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Patterns of distant brain recurrences after radiosurgery alone for newly diagnosed brain metastases: Implications for salvage therapy

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ABSTRACT

Introduction: Single modality radiosurgery (RS) is an established treatment option for patients with brain metastases (BM) with the aim of achieving optimal local control while avoiding toxicity from whole brain radiotherapy (WBRT). Published studies generally lack detailed data on distant brain recurrence (DBR) rates and characteristics. This study describes the patterns of DBR and consequences for salvage treatment in a group of patients treated with RS alone for 1–3 BM.

Materials and methods: Between 2002 and 2012, 443 patients were treated with RS alone in doses ranging 15–24 Gy in 1–3 fractions. Patient selection for RS was performed using triple dose gadolinium-enhanced MRI scans, obtained with slice distance of 2 mm (until 2008), 1.5 mm (2008–2012), and of 1 mm (from 2012). During follow-up, a DBR was observed in 147 patients, but in 20 of these patients (14%) these "new lesions" could retrospectively be seen on the planning MRI scan. These missed metastases had a median size of 2 mm, and in order to study real DBR patterns, these patients were excluded from analysis.

Results: Actuarial DBR rates at 6, 12 and 24 months in the remaining 423 patients were 21%, 41% and 54%, respectively, with a median time to DBR of 5.6 months. In 42% of DBR, a single new lesion was seen, in 70% there were $\leqslant$3 new lesions. Median diameter of the DBR was 6 mm; 97% of lesions were $\leqslant$30 mm. Salvage therapy was delivered in 82% of DBR patients, consisting of WBRT (46%), repeated RS (27%), or systemic treatment (9%). A RPA classification system (DBR-RPA), based on WHO performance status and interval between initial RS and diagnosis of DBR, was developed to estimate life expectancy after the development of DBR, which can be used to guide salvage therapy.

Conclusions: In this study of patients treated with RS alone, only 25% of treated patients needed salvage treatment for DBR, and ultimately only 18% of all patients underwent WBRT at any time during follow-up. A three-monthly MRI follow-up scheme identifies DBR at an early stage with respect to size and number of lesions, and most patients were asymptomatic at radiological diagnosis.

Radiosurgery (RS) is an established treatment modality for patients with a limited number of brain metastases (BM) in a good physical condition [1]. After single modality RS for oligometastatic BM, there is a substantial risk of developing distant brain recurrences (DBRs) of 52% up to 76%, which can cause neurologic morbidity or mortality [2,3]. High resolution imaging is useful to detect DBR at an early stage [4]. The incidence of DBR can be reduced by combining RS and whole brain radiotherapy (WBRT), but the randomized EORTC 22952–26001 study has confirmed previous reports showing that the addition of WBRT does not prolong overall survival in patients with up to 3 BM treated with RS or surgery [3,5]. Characteristics on DBR and salvage treatments have not been reported in detail.

The frequency of follow-up after RS for BM remains a matter of debate. The ASTRO guidelines for follow-up of these patients after RS do not specify the frequency and imaging protocol [6]. Within the EORTC 22952–26001 study, patients were imaged at every three month follow-up with MRI. At our center, MRI scans are similarly performed at 3 monthly intervals during the first 2 years, and every half year thereafter, as long as this is indicated by the clinical condition with consequences for salvage therapy.

This study was performed to assess the characteristics of DBR with respect to number, size and timing after RS alone, detected with such systematic follow-up, and to describe the frequency of salvage options used in a clinical setting.

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Materials and methods

Radiosurgery

In our institutional database, baseline characteristics, treatment details and follow-up data of newly diagnosed BM patients treated with Linac-based RS have been collected retrospectively [1]. According to our protocol, patients with 1–3 BM are eligible for RS as a single modality. Patient selection for RS alone was performed using triple dose gadolinium-enhanced MRI scans (1.5–2 Tesla), prior to 2008 obtained with 2 mm slice distance, from 2008 to 2011 with 1.5 mm slice distance, and from early 2012 with 1 mm slice distance. RS has been delivered using 5 dynamic conformal arcs on a Novalis (2002–2008) or Novalis TX (2008 onwards) linear accelerator (BrainLAB AG, Feldkirchen, Germany). Patient fixation was performed using the relocatable Gill–Thomas–Cosman frame (2002–2008), and as of 2008 using the BrainLAB's frameless mask system (BrainLAB, Feldkirchen, Germany). The RS target volumes consisted of the gross target volume contoured on the planning MRI with a 1 mm margin to correct for potential setup-inaccuracies. RS was prescribed using a 'risk-adapted' fractionation, with lesions $\leqslant 7.5\ cm^3$ receiving 21 Gy prescribed at the encompassing 80% isodose line. For lesions measuring 7.5–25 cm^3 or BM that were adjacent to the brainstem, the prescription dose was 18 Gy at the 80% isodose. For the largest lesions with volumes exceeding 25 cm^3, a single fraction of 15 Gy or 3 fractions of 8 Gy, both prescribed at the 80% isodoses were used. Follow-up included clinical visits and MRI scans at three-monthly intervals during the first two years of follow-up, and every half year thereafter as long as clinically indicated. Additional imaging was performed as indicated by neurological symptoms.

Follow up MRIs were co-registered with pretreatment planning MRIs to assess whether early DBRs had already been visible prior to RS in retrospect. The maximal diameter of the largest DBR at first diagnosis was determined on T1 gadolinium-enhanced axial MRI slices. The medical chart of the patient was consulted to determine if a patient was symptomatic or asymptomatic at the time of diagnosis of DBR. Moreover, considerations regarding the application and outcome of salvage treatments were noted.

Statistics

Survival was calculated from the date of RS, survival after DBR was calculated from the date of the MRI on which the DBR was diagnosed. Follow-up was calculated with the reverse Kaplan–Meier method [7]. Univariable Log-rank test and multivariable Cox regression analysis were used to determine risk factors for death after the diagnosis of DBR. Based on 2 significant risk factors for survival after DBR, a recursive partitioning analysis was done to divide the population into three groups: favorable, intermediate, and poor survival. All statistical analyses were performed using SPSS (version 19.0, IBM), using two-sided statistical testing at the 5% significance level.

Results

Between 2002 and 2012, a total of 443 patients with 595 newly diagnosed BM were treated with RS as a single modality. A total of 147 patients with DBR were identified. However, in 20 patients these "DBR" could be seen in retrospect on the stereotactic planning MRI scan. These missed metastases had a median size of 2 mm, and in order to study real DBR patterns, these patients were excluded from analysis. The remaining 423 patients had a median age of 62 years (range 16 up to 89 years) with the majority of patients (59%) having primary lung cancer. In total 271 (64%) of patients underwent RS for a single BM, 132 (31%) for two lesions and only 20 (5%) underwent RS for 3 lesions [1].

In the 423 analyzed patients, the median overall survival (OS) was 7.9 months, with OS rates of 58% and 15% at 6 and 24 months, respectively. The median follow-up duration was 29.7 months. A DBR was diagnosed in 127 (30%) of 423 treated patients. The median time from RS to development of DBR was 5.6 months (range 1.5–57.3 months), with actuarial DBR free survival rates of 79% and 46% at 6 and 24 months, respectively (Fig. 1). In a previous publication of this cohort of patients, a clinical nomogram was described for the prediction of DBR after RS [8].

At the time of DBR, the majority of patients (70%) had 1–3 new BM, with 42% presenting with only a single lesion (Fig. 2A). The median size of the largest new BM was 6 mm, with 77% of the patients having a new BM $\leqslant$1 cm, 92% $\leqslant$2 cm, and 97% $\leqslant$3 cm (Fig. 2B). Most DBRs were asymptomatic (65%) at the time of diagnosis; in 10% no record on the clinical status at the time of DBR could be found.

The median OS after diagnosis of a DBR was 6.1 months with OS rates of 25% and 7% at 12 and 24 months, respectively. In both univariate and multivariate analyses, the four characteristics that were predictive for survival at the time of diagnosis of DBR were WHO performance status, early occurrence of DBR (e.g. within 6 months after RS), diameter of the largest new brain metastasis, and the presence of extracranial metastases (Table 1).

Based on the above results, a recursive partitioning analysis (DBR-RPA) was developed for the prediction of OS after diagnosis of a DBR (Fig. 3). Patients with WHO performance status $\geqslant$2 were found to have the poorest prognosis with an OS of 3.4 months, i.e. DBR-RPA class III. At the next level, patients with WHO performance score 0–1 were divided with respect to the interval between the initial RS and the diagnosis of DBR. The most favorable subgroup (DBR-RPA class I) was patients with a long interval (i.e. $\geqslant$6 months) who had a median OS of 10.3 months. The intermediate DBR-RPA class II group with short interval between RS and DBR had a median OS of 5.4 months. The OS of the derived DBR-RPA groups was significantly different; ($p < 0.001$; Fig. 4). There appeared to be a balanced distribution of the DBR population over the prognostic groups, with 45 (35%) patients in DBR-RPA class I, 40 (32%) patients in DBR-RPA class II, and 42 (33%) in DBR-RPA class III.

Salvage therapy was eventually delivered in 104 patients (82% of DBR patients; 25% of all RS patients), consisting of salvage WBRT in 58 patients (46% of DBR patients; 14% of all patients), repeat RS in 34 patients (27% of DBR patients; 8% of all patients) or systemic

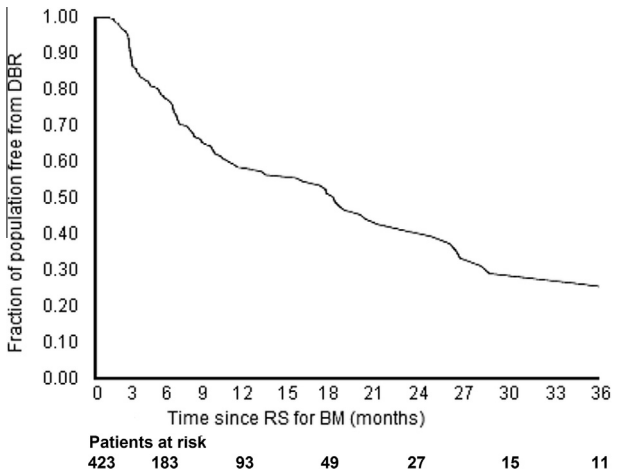

Fig. 1. Kaplan–Meyer analysis for risk of DBR after RS for BM ($N = 423$). *Legend:* DBR = distant brain recurrence, RS = radiosurgery, BM = brain metastases.