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**Prospective trial of gross-total resection with Gliadel wafers followed by early postoperative Gamma Knife radiosurgery and conformal fractionated radiotherapy as the initial treatment for patients with radiographically suspected, newly diagnosed glioblastoma multiforme**

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*Abbreviations used in this paper:* BCNU = 1; 3-bis(2-chloroethyl)-1-nitrosourea; CSF = cerebrospinal fluid; GBM = glioblastoma multiforme; GKS = Gamma Knife surgery; GTR = gross-total resection; KPS = Karnofsky performance scale; MGMT = O<sup>6</sup>-methylguanine-DNA methyltransferase; PCR = polymerase chain reaction; RPA = recursive partitioning analysis; RT = radiation therapy.

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*Object*

The purpose of this study was to determine whether increased local control and improved survival can be achieved in patients with glioblastoma multiformes (GBMs) who undergo aggressive resection, Gliadel wafer implantation, Gamma Knife radiosurgery (GKS), and fractionated radiotherapy (RT) as the initial treatment.

*Methods*

Thirty patients with radiographically suspected GBMs were screened for enrollment in a Phase I/II prospective clinical trial. Twenty-seven patients were eligible and underwent gross-total resection and Gliadel wafer implantation. Gamma Knife radiosurgery (12 Gy at 50%) was administered to the resection cavity within 2 weeks of surgery. Patients then received standard fractionated RT (total dose 60 Gy over 6 weeks). Temozolomide was prescribed for patients at the time of recurrence. Surveillance MR imaging, neurological examination, and quality-of-life evaluations were performed at 2-month intervals. To estimate the potential effects on the DNA repair mechanism, tumor tissue was analyzed with methylation-specific polymerase chain reaction analysis and immunohistochemical assays for *MGMT* gene promoter methylation and protein expression.

*Results*

The median survival for all patients was 50 weeks and the 2-year survival rate was 22%. When stratified into standard and high-risk patient groups, the median survivals were 76 and 33 weeks, respectively. Two patients remain alive at the time of this report with no clinical or radiographic evidence of disease at > 189 and 239 weeks posttreatment and excellent performance status. Local tumor control was achieved in 53% of patients, and local failure occurred in 47%. No acute early toxicity was noted; however, delayed symptomatic radionecrosis occurred in 47% of patients, which required repeated operations 9–24 months after the initial treatment. Delayed hydrocephalus requiring ventriculoperitoneal shunt placement occurred in 47% of patients. There was a significant difference in survival between patients whose tumors contained the methylated and unmethylated *MGMT* promoter, 103 versus 45 weeks, respectively ( $p = 0.0009$ , log-rank test).

*Conclusions*

The combination of aggressive resection, Gliadel wafer implantation, and GKS in addition to standard fractionated RT in selected patients resulted in increased local control and increased survival compared with a historical control group treated with surgery and involved-field RT alone. Delayed focal radionecrosis was increased to 47% in this series and was managed with steroids and repeated resection. Aggressive local tumor control with these multimodal therapies should be approached judiciously for a select group of high performance patients and the probability of developing symptomatic radionecrosis requiring surgery should be anticipated and fully disclosed to patients who undergo this treatment.

**KEYWORDS:** Gamma Knife radiosurgery; Gliadel wafer; glioblastoma multiforme; MGMT; resection.

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