Journal of the Neurological Sciences 387 (2018) 205–209

Contents lists available at ScienceDirect

Journal of the Neurological Sciences

journal homepage: www.elsevier.com/locate/jns

Radiation-induced meningiomas: A case-control study at single center institution

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ABSTRACT

Background: Our understanding of radiation induced meningiomas (RIM) is limited. It has been suggested that RIM harbor more aggressive cellular pathology and must be observed vigilantly. However, the actual recurrence rates of RIM compared to the sporadic meningiomas has yet to be defined.

Objective: We employ a single center case-control study to retrospectively assess recurrence rates between RIM ($n = 12$) and sporadic meningiomas ($n = 118$).

Methods: The criteria for the RIM group included the following: 1) History of intracranial clinical-dose radiation 2) Initial pathology other than meningioma, 3) Radiation administered greater than 5 years prior to meningioma onset. Recurrence rates, extent of resection and outcomes were analyzed.

Results: There was a significant difference in recurrence rates between the RIM group and sporadic meningioma: 50% vs. 5% respectively, $p = 0.004$. There was no significant difference in race, preoperative tumor volume, extent of resection, Ki67, or age between the two groups. Multivariate analysis demonstrated that size (OR 0.95 95%CI (0.92–0.99)), extent of resection (OR 1.08 95%CI (1.01–1.14)), WHO grade (OR 160.24 95% CI (6.32–74509)) and history of previous radiation (OR 1.28 95%CI (1.01–1.62)) were independent risk factors for recurrence. RIM patients had significantly higher proportion of atypical or malignant histology compared to sporadic patients ($p < 0.0001$).

Conclusion: RIM patients may have a higher predisposition for tumor recurrence than patients with sporadic RIM. The use of Ki67 indices may help identify patients with a higher risk of tumor recurrence. Prospective studies focusing on newly diagnosed patients with RIM may help identify an optimal surveillance and treatment plan.

1. Introduction

Early after the invention of the radiograph in the late 19th century, an association between radiation exposure and neoplasms was observed [1,2]. Several decades of research in the post-nuclear era identified meningiomas as common radiation-induced neoplasms in certain affected populations [3–6]. As this occurrence has become more widely accepted with more newly diagnosed patients, the clinical implications of radiation-induced meningiomas (RIM) remained unclear.

Several important management questions remain unanswered regarding histopathology, complications, recurrence rates and epidemiology of RIM. The paucity of data is largely due to the fact that most of our clinical experience has arisen from small clinical series and case reports [7–11]. The largest clinical series of RIM in the Tinea Capitis group (253 patients) suggested that RIM have an increased rate of recurrence compared to sporadic meningiomas, though their data was not statistically significant [12]. Other large studies fail to provide adequate follow-up or simply do not report recurrence rates for their patient series [13]. From this data, it has been theorized that RIM may harbor more aggressive cellular pathology and must be observed vigilantly [10]. However, the actual recurrence rates of RIM compared to the sporadic meningiomas has yet to be defined.

Here we present a case-control study at a single center institution designed to address the following objective: to compare recurrence rates, histopathology and outcomes between radiation induced meningiomas and a sporadic meningioma cohort.

2. Methods

The Institutional Review Board approved this study prior to

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https://doi.org/10.1016/j.jns.2018.02.033
Received 17 November 2017; Received in revised form 21 January 2018; Accepted 20 February 2018
Available online 21 February 2018
0022-510X/

retrospective review of patient data. No patient consent was needed due to the retrospective nature of our study. We screened over 2000 patients from 2000–2016, and excluded patients with insufficient follow-up or records. Consequently, 130 patients with intracranial meningiomas were isolated from an electronic billing database at a single tertiary care referral center with appropriate clinical and radiographic follow up. In all cases, a neuropathologist confirmed the diagnosis of meningioma using standard diagnostic classification systems (World Health Organization Classification System) [14]. All patients were initially screened into two main categories (radiation-induced) and sporadic (de novo). The criteria for including patients in the RIM group included the following:

1. History of intracranial clinical-dose radiation in the past (prophylactic, or therapeutic radiation).
2. Initial intracranial pathology that differed from meningioma
3. Radiation must have been administered greater than 5 years from meningioma onset.

Patients without a history of clinical radiation were defaulted to the sporadic group.

For all patients included, maximal safe resection was attempted when feasible. Patients without adequate follow-up/outcome data, operative reports, or hospitalization information were excluded. If follow-up was inadequate (< 6 weeks), patients were excluded.

Relevant demographic variables, radiation history, pathology, and operative data were included. Careful attention was given to ensure that adequate follow up was obtained on all patients. Extent of resection was determined by either post-operative imaging or by the surgeon's description in the operative report. Time to recurrence was recorded when applicable. Lesion volumetry was also estimated using approximations from standard formulas using a three-dimensional plane.

2.1. Statistical analysis

Wilcoxon and Fisher Exact tests were used to characterize ethnic subgroups to assess for significant discrepancies in age, incidence of comorbidities, extent of resection, and use of adjuvant therapy in sizeable sample groups ($n > 10$). Logistic regression (univariate and multivariate analysis) were performed to assess for risk factors for recurrence. P-value < 0.05 was considered statistically significant. R Statistic software was used for all statistical analysis (version 3.0.2, R Foundation for Statistical Computing).

3. Results

Our data was reported in accordance to the STROBE guidelines as previously mentioned by the EQUATOR network. RIM ($n = 12$) and sporadic group ($n = 118$) combined for a total of 130 patients for the study. Demographics were compared between the two groups and no statistical difference was identified between the two groups except for race where there was a larger proportion of white patients in the sporadic cohort ($p = 0.002$). Additionally, RIM patients had significantly higher proportion of atypical or malignant histology compared to sporadic patients (RIM: 41% vs. sporadic: 5%, < 0.0001) (Table 1). Males composed 28% ($n = 33$) and 42% ($n = 5$) of the sporadic and RIM group, respectively ($p = 0.33$). There was no statistical difference in calculated preoperative volumes between the sporadic group and RIM group (150 and 82 cc respectively, $p = 0.36$.) Extent of resection as calculated by Simpson grading system was not statistically different between the groups ($p = 0.20$) although proportionally more patients had a Simpson Grade 1 resection in the RIM group ($n = 9$, 75%) vs. sporadic ($n = 69$, 60%). The presence of multiple meningiomas was more common in the RIM group ($p < 0.0001$, $n = 7$, 58%) vs. the sporadic group ($n = 4$, 3%). Follow-up time between both groups was not statistically different between sporadic and RIM respectively (50 vs. 58 months, $p = 0.29$).

Table 1
Baseline characteristics of the 130 subjects with meningioma.

Patient characteristics	Sporadic ($N = 118$)	RIM ($N = 12$)	p-Value
Age (years) (IQR)	42 (37–47)	42 (31–48)	0.87
Gender			
Male n (%)	33 (28%)	5 (42%)	0.33
Female n (%)	85 (72%)	7 (58%)	
Race			
White n (%)	86 (73%)	7 (58%)	0.002
African American n (%)	29 (25%)	2 (17%)	
Hispanic n (%)	0 (0%)	3 (25%)	
Asian n (%)	3 (3%)	0 (0%)	
Size (cm) (IQR)	3.5 (2–5.3)	2.5 (1.8–4.8)	0.49
Volume (cc) (IQR)	150 (33–462)	82 (37–316)	0.36
Simpson			
I n (%)	69 (60%)	9 (75%)	0.18
II n (%)	27 (24%)	0 (0%)	
III n (%)	2 (2%)	0 (0%)	
IV n (%)	17 (15%)	3 (25%)	
Ki67 ($N = 59$)			
Low (< 5%)	38 (64%)	2 (17%)	
High	21 (36%)	10 (83%)	
Multiple meningiomas n (%)	4 (3%)	7 (58%)	< 0.0001
Hyperostosis n (%)	7 (6%)	2 (17%)	0.20
Follow-up (months)	50 (13–85)	58 (14–84)	0.29

Abbreviations: Interquartile range: IQR.
Wilcox test and Fisher test.

Recurrence rates were significantly different between both groups (sporadic = 5% vs. RIM = 50%, $p = 0.003$). Time to recurrence between the groups was not significantly different (28.01 months vs. 49.8 months, $p = 0.263$) (Fig. 1 and Table 2). A summary of features of the RIM subgroup are summarized in Table 3. Univariate analysis suggested a relationship between tumor recurrence and multiple factors including multiple meningiomas, WHO grade, preoperative tumor size, volume, extent of resection, and history of radiation (Table 4). Multivariate analysis however demonstrated that WHO grading ($p = 0.03$), preoperative tumor size ($p = 0.01$) and extent of resection ($p = 0.005$) were independently associated with tumor recurrence. Multivariate analysis revealed a trend towards recurrence in RIM patients ($p = 0.07$) (Table 5).

4. Discussion

In the late 19th century, the early effects of radiation were first identified. One of the earliest victims was a child who suffered an accidental gunshot wound and subsequently suffered from marked epilation after exposure to a roentgenogram [15,16]. Shortly after, Herman Muller in 1927 reported mutational changes that were induced by X-ray radiation in mosquitos. [17] Although nervous tissue was believed to be relatively resistant to radiation, the atomic bombs of Hiroshima and Nagasaki in the mid 20th century demonstrated clear radiation-induced neural changes. [18,19] Over the next several decades, it became apparent that patients with significant radiation exposure possessed faulty DNA repair mechanisms and thereby had a higher propensity for both hematological and solid neoplasms including meningiomas. [20]

After the Atomic Bomb Survivor Life Span study and Tinea Capitis study, radiation exposure was linked to an increased incidence of meningiomas. [10]. In the radiated Tinea Capitis group (253 cases), significant differences were noted between RIM and non-RIM patients (younger age at diagnosis, higher prevalence of calvarial tumors, higher proportion of multiple meningiomas). These long-term studies identified that a 36-year mean latency period for the development of radiation-induced meningiomas. However, time to recurrence (RIM: 5.8 vs. non-RIM: 5.3 years) and recurrence rates (18.2% vs. 14.6%) were not