Interval between planning and frameless stereotactic radiotherapy for brain metastases: are our margins still accurate?

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Abstract

Background and Purpose: Advances in intracranial stereotactic radiotherapy (SRT) have led to dramatically reduced planning target volume (PTV) margins. However, tumour growth between planning and treatment may lead to treatment failure. Our purpose was to assess the kinetics of tumour growth before SRT for brain metastases.

Material and Methods: this retrospective, monocentric study included all consecutive patients (pts) treated for brain metastases secondary to melanoma (ML) and non-small cell lung cancer (NSCLC) between June 2015 and May 2016. All pts underwent diagnostic brain imaging and a radiotherapy planning MRI, where GTV was delineated. Linear and exponential models were used to extrapolate a theoretical GTV at first day of treatment, and theoretical time to outgrow the PTV margins.

Results: Twenty-three ML and 31 NSCLC brain metastases (42 pts, 84 brain imaging scans) were analyzed. Comparison of GTV at diagnosis and planning showed increased tumour volume for 20 ML pts (96%), and 22 NSCLC pts (71%). The shortest time to outgrow a 1 mm margin was 6 days and 3 days for ML and 14 and 8 days for NSCLC with linear and exponential models respectively.

Conclusion: Physicians should bear in mind the interval between SRT planning and treatment. A mathematical model could screen rapidly progressing tumours.

Keywords: brain metastases, stereotactic radiotherapy, margins, interval

Importance of the Study

In a context of high precision and reduced margins, our study aims to assess the interval between planning and stereotactic radiotherapy of brain metastases, possibly responsible for undertreatment of tumours. We estimated tumour growth using linear and exponential models, in order to calculate a theoretical time to outgrow the PTV margins. This extrapolation has never been made. We found that tumour growth kinetic depended predominantly on histology and could be aggressively rapid. The present work underlined the necessity of personalizing treatment. Physicians should keep in mind time to treatment while reducing margins.

Introduction

Prognosis for non-small-cell lung cancer (NSCLC) and metastatic melanoma (ML) has recently dramatically improved thanks to targeted therapy and to immunotherapy [1]. But, the risk of spread to the central nervous system remains high with occurrence of brain metastasis for 40 to 60% of patients (pts) with metastatic ML. [2] On the other hand, more than 20% of lung cancers are associated with brain metastases at cancer diagnosis. [3] Hypo-fractionated SRT is considered to be a standard therapeutic option for pts with 1 to 5 brain metastases. [4] SRT provides a high gradient dose between tumour and surrounding tissue, and reduced PTV margins are used to spare the adjacent brain tissue. Therefore, to accurately delineate GTV, a fusion of magnetic resonance imaging (MRI) with the planning Computed Tomography scan (CT scan) is recommended. However, tumour growth between the planning CT scan and the first fraction of SRT might be responsible for an inaccurate coverage of the tumour, which may lead to treatment failure. Our purpose was to assess the kinetics of tumour growth between diagnostic imaging and planning MRI for brain metastases secondary to ML and NSCLC. We also evaluated, using mathematical models, the extrapolated size of the tumour at first day of treatment, and consequences in terms of inaccurate coverage of the tumour possibly leading to treatment failure. In addition, we estimated the theoretical interval for each tumour to outgrow the PTV margin.

Material and Methods

Patients. This retrospective, monocentric study included all consecutive pts treated with SRT for brain metastases secondary to ML or NSCLC between June 2015 and May 2016 at Bordeaux University Hospital, France. The eligibility criteria were: age > 18 years, histologically proved ML or NSCLC, and brain imaging data finding 1 to 5 brain metastases. Only non-resected metastases were analyzed. Pts with previous craniotomy were eligible if they had a new brain metastasis. Diagnosis of brain metastases was done on CT or MRI imaging and reviewed for confirmation by a multidisciplinary

board, including radiation oncologists, medical oncologists, neurosurgeons, and radiologists. Imaging consisted of cerebral CT scan or MRI with a contrast enhancement sequence. Pts with only one imaging scan available or with intra-tumoural bleeding were excluded. The institutional review board approved the study and the need for written informed consent was waived.

Radiation therapy. For SRT planning, all pts underwent a high-resolution, 3-dimensional T1-weighted gadolinium-enhanced MRI sequence, reconstructed every 1.0 mm. A CT scan was carried out for radiation therapy planning using a slice reconstruction every 1.0 mm and a field of 35 cm. A thermoplastic mask was used for immobilization. The Eclipse treatment planning system (Varian Medical Systems, CA version 13.5) was used to co-register the MRI and CT scan and to segment structures: optics, brainstem, spinal cord, retinas, brain, pituitary gland, GTV and PTV. Margins from GTV to PTV used in our institution were 2 mm. Dose was prescribed in order to ensure a minimal coverage of 90% of the PTV before validation of the treatment planning. SRT doses were 1 fraction of 20 Gy, 3 fractions of 9, 10 or 11 Gy or 5 fractions of 5 Gy depending on tumour size. Treatment was delivered using 6MV photons, by Elekta [T.M.] Versa HD [T.M.] associated with Fraxio [T.M.] system for stereotaxy. Exatrac [T.M.] system was used to adapt setting of the patient using a 6D rotation table for treatment.

Assessment. Baseline patient characteristics included KPS, RPA status, steroid treatment, number and location of brain metastases. Brain imaging consisted of MRI with gadolinium-enhanced sequences, or CT scan with intravenous contrast. Time at brain metastasis diagnosis, radiotherapy planning imaging and first day of treatment were recorded. The follow-up examinations consisted of an MRI scan every 3 months for 1 year and every 6 months thereafter. The primary endpoint was to assess the kinetics of tumour growth of brain metastases between diagnostic imaging and radiotherapy planning imaging, and to extrapolate the theoretical tumour volume at the time of SRT. Both types of imaging were implemented using the Eclipse system version 13.5. GTV was delineated on the basis of contrast enhancement by a radiation oncologist experienced in the treatment of brain metastases by SRT. GTV1, GTV2 and GTV3 corresponded respectively to GTV at diagnosis, on the planning imaging and the estimated volume at first day of treatment with linear extrapolation or exponential extrapolation.

The secondary endpoints were to assess tumour control and radiation induced toxicities during follow-up. Toxicity was scored according to the common terminology criteria for adverse events (CTACAE v4.0). A progressive disease was defined as a radiological progression without radio-necrosis criteria in accordance with the Response Assessment in Neuro-Oncology Brain Metastases (RANO-BM) working group. Radio-necrosis was diagnosed according to imaging features, such as increased contrast enhancement, non-progression of lesion over 4 months and reduced perfusion on dynamic MRI sequences.

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Statistical analysis. Linear extrapolation and exponential extrapolation were used to estimate the t minimum theoretical time allowing tumour diameter to increase by more than 4 mm (T-4mm) and more than 2 mm (T-2mm) from radiotherapy planning imaging. Univariate analysis was carried out on patient characteristics to analyze the predictive parameters of radio-necrosis

Results

Patients. Out of 103 pts treated for brain metastases by SRT between June 2015 and May 2016, 21 were treated for ML and 21 for NSCLC. Two pts were excluded because of lack of imaging data. The median age was 71.4 years old for ML pts (range 25-92) and 67.7 years old for NSCLC pts (range 48-82). Only 1 patient with ML was RPA class 1. Other patients were RPA class 2 for 17 ML pts (81%) and 16 NSCLC pts (76%) and class 3 for 3 ML pts (14%) and 5 NSCLC pts (24%). A systemic treatment was given at diagnosis for 14 ML pts (67 %) and 7 NSCLC pts (33%), including immunotherapy for 6 ML pts, targeted therapy for 5 ML pts and 1 NSCLC pt and conventional chemotherapy for 3 ML pts and 6 NSCLC pts. Brain metastases in ML or NSCLC pts were synchronous to ML or NSCLC diagnosis respectively in 3 and 11 cases, or metachrone in 18 and 10 cases, with a median time of 4.8 years [1- 40 years] and 2.1 [1 -9.5 years] for ML and NSCLC respectively (Table 1).

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Metastases. A total of 23 ML and 31 NSCLC metastases were analyzed from 42 pts. One NSCLC patient with 1 metastasis was excluded due to tumour bleeding. Location was supra-tentorial in 38 cases, cerebellar in 3 cases and mesencephalic in 1 case. Six pts had already received SRT for previous other brain metastases. One patient received previous whole-brain radiotherapy (30 Gy/10 fractions). All metastases analyzed had not been previously irradiated. Radiotherapy was delivered according to a monofraction scheme for 5 ML and 3 NSCLC metastases, 3-fraction scheme for 15 ML and 25 NSCLC metastases, or 5-fraction scheme for 3 ML and 2 NSCLC metastases (Table 1).

Assessment. Eighty-four brain imaging scans (67 MRI, 17 CT-scan) were analyzed. Comparison of imaging between diagnosis and radiotherapy planning showed increased tumour volume for 22 ML and 22 NSCLC metastases; stability for 1 ML and 7 NSCLC metastases, bleeding inside one NSCLC metastasis (excluded) and 1 metastasis volume decrease (Figure 1).

Median time between brain imaging at diagnosis and radiotherapy planning imaging was 24 days for ML and 29 days for NSCLC. Median time between radiotherapy planning imaging and first day of radiotherapy was 19 days for ML and for NSCLC. Median time between brain imaging at diagnosis and first day of treatment was similar for ML and NSCLC (Table 2). For each patient, tumour growth was calculated between diagnosis and treatment planning, and extrapolated between planning and SRT (Figure 2). Median GTV1 was 0.5 cm^3 for ML and 0.4 cm3 for NSCLC; median GTV2 was 1.5 cm^3 for ML and 0.8 cm^3 for NSCLC. GTV3 at first day of treatment for ML were significantly increased than NSCLC with linear and exponential model (respectively 2.1 cm^3 versus 1.2 cm^3 and 4.3cm^3 versus 1.6cm^3, p=0.05) (Figure 3).

The shorter T-4mm was 15 days or 6 days for ML and 32 or 15 days for NSCLC with respectively the linear or exponential models. Real time from planning imaging to first day of treatment was then compared to the theoretical time T4mm. Linear and exponential models showed respectively 2 ML

and no NSCLC and 11 ML and 1 NSCLC expected to outgrow the PTV margins on the first day of treatment. These metastases were potentially undertreated.

The shortest T-2mm was 6 days or 3 days for ML and 14 or 8 days for NSCLC with respectively the linear or exponential models. Twelve ML and 3 NSCLC were expected to outgrow the PTV margins during the first day of treatment according to the linear model whereas the exponential model predicted the same concern for 14 ML and 7 NSCLC.

Follow-up. Median follow-up was 12 and 17 months for ML and NSCLC pts respectively. Brain metastases were controlled at the end of the follow-up for all except two ML cases. One brain metastasis had a tumour bleeding 16 months after SRT. Four pts died from extracranial cancer progression (ML: 2 pts, NSCLC: 2 pts), and three ML pts died from new brain metastases. At 3 months, out of 39 patients alive, 11 had at least one new brain metastasis (ML: 5 pts, NSCLC: 6 pts). Acute toxicity included only one Grade 1 asthenia during treatment. Radio-necrosis was observed for 8/21 ML (36%) and 8/22 (36%) NSCLC, asymptomatic for 15 metastases and symptomatic for only one pt. Out of 8 (6 ML, 2 NSCLC) pts with steroids prescribed due to brain metastasis neurological symptoms, 3 (1 ML, 2 NSCLC) experienced radio-necrosis. 5 additional pts required steroids after radiation for symptomatic radio-necrosis. No effect of steroids on the tumor volume was observed. None of the patients with radio-necrosis received bevacizumab. No predictive parameter for radio-necrosis was found in univariate analysis.

Discussion

SRT is now considered to be the standard treatment for 1-3 non-resectable brain metastases and has dramatically changed the management of brain metastases. [5] Major advances in imaging and radiotherapy techniques enable high doses to be delivered to focal cancers, with reduced margins. [6] Current trends continue to focus on improvement of SRT accuracy. Nevertheless, concerns may be raised about potential risks of treatment failure due to tumour growth during the interval between treatment planning and initiation of SRT. This is the reason why we assessed tumour growth before

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treatment of ML and NSCLC brain metastases and the risk of inaccurate coverage of the tumour relating to time before SRT.

Radio-necrosis was observed in 8 of 21 irradiated MLs, symptomatic only in one case. Incidence of radio-necrosis is estimated from 10 to 25% [9, 10]. Using imaging-based diagnosis, Minniti et al. reported a 24% incidence of RN (14% symptomatic, 10% asymptomatic) [9]. Renal carcinoma, lung adenocarcinoma (ALK rearrangement specifically), HER2-amplied breast cancer, and BRAF V600 wild-type melanoma are suggested to present a higher risk of radio-necrosis [10]. These considerations could explain the present high rate of radio-necrosis. No predictive parameter was found in our study. [9] Our inclusion criteria excluded 2 rather specific situations of ML: bleeding before treatment that lead to cancellation of SRT and occurence of new ML or NSCLC between diagnosis and radiotherapy planning MRI. Indeed, delineation of bleeding tumour volume remained controversial and tumour evolution could not be predicted with linear or extrapolation model for this type of metastasis. Bleeding metastases are currently managed by neurosurgeons.

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Time from diagnosis to planning may result from the requirements of systemic treatments. This interval may also be explained by the poor availability of the SRT technique in some centres, and to the period before referring the patient to a stereotactic radiation unit. To our knowledge, the interval between diagnosis and initiation of SRT has not yet been assessed. In addition, the interval between radiotherapy planning and first day of treatment may differ between centres due to specific local organization. [7]

Two series reported the interval between treatment planning and radiosurgery for brain metastases. Seymour reported 82 pts with heterogeneous brain metastases. Time from radiation oncologist consultation to radiotherapy planning MRI was 28 days. Time from planning MRI to first day of treatment was 11 days. In most of the cases, diagnosis of brain metastases was established before the radiation oncologist consultation. Hence, our delays were roughly similar. In previous publications, local failure-free progression dramatically decreased when time from planning MRI to treatment was less than 14 days. [7] Garcia et al. reported a second series of 256 pts treated for brain

metastases with fixed frame radiosurgery (SRS). The mean time between diagnosis of metastases and MRI on day of treatment was 25 days. In this technique of fixed frame SRS, the treatment planning MRI was carried out the same day as the treatment. Growth of brain metastases was observed in 30% of patients, particularly for melanoma. However, local failure-free progression was not compromised when growth of brain metastases was observed before treatment planning. [8]

Our study showed a tumour progression for 82 % of brain metastases. As expected, time to outgrow a 1mm PTV margin (=T2mm) was short and clinicians should be careful with intervals when using 1mm margin from GTV to PTV. The choice of extrapolation model may lead to over or under estimation of the size of the tumour on the first day of treatment. No patient underwent brain imaging on the first day of treatment in order to validate our models. A prospective study with imaging on the first day of treatment would help statisticians and physicians to identify the best model for prediction of metastasis evolution. Interestingly, among the 2 patients who experienced a local failure, one was considered at risk of undertreatment according to our models. Time from planning imaging to treatment may lead to underestimation of the real GTV.[10] The present series highlights the need to reconsider our current management. To overcome this interval, one option could be to adapt the margin to the time to treatment. However, this may be considered non-ethical. [9] The other option is to reconsider the planning of the radiotherapy process.

Interestingly, we found a difference in tumour growth between ML and NSCLCC metastases. Initial median volumes were similar (0.50 and 0.45 cm3 respectively for ML and NSCLC), whereas median GTV2 was higher in melanoma (1.5 cm3) than in lung cancer (0.8 cm3). The slower tumour growth in lung cancer explained the 1 NSCLC with a long interval between diagnosis and treatment planning because of diagnostic doubt. This study highlighted that the heterogeneity between cancer types needs to be considered in brain metastases. Other studies will be necessary to identify rapid progression brain metastases that should be the treated earlier with SRT or surgery. On the other hand, brain metastases predicted to be slowly progressive could be treated with local or systemic treatment. [11]

Conclusion: Physicians should bear in mind the interval between SRT planning and treatment, especially using a 1mm margin. Growth of brain metastases is highly heterogenic between cancer types. A mathematical model could help to screen rapidly progressive tumours, in order to individualize treatment.

Compliance with Ethical Standards:

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Captions for all illustrations

Figure 1. Brain metastasis evolution from diagnostic imaging (A, C, E, G) to treatment planning imaging (B, D, F, H).

Figure 2. Evolution of brain metastases in ML and NSCLC. J0 corresponds to planning cerebral imaging, with corresponding GTV (GTV2) on Y axis. Negative part was time at diagnostic imaging for each brain metastasis with assessment of corresponding GTV (GTV1) on Y axis. Positive part was time/interval to SRT, associated for each metastasis to the predictive GTV (GTV3) at time to treatment (with linear extrapolation).

Figure 3. Box plots illustrative of GTV evolution at diagnosis (GTV1), at treatment planning (GTV2) and predictive of the first day of radiation (GTV3) for ML and NSCLC brain metastases.

Table 1. Characteristics of patients treated with stereotactic radiation for brain metastases secondary to ML or NSCLC.

Table 2. Characteristics of ML and NSCLC metastases time to treatment and evolution of tumour volume.

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