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Meningioma Screening with MRI in Childhood Leukemia Survivors Treated with Cranial Radiation

Purpose: Radiation induced meningioma (RIM) is a known late effect of cranial radiotherapy. Cranial MRI can detect small meningiomas, but its potential value as a screening tool is unknown.

Methods and Materials: MRI was used to screen asymptomatic survivors of childhood ALL treated with CRT ≥10 years previously. The incidence of RIM and outcomes of this group were compared with a historical cohort of survivors with the same exposure who underwent imaging only to investigate clinical signs or symptoms.

Results: 192 childhood leukemia survivors were included in this study, 86 in the screening group, 106 unscreened. Median time from RT to first screening MRI was 25 years. Screening MRI detected meningioma in 15 (17%) of screened survivors. In the unscreened group, 17 (16%) had neurologic symptoms leading to an MRI, 9 of whom (8.5%) were diagnosed with meningioma (p=0.06 for screened vs. unscreened crude rate). There was no significant difference between ~~Screened~~in size of detected meningiomas ~~patients had smaller tumours~~ (mean diameter 1.6cm with ~~-~~screening vs 2.6cm unscreened; p =0.13) ~~and a higher~~or cumulative incidence (6.0% vs. 3.6% at 25 years for screened vs. unscreened patients; p =0.77) ~~but neither achieved statistically significance~~. There were no significant differences in extent of resection between groups. There were 3 patients who had neurologic residual deficits in the unscreened group versus none in among screened patients (p= 0.25).

Conclusion: Screening MRI was able to detect small meningiomas that were not clinically apparent, however we could not demonstrate a significant improvement in the chance of total resection or a significant decrease in morbidity. A larger sample could clarify potential reduction in neurologic sequelae associated with screening.

Introduction

Childhood cancer survivors treated with cranial radiation (CRT) are at increased risk of developing meningioma (1-7), and s~~. Given the reported~~ ome investigators have reported aggressive biologic features ~~of~~ associated with radiation-induced meningioma (RIM)~~, and the sensitivity of MRI to detect meningioma~~ (8)~~,~~. Given the sensitivity of MRI to detect meningioma we piloted the use of MRI screening among asymptomatic survivors of childhood leukemia who had received CRT.

Material and Methods

Patients and Imaging

Patients eligible for screening were treated with CRT for leukemia ≥10 years previously, had no neurologic symptoms, and attended the long-term follow up clinic at [XXXX hospital] from January 1, 2013 to February 28, 2017. We compared outcomes for these patients with an unscreened historical control group comprised of patients with the same exposure who attended prior to the implementation of screening (January 1, 2005 to December 31, 2012). These patients underwent cranial MRI only if presenting with symptoms warranting investigation.

All patients were scanned using either a 1.5T Siemens Avanto-Fit or 3T Siemens Skyra-Fit MRI. The sequences included a sagittal T1 3D FSPGR (TR/TE 2300/2.27ms, FOV 25cm, 1mm slice thickness) gadolinium enhanced series and the corresponding axial and coronal reformations, axial FLAIR (TR/TE 9000/94ms, FOV 20cm, 4mm), diffusion (TR/TE 8000/97ms, FOV 22cm, 4mm slice thickness) and EPI-GRE (TR/TE 4000/30ms, FOV 24cm, 5mm slice thickness) series covering the entire brain.

Statistical Analysis

Chi-square test was used for comparison of non-continuous variables (Fisher test for frequency less than 5) and binomial exact methods were used to calculate 95% confidence intervals around proportions. Kaplan-Meier analysis was used to calculate the incidence of meningioma. The number needed to screen to prevent one neurologic complication was estimated as the reciprocal of the absolute reduction in risk of neurologic complication among screened versus unscreened patients.

Results

Detection of Meningioma

Patient characteristics are shown in Table 1 and in the Supplemental Materials. Among 86 screened survivors, mean age at leukemia diagnosis was 7 years, and the mean time to first MRI after CRT was 24 years. Unscreened patients (N=106) did not differ significantly from screened patients with respect to age at exposure, duration of follow-up, or CRT dose. Seventeen unscreened patients underwent MRI to investigate symptoms (16 had headaches, 2 vomiting, 2 dizziness, 1 papilledema and 1 visual disturbance; some had more than one sign or symptom).

Meningiomas were diagnosed in 15 (17.4%) screened and 9 (8.5%) unscreened patients ($p = 0.06$). No meningiomas were detected within 15 years of CRT, and the cumulative incidence in the screened and unscreened groups were 6.0% and 3.6% at 25 years, and 23.6% and 16.3% at 30 years ($p = 0.77$). RIMs were borderline smaller in the screened group (mean of greatest diameter 1.6cm vs. 2.6cm; $p = 0.13$).

Post-detection Management

Five (5.8%) screened patients underwent surgical resection (one following a period of observation) leading to a GTR in 4 (4.6%). Among unscreened patients, 4 (3.8%) underwent surgical resection, with GTR in 2 (1.9%) (p-values for both surgery and GTR rates >0.45). There

were two postoperative complications in the screened group (oral infection; wound hematoma not requiring evacuation) and one (cerebrospinal fluid leak) in the unscreened group (p = 0.2). None of the patients in the screened group were left with persistent neurologic complications (95% CI = 0-4%), while 3 patients (2.8%; 95% CI 0.6-8.0%) in the unscreened group had this outcome (p = 0.25). Using these rates, if the avoidance of persistent neurologic complication was the clinical intent of screening, 36 patients would require screening to avoid one persistent neurologic deficit. However, given the 95% confidence intervals around the complication rates, this number could be as high as 167, and we cannot exclude the possibility of worse neurologic outcome with screening.

Discussion

To our knowledge, this is the first study to evaluate the outcome of screening MRI for RIM among asymptomatic leukemia survivors treated with CRT. Completeness of surgical resection affects the local control of meningioma (9), and smaller tumors may potentially be more amenable to GTR with less morbidity (10). Prior studies have not evaluated the potential magnitude of a benefit that might occur with screening MRI as compared to imaging used only for symptom investigation. Although screening is recommended for several other RT-related late effects, the follow-up guidelines of the Children's Oncology Group make no recommendation for screening for RIM among these survivors, except for those with neurofibromatosis (11).

Compared to symptom-induced imaging, screening was associated with a non-signficant increased detection rate and reduction in the size of detected RIMs.. Importantly, however, comparison of the observed rate of diagnosed meningioma in the screened versus the unscreened patients is subject to both lead-time and length-time biases and possible over-diagnosis, and screening should be evaluated by its capacity to reduce clinically important morbidity. Screening was associated with small improvements in the rates of gross total resection,

surgical morbidity, and neurologic deficits between screened and unscreened survivors. The low rate of neurologic complications in the control group (<3%) would require a substantially larger sample size to demonstrate significant improvement in this outcome. For example, to have 80% power (with $\alpha = 0.05$) to detect a reduction in adverse neurologic outcome from 3% to 0.5% would require approximately 430 patients to be screened and compared with an equal number of controls.

Two studies reported on the use of cranial imaging among ALL survivors (9,10). Goshen found that 15 of 88 irradiated survivors (17%) were found to have meningiomas after a latency of 10 to 25 years. Only one patient had a postoperative complication. Some patients in this study underwent CT rather than MRI, however, and there was no distinction made between those undergoing imaging for asymptomatic screening versus for symptom investigation (9). Banerjee utilized MRI to describe the incidence of meningioma among 49 survivors of adult leukemia treated with CRT. Eleven (22%) out of 49 patients developed meningioma with a latency period of 14 to 34 years. Seven of eight patients who underwent surgery had a gross total resection, and 3 had postoperative complications. As with the prior study, there was no comparison among those undergoing imaging for screening versus symptom investigation (10).

We did not specify a post-detection meningioma management protocol, and so surgical resection rates may in part reflect variation in management approach among surgeons for similar tumours. Also, the use of historic controls may underreport minor persistent complications of meningioma treatment, and we did not administer quality of life questionnaire to screened patients; it is possible that the detection of asymptomatic RIM may have reduced quality of life among survivors.

Conclusion

Screening MRI was able to detect asymtpomatic meningioma in ALL survivors treated with CRT; however we could not demonstrate a significant improvement in total resection rate or a decrease in morbidity compared to controls imaged for symptoms. A larger sample could clarify potential reduction in neurologic sequelae associated with screening.

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Figure 1. Cumulative incidence of meningioma in childhood leukemia survivors following cranial radiation therapy.