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Case study

Early or late radiotherapy following gross or subtotal resection for atypical meningiomas: Clinical outcomes and local control

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ABSTRACT

We report a single institution series of surgery followed by either early adjuvant or late radiotherapy for atypical meningiomas (AM). AM patients, by WHO 2007 definition, underwent subtotal resection (STR) or gross total resection (GTR). Sixty-three of a total 115 patients then received fractionated or stereotactic radiation treatment, early adjuvant radiotherapy (≤4 months after surgery) or late radiotherapy (at the time of recurrence). Kaplan Meier method was used for survival analysis with competing risk analysis used to assess local failure. Overall survival (OS) at 1, 2, and 5 years for all patients was 87%, 85%, 66%, respectively. Progression free survival (PFS) at 1, 2, and 5 years for all patients was 65%, 30%, and 18%, respectively. OS at 1, 2, and 5 years was 75%, 72%, 55% for surgery alone, and 97%, 95%, 75% for surgery + radiotherapy (log-rank p-value = 0.0026). PFS at 1, 2, and 5 years for patients undergoing surgery without early adjuvant radiotherapy was 64%, 49%, and 27% versus 81%, 73%, and 59% for surgery + early adjuvant radiotherapy (log-rank p-value = 0.0026). The cumulative incidence of local failure at 1, 2, and 5 years for patients undergoing surgery without early External Beam Radiation Therapy (EBRT) was 18.7%, 35.0%, and 52.9%, respectively, versus 4.2%, 13.3%, and 20.0% for surgery and early EBRT (p-value = 0.02). Adjuvant radiotherapy improves OS in patients with AM. Early adjuvant radiotherapy improves PFS, likely due to the improvement in local control seen with early adjuvant EBRT.

1. Introduction

Meningiomas are the most common primary intracranial neoplasm, comprising about 30% of all reported brain tumors [1]. The WHO classifies meningiomas based on tumor behavior as: benign (WHO Grade I), atypical (WHO Grade II), or malignant (WHO grade III). Atypical meningiomas represent 4–35% [2–4] of meningioma and have a seven-to eightfold increase in recurrence rate and a significantly higher rate of mortality compared to benign meningiomas [2–6]. While gross total resection (GTR) (Simpson grade I, II, or III) or subtotal resection (Simpson grade IV or V) alone are standard treatment options for benign meningiomas, it is unclear if surgery alone is adequate for atypical meningiomas. Several series have demonstrated improved local control with immediate postoperative radiotherapy following surgery [7–9]; however, there is less evidence to support a benefit in overall survival (OS). Moreover, the cognitive toxicities of radiotherapy need to be considered when treating patients with relatively long life expectancy [10,11].

The data for radiotherapy after surgical management of a meningioma are somewhat controversial, particularly in the setting of GTR. Some retrospective studies support the role of adjuvant radiotherapy [7,12–15] while others do not [16,17] and most of these studies are limited by being retrospective series with a limited number of patients [14,18]. Further, these series have discrepancies in the extent of resection (EOR), timing of treatment, and criteria for atypical meningioma (AM) classification in the evaluated patient populations. Thus, a need exists for data evaluating the variables of timing and EOR separately in the setting of the new 2007 WHO classification guidelines.

Currently, no randomized clinical trials have been completed to provide clarity on the issue, although the RTOG has completed accrual of a single arm Phase II study (https://clinicaltrials.gov/ct2/show/NCT00895622) and the European Organization for

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Research and Treatment of Cancer (EORTC) is conducting a randomized phase III trial which is expected to be completed in 2024 [19].

The current series represents one of the largest single institution retrospective reviews evaluating the role of adjuvant radiotherapy following surgical management of an AM, and uniquely examines the effect of both EOR and timing on clinical outcomes. The goal of this study was to determine whether outcomes were affected by the timing of radiotherapy and if the efficacy of radiotherapy was affected by the EOR.

2. Methods

2.1. Patient population

This study was approved by the Wake Forest School of Medicine Institutional Review Board. The neuropathology database at Wake Forest was queried for all patients who received surgical resection of WHO grade II meningiomas between 1993 and 2014. Tumor grade was re-reviewed by neuropathology staff to assure that specimens met the 2007 WHO grading criteria for grade II meningioma. Patient characteristics and outcomes were determined using the patients' electronic medical records.

2.2. Treatment

All patients were treated with surgery (Sx), either GTR defined as Simpson grades I–III or STR defined as Simpson grades IV–V, at the time of initial diagnosis as determined by surgical operative reports. Simpson grade was determined based on the postoperative MRI. Following resection, patients were generally advised to have a consultation appointment with radiation oncology to determine if external beam radiation therapy (EBRT), Gamma Knife stereotactic radiosurgery (SRS), or observation were recommended post-surgical options. During the time period of the study, a total of 4 neurosurgeons and 5 radiation oncologists with varied treatment philosophies consulted with patients regarding possible adjuvant therapy. Due to the heterogeneity of treatment philosophies, a dichotomous patient population formed with some patients receiving early radiotherapy, and others receiving radiotherapy at time of failure. Patients opting for early EBRT received a mean of 31 fractions (range 28–35) with a median dose of 55.7 Gy (range 50.4–59.4 Gy); those treated with single-fraction SRS received a median dose of 14.5 Gy (range 12–18 Gy). Early radiotherapy (EBRT, SRS or both) were defined as $\leq$4 months after surgery, while late radiotherapy was defined as at the time of recurrence. Fourteen patients received a combination of both forms of radiotherapy, either early EBRT with late SRS, early SRS with late EBRT, early EBRT and early SRS, or late EBRT and late SRS. Two patients received repeat surgery.

2.3. Radiotherapy technique

For patients treated with external beam radiotherapy, the majority of patients were treated with a 3D conformal radiotherapy technique. Gross tumor volume (GTV) was defined as gross residual disease as well as the resection cavity. A 1.0 cm dural margin expansion and 0.5 cm parenchymal brain expansion were added to form the clinical target volume (CTV). A 3–5 mm planning target volume (PTV) margin was then added to account for patient setup uncertainty.

For patients treated with SRS, the patient was immobilized on the morning of treatment with a Leksell pin-based headframe. High resolution stereotactic magnetic resonance imaging (MRI) with contrast was acquired on the same day of treatment or. For patients with STR, the GTV generally consisted of treatment of the enhancing residual tumor, while for patients with GTR the GTV consisted of the tumor resection cavity.

2.4. Follow-up

Following initial treatment, patients underwent a follow-up MRI of the brain every 6 months for the first 2 years, and then annually after 2 years if there was no evidence of recurrence. All follow-up images were compared to images used for staging and evaluated for local failure and distant failure. Local failure was defined as either a histologically-proven recurrence or a 25% increase in the area of enhancement on axial slice MRI with a corresponding increase in perfusion on perfusion-weighted MRI. Distant meningioma was defined as a new meningioma at a site non-contiguous with the original tumor.

2.5. Toxicity

Toxicity was monitored by imaging and clinical follow-up and was defined as any unfavorable and unintended changed in the sign or symptom considered possibly, probably, or definitely related to radiosurgery. The Common Terminology for Adverse Events (CTCAE) version 4.0 was used to assign grading.

2.6. Statistical analysis

Patient characteristics were determined by group using means and frequencies. Overall survival (OS) was calculated as the time from surgery to death. Progression free survival was calculated as the time from surgery to death, local failure, or distant failure. Time to local failure was calculated as the time from surgery to local failure; participants who died prior to having a local failure were censored at the time of their death. For OS and PFS, patients who had not yet had an event where censored at the date of their last follow-up or five years post-surgery. Kaplan-Meier (KM) plots were created to evaluate the number of events within each level for variables of interest for all outcomes. Log-rank tests were used to test for differences in the survival curves by treatment type, both overall and within surgery type. Cox proportional hazards models were created using a forward selection process based on a list of predefined baseline covariates for the outcome of progression free survival. The list of possible covariates included age, gender, race, type of resection, meningiomatosis, and recurrence from an earlier tumor. Hazards ratios and 95 percent confidence intervals were derived from this Cox model and reported. Competing risks analysis was used to analyze the cumulative incidence of local failure as stratified by extent of resection and the use of adjuvant therapy. Statistical analysis was performed using SAS software version 9.4 (SAS Institute Inc., Cary, NC) and R 3.3.1 (R Foundation for Statistical Computing, Vienna, Austria).

3. Results

3.1. Patient characteristics

From August 1993 to August 2014, a total of 117 patients were treated for AM with either surgery alone or surgery + radiotherapy. Two patients were excluded from the study do to due concurrent diagnosis of Neurofibromatosis 2 as these patients have a different natural history from standard grade II meningiomas [20]. Fifty-two patients received Sx only and 63 also received radiotherapy. Other patient characteristics are summarized in Table 1. Median follow-up time was 36.9 months (range 0.01–226.0). The median patient

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