Outcome Evaluation of Patients with Limited Brain Metastasis From Malignant Melanoma, Treated with Surgery, Radiation Therapy, and Targeted Therapy

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■ OBJECTIVE: **The incidence of brain metastases from melanoma is increasing. Several effective treatment options are now available but what can be considered the optimal therapeutic strategy is not yet defined. We evaluated the outcome of patients with brain metastatic melanoma in terms of local control rate, brain distant progression, and overall survival.**

■ METHODS: **The present retrospective study includes only patients with limited brain metastases (≤4) who underwent surgery plus stereotactic radiosurgery (SRS), or SRS alone. Surgical resection was performed in patients with good Karnofsky performance score, single large brain lesions, controlled extracranial disease, and SRS alone in all other cases. Supramargical resection was performed in all patients. The prescribed radiotherapy doses were 24 Gy/1 fraction and 30 Gy in 3–5 fractions for lesions >2.5 cm. Clinical outcome was evaluated by brain magnetic resonance imaging performed 2 months after radiotherapy and then every 3 months.**

■ RESULTS: **From April 2011 to October 2015, 53 patients were treated. The median age was 54 years (range, 29–82 years). Most of patients had 1–2 brain metastases (86.8%). Twelve patients (22.6%) underwent surgical resection followed by SRS on the tumor bed, and 41 (77.4%) received SRS alone. The median follow-up time was 20.9 months (range, 5.7–61.3 months). The median, 1-, 2-, 3-year overall survival were 11.8 months, 47.2%, 28%, and 21.8%, respectively. Factors recorded as influencing survival were the number of brain metastases, the melanoma-specific graded prognostic assessment score, and BRAF mutated status.**

■ CONCLUSIONS: **Our data identifier a subset of patients with a more favorable outcome who could take advantage of a more aggressive local approach followed by targeted therapy.**

INTRODUCTION

Melanoma is the third most common cause of brain metastases (BMs) after lung and breast cancers.[1] The 5-year cumulative incidence of melanoma brain metastases (MBMs) is ≤10%, in approximately 20% of cases as the first appearance of disease, and about 45% of patients with metastases will develop BMs during the course of their disease.[2-5] Prognosis is poor with a median survival time and 1-year survival rate of 4–5 months and 10%–20%, respectively.[6,7] Although surgical resection followed by radiation therapy (RT) is the

Key words
- Brain metastases
- Local treatments
- Melanoma
- Radiosurgery
- Surgical resection

Abbreviations and Acronyms
BDP: Brain distant progression
BM: Brain metastase
CI: Confidence interval
GPA: Graded prognostic assessment
HSRS: Hypofrationated stereotactic radiosurgery
KPS: Karnofsky performance score
LC: Local control
MBM: Melanoma brain metastases
MRI: Magnetic resonance imaging
OS: Overall survival
RT: Radiotherapy
SRS: Stereotactic radiosurgery
WBRT: Whole brain radiation therapy

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mainstay treatment, this approach is usually offered to selected patients, with good performance status, a limited number of BMs, and controlled extracranial disease.[8,9] In a large Australian retrospective study, the investigators[6] showed improvement in median survival among patients treated with surgery (8.9 months) or surgery and postoperative radiotherapy (9.7 months) compared with RT (3.4 months) or supportive care alone (2.1 months). If on one side it is well established that surgical resection has to be aimed at complete excision to impact on local control, the optimal RT strategies are still debated. Whole brain radiation therapy (WBRT) has been the standard of care for the treatment of MBMs, but considering the relative radioresistance of melanoma cells when treated with small radiation doses, the risk of detrimental effect on quality of life and neurocognitive functions (~49%), and the absence of benefit on overall survival (OS), its use in clinical practice is questioned at present. Stereotactic radiosurgery (SRS) or hypofractionated stereotactic radiosurgery (HSRS), delivering higher doses in a single or few fractions, have largely replaced WBRT.[10-15] Recent findings showed that the association of local treatment and immune or targeted therapy could impact on brain control and survival.[16-22] Ipilimumab is a fully human monoclonal antibody that inhibits the function of cytotoxic T-cell-associated antigen 4 and enhances an immune response against melanoma cells. Retrospective analysis reported a sensitizing effect or even an abscopal effect for RT when used in conjunction with immunotherapy, but data are not yet ripe.[16-18] In BRAF- and MEK-mutated tumor, the use of their inhibitors, such as vemurafenib, dabrafenib, and trametinib, seem to be promising with reported objective responses in a range between 30% and 75%.[19-23] These results suggest that targeted drugs and RT-based techniques have high efficacy, although they need to be validated in randomized controlled clinical trials. Several effective treatment options are now available for patients with MBMs, but what can be considered the optimal therapeutic strategy is not yet defined. In this context, we analyzed the outcome of patients with limited brain metastasis from melanoma, with the aim to identity prognostic factors impacting on survival. These results could also supply data able to orient the future decision-making process.

METHODS

Patients and Treatments

The present retrospective study includes patients with limited brain metastases ($\leq$4) from primary melanoma treated with surgery plus HSRS, or SRS/HSRS alone, in relation to patients with general conditions and disease status. In detail these patients had 1) surgical resection followed by HSRS if Karnofsky performance score (KPS) was $\geq$70, controlled extracranial disease, single brain lesion with diameter $\geq$15 mm, presence of multiple BMs of which 1 conditioning mass effect and progressive neurological deficits, uncontrolled by medical therapy; 2) SRS alone in case of single BM <15 mm or multiple BMs $\leq$25 mm; and 3) HSRS alone in case of BMs >25 mm in patients with KPS <70 and uncontrolled extracranial disease. To define the appropriate therapy, each patient was evaluated by a multidisciplinary team including neurosurgeons, oncologists, and radiation oncologists. A supramarginal resection, defined as a microsurgical tumor excision with an extension of at least 5 mm larger as seen than enhancing T_1-weighted magnetic resonance imaging (MRI) sequences borders, was performed. In case of dural attachment, the dura mater removal was carried out at least 2 cm from the stalk in each direction. To precisely delineate the target volume for SRS or HSRS, enhanced T_1-weighted MRI sequences and postcontrast computed tomography scans were acquired and coregistered. The clinical target volume corresponded to the lesion or the tumor bed. A planning target volume was generated adding an isotropic expansion of 2 mm from the clinical target volume. All plans were optimized on the planning target volume. The prescribed total doses were 24 Gy/1 fraction and 30 Gy in 3–5 fractions for lesions >25 mm. After local treatments, different schemes of systemic therapy were used: chemotherapy with fotemustine, immunotherapy using ipilimumab, or BRAF inhibitor using vemurafenib, dabrafenib with or without MEK inhibitor such as trametinib.

Outcome Evaluation

Clinical outcome was evaluated by brain MRI performed 2 months after RT and then every 3 months. Local progression was defined as a radiographic increase of the enhancing abnormality in the irradiated volume, and brain distant progression (BDP) as the presence of new BMs outside the irradiated volume. Systemic disease was evaluated by contrast-enhancing computed tomography scan. Prognostic factors analyzed were age, gender, stage at diagnoses, presence of BRAF mutation, KPS, interval time between primary tumor diagnoses and appearance of BMs, recursive partial analysis class, melanoma-specific graded prognostic assessment (GPA) score, presence of other metastatic sites at time of BMs, number, location, and size of BMs, and administration of immune or targeted therapy after local treatments.

Statistical Analysis

Standard descriptive statistics (mean, standard deviation, and cross-tabulation analysis) were used to describe the general data behavior. Survival and recurrence time observations were plotted according to the method of Kaplan and Meier, starting from the date of BM diagnosis. The log-rank test was used to carry out the univariate analysis to investigate the prognostic role of individual variables. Groups were defined according to discrete volume of each variable. Multivariate Cox model was used as a method to estimate the independent association of a variable set with OS, local control (LC), and BDP. Statistical software used was STATA v. 13.1 (StataCorp, College Station, Texas, USA).

RESULTS

Patients and Treatments

From April 2011 to October 2015, 53 patients with limited MBMs were evaluated. Of these, 82 BMs were treated. Thirty-five were men and 18 women. The median age was 54 years (range, 29–82 years). At the time of primary melanoma diagnosis, 42 (79.2%) patients were in stage I-III and 11 (20.8%) in stage IV. BRAF mutation was present in 20 (37.7%) patients. The median interval time between the first diagnosis of melanoma and the appearance of BMs was 25.6 months (range, 0.0–315.1 months). Thirty-seven (69.8%) patients had other extracranial metastases in addition to MBMs and 16 (30.2%) had MBMs only. Most patients had a KPS