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Clinical Study

Effectiveness of radiotherapy for elderly patients with anaplastic gliomas

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ABSTRACT

Postoperative radiotherapy (RT) is utilized routinely in the management of anaplastic World Health Organization Grade III gliomas (AG), including anaplastic astrocytoma (AA) and anaplastic oligodendroglioma (AO). However, the optimal role of RT in elderly AG patients remains controversial. We evaluated the effectiveness of RT in elderly AG patients using a national cancer registry. The USA Surveillance, Epidemiology, and End Results database (1990–2008) was used to query patients over 70 years of age with AA or AO. Independent predictors of overall survival were determined using a multivariate Cox proportional hazards model. Among 390 elderly patients with AG, 333 (85%) had AA and 57 (15%) had AO. Approximately two-thirds of AA patients (64%) and AO patients (65%) received RT. Most AO patients (58%) and many AA patients (41%) underwent surgical resection; the remainder had biopsy. The median overall survival for all patients who underwent RT was 6 months (95% confidence interval [CI], 5–7 months) *versus* 2 months (95% CI 1–6) in patients who did not have RT. Patients who had gross total resection (GTR) plus RT had a median overall survival of 11 months (95% CI 7–14). Multivariate analysis for all patients showed that undergoing RT was significantly associated with improved survival (hazard ratio [HR] 0.52, $p < .0001$). AA tumor type (HR 1.37, $p = .03$) was associated with worse survival than AO tumor type; female sex (HR 0.59, $p < .0001$) and being married (HR 0.66, $p = .002$) significantly improved survival. Patients that underwent GTR had a significant reduction in the hazards of mortality compared to biopsy (HR 0.72, $p = .04$). Elderly AG patients undergoing RT had better overall survival compared to patients who did not receive RT. Treatment strategies involving maximal safe resection plus RT should be considered in the optimal management of AG in elderly patients.

1. Introduction

Anaplastic gliomas (AG), also known as World Health Organization (WHO) Grade III gliomas, are malignant brain tumors that include anaplastic astrocytoma (AA), anaplastic oligodendroglioma (AO), anaplastic oligoastrocytoma, and anaplastic ependymoma. AA and AO are the most common subtypes of AG, comprising 10–15% [1] and 4–7% [2] of all gliomas, respectively. The median survival of patients with AG ranges from 2 to 5 years, depending on tumor subtype [3]. However, older AA patients have significantly shorter survival, with 2 year survival rates of 6.4% (age 65–74 years) and 4.1% for patients over 75 years of age [4]. Similarly, the 2 year relative survival probability of AO patients between 65–74 years of age is 29.5% and 4.9% for AO patients older than 75 years of age. In spite of the poor survival prognosis and the challenges involved in the treatment of these patients, very little is known about this population's overall prognosis and optimal management mainly because they have been excluded from most large randomized trials.

Although a standardized treatment for AG has yet to be established, many physicians support treatment with maximal safe surgical resection followed by postoperative RT [5]. In the case of AO, some physicians are deferring the use of RT in patients where allelic co-deletions of chromosomes 1p and 19q (1p/19q co-deletion) are present [6], as adjuvant chemotherapy has been shown to improve survival in AO patients with 1p/19q co-deletion. Most clinical trials have shown modest benefits with respect to adjuvant chemotherapy in the treatment of newly diagnosed AA [7]. Despite a lack of support from clinical trials, many advocate treating AA with the Stupp regimen – adjuvant RT plus concurrent and

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adjuvant temozolomide (TMZ) following surgical resection, principally predicated on clinical outcomes from the glioblastoma multiforme (GBM) literature [8].

The optimal management of AG in the elderly is even more controversial as the risk and benefits of adjuvant treatment with RT and/or chemotherapy remain debated, particularly because of the poorer prognosis and higher frequency of comorbidities within this demographic. Proponents of adjuvant RT cite the dangerous myelosuppressive complications of chemotherapeutic agents, while those favoring chemotherapy maintain that the neurologic toxicity associated with RT in the elderly, such as significant cognitive impairment, outweighs its clinical benefits [9].

In order to help clarify the role of RT in the management of elderly AG patients, our study sought to assess the effectiveness of RT in patients greater than 70 years of age with newly diagnosed AA and AO.

2. Materials and methods

Patients were extracted retrospectively from the Surveillance, Epidemiology, and End Results (SEER) registry database. The SEER registry is maintained by the USA National Cancer Institute, which has collected incidence and survival data from up to 17 population-based cancer registries covering approximately 26% of the USA population since 1973. The database contains information on patient demographics, primary tumor site, histology, stage at diagnosis, treatment regimens including surgery, extent of surgical resection, and postoperative radiation treatment, as well as year of death. Our cohort included patients in all 17 registries from the SEER database between 1990 and 2008 that met our inclusion criteria.

We identified patients diagnosed with AA and AO according to International Classification of Disease for Oncology, Third Edition histology codes (codes 9401 for AA and 9451 for AO). Only patients over 70 years of age were included in this analysis. Only patients that received postoperative RT within 30 days after the date of surgery or biopsy were included. Patients without histological confirmation of tumor type were excluded from analysis. The total number of AA and AO patients documented in the SEER database before applying our inclusion criteria is reported in Supplementary Table 1. This preliminary analysis of all patients showed the ratio of AA *versus* AO tumor classification in 1970 and 1980 was not consistent with recent years (1990–2008). This relates to the inaccuracy with which AA and AO were classified in the 1970s and 1980s, a system which has since evolved and improved. For this reason, the current study opted to include only patients that were diagnosed between 1990 and 2008 even though initial analysis involved a larger cohort (1973–2008).

Demographic characteristics extracted from SEER included a patient's age, race, marital status, and sex. Clinical variables included extent of surgical resection, postoperative RT, combination therapy, number of primary tumors, and overall survival (OS). For the purpose of this study marital status was categorized as married *versus* unmarried. Furthermore, extent of resection was categorized as surgical resection (gross total resection [GTR], partial resection, and surgery not otherwise specified [NOS]) *versus* biopsy. Decade of treatment was divided into treatment received in the 1990s *versus* 2000s. Combination therapy was defined as surgical resection plus RT *versus* surgery alone. Tumor size was not included in this analysis due to the large amount of missing data for this variable (37.2%). Data regarding the use of adjuvant chemotherapy was not available in the SEER database. The main outcome of interest in this study was OS time, which was calculated from diagnosis date to date of death for deceased patients, or last follow-up visit for patients still alive. Observations were censored when a patient was alive at the time of last follow-up.

2.1. Statistical analysis

OS was compared between AA and AO patients via Kaplan–Meier estimates with log-rank tests used to compare survival distribution between these groups. Cox proportional hazards models were used to assess the prognostic value of patient, tumor, and treatment factors in predicting a patient's OS. Hazard ratios (HR), 95% confidence intervals (CI), and p values were reported throughout. A p value $\leqslant .05$ was considered to be statistically significant. All analyses were conducted with SAS software (version 9.2; SAS Inc., Cary, NC, USA).

3. Results

3.1. Demographics

A total of 390 elderly AG patients were analyzed in this study, 333 (85.4%) AA and 57 (14.6%) AO. The mean age of patients from both cohorts was 77 years old. Both AA and AO patients had similar characteristics (sex, race, marital status, tumor primaries, and RT rate) except for the distribution of extent of surgical resection. Most AA patients underwent a biopsy (58.9%), 13.8% had a partial resection, and GTR was achieved in 11.4% of patients. Biopsy (42.1%) followed by GTR (36.8%) and partial resection (19.3%) were the types of surgical rates observed in AO patients. AO patients underwent relatively more surgery plus RT (35.1% *versus* 27.6%) and GTR plus RT (22.8% *versus* 7.6%) than AA patients (Table 1).

3.2. OS

The median survival for all patients with AG ($n = 390$) was 4 months (Table 2), with 1, 2, and 3 year OS rates of 21.1%, 6.1%, and 4.4%, respectively. More specifically, the 1, 2, and 3 year OS rates for elderly AA patients ($n = 333$) were 19%, 5.5%, and 3.8%, respectively (Table 2). The 1, 2, and 3 year OS rates for elderly AO patients ($n = 57$) were 33.3%, 9.3%, and 7.4%, respectively. The median OS for elderly AO patients was significantly longer than elderly AA patients (6 months *versus* 4 months, $p < .006$) (Fig. 1).

3.3. Univariate analysis of survival in all AG patients

Univariate analysis for all 390 elderly AG patients showed that sex ($p = .007$), use of RT ($p < .0001$), extent of resection ($p = .0003$), and treatment regimen (surgery plus RT *versus* surgery alone *versus* GTR plus RT; $p < .0001$) were associated with significantly different survival distributions. Within this collective cohort, all female patients had a median OS of 5 months (95% CI 4–6) compared with 3 months (95% CI 3–4) for all male patients. The median OS for all patients who underwent RT was 6 months (95% CI 5–7) *versus* 2 months (95% CI 1–6) in patients who did not have RT. Patients who underwent GTR had the longest median survival (7 months, 95% CI 4–10), while those who had biopsy (4 months, 95% CI 3–4) and "other" surgery NOS (3 months, 95% CI 2–4) had the shortest median survival. All patients who underwent surgery plus RT had a median OS of 6 months (95% CI 5–9) while patients who underwent surgery alone had a median OS of 2 months (95% CI 2–3) (Fig. 2). Patients who underwent GTR plus RT had the highest median OS of 11 months (95% CI 7–14). Race, marital status, number of tumor primaries, and later decade of treatment did not significantly influence survival (Table 3).

3.4. Multivariate analysis of survival in all AG patients

Multivariate analysis for all patients revealed a 48% reduction in the hazards of mortality in patients receiving RT (HR 0.52, 95% CI