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Original Research Article

Significant tumor shift in patients treated with stereotactic radiosurgery for brain metastasis

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ABSTRACT

Introduction: Linac-based stereotactic radiosurgery (SRS) for brain metastases may be influenced by the time interval between treatment preparation and delivery, related to risk of anatomical changes. We studied tumor position shifts and its relations to peritumoral volume edema changes over time, as seen on MRI.

Methods: Twenty-six patients who underwent SRS for brain metastases in our institution were included. We evaluated the occurrence of a tumor shift between the diagnostic MRI and radiotherapy planning MRI. For 42 brain metastases the tumor and peritumoral edema were delineated on the contrast enhanced T1weighted and FLAIR images of both the diagnostic MRI and planning MRI examinations. Centre of Mass (CoM) shifts and tumor borders were evaluated. We evaluated the influence of steroids on peritumoral edema and tumor volume and the correlation with CoM and tumor border changes.

Results: The median values of the CoM shifts and of the maximum distances between the tumor borders obtained from the diagnostic MRI and radiotherapy planning MRI were 1.3 mm (maximum shift of 5.0 mm) and 1.9 mm (maximum distance of 7.4 mm), respectively. We found significant correlations between the absolute change in edema volume and the tumor shift of the CoM ($p < 0.001$) and tumor border ($p = 0.040$). Patients who received steroids did not only had a decrease in peritumoral edema, but also had a median decrease in tumor volume of 0.02 cc while patients who did not receive steroids had a median increase of 0.06 cc in tumor volume ($p = 0.035$).

Conclusion: Our results show that large tumor shifts of brain metastases can occur over time. Because shifts may have a significant impact on the local dose coverage, we recommend minimizing the time between treatment preparation and delivery for Linac based SRS.

Introduction

Brain metastases occur in approximately 10–30% of all cancer patients with solid tumors [1]. Different treatment modalities are available, including surgery, whole brain radiation therapy (WBRT), stereotactic radiosurgery (SRS) and best supportive care. Choice of treatment is based on patient related factors and tumor characteristics and is to be determined in multidisciplinary teams [2]. SRS is often the treatment of choice for patients with smaller tumors, limited number of lesions, and for patients with unresectable tumors or who are medically inoperable. The maximum tumor volume and the number of lesions that can safely be treated simultaneously with SRS is a subject of investigation [3,4]. Different systems are used for SRS, such as the Gammaknife®, Cyberknife® and Linac based systems [5]. Many institutes apply Linac-based SRS, which requires a robust positioning of the skull in SRS frames or image guidance based on CBCT with skull focused registration [6]. However, the variation of tumor location in time and the possible influence of steroids hereon are unknown. For Linac-based SRS the time between the pretreatment MRI and the actual treatment delivery may take several days in which tumor shifts can occur resulting in suboptimal target coverage.

Patients with brain metastasis often experience neurologic symptoms triggered by the tumor mass, and often by the surrounding edema. For patients with significant or symptomatic peritumoral edema, steroids (i.e. dexamethasone) are commonly

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prescribed. Although the mechanism is not entirely clear, studies show a decrease in radiographic edema after the administration of dexamethasone [7]. We hypothesize that a change (increase or decrease) of edema may have an impact on the tumor position.

To our knowledge, there is currently no literature available about the extent of tumor shifts in patients with brain metastases. In this work, we used the time between the diagnostic MRI and the radiotherapy planning MRI to study the changes in tumor volume, spatial location and edema volume as function of time.

Materials and methods

Patients

For this study we included 26 patients receiving a single fraction of SRS treatment for brain metastasis between October 2015 and February 2016 at the Netherlands Cancer Institute (NKI). Patients were excluded when the patient had previous WBRT, when the SRS was given to surgical cavity (i.e. post-resection), when the tumor location was not in the brain parenchyma or if one of the MRI sequences was not available. Information about steroid use and systemic cytotoxic treatment was retrospectively retrieved from the electronic patient file and binary scored (i.e., yes/no).

Imaging

The MR examination included a Fluid-attenuated inversion recovery (FLAIR) sequence and a T1 weighted sequence with contrast (T1w + c) for both the diagnostic MRI (MRD) protocol as for the radiation treatment planning MRI (MRRT) protocol. For 14 patients the MRD was performed at the NKI and 12 patients were referred from another hospital (with a MRD executed at the referring hospital). There were 8 different referring hospitals. Slice thickness of the MRD images varied from 0.9 to 6 mm for the T1w sequence and 4.4 to 6 mm for the FLAIR sequence. For the MRRT the slice thickness was 1 mm and 3.3 mm for the T1w + c and FLAIR sequence, respectively. The contrast agent (Dotarem, Guerbet, France, 15 ml) was injected using an automated injection pump (Spectris Solaris, Medrad Inc.). Details about chemical shift artifacts, deviations in localization due to gradient non-linearity and slice thickness are given in the Supplementary data (Table S1).

Registrations and delineations

In house developed software was used for registration and volume determination. Both the MRD and MRRT images were skull based rigidly registered with the planning CT scan (CTRT). Both the gross tumor volume (GTV) and edema were delineated by a single observer (EH) and reviewed by an experienced CNS radiation oncologist (GB).

The tumor was contoured on the T1w + c, and the peritumoral edema was contoured on the FLAIR sequence (Fig. 1).

For all delineations, the volume and volume change between MRD and MRRT were determined. To calculate the edema volume, the tumor volume was excluded by subtracting the intersection between the edema and the tumor.

Tumor shift

The magnitude of the tumor shifts was evaluated by two parameters: the displacement of the Centre of Mass (D^{CoM}) of the tumor on the MRD and MRRT (with CoM representing the central point of the tumor within its contour) and by the maximal perpendicular distance between the two tumor delineations on the MRD and MRRT ($D^{MRD\text{-}MRRT}$; Fig. 2).

For the $D^{MRD\text{-}MRRT}$, the delineation on MRD was used as the reference delineation and the delineation on MRRT as the target delineation. The delineations were automatically triangulated and resampled to 1 mm point spacing on the reference delineation. The distance perpendicular on the resample point of the reference scan towards the target scan was then automatically measured (Fig. 1).

$D^{MRD\text{-}MRRT}$ was corrected for tumor growth by subtracting the difference in radius between the two tumor contours from the maximum distance (assuming a spherical tumor with radius $r = (V/(^4/_3\pi))^{1/3}$ and isotropic growth).

To determine the influence/dependence of the tumor location on tumor shifts, the shortest distance of the tumor surface to the

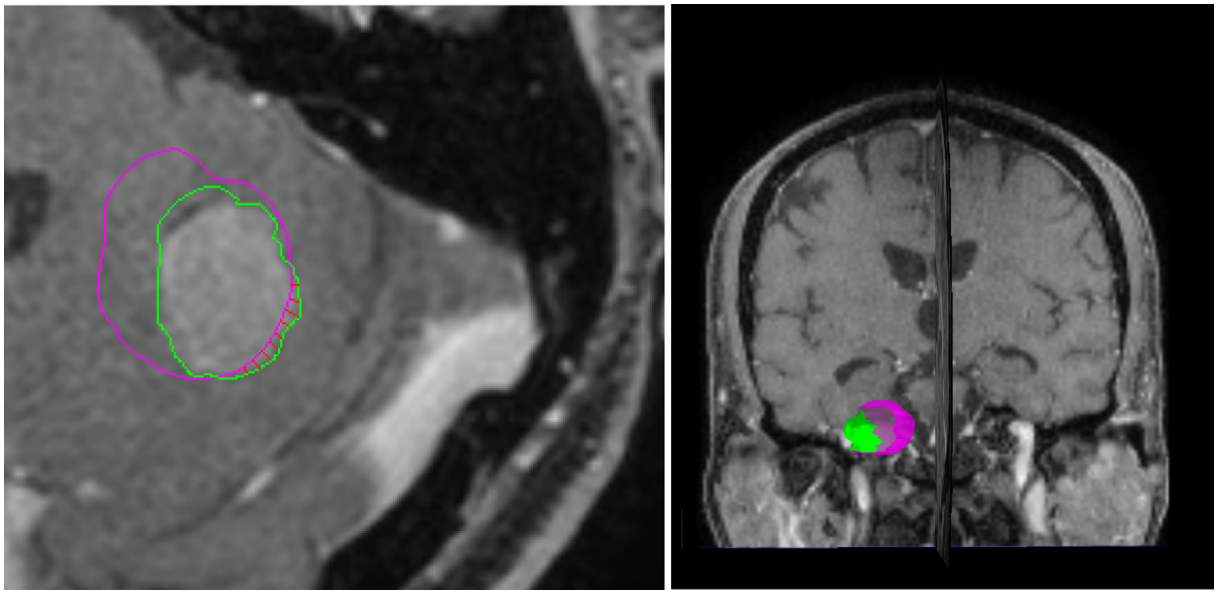

Fig. 1. Example of patient who received the day before the MRD one gift of dexamethasone and continued dexamethasone intake hereafter (2dd4mg). The MRRT was made 8 days later and the tumor contours overlaid on sagittal (left) and coronal (right) view of the MRRT T1w + c image. The pink contour is the reference contour from the MRD examination, whereas the green contour is delineated on the data from the MRRT examination. The red lines in the left image represent the positive distances between the two tumor surfaces. The right image shows a 3-dimentional depiction of these tumor contours. Here, the MRRT tumor volume which is shifted outside the MRD tumor volume is indicated in green. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

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