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Type 2 diabetes is an independent negative prognostic factor in patients undergoing surgical resection of a WHO grade I meningioma

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ABSTRACT

Objectives: In recent years, there has been increased recognition of the relationship between type 2 diabetes mellitus (DM) and poor outcomes following a variety of surgical procedures. We sought to study the role of type 2 DM as a prognostic factor affecting the long-term survival of patients undergoing surgical resection of a WHO Grade I meningioma.
Methods: We conducted a retrospective cohort study on 196 patients who had a WHO Grade I meningioma resected at our institution between 2001 and 2013. The medical record was reviewed to identify a pre-existing diagnosis of type 2 DM. Patient mortality was reviewed by medical record and Social Security Death Index (SSDI). Variables associated with survival in a univariate analysis were included in the multivariate Cox model if $P < 0.10$. Variables with probability values >0.05 were then removed from the multivariate model in a step-wise fashion.
Results: 33 (17%) patients had pre-existing diagnoses of type 2 DM prior to clinical presentation. Mean survival time in diabetic patients was 52.1 months compared to 160.9 months in non-diabetics. The decreased survival rate and time in patients with type 2 DM were found to be statistically significant ($p = 0.008$ and $p < 0.0001$, respectively). In a multivariate Cox analysis, a pre-existing history of type 2 DM was independently associated with decreased survival following the resection of a WHO Grade I meningioma ($HR = 2.6$, $p = 0.045$).
Conclusions: A pre-existing diagnosis of type 2 DM is an independent negative prognostic indicator following the resection of a WHO Grade I meningioma.

1. Introduction

Intracranial meningiomas are the most frequently diagnosed primary brain tumors, accounting for roughly 1/3 of all diagnoses [1,2]. The majority of meningiomas carry a favorable prognosis, and amongst the operative cases the risk of postoperative morbidity and mortality is fairly low [3–5]. However, a number of factors have been associated with higher risk of perioperative complications and long-term mortality. Patient age, tumor size, pathological grade, tumor location, and extent of surgical resection are previously identified prognostic variables in patients undergoing a meningioma resection [6–12].

In recent years, there has been increasing interest in the relationship between type 2 diabetes mellitus (DM) and outcomes in a number of brain tumor patient populations. In particular, in patients with high-grade gliomas, pre-existing diagnoses of type 2 DM and postoperative hyperglycemia have been identified as independent predictors of decreased survival [13–16]. We sought to study the role of type 2 DM in predicting the long-term

Abbreviations: BMI, Body mass index; CI, Confidence interval; DM, Diabetes mellitus; GTR, Gross-total resection; HR, Hazard ratio; KPS, Karnofsky Performance Status; MRI, Magnetic resonance imaging; SSDI, Social Security Death Index; WHO, World Health Organization.

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survival in patients undergoing surgical resection of a WHO Grade I meningioma.

2. Methods

2.1. Patient population

We conducted a retrospective cohort study on 196 patients who had a primary intracranial WHO Grade I meningioma resected at our institution between 2001 and 2013. For patients with a history of multiple meningioma resections at our institution, only data with regard to the initial resection was used in the study. Four attending neurosurgeons with specialized training in neurosurgical oncology performed all resections. All patients included in the study received a 1-week course of oral dexamethasone following surgical resection.

2.2. Data collection and study variables

Records of clinical and radiographic data were retrospectively obtained from the electronic medical record and entered into a REDCap database [17]. All such entries in the medical record were reviewed from the time of initial clinical presentation to date of last chart review, 9/14/2015. Patient age, gender, pre-existing diagnoses of type 2 DM, body mass index (BMI), peri-operative blood glucose levels, extent of surgical resection, tumor pathological grade, details of any radiation therapy, Karnofsky Performance Status (KPS) scores, and duration of follow-up were reviewed from the medical record.

Patient age was defined as age at time of operation. A *pre-existing diagnosis of type 2 DM* variable was created based on a clinical history of type 2 diabetes at least 6 months prior to the radiographic diagnosis of an intracranial meningioma. Patients with a history of type 1 DM were excluded from the study. Patients with new diagnoses of type 2 DM subsequent to clinical presentation and surgical resection of the meningioma were not designated as diabetics in this study. BMI was calculated from the preoperative patient assessment. A *preoperative blood glucose level* variable was defined based on the latest available fasting blood glucose prior to the date of surgery. A *postoperative blood glucose level* variable was defined as the patient's fasting blood glucose at the time of first postoperative outpatient clinical assessment. All blood glucose levels are reported in mg/dL.

Extent of surgical resection was classified as gross-total resection (GTR) or incomplete resection based on the interpretation of the immediate postoperative magnetic resonance imaging (MRI) scan by the neuroradiologist. Tumor grade was assigned as WHO Grade I, II, or III based on the neuropathologist's assessment of the tumor subsequent to the resection. Patients with WHO Grade II or III meningiomas were not included in the study. The medical record was also reviewed for any concomitant radiation therapy. Patients who had any radiation therapy of a meningioma were excluded from the study. KPS scores were assigned based on clinical assessment, both preoperatively at time of presentation and postoperatively at time of first postoperative clinic visit. A *duration of follow-up* variable was defined as the time between the operation and the last clinic visit with the attending neurosurgeon.

Patient mortality was reviewed by medical record and Social Security Death Index (SSDI) [18]. Phone calls to patient household were attempted if medical record and SSDI search results were equivocal. 3 patients with uncertain survival as of 9/14/2015 were excluded from the study. The dates and causes of death were recorded where applicable. When the exact date of death was not available, it was estimated as the first day of the month of confirmed mortality.

2.3. Statistical analysis

All information was de-identified prior to statistical analysis in Microsoft Excel (Redmond, WA, USA) and IBM SPSS Statistics (Armonk, NY, USA) [19,20]. Mean, standard deviation, and median were computed for continuous variables; frequency and percentage were computed for categorical variables. Descriptive statistics were performed using Fisher's exact test for categorical variables and Mann Whitney *U* test for continuous variables. Survival as a function of time after surgical resection was depicted using Kaplan-Meier survival analysis. The log-rank test was used to analyze the differences in the probability of survival between diabetics and non-diabetics. A multivariable Cox-proportional hazard logistic regression model was built to determine the predictors of survival. The independent variables including age, gender, pre-existing history of type 2 DM, BMI, preoperative blood glucose, postoperative blood glucose, pre-operative KPS, peri-operative change in KPS, and extent of surgical resection were included in the model. The variables with p value more than 0.05 were removed from the model in a step-wise fashion. For all analysis, a p-value of less than or equal to 0.05 was considered statistically significant.

3. Results

A total of 196 patients met the inclusion criteria and were evaluated in this study. The mean age at time of operative resection was 55.5 ± 13.9 years. The patient population included 152 (78%) females and 44 (22%) males. Mean BMI at time of surgical intervention was 30.1 ± 8.8. GTR of the meningioma was accomplished in 162 (83%) patients. The mean pre-operative KPS score was 76.8 ± 11.6 and patients experienced a mean increase in KPS score of 4.1 ± 14.2 postoperatively. Mean pre-operative blood glucose in all patients was 111.3 ± 37.2 mg/dL. Post-operatively, mean blood glucose had increased to 165.3 ± 31.9 mg/dL ($p < 0.001$). Mean duration of postoperative follow-up was 40.3 ± 32.4 months.

Thirty-three (17%) patients had pre-existing diagnoses of type 2 DM prior to clinical presentation and 163 (83%) were non-diabetics. Statistically significant differences were found between diabetics and non-diabetics with regard to age at time of operation, gender, mean BMI, peri-operative changes in KPS, in addition to mean pre-operative and post-operative blood glucose levels. No significant difference was noted between the two groups with regard to extent of surgical resection, mean pre-operative KPS, or duration of postoperative clinical follow-up. These findings are summarized in Table 1.

As of last chart review, we were able to confirm death in 8 (24%) patients with type 2 diabetes and in 12 (7%) non-diabetics. The relatively increased rate of mortality in type 2 diabetics was statistically significant ($p = 0.008$). Patients with diabetes had significantly lower mean survival time (52.1 ± 11.6 months) compared to non-diabetics (160.0 ± 22.7 months) ($p < 0.001$). A comparison of patient mortality between these two groups is provided via a Kaplan-Meier plot in Fig. 1.

In a multivariate proportional hazard cox-regression analysis, a pre-existing diagnosis of type 2 diabetes (HR = 2.7, 95% CI = 1.02-7.07, $p = 0.045$) and increasing age at time of operation (HR = 1.1, 95% CI = 1.03-1.12, $p = 0.001$) were independent predictors of decreased survival. Increasing peri-operative KPS scores (HR = 0.94, 95% CI = 0.91-0.96, $p = 0.0001$) were independently associated with increased survival. These findings are summarized in Table 2. Increasing BMI (HR = 1.01, 95% CI = 0.92-1.2, $p = 0.82$) and male sex (HR = 1.58, CI = 0.55-4.52, $p = 0.40$) were not found to be an independent predictor of mortality.