HIGHLY CONFORMAL CRANIOSPINAL RADIOTHERAPY TECHNIQUES CAN UNDERDOSE THE CRANIAL CTV IF LEPTOMENINGEAL EXTENSION THROUGH SKULL BASE EXIT FORAMINA IS NOT CONTOURED.

Article Outline

Highlights

- Highly conformal techniques can deliver craniospinal RT for medulloblastoma.
- Meninges and CSF extend through the skull base with cranial nerves.
- These structures receive inadequate dose if they are not specifically contoured.
- Posterior fossa foramina should be included in the craniospinal CTV.

Abstract

AIMS

Craniospinal radiotherapy (CSI) remains a crucial treatment for patients with medulloblastoma. There is uncertainty about how to manage meningeal surfaces and CSF that follow cranial nerves exiting skull base foramina. The purpose of this study was to assess plan quality and dose coverage of posterior cranial fossa foramina with both photon and proton therapy.

METHODS & MATERIALS

We analysed radiotherapy plans of 7 patients treated with CSI for medulloblastoma and primitive neuro-ectodermal tumours, and 3 with ependymoma (total n=10). Four had been treated with a field-based technique, 6 with TomoTherapy™. The internal acoustic meatus (IAM), jugular foramen (JF) and hypoglossal canal (HC) were contoured and added to the original treatment CTV (Plan_CTV) to create Test_CTV. This was grown to Test_PTV for comparison with Plan_PTV. Using Plan_CTV and PTV, proton plans were generated for all 10 cases. The following dosimetry data were recorded: Conformity (DSC) and homogeneity index (D_2-D_{98}/D_{50}) as well as median and max dose ($D_{2\%}$) to Plan_PTV, $V_{95\%}$ and minimum dose ($D_{99.9\%}$) to Plan and Test_CTV and PTV, $V_{95\%}$ and minimum dose ($D_{98\%}$) to foramina PTV's.

RESULTS

Proton and TomoTherapy™ plans were more conformal (0.87, 0.86) and homogeneous (0.07, 0.04) than field-photon plans (0.79, 0.17). However, field-photon plans covered IAM, JF and HC PTV's better than proton plans ($p = 0.002, 0.004, 0.003$ respectively). TomoTherapy™ plans covered the IAM and JF better than proton plans ($p = 0.000, 0.002$ respectively) but the result for HC was not significant. Adding foramen CTV/PTV's made no difference for field plans. Mean D_{min} dropped 3.4% from Plan to Test_PTV for TomoTherapy™ (ns), and 14.8% for protons ($p = 0.001$).

CONCLUSIONS

Highly conformal CSI techniques may underdose meninges and CSF in the dural reflections of posterior fossa cranial nerves unless these structures are specifically included in the CTV.

Keywords

Craniospinal radiotherapy, medulloblastoma, intensity-modulated radiotherapy, proton beam therapy, radiotherapy planning.

I. Introduction

High quality radiotherapy (RT) remains an important treatment for patients with medulloblastoma [1]. The literature reports a relationship between inadequate technique and patterns of relapse [[2], [3], [4]]. Although the majority of these tumours arise in the posterior cranial fossa, they are known to spread to leptomeningeal surfaces throughout the craniospinal axis (CSA) and the evolution of radiotherapy techniques used for medulloblastoma reflects this biology. Current standard practice includes a moderate dose of craniospinal irradiation (CSI), followed by a boost to the tumour bed in the posterior fossa, where historical data suggests the risk of relapse is higher [[5], [6]].

There has been rapid development in both technology and treatment technique for medulloblastoma. The classical 'field-based' approach whereby a parallel pair of opposed lateral photon fields are matched to the divergence of a posterior field is still used by many centres. Others have adopted 3D-conformal and intensity-modulated radiotherapy (IMRT) approaches [7]. Helical arc IMRT delivery offers an elegant solution to many of the technical challenges posed by CSI [8]. The potential of proton therapy for medulloblastoma has been considered for two decades [[10], [11]]. It has attractive advantages, especially in children, with the possibility of reduced dose to critical OAR's and a lower whole body integral dose [[12], [13]].

Studies report a high risk of medulloblastoma recurrence in the cribiform plate and inferior frontal and temporal lobes, when they were not included in the target volume, or when they were missed due to shielding of the eyes [[4], [14], [15], [16]]. These structures are therefore now included routinely in the Clinical Target Volume (CTV).

With the evolution of volume-based radiotherapy techniques, an unresolved issue is whether meningeal reflections of cranial nerves as they exit their respective skull base foramina should be included in the CTV. Field-based CSI protocols recommend a margin of 5mm below the cribiform plate and at least 10mm below the skull base elsewhere in order to cover cranial nerve meningeal

reflections. Recently published work has demonstrated that CSF and thus surrounding meningeal surfaces may be found over a centimetre beyond the internal table of the skull in the internal acoustic meatus (IAM), jugular foramen (JF) and hypoglossal canal (HC) [17]. This finding may be of interest for clinicians planning RT for patients with medulloblastoma.

The purpose of this study was to test the hypothesis that modern, volume-based conformal RT techniques underdose meningeal surfaces in the posterior fossa unless these structures are specifically included in the CTV.

II. Materials and Methods

This project was registered and approved as a service evaluation (Proposal No. 193) with the local oncology directorate and audit department.

a. Patient data sets

Patients treated with CSI for primitive neuro-ectodermal tumours at our institution between 2005 and 2014 were identified *(n=7)*. Another who received CSI following locoregional recurrence of ependymoma was identified, and to further increase sample size, 2 patients who underwent focal, posterior fossa RT for primary ependymoma were also included. In both cases CTV's were large, covering much of the posterior fossa, and were constrained by the internal table of the skull. Importantly, the CTV margins used included skull base foramina and extended beyond this constraint posing the same dosimetric question as seen with the 8 CSI cases. There were therefore 10 cases in total. All patients had been immobilised with a thermoplastic shell and undergone CT simulation (3mm CT slices). Details of patient characteristics, disease, treatment technique, dose and platform are all given in Table 1.

b. Re-planning and Dose Analysis

Treatment plans, including DICOM imaging files; structure sets and dose-cubes were drawn from archive and reloaded into virtual simulation software (PROSOMA 3.3, OSL, Shrewsbury, UK). Using published anatomical data [17], new contours and target volumes were constructed for each patient. Using bone density windows, a contour was drawn for each individual right and left IAM, JF and HC, to include all possible areas of CSF extension on bone density windows - each volume was drawn and saved as a separate structure; R_IAM, L_IAM, R_JF, L_JF, R_HC, L_HC. The Boolean operator function in PROSOMA was used to fuse these separate volumes with Plan_CTV, and saved as Test_CTV. Test_CTV was grown isotropically by 5mm to a final PTV (Test_PTV) and each foramen CTV was grown by 5mm to an individual PTV (Figure 1 A-D). The treatment plan dose-cube was reloaded, individual dose volume histograms (DVH's) were produced for each structure and dosimetric information recorded.

To compare the quality of treatment plans to the original target volume, we recorded near max dose ($D_{2\%}$), and median PTV dose, to Plan_PTV. We also calculated dose homogeneity and conformity; homogeneity was calculated using $(D_{2\%} - D_{98\%})/D_{50\%}$ according to ICRU 83 and conformity was calculated using the Dice Similarity Coefficient (DSC), given as $2(A \cap B)/(A+B)$, between the Plan_PTV and the 95% isodose line [[18], [19]].

To compare CTV and PTV dosimetry before and after addition of posterior fossa cranial nerve foramen volumes, $V_{95\%}$ and minimum dose ($D_{99.9\%}$) were recorded. For each foramen PTV, $V_{95\%}$ and minimum dose (D_{98}) were measured. $D_{99.9}$ was chosen for composite PTV and CTV volumes as the Plan_PTV volumes ranged from 280 to 2040cc (median 378cc), and we were interested to see a genuine 'minimum' dose. Foramen PTV volumes were generally < 10cc, thus D_{98} was used.

Anonymised DICOM files and structure sets were encrypted and sent by secure link to a colleague at a collaborating proton beam therapy centre. These files were loaded into their planning system (Raystation 4.7, Raysearch Laboratories AB, Stockholm, Sweden). Pencil beam scanning

protontherapy plans using a local cochlea sparing protocol (objectives: max dose 50Gy, mean dose 30Gy, compromise of PTV, but not CTV, permissible if necessary) were produced for all 10 cases, aiming to adequately cover the original Plan_CTV's. Once these plans were generated, amended target volumes including posterior fossa foramen PTV's, Test_CTV and Test_PTV were loaded, DVH data was derived and returned to the first author for analysis.

c. Statistical Analysis

Statistical analysis was performed using IBM SPSS Statistics v 23.0. Paired t-tests were used to compare minimum doses to both planned (treated) composite volumes and foramen PTV's with both photon and proton plans. The same method was used to test the significance of adding foramen volumes (to both CTV and PTV) for all 3 treatment techniques. A significance level of 0.05 was used for all analyses and Bonferroni corrections were used to account for multiple testing.

III. Results

a. Composite volumes

Using level 3 reporting metrics [18], both TomoTherapy™ and protons produced higher quality treatment plans than a field-based photon technique. Median dose for field plans was ranged from 101.6% to 104.8%. Median doses for TomoTherapy plans were between 99.4% and 100.2% and proton plans ranged from 99.8% to 100.1%. The mean near-maximum dose ($D_{2\%}$) for field plans was 108.7% (range 105.5% - 111%) compared with 101.2% (range 100.8% - 101.9%) for TomoTherapy, and 103.3% (range 101.7% - 104.8%) for protons. Mean homogeneity index for field plans was 0.17 (range 0.083 – 0.41) compared with 0.042 (0.022 – 0.073) for TomoTherapy and 0.072 (0.048 – 0.091) for protons. Proton plans were the most conformal; the mean DSC was 0.87 for proton plans compared with 0.86 for TomoTherapy and 0.79 for field-based photon plans. Coverage of Plan_PTV (as measured by $V_{95\%}$) was generally satisfactory with all treatment techniques. One field plan (case 3) had a $V_{95\%}$ of 92% - areas of relative under-dosing were laterally over the cranial vault due to build-up.

Figure 2 shows the effect of adding posterior fossa foramen to the dosimetry of both CTV's and PTV's for all 3 techniques. Adding these structures made no difference to PTV $V_{95\%}$, minimum PTV or CTV dose for any of the 4 field-based treatment plans. These data do show one outlier case (case 3) where target coverage was poor both with and without posterior cranial nerve volumes for reasons described. Adding posterior fossa cranial foramen volumes caused a drop in PTV $V_{95\%}$ (100 to 98.2%) in 1 of 6 cases planned and treated with TomoTherapy. Two cases saw a drop in PTV minimum dose of greater than 2% - case 7 (97.2% to 92.4%) and case 8 (96% to 81.6%). Mean PTV D_{min} dropped 3.4% from Plan to Test_PTV for TomoTherapy plans, and this difference was not statistically significant (p=0.20). Only case 8 saw a drop in CTV minimum dose (97.3% to 92.7%).

The consequences of adding posterior fossa foramen to CTV's were greater with proton plans. The effect on $V_{95\%}$ was subtle, but 9 of 10 cases saw a lower $V_{95\%}$ with Test_PTV than Plan_PTV (mean drop 1.1%, range 0 – 3.5%). The effect on minimum PTV dose was more pronounced; half of the proton plans saw >20% drop in minimum dose. Mean Test_PTV minimum dose was 70.9%, compared with 85.7% for Plan_PTV. This difference was statistically significant (p=0.001). Dosimetric differences with CTV's were smaller but still apparent. Six of 10 plans saw a drop of <1%, but case 10 saw a drop of 8.9% (98.4% to 89.5%) from Plan_CTV to Test_CTV, whilst case 8 saw a large drop of 23.2% (95.9% to 72.7%). Mean minimum CTV dose dropped from 97.1% to 93.5%, but this was not statistically significant (p=0.17).

We compared minimum doses to composite volumes with both photon and proton techniques for all 10 patients. Mean minimum doses for field technique cases (1-4) were 76.2% (photons) vs. 91.5% (protons), and 93.2% (photons) vs. 97.1% (protons) for Test_PTV and Test_CTV respectively. Neither difference was statistically significant. For cases 5-10 (TomoTherapy) the respective values for Test_PTV and Test_CTV were 89.8% (photons) vs. 70.8% (protons), and 95.5% (photons) vs. 91.6% (protons). The p value for Test_PTV D_{min} TomoTherapy vs. protons was 0.03 suggesting significance. However, once a Bonferroni correction for 4 significance tests on the Test_volume data is taken into account, $\alpha = 0.0125$ thus the null hypothesis must not be rejected.

b. Individual Foramina

Dosimetry results for the IAM, JF and HC PTV's as separate structures are shown in Figure 3. These structures were well covered by field-based photon plans - the $V_{95\%}$ to each foramen PTV was 100% for all field plans. Significant differences between field-photon and proton plan minimum doses were found for all 3 foramen PTV's (IAM p = 0.002, JF p = 0.004, HC p = 0.003). TomoTherapy plans covered the IAM well. Only 1 plan (left IAM, case 7) had a $V_{95\%}$ and minimum dose <90%, and mean D_{min} was 95.8%. IAM coverage with protons was less good, mean D_{min} was 72.3% (range 47.9% - 96.8%) and this difference was significant (p = 0.000). Jugular Foramen coverage with TomoTherapy plans was slightly less good; mean D_{min} was 94% and minimum dose was < 95% for 5/12 foramen – the lowest doses being 80.4% and 85.9% respectively for left and right JF for case 8. Minimum doses were lower still with proton plans; mean D_{min} was 78.5% (range 36.8% to 97.8%). This difference was also significant (p=0.002). The structure with lowest mean D_{min} with TomoTherapy plans was the HC PTV. D_{min} was < 95% for half of these structures and mean D_{min} was 93.9% (range 80.8% - 99%). Minimum HC PTV doses were lower with protons (D_{min} mean 89.1% (range 62.9% - 98.9%). Comparing TomoTherapy and proton plans for HC PTV gives a p value of 0.049, but this does not reach significance at the 0.05 level due to Bonferroni correction.

To prove that low doses to small cranial nerve foramen PTV's affect the dosimetry of much larger Test_CTV and Test_PTV's, we constructed a scatter-plot (Figure 4) comparing the mean D_{min} for all foramina combined, with the drop in D_{min} from Plan_PTV to Test_PTV and found that these parameters are indeed correlated (r^2=0.65). We went on to construct Dose Volume Histograms (DVH's) for the 2 patients with the greatest differences between photon and proton plans; these are shown in Figure 4. For case 1 (Caption A), the proton plan covered the CTV well, but there was a noticeable shoulder on the PTV curve due to low foramen doses. Case 8 (Caption B), had low foramen doses for both photon and proton plans, but the CTV curve has more of a shoulder with protons than photons and this effect is greater with the PTV curves. The underdosing of foramen

PTV's (and therefore Test_PTV's) with proton plans, and to a lesser extent TomoTherapy is demonstrated visually in Figure 6.

IV. Discussion

Work on the detailed anatomy of the IAM, JF and HC using FIESTA MRI has clearly demonstrated CSF beyond the internal table of the skull, which many clinicians would consider to be a CTV surrogate [17]. This study is the first to investigate the dosimetric implications of failure to include leptomeningeal reflections of posterior fossa cranial nerve foramina in the CTV of CSI treatment plans for medulloblastoma. Specifically, we have demonstrated that this problem is potentially more significant with highly conformal RT techniques.

There are many advantages to using highly conformal RT techniques for patients with medulloblastoma, and recent research in this field has focussed on how best to use technological advances to spare organs at risk (OAR's) and reduce long-term toxicity [[20], [21], [22], [23]]. Helical IMRT solutions spare OAR's better than 3D conformal or fixed field IMRT plans [7], and proton plans offer even greater capacity to reduce dose to most OAR's including eyes, cochlea, thyroid, heart and gonads [[10], [11], [24]]. Modelling data suggest that these dosimetric advantages will translate to lower cardiac morbidity and second cancer risk [[12], [25]], and the possible magnitude of these benefits have prompted debate within the community as to whether proton therapy is the only ethical approach to delivering CSI in children [26]. The drive to minimise treatment related morbidity is both laudable and important, but the primary aim must remain disease eradication for these highly curable tumours.

Our results show that field-based photon plans adequately cover leptomeningeal surfaces in the IAM, JF and HC, regardless of whether or not they are specifically contoured. Helical arc photon therapy plans with TomoTherapy show good coverage of the IAM but potentially significant under-dosing of meningeal surfaces in the JF and HC in 1 of 6 patients. The effect of increasing conformity

is manifestly more obvious with proton plans, where the lowest recorded D_{min} for IAM, JF and HC PTV's were 47.9%, 36.8% and 62.9% respectively, and this effect is well visualised in Figure 6. The question of how relevant low doses to small components of a much larger structure on overall dosimetry has also been addressed. The data in figure 2 show that adding posterior fossa foramina to composite CTV and PTV for proton plans made a noticeable difference to minimum dose. For proton plans, there appears to be a relationship between cases that saw the lowest foramen doses, and those in which differences between Plan and Test CTV and PTV doses are apparent. This same effect is also seen in the DVH's in Figure 5.

Recent data on medulloblastoma relapse suggest that the posterior fossa remains a high-risk site, despite modern RT protocols that boost this region. One single institution series, (median age 7, range 0-50, n=106) found an overall relapse rate of 27%, of which 41% involved the posterior fossa [27]. Another study looking at paediatric patients from two centres (one USA, one Canadian, 89 medulloblastoma) found overall relapse rates of 29%, with 27% of these in the posterior fossa [28]. A study that looked at 20 adult patients found that 71% of the recurrence in their series involved the posterior fossa [29]. To the best of our knowledge however, there are no data specifically pertaining to marginal recurrence of medulloblastoma in the structures discussed in this study. Furthermore, an early report directly comparing outcomes of patients undergoing treatment with photon and proton techniques showed no significant differences between techniques [30].

Our data show that compared to field-based photon CSI plans; TomoTherapy and proton plans give lower median and maximum doses to the PTV, better target conformity and dose homogeneity within that target. Nonetheless, we have also demonstrated that the CSF and meninges found in the foramina of the posterior fossa are under-dosed with highly conformal RT techniques, unless they are specifically contoured, and that this may have a small but noticeable effect on the overall dosimetry of the treatment plan.

The limitations of this study are firstly that it is based on a small and heterogeneous case series, and to increase sample size 2 patients who had not undergone CSI were included. Importantly however, the CTV's used in these cases closely resembled a typical phase II for a medulloblastoma plan, and the margins used extended beyond their skull base constraints into skull base foramina. Because of its design, we have not been able to directly compare these dosimetric effects in field based and TomoTherapy plans. In conducting this study, we found that there was inconsistency in the way that CTV's were contoured around these structures. In some cases, the Plan_CTV did already include part or all of the IAM and JF. Whilst this makes the point that there is a need for anatomical and dosimetric data to guide segmentation, it may have weakened the findings of our study.

Finally, this study has not looked at doses to OAR's. The proton plans in this study were generated with a cochlea-sparing protocol, whilst the photon plans were not. This may slightly reduce the strength of direct plan comparison, but accurately reflects the current clinical dilemma. Published FIESTA MRI data and a previous surgical study prove that dura and CSF are present to the fundus of the IAM [[17], [31]]. Equally, the risk of sensorineural deafness rises sharply with doses above 40-45Gy [[32], [33]]. It has been shown that 3D conformal and IMRT photon techniques can spare the cochlea relative to field based photon plans [34], and that proton plans are better still [[24], [35]]. These dosimetric advantages seemingly translate to clinical benefit, which may in turn have long-term economic benefit [[36], [37]]. However, these studies do not explicitly describe how the CTV was constructed around the IAM. Images from St Clair et al. [24] suggest that the IAM's were not included in the CTV in this study. In the era of protons, cochlea sparing is technically possible, but there is ongoing debate within the neuro-oncology community as to how this should be prioritised, particularly for CSF positive medulloblastoma.

Our data show that however conformal the RT technique, it is not possible to simultaneously treat meninges/CSF in the IAM, and keep cochlea dose below tolerance. We suggest that the full IAM should be contoured as CTV. However, oncologists must weigh the balance between cure and

morbidity, and prioritising cochlea sparing for lower risk patients by using exclusion structures during the planning process may be justified. Promising work on molecular risk stratification may help to inform such decisions [38], and there is a clear need for careful long-term follow up of patients treated with CSI.

V. Conclusions

This study has shown that the meningeal reflections and CSF surrounding cranial nerves VII-XII as they pass into posterior fossa skull base foramina are underdosed by highly conformal RT techniques, unless they are specifically included in the CTV. Such findings may have implications for tumour control and it is essential to monitor relapse patterns for patients treated for medulloblastoma. We have not addressed the impact that such inclusion would have on dose to OAR's, specifically the cochlea, but this is a subject for further work.

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VIII. Conflicts of interest:

None.

IX. References

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X. Table & Figure captions

Table 1: Case Details

Figure 1: Re-contouring procedure. (A) Contouring right and left HC's. (B) Adding to Plan_CTV to create Test_CTV. (C) Growing Test_CTV to Test_PTV. (D) Growing foramen PTV's.

Figure 2: Composite volume coverage, photon and proton plans. (A) PTV V95%. (B) PTV Minimum Dose (D99.9%). (C) CTV Minimum Dose (D99.9%).

Figure 3: Individual foramen coverage, photon and proton plans. (A) Internal Acoustic Meatus. (B) Jugular Foramen. (C) Hypoglossal Canal.

Figure 4: Scatter plot showing relationship between minimum foramen dose and fall in Plan_PTV to Test_PTV.

Figure 5: Dose Volume Histograms for Test_CTV & Test_PTV for photon and proton plans. (A) Case 8 – TomoTherapy. (B) Case 1 – Field.

Figure 6: Dose wash for case 1 field (A) and proton (B) plans, case 8 TomoTherapy (C) and proton (D) plans. Colour-scheme: dark red 107%, light red 95%, orange 90%, yellow 80%, lime 70%, green 60%.