Comparison Between Surgical Resection and Stereotactic Radiosurgery in Patients with a Single Brain Metastasis from Non–Small Cell Lung Cancer

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BACKGROUND: **The management of patients with single brain metastasis (BM) from non–small cell lung cancer (NSCLC) is controversial. Surgical resection (SR) with adjuvant irradiation and stereotactic radiosurgery (SRS) are performed in the treatment of such lesions. This study compared both modalities in terms of tumor control and survival.**

METHODS: **During the period 2004–2011, 115 patients with single BM from NSCLC were treated with SR or SRS at our institution. Median patient age was 61 years. SR was performed in 43 patients, and SRS was performed in 72 patients. Most patients who underwent SR had adjuvant irradiation. Of patients, 63% in the SR group and 56% in the SRS group had synchronous presentation of BM and lung primary tumor. Thoracic disease was managed with curative intent in 60% of patients in the SR group compared with 50% of patients in the SRS group.**

RESULTS: **Median follow-up was 10.2 months. Local control was 72% in patients in the SR group and 79% in patients in the SRS group ($P = 0.992$). Median survival for patients in the SR group was 13.3 months, and median survival for patients in the SRS group was 7.8 months ($P = 0.047$). Multivariate analyses revealed aggressive treatment of the primary NSCLC as an independent factor associated with prolonged survival in patients undergoing SR. In the SRS group, patients with metachronous metastasis showed a better prognosis. Metachronous presentation was associated with more aggressive management of the primary tumor.**

CONCLUSIONS: **In this study, patients with single BM undergoing SR had a survival advantage. However, because SR and SRS achieved comparable local control of BM, patients receiving SRS should benefit from an equally aggressive treatment of the primary NSCLC, as thoracic management was the most important predictor of survival.**

INTRODUCTION

Brain metastasis (BM) accounts for most malignant intracranial tumors. Lung cancer is the most common primary site of origin (17). The histologic subgroup of non–small cell lung cancer (NSCLC) constitutes approximately 80% of all lung cancers. During the course of their disease, 25%–50% of patients with NSCLC develop at least 1 BM (7, 9, 23).

Despite the poor prognosis of patients with single BM from NSCLC, aggressive management of such lesions is now the common trend among oncologists. Stereotactic radiosurgery (SRS) and surgical resection (SR) are effective management modalities for single BM (4, 7, 9, 11, 23). SR is usually preferred in larger, symptomatic lesions or when histologic diagnosis is needed. SRS is less invasive and is used for surgically inaccessible lesions or when patients are deemed ineligible to undergo surgery because of numerous comorbidities or advanced disease. Many patients fall somewhere in between those extreme situations, with surgically accessible lesions of small to moderate size, and optimal management is controversial in these situations. This study was conducted to assess the outcomes of initial treatment with SRS or SR in terms of local control, morbidity, and survival in patients with a single BM from NSCLC. When referring to SR in

Key words
- Gamma Knife radiosurgery
- Non–small cell lung cancer
- Single brain metastasis
- Stereotactic radiosurgery
- Surgical resection

Abbreviations and Acronyms
BM: Brain metastasis
MRI: Magnetic resonance imaging
NSCLC: Non–small cell lung cancer
SR: Surgical resection
SRS: Stereotactic radiosurgery
WBRT: Whole-brain radiation therapy

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the text, postoperative irradiation is implied because it is the standard of care at our institution.

MATERIALS AND METHODS

Between January 2004 and December 2011, 115 patients were managed with upfront SRS or SR for a single BM from a primary NSCLC at the Centre Hospitalier Universitaire de Sherbrooke. The charts of patients were reviewed along with the Gamma Knife SRS database, which is prospectively collected at the time of patient follow-up by neurosurgeons at our institution. Informed consent from the subjects of the study and local ethics committee approval were obtained.

Patient Characteristics

Patient characteristics are presented in Table 1. All patients had a single BM detected by magnetic resonance imaging (MRI). Patients were grouped according to their initial management strategy. Taking patient preference and general medical condition into account, in most cases with brain metastasis of appropriate volume (maximum diameter <3 cm), SRS was the preferred management strategy. SRS was also favored for tumors in eloquent locations (primary motor, somatosensory, visual, and speech areas; basal ganglia; thalamus; and brainstem). Patients presenting with a very large metastasis, symptomatic focal mass effect, or intracranial hypertension unresponsive to corticosteroids were treated with SR as is dictated by standard of care. SRS was performed in 72 patients, and SR was performed in 43 patients. In the SR group, 39 patients received some form of adjuvant irradiation, consisting of tumor bed SRS ($n = 21$), whole-brain radiation therapy (WBRT) ($n = 10$), and combination of tumor bed SRS and WBRT ($n = 7$). Adjuvant management was chosen based on tumor bed dimensions and patient condition. Since 2008, tumor bed SRS has been our preferred adjuvant irradiation technique for tumor beds of maximal diameter <5 cm. WBRT was used in combination with SRS when the tumor bed remained too large on treatment planning MRI. Before 2008, WBRT was alternatively used alone based on the preference of the treating radiation oncologist. No patient in the SRS group had WBRT as part of the initial management plan. Regular follow-up evaluations were conducted in all patients. Repeat imaging was conducted 2 months after treatment and at 3-month intervals thereafter if there was no evidence of recurrence. Follow-up MRI was performed for assessment of metastasis response to initial treatment, which was based on the Response Assessment in Neuro-Oncology criteria (8). Briefly, disappearance of a lesion is a complete response; >50% regression is a partial response; and >25% increase in size, unless transient, is progressive disease. All other changes are considered stable disease. Salvage treatment was performed if needed for local and distant brain recurrences (Table 2).

Median patient age at the time of treatment was 61 years (range, 39–86 years), and 46% of patients were men. Median maximal diameter of BM in patients in the SR group was 3.7 cm (range, 2.0–6.0 cm). In the SRS group, the median maximal tumor diameter was 2.0 cm (range, 0.6–3.2 cm). Histologic confirmation of NSCLC was obtained in all patients either with the BM surgical specimen or with biopsy of the primary tumor. In 67 patients, synchronous diagnosis of the primary NSCLC and BM was obtained, and metachronous diagnosis was obtained in 48 patients. Synchronous diagnosis was defined by an interval of <6 weeks between diagnoses of the primary and cerebral tumors. Systemic evaluation of most (79%) patients was performed using positron emission tomography scans. The TNM staging of the disease was subsequently determined according to the most recent staging classification of the American Joint Committee on Cancer (3). As a result of inadequate documentation, it was impossible to determine the original disease stage for 9 patients. When stratified according to the Radiation Therapy Oncology Group recursive partitioning analysis (6), 13% of patients were in class I, 74% were in class II, and 13% were in class III. Most patients in the SR (76%) and SRS (71%) groups had a recursive partitioning analysis class II classification, and this was similar between the groups. At the time of diagnosis of BM, 102 patients had related symptoms, including seizures, focal deficits, headache, and altered level of consciousness. Only 13 patients were neurologically intact at the time of diagnosis of their cerebral disease. Patients were considered as having thoracic management with curative intent if they had undergone SR; radiotherapy with curative intent with or without chemotherapy; or triple-modality treatment including surgery, radiotherapy, and chemotherapy of the primary NSCLC. Patients undergoing palliative radiotherapy or chemotherapy were considered to have medical palliative treatment. For the management of systemic disease, 60 patients originally had treatment with curative intent, 33 had palliative management, and 18 had supportive care only. In 4 patients who were originally treated at other institutions, exact treatment of the primary NSCLC could not be determined. Of surgical patients treated with RS, 53% ($n = 23$) underwent curative intent treatment compared with only 41% ($n = 28$) of patients treated with SRS ($P = 0.281$).

Radiosurgery Procedures

The radiosurgery procedure was performed a median of 2 weeks after the diagnosis of BM (range, 1–15 weeks). All treatments were done using a Leksell Gamma Knife model 4C or Perfexion (Elekta Instruments AB, Atlanta, Georgia, USA) under local anesthesia with conscious sedation. A volumetric contrast-enhanced magnetization-prepared rapid gradient echo MRI sequence with three-dimensional reconstruction was used for dose planning. Using Leksell GammaPlan (Elekta Instruments AB) software, a radiosurgical plan was devised using a median of 6 isocenters (range, 1–26) to cover the total tumor volume. The median treatment volume was 4.4 mL (range, 0.1–16.3 mL). The median maximal dose was 36 Gy (range, 20–48 Gy). The median marginal dose was 18 Gy (range, 12–24 Gy). The 50% isodose line was used most often for the prescription.

Statistical Analyses

Statistical analyses were performed using commercially available software (IBM SPSS Statistics version 20; IBM Corp., Armonk, New York, USA). Patient characteristics were compared using χ^2 test. Mann-Whitney test was used to compare continuous variables. When frequencies were ≤5, Fisher exact test was used. The following factors were assessed for their impact on survival and local control: age, gender, Karnofsky performance scale score, Eastern Cooperative Oncology Group score, histology, time elapsed between diagnoses, TNM staging, BM localization and