Meningiomas are relatively common extra-axial primary neoplasms that arise from arachnoid cap cells in the outer layer of the leptomeninges of the cranial and spinal compartments [1-4]. They are found in any area of the central nervous system (CNS) but are most common over the cerebral convexities or at the cranial base [4]. Meningiomas comprise approximately 33% of all primary brain tumors and the overall incidence in the general population is 2.3/100,000 people [1-4]. The incidence of intracranial meningiomas increases with each decade of life of intracranial meningiomas increases with each decade of life [4-8,10]. Meningiomas are categorized by the World Health Organization (WHO) into three grades that reflect increasing histological anaplasia and portend increasingly aggressive tumor behavior with greater risk of recurrence [6,16,17]. Other grading systems exist, including the Mayo system based on similarly objective histological criteria but the WHO system is most accepted [16,17]. A higher percentage of meningiomas in patients under the age of 20 years are histologically atypical [4-16]. Other meningiomas and intraventricular and infratentorial meningiomas are also more common in the younger age groups [4-7].

Meningiomas may occur sporadically or as part of a familial syndrome such as neurofibromatosis 2 (NF2), meningioangiomatosis (MA), or Gorlin's syndrome [1,6,9]. Genetic studies suggest meningiomas are clonal outgrowths from a single mutated cell and are frequently associated with chromosomal abnormalities which increase in frequency and complexity with increasing histological grade [1]. Deletion or inactivation of the NF2 gene on chromosome 22 is frequently seen in sporadic meningiomas [4-10]. Meningiomas are analyzed according to the World Health Organization (WHO) grading system, which includes grades I, II, and III. Grade I meningiomas are the most common and are characterized by well-differentiated tumor cells with minimal atypical features. Grade II meningiomas are characterized by increased cellularity and atypia, while grade III meningiomas are characterized by extensive cellular pleomorphism and mitotic activity.

Intracranial meningiomas are rare in individuals under age 30 years. The purpose of this study was to analyze the demographics and clinical features of intracranial meningiomas in individuals under age 30 years. A retrospective analysis of clinical, radiographic, and pathology data of patients under age 30 years who presented with an intracranial meningioma was performed.

Results: Thirty five patients met the criteria. Mean age was 25 years, 11 were male and 24 female. Five patients had previous radiation exposure. The presenting symptom was headache in 16 patients (45.7%) and seizure in 9 (25.7%). Cranial base tumors comprised 74%; 26% were supratentorial. Simpson grade 1 or 2 resection was achieved in 16 patients (48.5%); grade 3 or 4 resection was achieved in 17 patients (51.5%). Tumor pathologic grade was WHO grade I in 27 (77.1%), grade II in 6 (17.1%) and grade III in 2 patients (5.7%). Postoperative radiation therapy for tumor progression was administered in 13 patients. Radiographic follow-up was available in 26 patients at an average of 6.1 years after surgery; of these, 14 had no recurrence or progression of residual tumor while 12 had recurrence or progression. Recurrence was more common in patients with WHO grade II and III tumors and radiation-induced meningiomas. Recurrent tumors tended to have a higher WHO grade.

Conclusion: In this group of intracranial meningiomas in individuals <30 years, ionizing radiation was a risk factor and tumors were more common in females. A higher percentage of WHO grade II and III tumors at presentation and recurrence was noted. Recurrent tumors were more common in patients with higher WHO grade and in radiation-induced meningiomas.

Keywords: Meningioma, young adults, risk factors, radiation induced meningioma
meningiomas, although 1p, 6q, 14q, and 18q deletions have also been reported [1,5-9]. Older patients tend to have sporadic tumors while patients under the age of 20 years tend to have meningiomas associated with one of these three syndromes [1,6,9]. Among exogenous factors, cranial ionizing radiation is the only exposure that confers an increased risk of intracranial meningioma formation [1,4,6,14-16]. Individuals are exposed to cranial ionizing radiation in various forms; it may be administered during the course of diagnostic studies, or as part of a therapeutic prophylactic or treatment protocol, or accidental exposure from inadvertent or accidental environmental sources may occur [4,6,8].

Previous studies have evaluated the demographics and clinical features of meningiomas in individuals under the age of 20 years [5-7,9-13,18]. This captures most meningiomas that occur as part of a familial syndrome or the rare sporadic meningioma in young individuals. However, given the long latency of post-radiation meningiomas, these tumors may not occur until the third decade of life. In addition, there are no studies that look at the occurrence of cranial base meningiomas in children and young adults. Our practice has a strong representation of cranial base tumors. The purpose of our study was to evaluate the demographics, risk factors, clinical presentation, radiological findings, histological findings, biological behavior, recurrence rates, and long-term outcome in patients who underwent initial surgical resection of a meningioma in the first three decades of life (<age 30 years) over the past 30 years at our institution.

**Methods**

Approval from the Institutional Review Board at Loyola University Medical Center/Stritch School of Medicine was obtained. A retrospective review of all cases of pathologically confirmed meningioma within the intracranial compartment in individuals under the age of 30 years at initial diagnosis treated at our institution over the past 30 years was performed. Patients were identified by clinical record review, ICD coding data, or from the neuropathology database. Each chart was reviewed for patient demographics, presenting symptoms and signs, tumor location and size, imaging findings, extent of surgical resection, histopathological findings, radiographic follow-up, tumor recurrence, and clinical outcome. The presence of genetic risk factors and exposure to cranial radiation was noted. Extent of tumor resection was determined by a review of the surgeon’s intraoperative impression and postoperative imaging studies when available and graded as per the Simpson grading system. Tumor histopathology and WHO grading was recorded along with the Ki-67 labeling index and progesterone receptor status, when available. Recurrence of tumor was defined as reappearance of tumor on imaging studies following Simpson Grade 1 or Grade 2 resection. Regrowth or progression of tumor was defined as any increase in size of known residual tumor on follow-up radiographic imaging. The need for repeat surgical intervention or use of radiation therapy following surgery was recorded. Length of follow-up was recorded along with Eastern cooperative oncology group (ECOG) performance score based on available clinical information at last evaluation.

Standard descriptive statistics are reported (Mean± standard deviation for numerical variables and frequency count and percentage for categorical variables). Kaplan-Meier method was used for analysis of time to recurrence or progression and Cox proportional hazards model was used to examine the association between recurrence or progression and WHO grade while controlling for age and sex. Ordinal logistic regression was used to assess the effect of WHO grade and extent of resection on ECOG score at last follow-up while controlling for age and sex. A prospectively determined p value equal to or less than 0.05 was used to imply a statistically significant difference. All statistical analysis was carried out using the SAS software package version 9.2 (SAS Institute Inc., Cary, NC).

**Results**

We identified 35 patients under the age of 30 years who were diagnosed with an intracranial meningioma at our institution over the past 30 years (Table 1). Mean age of the patients was 25 years (range 5-30 years) at the time of their initial surgery. Eleven were male (31.4%) and 24 were female (68.5%) and they underwent a total of 49 procedures. None of the patients had a diagnosis of neurofibromatosis or any other tumor syndrome. Five patients had previous exposure to ionizing radiation: two had childhood (at ages 5 and 6 years respectively) therapeutic prophylactic radiation for acute lymphocytic leukemia (ALL), one received craniospinal axis radiation at age 3 years for a posterior fossa medulloblastoma, one underwent radiation for the same tumor five years before presentation at our institution, and one patient had accidental exposure to environmental radiation. The latency period between radiation exposure and meningioma development in the two patients who received prophylactic cranial radiation for ALL was 24 and 25 years respectively and for the patient who received cranial radiation for medulloblastoma, it was 25 years. The latency period for the patient exposed to accidental environmental radiation was 20 years.

The most common presenting symptom was headache in 16 patients (45.7%) followed by seizure in 9 (25.7%), vision changes in 7 (20%), weakness in 3 (8.5%), and cranial nerve palsy in 2 (5.7%). Tumors were located in the posterior cranial fossa in 10 (28.5%), anterior cranial fossa in 9 (25.7%), at the sphenoid ridge in 7 (20%), and convexity or parafalcine location in 4 each (11.4% each). One tumor was located within the ventricle (2.9%). The average size of the tumor was 3.6 cm (Standard deviation: 1.74). Multiple meningiomas were noted in four patients (11.4%); two of these patients has previous radiation exposure. Time from diagnosis to surgery averaged 1.5 years. Six patients had had previous resections at outside institutions and one had previous radiation therapy to the same tumor without tissue diagnosis. In these seven
Table 1. Demographic and Clinical data for the 35 patients who presented with intracranial meningiomas at <30 years of age.

| Age group | Length of study | Number of patients | Average age | Sex ratio | Genetic syndrome | Radiation exposure | Presenting symptoms and signs | Location of tumors | Average size | Multiple tumors | Previous treatment | Simpson Grade of Resection (29 patients) | WHO Grade of Tumor | Radiographic followup | Average follow-up | ECOG at last follow-up |
|-----------|----------------|--------------------|-------------|-----------|------------------|-------------------|-------------------------|---------------------|-------------|----------------|------------------|----------------------------------------|----------------|-------------------|----------------|-------------------|
| <30 years | 30 years       | 35                 | 25.7 years (Range 5-30 years) | Male 12 : Female 23 Male 34.2% Female 65.8% | None            | 5 patients        | Headache 16 (45.7%) Seizure 9 (25.7%) | PCF 10 (28.5%) ACF 9 (25.7%) | 3.63 cm       | 3 (8.5%)        | Surgery 6 patients | Grade I: 8 (27%) Grade II: 6 (21%) | Grade I: 36 (73.4%) Grade II: 8 (16.3%) | No recurrence 8 (32%) Stable residual: 10 (40%) | 6.5 years | Grade 0: 7 (30%) Grade 1: 12 (52%) |

PCF: Posterior cranial fossa; ACF: Anterior cranial fossa; WHO: World Health Organization

patients, the indication for surgery was progression of tumor on radiographic imaging studies (Table 1).

Accurate estimation of resection by the Simpson grading system was possible in 33 of the 35 patients. Grades 1 and 2 were considered together; similarly, grades 3 and 4 were grouped together. Simpson grade 1 or 2 resection was achieved in 16 patients (48.5%) and Simpson grade 3 or 4 resection was achieved in 17 patients (51.5%). No patient had a Simpson grade 5 (biopsy only) resection. All the tumors had histopathological features consistent with a diagnosis of meningioma. Documentation of brain invasion was available in 26 patients; of these four patients had documentation that suggested brain invasion noted at the time of surgery. Tumor pathologic grade in the 35 initial surgical specimens were WHO grade I in 27 (77.1%), grade II in 6 (17.1%) and grade III in 2 patients (5.7%). Ten patients had more than one surgical procedure due to tumor recurrence producing 14 additional surgical specimens. Thus, when considering the total pathology database of 49 surgical specimens, WHO grade I tumors were noted in 36 (73.4%), WHO II in 8 (16.3%), and WHO III in 5 (10.2%). Information about progesterone receptor status was available in 15 patients. All these 15 specimens were progesterone receptor positive at the time of initial resection. In one patient, the recurrent tumor resection specimen converted to progesterone receptor negative at the second surgery. Monoclonal antibody MIB-1 Ki-67 labeling index information was available in 15 patients and ranged from 1.5-20%. In 9 (60%) patients, the Ki-67 labeling index was greater than 5%. In 33 patients, information was available about postoperative adjuvant radiation therapy. Of these, 13 patients (37.1%) had postoperative adjuvant radiation therapy; in 9 of these patients, the tumors were WHO grade I and in 4 patients, they were WHO grade II or III.

Clinical follow-up for all patients averaged 6.5 years. There were no deaths recorded in any patient with documented follow-up. Follow-up information permitted ECOG score estimation in 23 patients. ECOG 0 was noted in 7 patients (30%), ECOG 1 noted in 12 (52%), ECOG 2 in 3 (13%), and ECOG 3 in 1 patient (5%) (Table 2). Immediate or early postoperative complications after initial surgery included cranial nerve palsy in 8 patients (16.6%), cerebrospinal fluid (CSF) leak in 5 patients (10.4%), hemiparesis in 4 patients (8.3%), wound infection in 2 patients (4%), hydrocephalus, subdural hematoma, new postoperative seizures and brainstem infarct in 1 patient each (2% each) (Table 3). Among patients with cranial nerve palsy, three of eight improved and among patients with weakness, two of four patients improved. Four of the five patients with a CSF leak required operative repair.
There were two other patients that needed a return to the operating room: one for delayed presentation of a chronic subdural hematoma, and one porencephalic cyst associated with hydrocephalus that eventually required shunting for persistent symptoms. One other patient had a CSF leak that resolved with a lumbar drain. The patient with a brain stem infarct required long-term assistance including tracheostomy and gastrostomy, and one patient with multiple cranial nerve deficits required tarsorrhaphy. The two wound infections resolved local debridement and antibiotics.

Radiographic follow-up was available in 26 patients at an average of 6.1 years after surgery. Of these 26 patients, 5 had Simpson grade 1 or 2 removal and no recurrence, 9 had Simpson grade 3 or 4 removal and no recurrence. Six patients had Simpson grade 1 or 2 removal and had recurrent tumors and six had Simpson grade 3 or 4 removal and recurrent tumor.

Table 2. Eastern cooperative oncology group (ECOG) score [96].

| Grade | Number of Patients (Percentage) | ECOG Functional Status |
|-------|---------------------------------|------------------------|
| 0     | 7 (30%)                         | Fully active, able to carry on all pre-disease performance without restriction |
| 1     | 12 (52%)                        | Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work |
| 2     | 3 (13%)                         | Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours |
| 3     | 1 (5%)                          | Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours |
| 4     | 0                               | Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair |
| 5     | 0                               | Dead |

ECOG: Eastern Cooperative Oncology Group

Table 3. Summary of Postoperative Complications.

| Complication                  | Frequency |
|-------------------------------|-----------|
| Cranial nerve palsies         | 8 (16.6%) |
| Improved                      | 3         |
| CSF leak                      | 5 (10.4%) |
| Requiring operative repair    | 4         |
| Weakness                      | 4 (8.3%)  |
| Improved                      | 2         |
| Wound infection requiring antibiotics | 2 (4%) |
| Hydrocephalus, shunted        | 1 (2%)    |
| Subdural hematoma             | 1 (2%)    |
| Ventilator-dependent stroke   | 1 (2%)    |
| New seizures                  | 1 (2%)    |

Of the patients with no recurrence following surgery and with adequate radiographic and clinical follow-up, 12 were WHO grade I and one was a WHO grade II and one a WHO grade III tumor. The former of these two patients had follow-up for 3 years and the latter was lost to follow-up after just one year. On the other hand, the follow-up for the group of 12 patients with WHO grade I tumors and no recurrence averaged 6.5 years. Of the six patients who had Simpson grade 1 or 2 removal and had recurrent tumors, five were WHO grade I and one was WHO grade II. In this subgroup, follow-up for the WHO grade I tumors averaged 5.6 years, while the single patient with a WHO grade II tumor was found to have a recurrence just 3 months after a Simpson grade 1 or 2 resection.

In all, 12 patients had evidence of tumor recurrence or regrowth of residual tumor on follow-up imaging studies (Table 4). Follow-up in these patients averaged 5 years, the average age was 25 years, six were male and six female, two had previous cranial radiation therapy for ALL, and one was exposed to environmental radiation, seven had WHO grade I tumors and five had WHO grade II tumors, nine were cranial base tumors and three supratentorial tumors. The average size of the tumors was 4.2 cm, two patients had evidence of brain invasion at the time of surgery and six had undergone a Simpson grade 1 or 2 resection. The Ki-67 labeling index was reported in seven of these patients and ranged from 5-20%. Five required adjuvant radiation therapy.

The subset of five patients with radiation exposure prior to surgery in our series of 35 patients are listed (Tables 5a and 5b). Of these, four tumors were categorized as radiation-induced meningiomas (RIM) and one patient received fractionated radiation prior to surgery to a skull base tumor that had radiographic features suggestive of a meningioma but no histological confirmation at that time; this patient was excluded from the group of RIM. The group of four patients with RIM had three males and one female. Two patients had received childhood radiation for ALL and one had received radiation for treatment of a medulloblastoma. One patient was exposed to accidental environmental radiation from a nuclear facility meltdown. The average age was 29.3 years and the tumors presented after an average latency period of 23.5 years. Three of these tumors were skull base tumors and one was supratentorial; the average size of the tumors was 4.08 cm. Two patients had multiple meningiomas. Brain infiltration was reported in two patients at the time of surgery. Two were WHO grade II tumors and two were WHO grade I. The Ki67 labeling index ranged from 2-10% (average 4.75%). All the tumors were positive for progesterone receptors. All four patients had a Simpson grade 1 or 2 resection and despite that three of these tumors recurred. Follow up in this group of RIM averaged 5.5 years. At last follow-up, three patients were doing well with an ECOG score of 0 and one had an ECOG score of 2 (ambulatory and capable of self-care but unable to work).

One patient in this group of RIM was exposed to radiation...
Table 4. Summary of cases with tumor recurrence.

| Age (Years) | Sex | Risk factors | Location | Size (cm) | Brain infiltration | WHO Grade | Ki67 LI | PR | Extent of Resection | Adjuvant treatment | F/U (yr) | ECOG at last F/U |
|-------------|-----|--------------|----------|-----------|-------------------|-----------|--------|----|-------------------|------------------|---------|-----------------|
| 5           | F   | None         | ST       | 6.5       | -                 | I         | -      | Unk| GTR               | None             | 1       | Unknown         |
| 30          | M   | TR           | ACF      | 2.9       | Yes               | II        | 10     | +   | STR               | SRT             | 5       | 2               |
| 30          | F   | None         | ST       | 3.1       | No                | II        | 5      | +   | GTR               | SRT / SRS        | 0.25    | 2               |
| 27          | M   | None         | ACF, MCF, PCF | 4 | -                 | II        | -      | Unk| STR               | Unknown          | Unknown | Unknown         |
| 20          | F   | None         | ACF, MCF | -         | -                 | II        | 20     | +   | STR               | None             | 4       | Unknown         |
| 29          | M   | ER           | ACF      | 8         | Yes               | I         | 2      | +   | GTR               | SRT / SRS        | 7       | 0               |
| 27          | F   | None         | ACF, MCF, PCF | 1 | No                | I         | -      | Unk| STR               | SRT             | 7       | 2               |
| 24          | M   | Previous radiation | ACF, MCF | 5 | No                | II        | 10     | +   | STR               | SRT             | 6       | 1               |
| 17          | F   | None         | ACF      | 4         | No                | I         | 7      | +   | GTR               | None             | 8       | 1               |
| 30          | M   | TR           | ST       | 2.9       | No                | I         | 5      | +   | GTR               | None             | 6       | 0               |
| 30          | F   | None         | ACF      | -         | No                | I         | -      | Unk| GTR               | None             | 6       | 0               |
| 30          | M   | None         | ACF      | -         | Unk               | I         | Unk    | Unk| STR               | None             | Unknown | Unknown         |

(M: Male, F: Female, ST: Supratentorial, SB: Skull base, Unk: Unknown, WHO: World Health Organization, PR: Progesterone receptor, SRT: Stereotactic radiotherapy, SRS: Stereotactic radiosurgery, F/U: Followup, ECOG: Eastern cooperative oncology group)

Table 5a. Summary of Patients with Cranial Radiation Exposure.

| Patient | Age at Presentation (Years) | Sex | Radiation exposure | Latency period (Years) | Location | Size (cm) | Number | Brain infiltration |
|---------|-----------------------------|-----|--------------------|------------------------|----------|-----------|--------|-------------------|
| 1       | 30                          | M   | Treatment of ALL   | 24                     | ACF      | 2.9       | M      | Yes               |
| 2       | 29                          | M   | Environmental      | 20                     | ACF      | 8         | S      | Yes               |
| 3       | 28                          | F   | Medulloblastoma    | 25                     | PCF      | 2.5       | S      | No                |
| 4       | 30                          | M   | Treatment of ALL   | 25                     | ST       | 2.9       | M      | No                |

Table 5b. Summary of Patients with Cranial Radiation Exposure.

| Patient | WHO Grade | Ki67 LI | PR Simpson Grade | Postoperative complications | Adjuvant treatment | Recurrence | F/U (yr) | Progression at last FU | ECOG at last FU |
|---------|-----------|---------|------------------|----------------------------|-------------------|-------------|---------|------------------------|-----------------|
| 1       | II        | 10      | +                | 2                          | Yes               | SRT         | Yes     | 5                      | Yes             | 2               |
| 2       | I         | 2       | +                | 1                          | No                | SRT / SRS   | Yes     | 7                      | Yes             | 0               |
| 3       | II        | 2       | +                | 2                          | No                | None        | No      | 4                      | No              | 0               |
| 4       | I         | 5       | +                | 1                          | No                | None        | Yes     | 6                      | Yes             | 0               |

from the Chernobyl disaster at age 9 years. He presented with a large anterior cranial fossa lesion at age 29 years (Figure 1A) and underwent surgery. We were able to get a Simpson grade 1 resection that included all the involved bone and dura and then reconstructed the dura and calvarial defects with synthetic materials (Figure 1B). He recovered nicely after surgery. The initial pathology report suggested that this was a WHO grade I meningioma. However, given his history of radiation exposure, a second pathology review was performed and the final pathology was an atypical meningioma, WHO grade II, negative for progesterone receptors, with the Ki-67 labelling index elevated to 11% in some areas of the tumor, and deletions of chromosomes 1p and 22q on fluorescence in-situ hybridization (FISH). During the postoperative healing phase, he was noted to have a recurrence of tumor at six months from surgery (Figure 1C). He received fractionated
radiotherapy to the entire tumor bed with a boost to the focal region of recurrent tumor with regression of this recurrent tumor (Figure 1D). At three years from surgery, he was noted to have a small, asymptomatic recurrence without mass effect (Figure 1E). This was treated with stereotactic radiosurgery with good response and no further recurrence noted on imaging approximately six years from his initial surgery (Figure 1F).

Analysis of time to recurrence or progression for the group of 24 patients with adequate radiographic follow-up was assessed using the Kaplan-Meier method. Difference between groups of WHO grade was compared by the two-sided log-rank test. A significant difference by WHO grade was noted (p=0.0009) (Figure 2).

Figure 2. Kaplan-Meier analysis of time to recurrence or progression. Difference between groups of WHO grade was compared by the two-sided log-rank test. A significant difference by WHO grade was noted (p=0.0009).

Ordinal logistic regression was used to assess the association between ECOG score at last follow-up and categorical predictors, namely WHO grade and extent of resection. Statistical adjustments were made for age and sex. The WHO grade was once again a significant predictor of outcome (p=0.03). A WHO grade II or III was 13.54 times (95% CI: 1.28-143.15) more likely than a WHO grade I to receive a higher score (Figure 4). Among 17 patients with WHO grade I, 16 (94%) had an ECOG score of 0 or 1 at last follow-up, while among 6 patients with WHO grade II or III tumors, 3 (50%) had an ECOG score of 0 or 1 at last follow-up. Extent of resection was not a significant predictor of outcome as assessed by the ECOG score (p=0.20).

Discussion

Meningiomas in patients under the age of twenty are more frequent in males, and may be associated with genetic syndromes such as NF2 [5,7,9,19-32]. By contrast, among older patients, meningiomas are more common in females and less commonly associated with genetic syndromes. There is also a higher frequency of WHO grade II and WHO grade III tumors in the <20 year age group than seen in older age groups and they are more frequently multiple. [5,6,23,26,30,31,33] Ionizing radiation is a risk factor for both pediatric and adult patients because of the long latency period involved in the development of post-radiation brain tumors; other possible etiological factors such as cranial trauma or viruses have not been conclusively shown to have a role in the pathogenesis of meningiomas [5,6,19,23,25,26,30,31,33]. Most of the studies in the literature focus on the clinical and histological characteristics of meningiomas in patients <20 years of age (Table 6). This study extends that window by one decade and...
Figure 3. Multivariate Cox proportional hazard model was used to examine the association between recurrence/progression and potential risk factor WHO grade. Statistical adjustments were made for age and sex. Hazard ratio with 95% confidence interval was reported. There was a strong prognostic effect of WHO grade on recurrence/progression (p=0.0094). The hazard rate of WHO grade II-III was 12.88 times (95% CI 1.87–88.76) that of WHO grade I.

permits an analysis of a slightly different patient population.

Genetic predisposition to intracranial meningioma
Meningiomas occur sporadically or as part of a familial syndrome such as NF2. This association is more pronounced in individuals <20 years of age. [5-7,23,26,30,31,33]. Other genetic syndromes that predispose to intracranial meningioma formation include MA, Gorlin’s syndrome, and Down’s Syndrome [6]. Meningioangiomatosis (MA) is a rare condition in which proliferation of arachnoidal tissue, fibroblasts and microvasculature is seen [34]. Meningiomas seen with MA tend to be WHO grade 1 lesions and slightly more common in males. Gorlin’s syndrome or multiple basal cell carcinoma syndrome, is an autosomal dominant condition characterized by defects in the PTCH gene on chromosome 9 [6,9]. Defects in multiple body systems are seen along with an increased risk of intracranial meningioma development [6,34].

The association of intracranial meningiomas with NF2 is most commonly observed. With NF2, loss of heterozygosity of the NF2 gene on Chromosome 22q12.2, a tumor suppressor gene that encodes the protein merlin that links membrane receptors to the cytoskeleton, is frequently seen. Depletion of merlin constitutively activates mTORC1 signaling, turning on cell cycling and promoting cell survival [35]. In NF2 patients, after vestibular schwanomma, meningioma is the second most common neoplasm and is seen in 53% of patients [34]. Patients with the Wishart variant of NF2 may be at even greater risk of developing a meningioma and do so at an earlier age [6]. Meningiomas seen in association with NF2 have a propensity to arise from the optic nerve sheath and within the spinal canal and are more frequently multiple [9,24]. Loss of NF2 gene expression is ubiquitous in NF2 patients with meningiomas, while this is seen in 40-60% of all sporadic meningiomas. It is possible that this genetic change may play a crucial role in meningioma formation, even in the absence of the NF2 syndrome [9,22,24,36-38]. None of the patients in this study had any predisposing genetic syndrome or genetic factors. This was in contrast to what was reported by other authors.
Table 1. Analysis of Maximum Likelihood Estimates

| Parameter          | DF | Estimate | Standard Error | Wald Chi-Square | Pr > ChiSq |
|--------------------|----|----------|----------------|-----------------|------------|
| Intercept          | 4  | -2.4947  | 2.5363         | 0.9675          | 0.3253     |
| Intercept          | 2  | -0.6502  | 2.3904         | 0.0740          | 0.7856     |
| Intercept          | 1  | 2.6251   | 2.5095         | 1.0943          | 0.2955     |
| Age                | 1  | -0.1103  | 0.0879         | 1.5766          | 0.2093     |
| Sex                | M  | -0.1045  | 0.9303         | 0.0126          | 0.9105     |
| WHO Grade          | 2-3| 2.6053   | 1.2033         | 4.6876          | 0.0304     |
| Extent of Resection| STR| 1.2193   | 0.9524         | 1.6393          | 0.2004     |

Table 2. Odds Ratio Estimates

| Effect       | Point Estimate | 95% Wald Confidence Limits |
|--------------|----------------|---------------------------|
| Age          | 0.896          | 0.754 - 1.064             |
| Sex          | M vs F         | 0.901 - 5.578             |
| WHO Grade    | 2-3 vs 1       | 13.536 - 143.146          |
| Extent of Resection | STR vs GTR | 3.385 - 21.888          |

Figure 4. Ordinal logistical regression was used to assess the association between ECOG at last follow-up and categorical predictors WHO grade and extent of resection. Statistical adjustments for sex and age were made. Score test was used to assess the proportional odds assumption. WHO grade was a significant predictor (p=0.03). A WHO grade II-III had 13.54 times (95% CI 1.28 – 143.15) the odds of receiving a higher score than WHO grade I.

when studying patients with intracranial meningiomas under the age of 20 years [6]. The average age in those studies was between 10 and 15 years, [5,6,18,23,26,30,31,33] while the average age in our patient cohort was 25 years. It is possible that this is a reflection of the referral pattern to our practice and the representation of a more adult population accounted for this difference.

Ionizing radiation and intracranial meningioma

High energy ionizing radiation has the capacity to cause direct cellular DNA damage or indirect free-radical mediated DNA damage [4,39-42]. This form of radiation is in the high frequency, short wavelength end of the electromagnetic spectrum. Exposure less than 10 Gy is considered low grade while exposure above 10 Gy is considered high grade [42-47]. While cranial ionizing radiation can cause local effects such as alopecia, scalp atrophy, or microcephaly, it is also a recognized risk factor for the development of secondary intracranial tumors, in particular meningiomas [1,9,14,15,27-29,41-47]. Ionizing radiation may be administered as part of a therapeutic treatment plan, or a patient may be exposed to it during diagnostic studies such as computed tomography (CT) scans or x-ray angiographic studies [1,4]. Angiography, in particular, may result in high exposure doses for both the patient and the practitioner if performed without adequate lead shielding. Even dental x-rays may confer an increased risk particularly when administered to children under the age of 10 years, and may be particularly associated with the occurrence of meningiomas on the tentorium or below it [1,4,8,44]. Radiation therapy, administered as part of a treatment plan such as for patients with medulloblastomas or pituitary adenomas, may increase the risk of meningioma formation.
Table 6. Literature review of intracranial meningiomas in children and young adults.

| Authors       | Age group | Time period (years) | # of Patients | Seizure Motor deficit | CN palsy | Raised ICP | Headache Loss of vision | Ataxia Syndrome Previous Radiation |
|---------------|-----------|---------------------|---------------|-----------------------|----------|------------|------------------------|-------------------------------------|
| Germano, 1994| 0-20y     | 42                  | 23            | 25%                   | 33%      | NS         | NS                     | NS                                  |
| Erdingler, 1998| 0-15y    | 26                  | 29            | NS                    | 21%      | 14%        | NS                     | NS                                  |
| Rushing, 2005 | 0-20y     | 22                  | 87            | 33%                   | 10%      | NS         | 13%                    | 10%                                 |
| Gao, 2009     | 0-18y     | 15                  | 54            | 35%                   | 22%      | 26%        | 30%                    | 37%                                  |
| Menon, 2009   | 0-20y     | 27                  | 38            | 76%                   | 39%      | 13%        | 71%                    | NS                                  |
| Thuins, 2012  | 0-18y     | 35                  | 72            | 28%                   | NS       | NS         | 36%                    | 14%                                  |
| Santos, 2012  | 0-18y     | 16                  | 15            | 20%                   | NS       | NS         | 20%                    | 40%                                  |
| Ravindranath, 2013 | 0-18y | 24                  | 31            | 36%                   | 36%      | 9%         | 32%                    | 6%                                  |
| LUMC, 2013    | 0-30y     | 30                  | 35            | 26%                   | 9%       | 6%         | NS                     | 46%                                 |

| Authors       | Supratentorial | Infratentorial | Multiple | GTR | WHO I | WHO II | WHO III | F/U | Recurrence | Good Outcome |
|---------------|----------------|---------------|----------|-----|-------|--------|---------|-----|------------|--------------|
| Germano, 1994| 70%            | 13%           | NS       | 60%| 71%   | 29%    | -       | 12.9y | 0          | 100%         |
| Erdingler, 1998| 81%            | 19%           | 7%       | 86%| 94%   | 3%     | 3%      | 6.5y  | NS         | NS           |
| Rushing, 2005 | 76%            | 16%           | NS       | 62%| 71%   | 24%    | 5%      | 6.5y  | 19%        | NS           |
| Gao, 2009     | 70%            | 28%           | NS       | 72%| 82%   | 11%    | 7%      | 5y    | 30%        | 82%          |
| Menon, 2009   | 49%            | 32%           | 7%       | 49%| 73%   | 22%    | 5%      | 5y    | 18%        | 84%          |
| Thuins, 2012  | 58%            | 18%           | 6%       | 55%| 74%   | 18%    | 8%      | 5y    | 26%        | 5y PFS 56%, OS 84% |
| Santos, 2012  | 50%            | 17%           | 20%      | 80%| 73%   | 27%    | -       | 5y    | 33%        | 80%          |
| Ravindranath, 2013 | 51% | 49%           | 6%       | 83%| 64%   | 36%    | -       | 4y    | 64%        | 81%          |
| LUMC, 2013    | 71%            | 29%           | 9%       | 48%| 73%   | 16%    | 10%     | 6.5y  | 12%        | NS           |

ICP: Intracranial pressure, GTR: Gross total resection.

Therapeutic cranial radiation may be administered prophylactically in some instances such as in the treatment of ALL patients at high-risk for CNS relapse or small-cell lung cancer patients [41-43,45-51]. At times, it is considered in the management of non-small-cell lung cancer patients as well [42]. The life expectancy of lung cancer patients, both small-cell and non-small-cell, may be shorter than the latency period for the development of an intracranial tumor and hence, this patient population is rarely considered in this context. On the other hand, children with ALL who receive prophylactic cranial radiation at a young age, frequently in the first decade of life, are uniquely susceptible to developing intracranial tumors such as meningiomas as they have excellent long-term survival with current chemotherapy and radiation therapy treatments [27-29]. In addition, arachnoidal tissues in children may be uniquely susceptible to the oncogenic effects of ionizing radiation [25]. Age at exposure also has an impact on the latency period of tumor development and the type of tumor that develops. Exposure below age 20 years may predispose to meningioma development while exposure above the age of 20 years may predispose more towards sarcoma development [50].

Acute lymphoblastic leukemia (ALL) is one of the most common cancers in children and comprises 23% of all malignancies in children <15 years of age [41,45,46]. Risk factors for the development of ALL include prenatal exposure to x-rays or post-natal exposure to high-dose radiation. Among genetic factors, NF also confers an increased risk of ALL development. Patients are treated with induction chemotherapy that continues into a consolidation and maintenance phases and >90% achieve remission with >80% expected to be long term survivors [41,45,46]. The CNS, and testes in males, is considered a sanctuary site that is relatively impermeable to the effects of systemic chemotherapy. Involvement of the CNS is seen in 3% of patients at initial presentation and without prophylactic treatment, most high risk patients will develop CNS disease.
Tinea capitis was treated with scalp radiation as per the Adamson-Kleinbock technique \[42\]. The success of intrathecal chemotherapy to supplement systemic chemotherapy protocols has spurred ongoing trials seeking to eliminate cranial radiation altogether from ALL protocols. Prophylactic cranial radiation is hence administered to patients in a high-risk category \[15,27,41-43,45-47\]. Ionizing radiation exposure may also occur accidentally from environmental sources or following natural disasters that cause breakdown of facilities that release damaging radiation into the air, ground, or water. Atomic bomb survivors and those exposed to large doses of radiation from accidental causes such as the nuclear plant meltdown at Chernobyl are at risk of development of cranial or non-CNS malignancies \[39,44,52\].

Tinea capitis is a relatively common fungal infection of the scalp caused by the Trichophyton species \[42,47,53,54\]. Prior to 1960, Tinea capitis was treated with scalp radiation as per the Adamson-Kleinbock technique \[42,47\]. Estimates of exposure were 5-8 Gy to the scalp, 1.5 Gy to the brain, and 0.7 Gy to the cranial base and a 10-fold relative risk of developing an intracranial meningioma has been reported in this population \[1,53\]. Sadetzki et al., reported 253 cases of RIM from among a cohort of 11,000 children treated as per this protocol for tinea capitis \[54\]. When compared to a similar group of non-RIM meningiomas, these tended to occur in younger patients, were more commonly seen \[14,15,27-29,41-43,45-47\]. NF2 mutations or chromosome 22 abnormalities are uncommon while chromosome 1p, 6q, and 7p deletions are more commonly seen \[17,42,54,55\]. The incidence of RIM also may increase with increased length of follow-up \[27,29\]. The cumulative actuarial risk of developing a RIM is 0.53% at 10 years, 1.2% at 20 years and 8.8% at 25 years \[29\]. The latency period for the development of a RIM is between 20-35 years and varies depending on age at exposure and the total dose; higher doses and younger ages portend shorter latency periods \[4,25,42,47\]. In rare instances, it may be even shorter; Choudhary et al., reported one case of RIM that occurred after a latency period of just 14 months \[50\]. Others estimate latency periods of 10.8 years for pediatric patients and 18.7 years for adult patients \[29,49\].

Five of the 35 patients in this study had a history of previous radiation exposure. Two of the five had received prophylactic cranial radiation as part of a treatment protocol for ALL and one patient received craniospinal axis radiation for treatment of a posterior fossa medulloblastoma. One patient had received previous radiation therapy to a cranial base meningioma that was already present. Of the two patients who received prophylactic cranial radiation for ALL, one had an anterior cranial base tumor that was WHO grade II and recurred multiple times. One patient in this study had exposure to a large dose of radiation from a nuclear power plant accident and environmental contamination as a child, but the exact dose he received was not discernible. The average latency period for the patients who had therapeutic or environmental exposure to radiation in this series was 23.5 years. None of the patients in our study had a history of tinea capitis or received cranial radiation for this indication.

Demographics of patients and location of tumors

Pediatric meningiomas are characterized by a slight male predominance as compared to meningiomas in adults wherein a female predominance is noted \[1,4-6,18\]. The increase in female to male ratio gets more pronounced with increasing age \[1,4-6,18\]. In this series where the average age of the patients was 25 years and none of the patients had any syndromic abnormalities, females outnumbered males almost 2:1. It is possible that these variables portend a trend towards female predominance; that is, intracranial meningiomas in young adults without syndromic associations may be more common in women. The average age among the 12 patients with recurrent tumors was 25 years and in this subgroup as well females outnumbered males. The average age among patients with radiation induced tumors was 29.3 years; slightly older than the rest of the cohort which may be because they presented after an average latency period of 23.5 years following radiation exposure.

The cerebral convexity is the most frequent location for adults with intracranial meningiomas. By contrast, some...
authors report intraventricular and infratentorial meningiomas are more common in children [5,7,9]. Other series reach varying conclusions; Germano et al., reported 23 cases of intracranial meningiomas in children under age 20 years and noted that 2/3rds were supratentorial in location, and 13% were intraventricular [18]. In the series of 87 patients reported by Rushing et al., 64% of the tumors were supratentorial, 16% infratentorial, and 12% intraventricular [6]. In the series reported by Amirjamshidi et al., 75% of the meningiomas were supratentorial [9]. Meningiomas with a lack of dural attachment are more frequent in children [5]. In our series, 26 of the 35 patients (74.28%) of the tumors were cranial base neoplasms and only one was located within the ventricle. This may be a reflection of the referral pattern to our institution which has a high representation of cranial base cases.

Surgery, histopathology and recurrence of tumor
Large meningiomas that cause significant mass effect on adjacent parenchyma are best surgically removed along with their dural base and involved bone; this is categorized as a Simpson grade 1 resection [56-58]. In the event that the dura cannot be removed, it is coagulated constituting a Simpson grade 2 removal [56-58]. These are probably the best options for a patient with a meningioma, if they can be safely executed [56-58]. Large lesions that invade or are intimately associated with critical structures such as the cavernous sinus may be debulked and the residual component monitored with radiographic imaging studies or treated with radiosurgery or radiotherapy in the event of radiographic progression [59,60]. Radiosurgery is an option for meningiomas that are small (<3cm) but show radiographic progression, or if they are located in a surgically inaccessible location or location where the risk of surgical intervention is significant [61-67]. It is also an option for residual meningiomas that show radiographic progression but cannot be removed surgically [59,60,63]. A meningioma that is small and not causing significant mass effect on the adjacent parenchyma in an asymptomatic patient may be observed with serial imaging studies and clinical follow-up [68,69].

Accurate estimation of resection by the Simpson grading system was possible in 33 of the 35 patients; this was based on a review of the operative notes and postoperative imaging when available. Simpson grade 1 or 2 resection was achieved in only 16 patients (48.5%). This number is lower than the resection rates achieved with supratentorial convexity meningiomas but consistent with other major published series of cranial base neoplasms; >60% of tumors in this series were cranial base meningiomas [26,70]. Similarly, morbidity following surgery may be a function of tumor location and relationship to critical neurovascular structures and treatment modality. Superficial convexity lesions have a significantly lower morbidity associated with surgery than cranial base lesions that are in proximity to critical neurovascular structures. The most common complication in this series was cranial nerve palsy that was observed following surgery in 8 (16.6%) patients and that was permanent in 5. Cerebrospinal fluid leakage was noted in 5 (10.4%) patients and required operative repair in 4. Other complications included motor weakness in 4 (8.3%) patients that was permanent in 2. Wound infection occurred in 2 (4%) patients while one patient developed hydrocephalus that required a permanent CSF diversion.

Recurrence after surgery is related to the extent of resection and WHO grade of the tumor [60,67,71-76]. Recurrence rates of RIM are higher even after Simpson grade 1 or 2 resections [55]. In Al-Mefty’s series of 16 patients with RIM, all the tumors recurred after first resection. A second recurrence was noted in 62% and a third recurrence in 17% [55]. The final pathology results in our series reflected a higher proportion of WHO grade II (16.3%) and WHO grade III (10.2%) tumors than seen in older adults but was similar to reported rates in series of intracranial meningiomas in individuals <20 years age (Table 6). Adjuvant radiotherapy was administered to residual tumors or the tumor bed in 10 (28%) patients and all these patients had WHO grade II or III tumors. Radiation exposure and WHO grade had an impact on recurrence in this series. Among the 12 patients who had evidence of tumor recurrence or regrowth of residual tumor on follow-up imaging studies (Table 4), two had previous cranial radiation therapy for ALL, and one was exposed to environmental radiation, seven had WHO grade I tumors and five had WHO grade II tumors. In addition, recurrence was more common with cranial base tumors as we were not able to achieve as complete a resection with these as with supratentorial convexity meningiomas.

In contrast to what is reported in the literature, we observed a higher rate of recurrence with RIM. The patient treated with craniospinal axis radiation for medulloblastoma had a WHO grade II meningioma that recurred once. The patient with environmental exposure had a WHO grade II tumor in the anterior cranial fossa that recurred twice. The patient who received neoadjuvant radiation five years before his eventual surgery for significant radiographic progression prompting the first surgery that revealed a WHO grade II meningioma and required two additional surgeries for significant recurrent tumor following Simpson grade 4 resections. This was a lesion located at the petrous apex with involvement of the cavernous sinus and basilar perforators. Tumor pathologic grade also had a trend towards higher WHO grades on recurrence. The distribution of WHO grades in the 35 initial surgical specimens was WHO grade I in 77.1%, grade II in 17.1% and grade III in 5.7%. When considering the additional 14 surgical specimens, the distribution was WHO grade I in 73.4%, WHO II in 16.3%, and WHO III in 10.2%.

Estrogen and progesterone receptor status of meningiomas are purported to have prognostic significance and may suggest the increased frequency of these tumors in women and the increase in growth during pregnancy and following menopause. [77-86] Progesterone receptor positivity is more common in grade 1 tumors and is a good prognostic sign.
Increased estrogen receptor expression may correlate with chromosome 14 and 22 alterations, molecular markers identified in meningothelial cell neoplastic transformation. At times, meningiomas may regress with cessation of progesterone agonist medications. However, there is no evidence that exogenous hormone use increases the risk of developing meningiomas. Progesterone receptor status may be more prevalent with increasing age at diagnosis of a meningioma. This data was only available in 13 patients in our study and 12 of them had tumors that stained positive for progesterone receptors. Given the limited numbers, progesterone receptor status information was inadequate to make firm conclusions of its impact on tumor recurrence. The Ki-67 labeling index is an estimate of the proliferating cells within a tumor. It thus reflects cells in all phases of the cell cycle except the G0 phase. The MIB-1 monoclonal antibody is used to stain the Ki-67 antigen and the labeling index is a subjective histopathological estimate that estimates the growth potential of a tumor. Similarly, with meningiomas, higher Ki-67 labeling indices are concordant with higher tumor grades and predictive of tumor regrowth or recurrence. With meningiomas, higher Ki-67 labeling indices are observed in males, recurrent tumors, and those located in a skull base location. Age is not considered to be a factor in the Ki-67 labeling indices of meningiomas, and when increased Ki-67 labeling indices are noted in childhood meningiomas, it is postulated that it does not predict recurrence or prognosis.

The selection of radiation therapy for a radiation-induced neoplasm may seem counter-intuitive but has been reported previously by other authors with varying degrees of success. In general, these options are considered for recurrent progressive lesions in surgically inaccessible areas. In our patient with a RIM following environmental exposure, we employed the option of fractionated radiotherapy at the first recurrence because it was our intent to treat the entire tumor bed as this was a WHO grade II neoplasm. The subsequent recurrence was small and focal and stereotactic radiosurgery was effective and considered less morbid than surgery (removal of synthetic cranioplasty and dural reconstructive implants). The patient responded well to the treatments without additional morbidity. Both fractionated radiotherapy and stereotactic radiosurgery have been reported as treatments for RIM. Single fraction radiosurgery may be more effective than fractionated treatments but each case has to be carefully assessed to determine which modality is more suitable.

The purpose of this study is to shed light on the demographics and clinical characteristics of meningiomas in patients below 30 years of age. It does have certain limitations, particularly because the data sampling extended back 30 years and some patients lacked adequate histological grading, immunohistochemical analysis, or proliferative index estimation, or were lost to clinical and radiographic followup. However, despite these constraints it does provide some useful information. In particular, with the average age of the patients being 25 years, there was a female predominance as opposed to male predominance observed in meningiomas in individuals less than 20 years of age. The distribution of WHO grades paralleled that observed in patients under 20 years with a higher representation of WHO grades II and III than seen in older adults. The Ki-67 labeling index tended to be higher but this information was not available in sufficient numbers of patients to draw firm conclusions. The WHO grade had a significant impact on outcome. Previous radiation exposure and WHO grade II and III tumors had higher recurrence rates.

Conclusion
When analyzing meningiomas in the first three decades of life in an adult practice with a strong representation of cranial base cases, we observed an average age at presentation of 25 years with a female predominance. A greater proportion of cases were WHO grades II and III compared to what is seen in older adults. Previous radiation exposure and higher WHO grade increased the risk of recurrence and tumors tended to be of a higher WHO grade at recurrence.

List of abbreviations
CNS: Central nervous system
WHO: World Health Organization
NF2: Neurofibromatosis 2
MA: Meningioangiomatosis
ECOG: Eastern cooperative oncology group
ALL: Acute lymphocytic leukemia
CSF: Cerebrospinal fluid
RIM: Radiation-induced meningioma
FISH: Fluorescence in-situ hybridization
CT: Computed tomography
MRI: Magnetic resonance imaging

Competing interests
The authors declare that they have no competing interests.

Authors’ contributions

| Authors’ contributions | VCP | ECP | EM | KB | RG | DEA |
|------------------------|-----|-----|----|----|----|-----|
| Research concept and design | ✓ | ✓ | --- | --- | --- | --- |
| Collection and/or assembly of data | ✓ | ✓ | --- | --- | --- | --- |
| Data analysis and interpretation | ✓ | --- | --- | --- | ✓ | --- |
| Writing the article | ✓ | --- | ✓ | ✓ | --- | --- |
| Critical revision of the article | ✓ | --- | ✓ | ✓ | --- | ✓ |
| Final approval of article | ✓ | --- | ✓ | ✓ | --- | ✓ |
| Statistical analysis | --- | --- | --- | ✓ | --- | --- |

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