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Clinical Study

Impact of the number of metastatic brain lesions on survival after Gamma Knife radiosurgery

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ABSTRACT

Effectiveness of Gamma Knife radiosurgery (GKRS: Elekta AB, Stockholm, Sweden) for patients with metastatic brain disease and the prognostic factors influencing their survival were analyzed in a 5 year retrospective data analysis (July 2001 to June 2006). Kaplan–Meier survival curves were constructed using univariate and multivariate analyses with the respective salient prognostic factors. This study analyzed data on 330 patients with brain metastases who underwent GKRS. Lung carcinoma (55%) was the most common primary cancer followed by breast (17.8%), melanoma (9.4%), colorectal (4.8%) and renal (3.9%). The median survival for all patients was 8 months. Survival ranged from 13 months for breast metastases, 10 months for renal, and 8 months for lung to 5 months for colorectal and melanoma. Mean age of patients was 58.5 years (range 18–81). Melanoma patients were younger with a mean age of 49 and also had the highest number of lesions (3.8) when compared to patients with renal (2.5), lung (2.8), colorectal (3) and breast (3.6). When stratified according to the number of lesions patient survival was 8 months (one to three lesions), 7.5 months (four or five lesions) and 7 months (six lesions or more). Mean Karnofsky Performance Status score (KPS) was 77 and survival dropped significantly from 8 months to 4.5 months if KPS was less than 70. Survival improved with a KPS of 70 or more, regardless of the number of lesions treated. Selection of patients based on the number of lesions may not be justified. A prospective trial is required to further define the prognostic factors affecting survival.

1. Introduction

Cancer is a major public health burden in the USA as in other countries. Currently, one in four deaths in the USA is due to cancer [1]. Brain metastases affect 20–40% of all cancer patients and forms the most common subtype of intracranial tumor pathology [2–4]. Metastatic brain tumors represent an increasingly common complication of systemic cancer with an incidence in excess of 170,000 cases per year in the USA [3,5]. In 2013, an estimated 23,130 new cases of primary brain and other nervous system tumors were reported in the USA [1]. Metastatic brain tumors are diagnosed eight times more frequently than primary brain tumors. This number, however, is likely to increase as a result of improved overall survival in cancer patients and more accurate detection through modern neurological imaging modalities [6].

Nevertheless, management of brain metastases is still an ongoing problem for neurosurgeons and oncologists. Left untreated, the estimated mean survival for patients with cerebral metastases is between 4 weeks and 6 months, depending on the histopathology, age of the patient, presence of extracranial disease, and Karnofsky Performance Status score (KPS) [7].

Traditionally, treatment options for patients with brain metastases have included medical management with systemic corticosteroids, surgical resection and fractionated whole brain radiation therapy (WBRT). In most documented series, the use of WBRT extends survival by 3–5 months. To elucidate, in the early 1990s, work done by Patchell et al. and Noordijk et al. [8,9] showed improved survival rates achieved with surgery after WBRT for single metastatic brain tumors. However despite its potentially beneficial role, surgical resection is often seen as a non-feasible option due to tumor multiplicity, lesion location and sometimes the grim preoperative medical condition of patients secondary to associated co-morbidities. Over the years, stereotactic radiosurgery (SRS) has been increasingly used for single and multiple metastatic brain

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lesions. Kondziolka et al. [10] have demonstrated promising results using Gamma Knife radiosurgery (GKRS: Elekta AB, Stockholm, Sweden) followed by WBRT for multiple brain metastases, with patient survival comparable to surgical resection with WBRT.

The purpose of this retrospective study was to analyze the effectiveness of GKRS for patients with metastatic brain disease and by doing so identify the prognostic factors affecting their survival. We evaluated the extent of impact that factors such as primary tumor location, KPS and the number of metastatic brain lesions have on overall survival. We were intrigued to determine if the selection of patients based on the number of lesions was justified.

2. Clinical material and methods

2.1. Study inclusion criteria

Between July 2001 and June 2006, 330 consecutive patients with single or multiple brain metastases underwent GKRS at State University of New York, Upstate Medical University, Syracuse, NY, USA. The Gamma Knife center at our institution is the first in Upstate New York and has been functional with a Leksell Gamma Knife since 1998. All patients were treated on model B using the same radiation source while a new Perfexion Gamma Knife unit (Elekta AB) is now operational.

All records were reviewed retrospectively and data regarding patient age, sex, primary diagnosis, KPS and the number of lesions was recorded on a database. These 330 patients harbored a total of 988 brain tumors that were all treated with GKRS. The mean age of the patients was 58.5 years (range 18–85 years). The majority were females 193 (58.8%) while 136 (41.2%) were males. Lung carcinoma (55%) was the most common primary cancer subtype, seen in 181 patients. This was followed by breast cancer (17.8%) with 59 patients. There were 31 patients with melanoma (9.4%) metastases. The other groups included colorectal cancer (4.8%) and renal cell cancer (3.9%). Of the remaining, 30 patients had other/unknown primary diagnosis.

In total, 120 patients (36.3%) had solitary brain tumors while the rest had multiple lesions. We divided the patients into subgroups based on the number of lesions on presentation. These subgroups included patients with single (solitary) metastases, two or three lesions, four or five lesions, and patients with six or more lesions. There were 25 patients (7.5%) with six or more lesions on presentation with 10 patients harboring more than 10 lesions (Fig. 1). The mean number of lesions was highest for melanoma (3.8) followed by breast (3.6), colorectal (3), lung (2.8) and renal (2.5).

All patients who underwent SRS for brain metastases were also assessed preoperatively for functional status and classified according to their KPS. The mean KPS was 77 and ranged from 30 to 100. Diagnosis of brain metastases was confirmed with MRI before undergoing GKRS in all patients.

Patient population referred for SRS may not include all patients with metastatic brain tumors that may have been treated with other modalities thus affecting patient outcomes.

2.2. Radiosurgery technique

SRS involved use of the Leksell Gamma Knife model B. The Leksell stereotactic frame (Elekta AB) was applied over the patient's head after application of a local anesthetic with mild sedation. All patients underwent stereotactic contrast enhanced brain MRI and planning was carried out with Leksell Gamma Plan software (Elekta AB).

The neurological surgeon, radiation oncologist and medical physicist were involved in dose selection and planning. Tumor volume ranged from 0.09 to 27.8 cm^3. The marginal radiation dose prescription ranged from 10–28 Gy (mean 16.8 Gy). A 50% isodose line was used in most cases to conform the dose to tumor margins. The patients were discharged within 24 hours after radiosurgery.

2.3. Statistical analysis

The Kaplan–Meier method was used for constructing survival curves using univariate and multivariate analyses with salient prognostic factors. This was achieved using the GraphPad Prism software (GraphPad Software, San Diego, CA, USA) and differences in survival between subgroups were analyzed by logrank test analysis (GraphPad Software). We attempted to determine the factors that had a statistically significant impact on patient survival. A probability value $p \leqslant 0.05$ was deemed statistically significant.

3. Results

3.1. Overall survival

The overall median actuarial survival time from date of radiosurgery was 8 months (Fig. 2). Of the 330 patients with brain metastases who underwent GKRS, 258 patients died while 72 remained alive at the time of this retrospective study. Survival depended on primary tumor type and ranged from 5 months to 13 months (Table 1). The best survival time of 13 months was found in patients with breast cancer metastases followed by

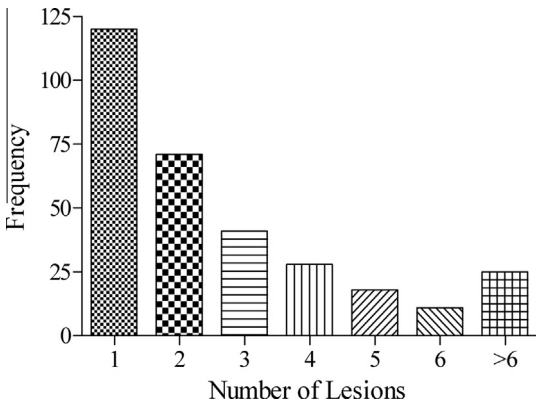

Fig. 1. Bar graph demonstrating the frequency of the number of lesions ranging from solitary to more than six lesions per patient.

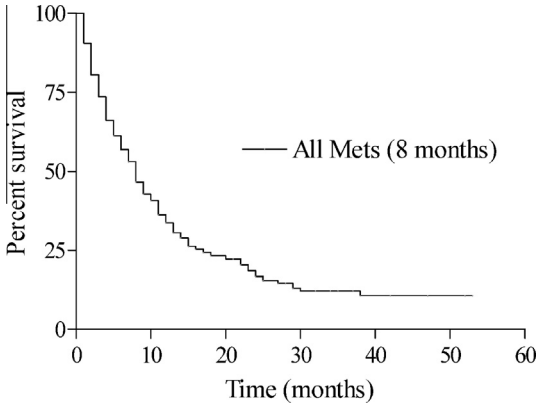

Fig. 2. Kaplan–Meier curve showing overall median survival time of 8 months for all patients regardless of primary site after brain metastases radiosurgery. Mets = metastases.