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Clinical Study

Meningioma after radiotherapy for malignancy

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ABSTRACT

Complications of radiation exposure have gained importance with increasing cancer survivorship. Secondary malignancies have been associated with cranial radiation exposure. We present our experience with intracranial radiation-induced meningioma (RIM) and discuss the implications of its presentation and natural history for patient management. Patients diagnosed with meningioma who had received radiation therapy between 1960 and 2014 were identified. Records were retrospectively reviewed for details of radiation exposure, previous malignancies, meningioma subtypes, multiplicity and pathologic descriptions, treatment and follow-up. Thirty patients were diagnosed with RIM. Initial malignancies included acute lymphocytic leukemia (33.3%), medulloblastoma (26.7%) and glioma (16.7%) at a mean age of 8.1 years (range 0.04–33 years). The mean radiation dose was 34 Gy (range 16–60 Gy) and latency time to meningioma was 26 years (range 8–51 years). Twenty-one patients (70%) underwent surgery. Of these, 57.1% of tumors were World Health Organization (WHO) grade I while 42.9% were WHO II (atypical). The mean MIB-1 labeling index for patients with WHO I tumors was 5.44%, with 33.3% exhibiting at least 5% staining. Mean follow-up after meningioma diagnosis was 5.8 years. Mortality was zero during the follow-up period. Meningioma is an important long-term complication of therapeutic radiation. While more aggressive pathology occurs more frequently in RIM than in sporadic meningioma, it remains unclear whether this translates into an effect on survival. Further study should be aimed at delineating the risks and benefits of routine surveillance for the development of secondary neoplasms after radiation therapy.

1. Introduction

After the discovery of X-rays in the late 1800 s, radiation for an array of applications became increasingly widespread in the early twentieth century. Shortly after its inception, it became clear that radiation could also have harmful effects, though its potential to induce malignancy did not come to the forefront until the extensive exposures associated with atomic explosions in Hiroshima and Nagasaki [1].

Meningioma as a consequence of radiation exposure has been described in multiple settings. Secondary neoplasia has been shown to be a dose-dependent phenomenon, whether accidental or for intended therapeutic purposes [1–4]. Although the definition of radiation-induced meningioma (RIM) is not standardized, meningioma within a previously irradiated field is the most broad and common diagnostic criterion [1]. As we consider the clinical implications of RIM, the effects of radiation dose on subsequent management decisions cannot be ignored. Standard follow-up surveillance for patients receiving radiation is not well established, and the amount of radiation exposure has a significant impact on the potential for subsequent complications. Studies performed over the last 20 years have focused on large population-based exposure studies [4], low dose exposures with long-term follow-up [2] and individual reports or small series of cases after therapeutic radiation [5–10].

While these studies have established a relationship between radiation dose and the development of meningioma, and a trend

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toward more aggressive pathologies, a cohort of patients who have developed meningioma after high dose radiation for prior malignancy has not been explored in detail. We present a series of patients who developed RIM after therapeutic radiation and discuss potential implications for screening procedures and management of these individuals.

2. Methods

This study was approved by the Memorial Sloan Kettering Cancer Center Institutional Review Board. Patients were identified by query of the institution's electronic medical records. Brain tumor diagnosis data was used, with data available from 1991–2014, to identify patients with a diagnosis of meningioma of any pathologic subtype who had also received prior radiation therapy for malignancy. These patients were screened for timing of radiation therapy greater than 5 years prior to meningioma diagnosis documented in the patient record, for which records were available dating back to 1960. Further screening selected patients whose radiation field included the meningioma site and a latency period of 5 years or greater in order to exclude coincidental sporadic meningioma.

Thirty patients were identified with radiation exposure occurring between 1960 and 1997. Meningioma diagnoses occurred between 1997 and 2014. Patient records were retrospectively reviewed and data collected regarding dates, doses and fields of radiation exposure, previous malignancies, meningioma subtypes, multiplicity and pathologic descriptions, treatments and follow-up. Pathology data was reviewed to ensure that assigned World Health Organization (WHO) grade was consistent with the 2007 criteria. MIB-1 labeling was recorded when available, as standard practice at this institution is to measure this index of proliferation for WHO I meningioma. MIB-1 index was measured by an attending pathologist by manual count using an ocular grid superimposed over an area containing >1000 tumor cells. Recurrent RIM was defined as meningioma reoccurring at the same site after complete resection.

Descriptive statistics such as frequencies, medians, means, and ranges were utilized for characterization of the population under study. Correlation between total radiation dose to the meningioma site and latency in this series was analyzed by Pearson correlation coefficient. Correlations between receipt of chemotherapy and categorical characteristics of interest (WHO grade, and age at radiation dichotomized at 5 years) were examined with Fisher's exact test. Correlations between receipt of chemotherapy and continuous characteristics of interest (latency and MIB) were analyzed with the Wilcoxon rank sum test. All p-values were two-sided with a level of significance less than 0.05 and all statistical analyses were done in SAS (version 9.4, SAS Institute, Cary, NC, USA).

3. Results

Thirteen women and 17 men were diagnosed with RIM. The mean age at diagnosis of the primary malignancy was 8.1 years (range 0.04–33 years). Common initial malignancies included acute lymphocytic leukemia (33.3%), medulloblastoma (26.7%), and glioma (16.7%) and the mean radiation dose was 34 Gy (range 16–60 Gy, Table 1). The mean age at RIM diagnosis was 34.7 years (range 12.2–57.7), and mean latency time to meningioma diagnosis was 26 years (range 8–51 years, Table 2).

Patients were most commonly asymptomatic at diagnosis (60.0%), while 26.7% of patients presented with headache and a smaller number with other signs and symptoms (Table 2). There was no difference in latency time between patients receiving radiation under or over the age of 5 years ($p = 0.95$) and no correlation between radiation dose and latency time ($r^2 = 0.11$, $p = 0.64$). Patients receiving chemotherapy had a significantly later date of primary diagnosis (72% after 1983 *versus* 18% before 1983, $p = 0.0047$) and shorter latency period between radiation therapy and meningioma diagnosis than those who were not treated with chemotherapy for their first malignancy (21 *versus* 32 years, $p = 0.03$, Table 3). Supratentorial meningiomas comprised 80.0%, while the remainder were intraventricular or occurred in the posterior fossa (Table 4).

Twenty-one patients (70.0%) were treated with surgical resection, one patient (3.3%) was treated with radiation therapy and eight (26.7%) were observed without intervention (Table 2). Of those undergoing surgical resection, 57.1% were WHO I and 42.9% were WHO II (Table 5). The mean MIB-1 labeling index for patients with WHO I tumors was 5.44%, with 33.3% exhibiting $\geqslant$5% staining (Table 6). The mean number of meningiomas per patient in the cohort was 1.6 (range 1–6). Ten patients had multiple lesions. The mean duration of follow-up after meningioma

Table 1
Characteristics of initial presentation and management of 30 patients undergoing radiation therapy and subsequently developing meningioma

Characteristic	Value (%)
Sex	
Male	17 (56.7)
Female	13 (43.3)
Age in years	
Mean	8.1
Median	6
Range	0.04–33
Primary malignancy	
Acute lymphocytic leukemia	10 (33.3)
Medulloblastoma	8 (26.7)
Glioma	5 (16.7)
Retinoblastoma	2 (6.7)
Ependymoma	2 (6.7)
Lymphoma	1 (3.3)
Neuroblastoma	1 (3.3)
Sarcoma	1 (3.3
Radiation dose	
Mean	34 Gy
Median	34 Gy
Range	16–60 Gy

Table 2
Characteristics of 30 patients at radiation-induced meningioma diagnosis and management

Meningioma characteristics	Value (%)
Age at presentation in years	
Mean	34.7
Median	33.6
Range	12.2–57.7
Latency period in years	
Mean	26
Median	23
Range	8-51
Presenting signs/symptoms	
Asymptomatic	18 (60.0)
Headache	8 (26.7)
Seizure	1 (3.3)
Focal deficit	1 (3.3)
Visual loss	2 (6.7)
Physical deformity	1 (6.7)
Neck pain	1 (6.7)
Unknown	1 (6.7)
Management	
Observation	8 (26.7)
Surgical resection	21 (70.0)
Radiation therapy	1 (3.3)