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Age-Related Changes in Frontal Lobe Anatomy Require Alternatives to Opposed Lateral Fields

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Abstract

Purpose: To define the temporofrontal angle (TFA), determine the age and gender-related variability of the TFA, and discuss implications of those findings for radiation therapy (RT).

Patients and Methods: Treatment-planning software computed tomography images for 122 patients were analyzed for frontal lobe excursion anteriorly between the orbits, defined as the TFA. The TFA, including its anterior and lateral components, was compared as a function of both age and gender.

Results: The TFA decreased linearly in pediatric patients ($P < .001$); however, that linear relationship disappeared after age 20 ($P = .84$). Both male and female pediatric patients showed decreased frontal lobe projection as a function of age (male, $P < .001$; female, $P = .001$). Pediatric females, but not pediatric males, displayed an age-related increase in the lateral projection of their anterolateral temporal lobe ($P = .001$).

Conclusion: Because frontal lobe position relative to the ocular globes varies with age and the frontal lobe can serve as a sanctuary site in some tumor types, it is essential that innovative RT approaches be used for orbital sparing while effectively treating the frontal lobe in very young children. Proton therapy may be optimal in this context. Moreover, differences in neuroanatomic development between the genders dictate careful attention to each patient's anatomy during RT treatment planning.

Keywords: craniospinal radiation; temporofrontal angle; cribriform plate; pediatric radiation therapy; orbital radiation

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Introduction

For nearly 6 decades, craniospinal irradiation (CSI) has been used to treat patients at risk for cerebrospinal axis metastasis [1]. Benefits of CSI have been documented for patients with metastatic primary central nervous system malignancies, such as medulloblastoma, ependymoma, astrocytoma, and pineoblastoma, as well as hematologic malignancies, such as acute lymphoblastic leukemia with central nervous system involvement [2–8]. Supratentorial failure of CSI in patients with medulloblastoma has been reported to occur in the region of the cribriform plate [9–14]. A number of causes for this phenomenon have been proposed, including gravity-dependent settling of tumor cells and "cold spots" in the radiation field [15].

A study by Weiss et al [16] found that with the use of lateral, opposed, 6-MV photon beams, 95% of the cribriform plate received only 85% of the prescribed dose. By

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decreasing the length of the eye block, a sufficient dose could be delivered to the cribriform plate; however, that improvement comes at the expense of higher radiation doses to the lens. With the introduction of advanced treatment modalities, such as intensity modulated radiation therapy (RT), image-guided RT, and proton beam therapy, clinicians may now deliver radiation with better sparing of the surrounding tissue [17, 18].

In our practice, which consists largely of pediatric central nervous system malignancies, we noticed that, when planning CSI, orbital sparing was more difficult in some patients than it was in others. Specifically, the difficulty arose for patients with frontal lobes extending relatively further anteriorly between the orbits. Initially, that discrepant anatomy among our patients seemed random. However, we anecdotally noticed that patients with difficult-to-treat, anteriorly projecting frontal lobes tended to have small frontal sinuses.

The frontal sinuses continue developing from birth until late adolescence [19]. Thus, when compared with their older counterparts, younger patients generally have smaller, less-developed frontal sinuses. As the frontal sinuses and the face, in general, mature, the frontal lobe of the brain has less relative anterior extent. Because of our patient population, we had a unique opportunity to investigate age-related changes in frontal lobe anatomy and to discuss the implications of those changes on radiation-treatment planning. Accordingly, we hypothesized that younger patients tended to have frontal lobes that were more difficult to treat and might require the use of advanced treatment modalities.

Patients and Methods

Patient Selection

After institutional review board approval, Indiana University Health Proton Therapy Center medical records were queried for all patients receiving cranial spinal irradiation for any reason or with insurance billing codes for any cranial malignancy between June 2010 and August 2011. A total of 122 patients were identified. Scans were available for 114 (93%) of those patients. The patients were divided into 2 groups: pediatric patients (age $\leq$ 20 years) and adult patients (age $>$ 20 years). Patient characteristics are reported in Table 1.

Temporofrontal Angle Determination

Each patient's computed tomography planning scan was loaded into Eclipse treatment planning software (version 10.0, Varian Medical Systems, Palo Alto, CA, USA). The image used was the axial view at the level of the orbital roof (Figure 1). The methodology for calculation of the temporofrontal angle (TFA) requires measurement of 2 anatomic segments.

Segment A represents the frontal lobe excursion. That segment consists of the distance from the posterior orbit to the most anterior aspect of the frontal lobe, in this case (Figure 1), 3.2 cm. Segment B represents the maximal distance of the anterior temporal lobe from midline at the posterior orbit. Figure 1 reveals a value of 4.53 cm. The TFA (θ) was obtained from those 2 perpendicular segments. In this case, arc tan(A/B) yields a θ of 35%.

For patients scanned with a significant degree of head flexion, segment A more accurately represents the hypotenuse formed by the true frontal lobe excursion in the axial plane of the orbits and a caudal-rostral component of the head tilt (Figure 2). As the degree of flexion increases, so does that caudal-rostral component. Thus, in patients scanned with excessive head flexion, the true anterior-posterior projection of the frontal lobe is

Table 1. Patient characteristics.

Characteristic	Average	Standard deviation
Age, y		
All	17	17
$\leq$ 20	9	5
$>$ 20	43	14
	No.	**%**
Gender		
All		
Male	60	52.6
Female	54	47.4
Gender, age $\leq$ 20, y		
Male	46	52.9
Female	41	47.1
Gender, age $>$ 20		
Male	14	51.9
Female	13	48.1
Age group, y		
$<$ 2	8	7
2–4	23	20
5–7	12	11
8–10	15	13
11–14	13	11
15–17	12	11
18–20	4	4
21–30	7	6
31–50	14	12
$>$ 50	7	6
Total	114	100.0

overestimated. To compensate for that, we normalized the degree of flexion versus the extension for all patients by adjusting the length of Segment A before calculating θ.

Age-Distribution Calculations

The TFA values obtained were analyzed in Microsoft (Redmond, WA, USA) Excel 2003 by patient age. All graphs and statistical values were produced on GraphPad (Prism 4.0, GraphPad Software, Inc, La Jolla, CA, USA).

Results

Anatomy as a Function of Age

As expected, we found that younger patients tended to have frontal lobes that projected more anteriorly ($P < .001$). Older patients' frontal lobes often projected less than 1.0 cm anterior to the posterior orbit. The coefficient of determination of that relationship was relatively weak ($r^2 = 0.3869$). The second component of the TFA—the distance between the midline and the anterolateral-most portion of the temporal lobe—was between 3.0 and 4.0 cm in almost all patients, regardless of their age. There was a very weak, but significant, relationship between that distance and age ($r^2 = 0.08508$, $P = .002$).

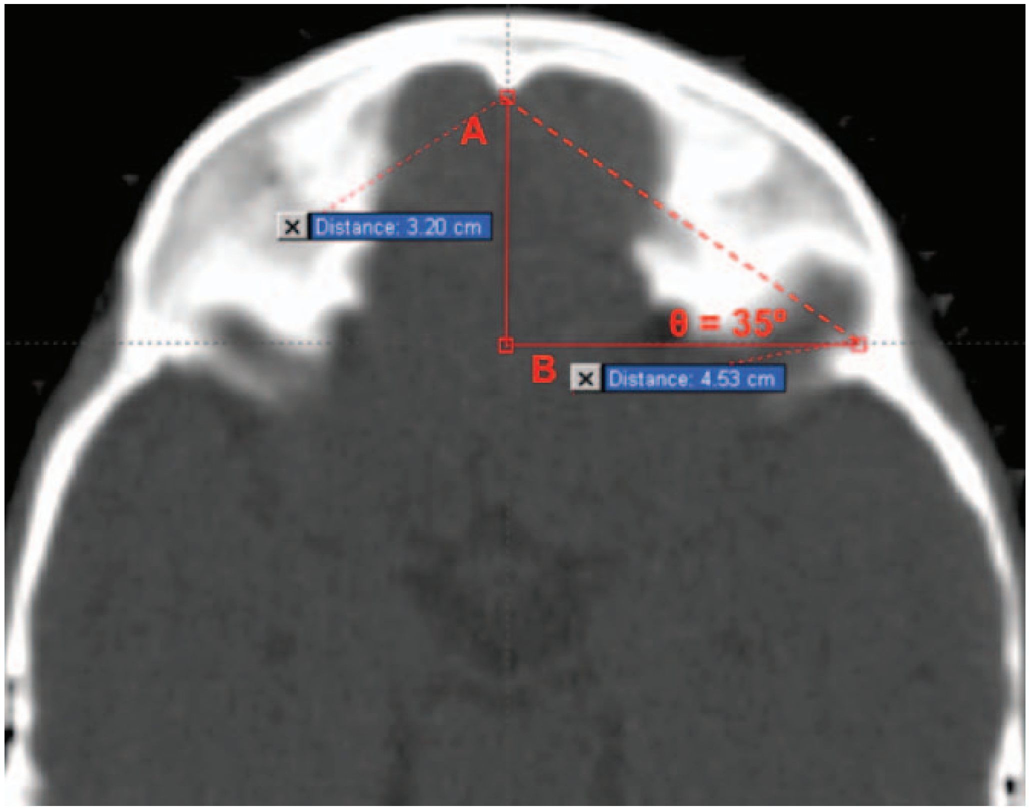

Figure 1. The value of θ is dependent on the values of the measurements A and B. The value of θ in this patient, before correction for head flexion/extension, was 35.2° z.

Anatomy as a Function of Gender

Frontal lobe excursion decreased significantly with age in both pediatric, male and female patients (Figure 3; male, $P < .001$ and female, $P < .001$, respectively), the association was stronger in males than it was in females (male, $r^2 = 0.4911$ and female, $r^2 = 0.2590$, respectively). However, there was no statistically significant difference in the best-fit lines as determined by a comparison of their slopes ($P = .17$). We then analyzed adult patients. For adults, neither males nor females retained a significant relationship between frontal lobe excursion and age (male, $P = .19$ and female, $P = .70$, respectively), with poor fit for both (male, $r^2 = 0.1403$ and female, $r^2 = 0.01419$, respectively). There was no statistically significant difference in the best-fit lines, as determined by a comparison of their slopes ($P = .18$). Frontal lobe maturation in men may continue until age 50, after which degeneration ensues [20]. Accordingly, that association may have become statistically significant if more of the adult patients had been included in our study.

Pediatric patients displayed a gender-related dichotomous function between temporal lobe position and age. The distance of the anterolateral temporal lobe from the midline in male pediatric patients was independent of age ($P = .32$, $r^2 = .02221$). On the other hand, female patients tended to have a greater distance between the midline and the anterolateral projection as they aged ($P < .001$, $r^2 = 0.3082$). When comparing the best-fit lines for male and female pediatric patients, we observed a significantly greater best-fit slope in females than in males (Figure 4, $P = .03$). Although gender has been shown to

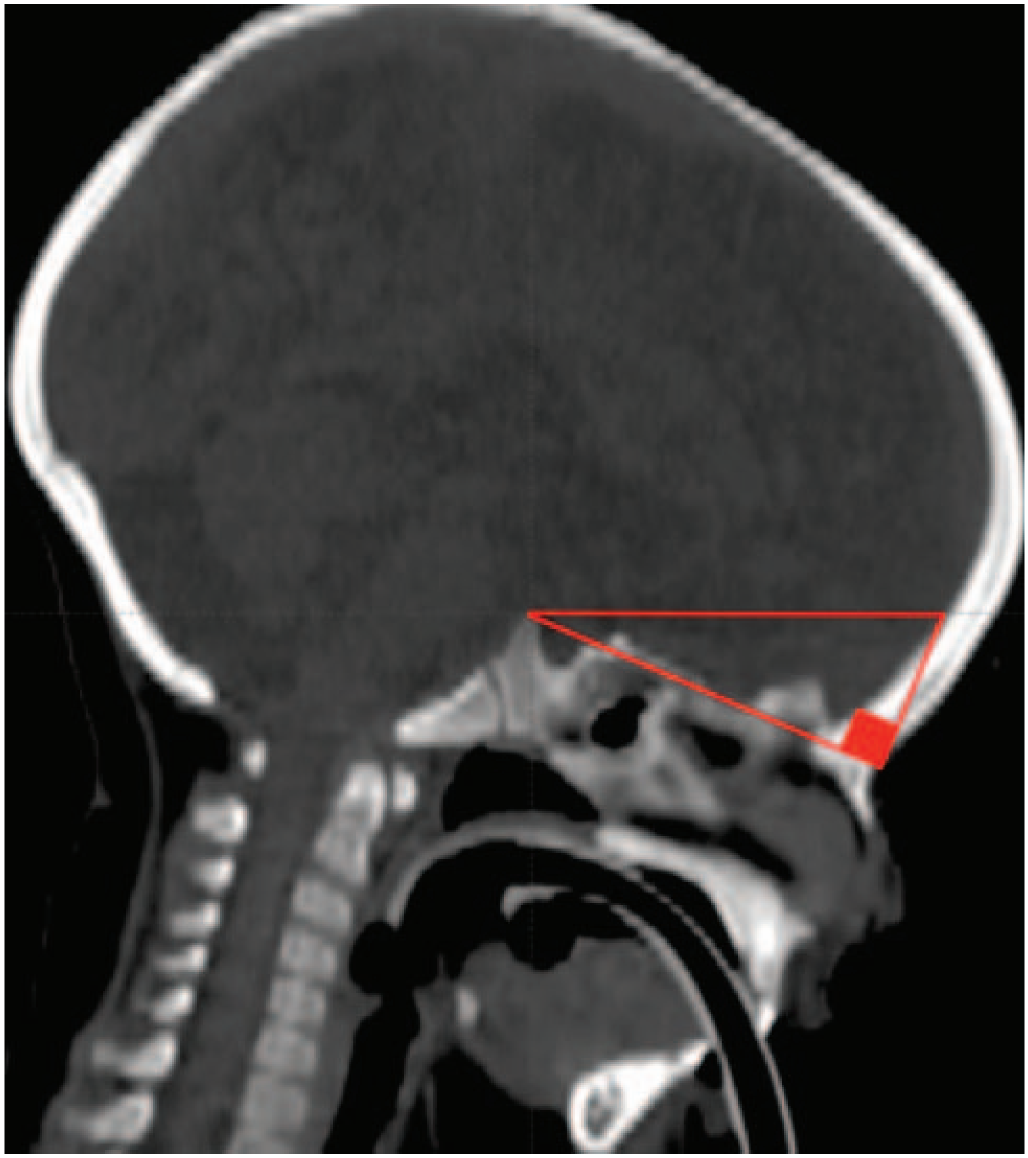

Figure 2. Correction of temporofrontal angle for head position. Sagittal head computed tomography (CT) scan at the midline was used to measure the positions of the nasion and the posterior clinoid process. Those coordinates were then used to determine the relative degree of flexion versus extension of the head. A cosine of that angle was applied to the measured hypotenuse to compensate for overestimation of that component on CT scan measurements.

affect grey and white matter volumes, corpus callosal areas, ventricle volumes, and overall volume, we are the first, to our knowledge, to illustrate simultaneous age-gender–specific changes in the temporal lobe anatomy [21–23].

Again, we performed an identical comparison in adult patients. Both male and female patients exhibited a trend for increased distance of anterolateral temporal lobe from the midline as a function of age. That trend was significant and moderately correlated in adult, female patients ($P = .02$, $r^2 = 0.4124$) but was insignificant in adult, male patients ($P = .46$, $r^2 = 0.04620$). There was no significant difference in the slopes of the best-fit curves ($P = .45$).

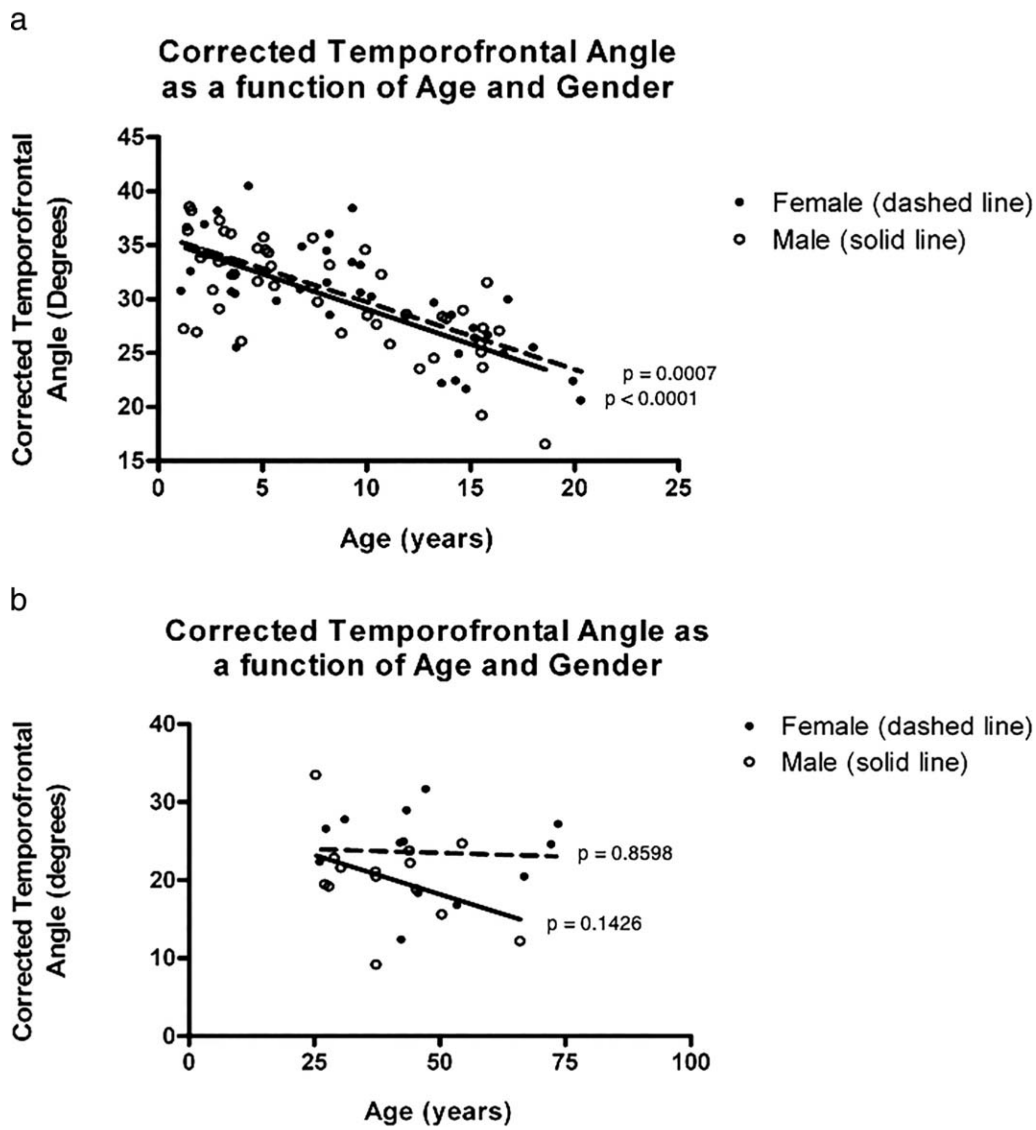

Figure 3. The temporofrontal angle (TFA) decreases as a function of age before and during adolescence, after which, the TFA stabilizes. Graphs illustrate (a) pediatric patients and (b) adult patients.

Temporofrontal Angle Correlation with Age, Independent of Gender

The TFA decreased in all patients as age increased ($P < .001$, $r^2 = 0.4098$), largely because of the effect of the pediatric population. When TFA was plotted stratifying patients into 2 age groups, adults (age $>$ 20 years; n $=$ 27; 24%) and children (age $\leq$ 20 years; n $=$ 87; 76%), the relationship remained significant for children ($P < .001$), but not for adults ($P = .84$) (Figure 3).

Both boys and girls exhibited a decrease in the TFA as a function of age ($P < .001$). Additionally, the TFA correlated moderately well with age in both male and female pediatric patients (male, $r^2 = 0.4926$ and female, $r^2 = 0.5225$, respectively). When plotting TFA as a

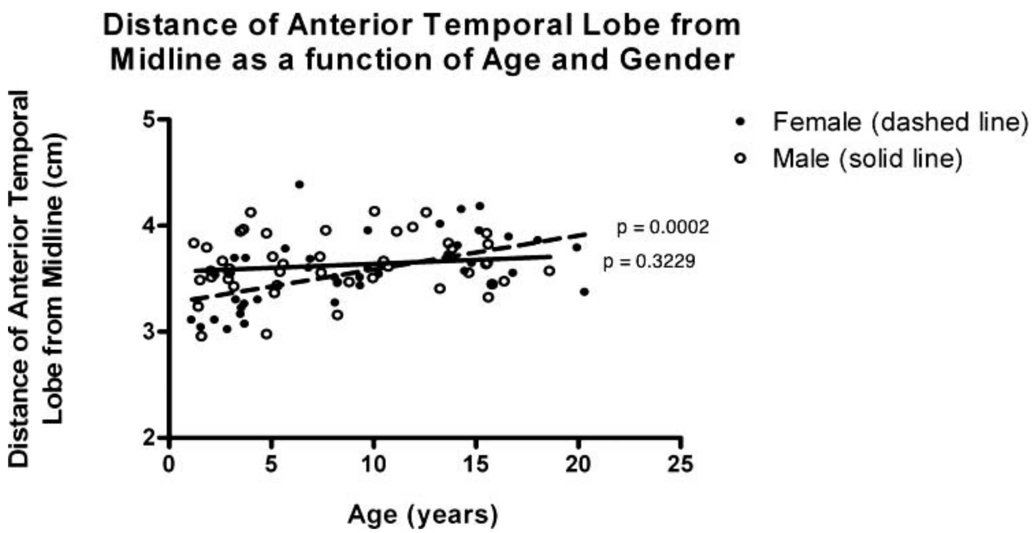

Figure 4. Lateral projection of the anterofrontal portion of the temporal lobe gradually increases with age in female pediatric patients but not in male pediatric patients.

function of age in adult patients, neither gender exhibited a significant relationship (adult males, $P = .14$; adult females, $P = .86$).

Discussion

The extension of pediatric frontal lobe between the globes—especially pronounced in young children—forces a reconsideration of traditional whole brain fields for pediatric RT, commonly used with leukemia and as part of craniospinal RT. Whether the isocenter is placed in the middle of the brain or at the bony canthus, traditional, opposed lateral beams have a poor dosimetric profile with doses to the parotid glands, eyes, and lenses. In fact, we have found that proper inclusion of the frontal lobe with opposed laterals may require coverage of the entire globe, with flash anteriorly. That is clearly suboptimal because that dose to lens and conjunctiva becomes the price of sufficient frontal lobe coverage.

Thus, in pediatric patients receiving cranial irradiation, determination of frontal lobe extension is mandatory. This anatomic assessment must occur before beam selection to avoid excess dose to organs at risk, as well as "hot" and "cold" spots in the RT field.

Conclusion

Defining the TFA in this article was employed as a means of making absolute measurements so that we could evaluate the significance of anatomic changes to the frontal lobe, a potential sanctuary site for tumor cells, with age. The results of this study point to the need to exercise extreme caution in pediatric RT in very young children. Proton therapy allows for beam selection that may reflect the anatomic variation of younger patients in a superior fashion to conventional RT.

ADDITIONAL INFORMATION AND DECLARATIONS

Conflict of Interest Disclosure: The authors have no conflicts of interest to disclose.

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