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Clinical Study

Tumor resection with carmustine wafer placement as salvage therapy after local failure of radiosurgery for brain metastasis

Frank Mu [a,*], John T. Lucas Jr. [a], Jonathan M. Watts [c], Annette J. Johnson [c], J. Daniel Bourland [a], Adrian W. Laxton [b], Michael D. Chan [a], Stephen B. Tatter [b]

[a] Department of Radiation Oncology, Wake Forest School of Medicine, Medical Center Boulevard, Winston-Salem, NC 27157, USA
[b] Department of Neurosurgery, Wake Forest School of Medicine, Winston-Salem, NC, USA
[c] Department of Radiology, Wake Forest School of Medicine, Winston-Salem, NC, USA

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ABSTRACT

Prolonged survival in brain metastasis patients increases recurrence rates and places added importance on salvage therapies. Research examining carmustine polymer wafers as an adjuvant therapy for brain metastasis is limited. We present a single institution retrospective series documenting the use of BCNU wafers placed in the cavity of resected recurrent brain metastases that had failed prior stereotactic radiosurgery (SRS). Between February 2002 and April 2013, a total of 31 patients with brain metastases failed SRS and underwent resection with intracavitary placement of carmustine wafers. Clinical outcomes including local control, survival, cause of death, and toxicity were determined from electronic medical records. Kaplan–Meier analysis was performed to assess local control and survival. Imaging features were reviewed and described for patients with serial post-operative follow-up imaging examinations over time. Overall survival at 6 months and 12 months was 63% and 36%, respectively. Fourteen of 31 patients (45%) died from neurologic causes. Local control within the resection cavity was 87% and 70% at 6 and 12 months, respectively. Five patients (16%) underwent further salvage therapy following carmustine wafer placement after local failure. Resection cavities of all six patients with follow-up imaging showed linear peripheral enhancement. Pericavity and wafer enhancement was present as early as the same day as surgery and persisted in all cases to 6 months or longer. Carmustine polymer wafers are an effective salvage treatment following resection of a brain metastasis that has failed prior SRS. For patients with successful local control after wafer implantation, linear enhancement at the cavity is common.

1. Introduction

Patients with brain metastases are experiencing increased survival times because of improved therapies for extracranial disease [1], earlier detection of brain metastases [2], and more effective therapies for brain metastases [3]. This improvement in survival places increased importance on salvage therapies for brain metastases, since local recurrence occurs at a higher rate for patients with prolonged survival. While surgery can be performed in the salvage setting after failure of radiosurgery or whole brain radiotherapy, the local recurrence rate after resection alone for a brain metastasis is 19–46% [4]. Recurrence of the brain metastasis even after gross resection is thought to be the result of microscopic tumor cells that lie just outside the resection cavity or have infiltrated normal-appearing brain tissue. For this reason, radiosurgery and whole brain radiotherapy have commonly been used as adjuvant therapy after resection of a brain metastasis in order to decrease the likelihood of failing within the resection cavity.

A disadvantage of further radiotherapy as adjuvant therapy after resection of a recurrent brain metastasis is the limited lifetime tolerance of brain tissue to radiation, which results in a cumulative risk of radiation necrosis. An adjuvant treatment option that does not require radiotherapy is the application of carmustine (1,3-bis[2-chloroethyl]-1-nitrosourea or BCNU) polymer wafers. The advantage of these wafers is that they deliver a high concentration of chemotherapy at the predominant location of treatment failure. Several studies have demonstrated the efficacy of carmustine polymer wafers on primary malignant brain tumors [5,6], although the scientific literature describing the use of carmustine wafers for adjuvant treatment of brain metastases is limited [7].

We present a single institution retrospective series documenting the use of BCNU wafers placed at the resection cavity of resected recurrent brain metastases that had failed prior stereotac-

* Corresponding author. Tel.: +1 704 650 5039.
E-mail address: fmu@wakehealth.edu (F. Mu).

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tic radiosurgery. The purpose of this study is to examine the effectiveness of carmustine wafers in maintaining local control within the cavity. Additional outcomes of interest, which are descriptively summarized, include survival, likelihood of neurologic death, and patterns of failure of recurrent brain metastases treated with this modality.

2. Materials and methods

2.1. Data acquisition

This retrospective study was approved by the Wake Forest University Institutional Review Board. The Wake Forest University Department of Radiation Oncology Gamma Knife Tumor Registry was searched for all patients who received radiosurgical treatment for a brain metastasis and later underwent craniotomy with carmustine wafer placement (Gliadel Wafer, MGI Pharma, Bloomington, MN, USA). Between February 2002 and April 2013, a total of 31 consecutive patients with brain metastases who failed radiosurgery and underwent surgical resection with intracavitary placement of carmustine polymer wafers were identified. Patients were considered to have failed locally if failure was pathologically proven or if there was evidence of enlargement in volume by at least 25% of the enhancing nodularity at the cavity. Electronic medical records were reviewed to determine patient characteristics including age, sex, race, date of diagnosis, prior whole brain radiotherapy, date of first brain metastasis, date of radiosurgery, size of metastasis at radiosurgery, marginal dose, date of treatment failure, and date of craniotomy. Outcomes such as local control, toxicity, development of leptomeningeal disease and cause of death were also determined from electronic medical records. Table 1 summarizes the patient characteristics in this study.

2.2. Radiosurgery technique

Prior to treatment failure, all patients had been treated with Gamma Knife radiosurgery (Leksell Model C unit prior to May 2009, Leksell Gamma Knife Perfexion unit after May 2009; Elekta AB, Stockholm, Sweden). Prior to radiosurgery, patients underwent a high-resolution contrast-enhanced stereotactic MRI study of the brain. Treatment planning was performed using the Leksell GammaPlan Treatment Planning System (Elekta AB). Dose prescription was determined based on size and volume of each metastasis, generally following the guidelines published by Shaw et al. for single fraction radiosurgical treatment of brain metastases [8]. The median marginal dose of the previously treated lesion was 18 Gy (range 10–24 Gy) and the median resected volume at the time of stereotactic radiosurgery failure was 4.9 cc (range 0.2–53 cc).

Table 1
Patient characteristics

	Number (%)
Patients	31
Median age, years	55 (range 29–75)
Sex	
Female	16 (52%)
Male	15 (48%)
Primary disease site	
Non-small cell lung	13 (42%)
Small cell lung	3 (10%)
Melanoma	4 (13%)
Breast	8 (26%)
GI	2 (6%)
Thyroid	1 (3%)
Median tumor volume prior to resection	4.9 cc (range 0.2–53)
Treatment history	
Prior whole brain radiotherapy	8 (26%)
Prior median Gamma Knife[a] margin dose	18 Gy (range 10–24)

GI = gastrointestinal.
[a] Elekta AB, Stockholm, Sweden.

2.3. Carmustine wafer placement

Carmustine wafer was placed at the time of salvage craniotomy if the frozen section was consistent with recurrent brain metastasis. Three of 31 patients underwent carmustine wafer placement after frozen section suggested recurrent metastasis but had a final pathology consistent with radiation necrosis. Carmustine wafer placement was not performed if there was a gross communication between the resection cavity and the ventricular system, or if the resection cavity was of insufficient size to fit a carmustine wafer. The cavity was lined with a single layer of carmustine wafers. A maximum of eight wafers were used per patient; fewer were used if the cavity was of insufficient size to accommodate eight wafers. Wafers were placed equidistant from each other within the cavity. If wafers appeared mobile at time of implantation, they were covered with a single layer of surgical cellulose to hold them in place.

2.4. Patient follow-up, response assessment, and salvage therapy

Patients were followed with a repeat MRI of the brain approximately 6 weeks after craniotomy and then approximately every 3 months thereafter. Local failure was defined as either a pathologically-proven recurrence within the resection cavity, growing nodular enhancement outside of the expected region of carmustine penetration, or by clinical characteristics of local treatment failure. Local failures were treated with further surgical excision, or whole brain irradiation. Neurological death was defined as had been reported by Patchell et al. [4].

2.5. Prospective imaging review

Imaging was prospectively reviewed by consensus between a neuroradiology fellow and a neuroradiologist with 17 years of experience. Both physicians were blinded to patient outcomes and tumor pathology. Imaging follow-up of this patient population is complicated by the variable appearances of the surgical cavity (pericavity infarct and/or blood products/local reaction to a residua of carmustine wafers); concurrent or preceding radiotherapy, surgery, and chemotherapy; various imaging intervals (which were appropriately tailored to patient condition); and lack of tissue confirmation in the majority of cavities. Imaging features were thus described only for patients who had serial post-operative follow-up imaging examinations over time. As the goal of prospective imaging review was to describe treatment-related changes over time, patients were required to have 6 months of imaging follow-up in order to be included in the imaging review.

2.6. Statistical analysis

Time to event data were summarized using Kaplan–Meier plots. Primary endpoints included time to local failure and time to death. All analyses were done using SAS version 9.2 (SAS Institute, Cary, NC, USA).

3. Results

3.1. Survival

Overall survival at 6 and 12 months from time of carmustine wafer placement was 63% and 36%, respectively (Fig. 1A). Median