases (BM) are an advanced stage cancer manifestation that eventually affects up to 30% of cancer patients. They predominantly originate in lung, breast, skin, colon and kidney cancers and, given the change in demographics in industrialized countries with increased cancer frequencies and concomitantly improved diagnostic sensitivities, the incidence is believed to further rise [1,2]. Treatment options for BM include surgery, whole-brain radiotherapy (WBRT) and stereotactic radiosurgery [1]. Chemotherapy plays a limited role as BM generally show a high degree of intrinsic and extrinsic (blood–brain barrier) drug resistance [3]. Although diverse prognostic factors (e.g., age, KPS, controlled primary, no extracranial metastases) [4] are important in choosing a suitable treatment option [5], WBRT with or without (radio-)surgery is applied in most cases [1,2]. Adjuvant WBRT reduces the risk of recurrent BM and improves quality of life but does not prolong overall survival [6], except in patients with single BM [7].

Beside therapeutic WBRT, prophylactic WBRT (prophylactic cranial irradiation, PCI) is widely used in patients with small-cell lung cancer (SCLC) and has been shown to prolong overall survival even if only a mild response to chemotherapy was seen [8]. The use of PCI in patients with non-small-cell lung cancer (NSCLC) is currently discussed as it may reduce the incidence of BM, but does not prolong overall survival [9,10].

Irradiation of the brain does not only bear the risk of inducing acute (partially mass-associated) side effects such as nausea, hair loss, vomiting and fatigue, but also causes long-term neurocognitive deficits [1,11,12]. Although neurocognitive disorders after PCI/WBRT also have a multifactorial etiology based on a patient's individual medical history (preceding chemotherapy, pre-existing vascular damage e.g., from smoking, local reactions/edema) [13,14], it is currently believed that they are mostly caused by a loss of neural stem cells in the hippocampal areas [15]. Multipotent and self-renewing neural stem cells are found in the subgranular zone of the adult hippocampus and in the subventricular zone of the lateral ventricles [16]. The hippocampus plays an important role in memory consolidation and emotional learning (contextual fear conditioning) [17,18]. The disruption of neurogenesis in the subgranular zone or damage to the hippocampus can lead to impaired short- and long-term memory, learning and contextual

* Corresponding author. Address: Department of Radiation Oncology, Universitätsmedizin Mannheim (UMM), Medical Faculty Mannheim, Heidelberg University, Theodor-Kutzer-Ufer 1-3, 68167 Mannheim, Germany.
E-mail address: frank.giordano@umm.de (F.A. Giordano).
[1] These authors contributed equally to this work.

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fear conditioning [19–22]. In line with this, irradiating the brain decreases neurogenesis in the hippocampus which leads to impaired hippocampal-dependent learning and memory [23–25].

To prevent radiation-induced loss of neuronal stem cells, hippocampal-sparing (HS) radiation techniques have been developed and first data from helical tomotherapy or LINAC-based intensity-modulated radiotherapy (IMRT) have proven the feasibility of the approach [26,27]. Currently, there is an increasing enthusiasm in investigating HS-WBRT in the hope of providing clinical evidence to how it may be less detrimental on cognitive functions and the patients' QoL [11,28]. If this theory is correct, a re-assessment of risks and benefits of PCI is necessary in diseases in which the BM rate is considered high but in which PCI is up to date reluctantly used (e.g., in NSCLC) due to potential treatment-related toxicity. HS-WBRT may however bear the risk of missing micrometastases and thereby undertreating cancer patients. Recent studies described the hippocampus and limbic circuit to be a rare site of BM [29,30], but did not discriminate between the *center* of a mass (CoM) which can be seen as the initial focal point of metastatic settlement and the *border* of a mass. We propose that this distinction is necessary to comprehensively assess the risk of undertreating patients with HS-WBRT. We also aimed to explore the magnitude of relapse risk in the spared region surrounding the hippocampus due to delivering sub-therapeutic dose to it.

Material and methods

Patient selection

We retrospectively analyzed 100 randomly selected patients with BM of various cancers that were being treated at the Department of Radiation Oncology of the Medical Centre Mannheim between 2008 and 2011. An exclusion criteria was pre-treatment (of any kind) for BM. There was no cut-off for the total number of metastases found in a single patient.

Mapping of metastases

For each patient, T1-weighted, gadolinium contrast-enhanced axial MRIs were registered into the treatment planning system Oncentra MasterPlan® (Nucletron BV, Veenendaal, The Netherlands) and all metastases found were contoured together with both hippocampi according to the RTOG 0933 hippocampal atlas [31]. The MRIs were saved as Digital Imaging and Communication in Medicine (DICOM) files, transferred to another computer and reconverted. We calculated the distance in mm from the center of mass (CoM) of each metastasis to the closest of both hippocampi using the computer program MATLAB® (MathWorks, Natick, MA, USA). For each primary tumor entity, a heat map was generated by normalizing the patient's MRIs to the MRI of a healthy brain. The individual brains were realigned in order to remove "head tilt" related effects. We normalized each patient brain without the BM to a standard brain template which was provided by the Statistical Parametric Mapping software SPM8© (Wellcome Trust Centre for Neuroimaging at UCL, London, UK). The resulting normalization information from the SPM8© software was applied to the BM mask of the individual MRIs as well. We interpolated the patient brain images to the same resolution as the standard brain template. By accumulating the metastasis occurrence for each voxel of the normalized MRIs we generated a heat map of all patients and heat maps for each primary tumor entity.

Treatment planning

We created hippocampal sparing IMRT plans for 10 randomly selected patients with Monaco 3.0 (Elekta AB, CMS software, St. Louis, USA). All plans were calculated following the dose constrains in the RTOG guideline [32] to a dose of 30 Gy in 10 fractions. The technique used consisted of eight volumetric modulated arcs (VMAT) at four table positions, two full arcs (360°) at 0° table position and six partial arcs (140°) at 45°, 90° and 315° table position. This approach resulted in very steep dose gradients around the spared hippocampal avoidance volumes with satisfactory coverage and homogeneity to the PTV while maintaining acceptable delivery time efficiency. The longitudinal dose distribution from the inside of the hippocampi (−0.2 cm) to a 0.25 cm distance was established based on calculations performed with the Monaco software. For each dose at a corresponding distance d the EQD2 using an α/β ratio of 10 Gy ($EQD2_{\alpha/\beta 10}$, LQ-model) was calculated and a dose–distance relation fitting curve using Microsoft Excel was established.

Calculation of the risk of brain metastases after PCI

We focussed on SCLC and NSCLC, for which dose–response ratios are well described from large randomized studies that investigated the benefit of PCI. For SCLC, data were provided in the meta-analysis of Aupérin et al. [33] as well as additional data from Le Péchoux et al. [34] and Slotman et al. [35]. For NSCLC, we used data from Gore et al. [10], Cox et al. [36], Umsawasdi et al. [37], Russell et al. [38], Jacobs et al. [39], Stuschke et al. [40] and Pöttgen and colleagues [9]. For each dose applied in a study, we calculated the corresponding $EQD2_{\alpha/\beta 10}$ (LQ-model) and plotted it against the associated/reported relative risk (RR) for BM. Dose–response curves were fitted by a logistic function using the non-linear modeling function of the JMP Statistical Discovery® Software (SAS Institute GmbH; Böblingen, Germany).

Results

The study presented here aimed to establish a model that allows estimating the additional risk introduced by sparing the hippocampus during WBRT (Supplementary Fig. 1a).

Collective

A total of 856 BM were contoured in 100 patients, with the numbers of metastases per patient ranging from 1 to 116. The male-to-female ratio was balanced with $n = 57$ male and $n = 43$ female patients. The mean age was 64 (range: 44–84) years for men and 63 (47–85) years for women (Supplementary Fig. 1b). In male patients, the most common primary tumors were NSCLCs ($n = 25$), followed by malignant melanomas MM; ($n = 13$), SCLCs ($n = 6$), renal cell carcinomas ($n = 4$), colorectal cancers ($n = 3$), cancers of unknown primary (CUP; $n = 3$), adenocarcinomas of the esophago–gastric junction (AEG; $n = 2$) and prostate cancers ($n = 1$). In female patients, BM most often originated from breast cancers ($n = 13$), followed by NSCLCs ($n = 11$), melanomas ($n = 6$), SCLCs ($n = 5$), renal cell carcinomas ($n = 2$), ovarian cancers ($n = 2$), mediastinal carcinoids ($n = 1$), not-specified lung cancers (LC-NOS; $n = 1$), CUPs ($n = 1$) and AEGs ($n = 1$).

Gross locations of metastases

BM were seen to be non-homogenously distributed with a preference for the frontal lobe (26% of all BM), the cerebellum (26%) and the parietal lobe (20%, Supplementary Table 1). We also noted that metastases derived from NSCLC and MM were in average slightly larger than those arising from SCLC and breast cancer (average size of NSCLC metastasis: $3.9 \pm 12.3\ cm^3$; MM: $2.5 \pm 8.9\ cm^3$; SCLC: $1.9 \pm 8.9\ cm^3$; breast cancer: $2 \pm 6.5\ cm^3$; Supplementary Fig. 2). The apparently high number of metastases in the cerebellum has been also observed in previous mapping studies [26,41].