Impact of Resecting Radiation Necrosis and Pseudoprogression on Survival of Patients with Glioblastoma

Rachel Grossman[1], Nir Shimony[1], Uri Hadelsberg[1], Dov Soffer[2], Razi Sitt[1], Natan Strauss[3], Benjamin W. Corn[3], Zvi Ram[1]

■ INTRODUCTION: **Radiation necrosis (RN) and pseudoprogression are known as postradiation treatment effects and may simulate tumor progression. The disease course of glioblastoma patients who had developed RN and the impact of resecting RN on survival have not been evaluated. This study examines the clinical course of patients considered candidates for repeat surgery for a recurring brain mass proven to be RN and compared these with patients who had true tumor recurrence at surgery.**

■ METHODS: **Of 159 patients with glioblastoma who were reoperated on because of a presumed recurrent tumor requiring repeat surgery, 18 had RN as the major component of the resected mass. The characteristics and outcome of these 18 patients were retrospectively analyzed and compared with patients in whom active and bulky tumor was found during surgery.**

■ RESULTS: **Radiation necrosis occurred significantly earlier than true tumor recurrence. Patients with RN harbored larger lesions and were significantly more symptomatic before the second surgery. Most patients with RN who underwent GTR of the lesion in the second operation experienced faster resolution of the surrounding edema compared with patients who underwent STR or biopsy only. There was no significant difference in survival between the 2 groups.**

■ CONCLUSIONS: **These data provide an opportunity to examine the clinical course of a selected group of patients with histologically verified RN. Although RN is associated with more severe neurologic symptoms that improve after surgery, its occurrence or surgical removal carries no survival advantage compared with patients who undergo a repeat operation for true tumor recurrence.**

INTRODUCTION

Radiation therapy is part of the standard treatment for patients with newly diagnosed glioblastoma multiforme (GBM),[1] along with concurrent treatment with temozolomide, and has been shown to prolong survival in these patients.[1] However, radiation therapy may cause radiation necrosis (RN) that typically occurs several months post treatment and is characterized by new enhancement at the treatment site and severe perilesional edema. When occurring early after chemoradiation, radiologic changes suggestive of tumor recurrence may in fact represent "pseudoprogression," a nontumoral treatment effect that subsides with time.[2] Differentiation between RN and tumor progression poses a diagnostic dilemma. The incidence of observing post-treatment radiologic changes that may represent RN and pseudoprogression phenomena is steadily increasing.[3-5] Radiation necrosis, tumor recurrence, and pseudoprogression cause destabilization of the blood-brain barrier. Thus, the appearance of post-treatment enhancing magnetic resonance changes is a nonspecific phenomenon. Attempts have been made to employ various advanced

Key words
- Craniotomy
- Glioma
- Outcome
- Pseudoprogression
- Radiation necrosis

Abbreviations and Acronyms
GBM: Glioblastoma multiforme
GTR: Gross total resection
KPS: Karnofsky performance scale
MRI: Magnetic resonance imaging
PET: Positron emission tomography
RN: Radiation necrosis
STR: Subtotal resection
WHO: World Health Organization

From the Departments of [1]Neurosurgery and [2]Pathology and [3]Institute of Radiotherapy, Tel Aviv Medical Center, affiliated with the Sackler Faculty of Medicine, Tel-Aviv University, Tel-Aviv, Israel

To whom correspondence should be addressed: Rachel Grossman, M.D. [E-mail: rachelgr@tasmc.health.gov.il]

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imaging modalities, such as diffusion imaging techniques, magnetic resonance spectroscopy (MRS), perfusion imaging techniques, and positron emission tomography (PET), to differentiate viable tumor from treatment changes, but with limited success.[6-10]

Pseudoprogression, a self-limiting process, is characterized by new enhancement that usually occurs within 2–5 months after treatment before spontaneously resolving by clinical and radiographic criteria.[3-5] Radiation necrosis occurs usually between 3 and 12 months post chemoradiation treatment and is characterized by cell necrosis and endothelial apoptosis, as well as increased vascular permeability, edema, and gliosis.[6,9,11] These conditions may of course overlap, which makes differentiating true tumor recurrence from necrosis even more difficult.[2] The treatment paradigm for each entity is different. In the case of tumor recurrence, patients may benefit from repeat surgical resection and further oncologic treatment.[12] In the case of RN, the management is usually conservative with several treatment options, including antiplatelet agents, anticoagulants, hyperbaric oxygen, high-dose vitamins, corticosteroids, or bevacizumab.[6,13,14] In the case of a symptomatic lesion resistant to medical treatment, surgical resection is a valid treatment option. The clinical impact of surgical resection of radiation-induced necrosis or pseudoprogression has not yet been described.

Obviously, the majority of GBM patients with a presumed progression (or pseudo progression) never undergo a second operation. Accordingly, our data are not representative of the entire cohort of patients diagnosed with GBM but rather provide insight into a selected patient population considered appropriate for a repeat operation and in whom the resected mass consisted of necrosis rather than viable tumor.

METHODS

Patient Selection

The study was approved by the institutional review board (approval TLV-0626-11). All patients who had been operated on for a presumed recurrence of GBM at the Neurosurgery Department, Tel-Aviv Medical Center, from 2003 to 2011, were included in this study. The treatment of a patient with GBM followed the guidelines of the Radiating Therapy Oncology Group (RTOG) (i.e., 2 Gy, administered daily, 5 days per week, to a total of 60 Gy over 6 weeks).[1] All specimens were examined by a neuropathologist and diagnosed according to the World Health Organization (WHO) criteria.[15] Since our cohort of patients was treated before the era of the RANO criteria, we have used the Macdonald criteria to define tumor recurrence. The diagnosis of RN was based on commonly accepted criteria.[8,11,16] Because complete eradication of tumor is exceedingly rare, most commonly there is a mixture of both residual and recurrent tumor and RN.[8,11,16] Thus, RN was considered the primary diagnosis on the basis of previously established criteria[11] only if the resected specimen comprised <20% residual/recurrent viable tumor and >80% was diagnosed as necrosis.[8]

Clinical Variables

Clinical and demographic data were retrieved from the hospital database, and data on demographics, presenting symptoms, medical comorbidities, neuroimaging findings, and postoperative course were extracted from patients' charts. Magnetic resonance imaging (MRI) studies were reviewed, and lesion location was documented. The Karnofsky performance scale (KPS) was used to assess functional status, and the scoring was dichotomized as being above and below 70. Lesion size was calculated by the maximal diameter on T1-weighted, contrast-enhanced images. Postoperative mortality and surgery-related complications were recorded, if occurred, within 30 days after surgery. The extent of resection was calculated on the basis of a postoperative MRI scan performed within 48 hours after surgery and categorized into gross total resection (GTR, >95% resection of the residual enhancement of the lesion) or subtotal resection (STR, >90% resection of the residual enhancement of the lesion).

STATISTICAL ANALYSIS

Descriptive statistics were given as median, mean, and standard deviation (SD). The chi-square or Fisher's exact test was used to examine group differences in categorical variables. A case-control study was performed to compare survival in cases of tumor recurrence versus RN. Survival as a function of time from diagnosis to death (overall survival), time from initial diagnosis to presumed tumor recurrence, and time from presumed tumor recurrence to death was calculated and expressed according to the estimated Kaplan-Meier method. All statistical analyses were performed using SAS for Windows 9.2, and P values <0.05 were considered statistically significant.

RESULTS

Patient Characteristics

One-hundred and fifty-nine patients out of 773 patients (20.6%) who were operated on for resection of GBM underwent reoperation for a presumed tumor recurrence at the designated time period of the study. One-hundred and forty-one patients (88.7%) had pathologically proven tumor recurrence (mean age ± SD 57.1 ± 11.1 years), and they were compared with 18 patients (11.3%) with a histopathologic diagnosis of RN based on the previously described criteria,[11] (57.2 ± 9.7 years, $P = 0.9$, **Table 1**). There was a slight male predominance in the recurrent glioblastoma group (62.2%) and a female predominance in the RN group (58.8%, $P = 0.09$). Most patients in both groups had a KPS score >70 before the second surgery, with a slightly higher percentage in the RN group (82.3% vs. 67.7%, $P = 0.2$). There was no difference between the 2 groups in the rate of comorbidity status ($P = 0.7$). There was no difference in the radiation doses between both groups (5249 cGy and 5301 cGy for tumor recurrence and RN respectively, $P = 0.9$) or volumes of radiation as calculated by the enhancing region (98.3cc and 89.9cc for the RN and tumor recurrence, respectively, $P = 44$). Radiation necrosis or tumor recurrence appeared consistently at the site of the previously operated tumor in all patients. The most common lesion site in both groups was the temporal lobe, followed by the frontal, parietal, and occipital lobes. The RN lesions were significantly larger compared with the recurrent GBM lesions (88.2% had tumor diameter >40 mm in the RN group vs. 62.3% in the recurrent tumor group, $P = 0.03$). Fourteen of the 18 patients with RN exhibited new neurologic symptoms before their second operation. Seven patients suffered