TITLE PAGE

Full Title:

FAST IMAGING EMPLOYING STEADY-STATE ACQUISITION (FIESTA) MRI TO INVESTIGATE CEREBROSPINAL FLUID (CSF) WITHIN DURAL REFLECTIONS OF POSTERIOR FOSSA CRANIAL NERVES.

Abbreviated Title:

FIESTA MRI FOR DURAL REFLECTIONS OF POSTERIOR FOSSA CRANIAL NERVES.

Abstract

Objectives:

There is no consensus approach to covering skull-base meningeal reflections - and CSF therein - of posterior fossa cranial nerves (CN's VII-XII), when planning RT for medulloblastoma and ependymoma. We sought to determine whether MRI and specifically FIESTA sequences can answer this anatomical question and guide RT planning.

Methods:

Ninety-six posterior fossa FIESTA sequences were reviewed. Following exclusions, measurements were made on the following scans for each foramen respectively (left, right); internal acoustic meatus (IAM) (86, 84), jugular foramen (JF) (83, 85) and hypoglossal canal (HC) (42, 45). A protocol describes measurement procedure. Two observers measured distances for 5 cases and agreement was assessed. One observer measured all the remaining cases.

Results:

IAM and JF measurement inter-observer variability was compared. Mean measurement difference, between observers was -0.275mm (s.d. 0.557). IAM and JF measurements were normally distributed. Mean IAM distance was 12.2mm (95% CI 8.8 - 15.6), JF was 7.3mm (95% CI 4.0 - 10.6). The HC was difficult to visualise on many images and data followed a bimodal distribution.

Conclusions:

Dural reflections of posterior fossa CN's are well demonstrated by FIESTA MRI. Measuring CSF extension into these structures is feasible and robust; mean CSF extension into IAM and JF was measured. We plan further work to assess coverage of these structures with photon and proton RT plans.

Advances in Knowledge:

We have described CSF extension beyond the internal table of the skull into the IAM, JF & HC. Oncologists planning RT for patients with medulloblastoma and ependymoma may use this data to guide contouring.

Introduction

Clinical Setting

High-quality radiotherapy (RT) remains a crucial aspect of treatment for medulloblastoma and there is clear data linking inadequate technique to recurrence to.[1-5] These tumours arise infra-tentorially, within the cerebellum or in the vicinity of the fourth ventricle. Their typical pattern of spread is to meningeal surfaces, frequently loco-regionally in the posterior fossa.[6,7] The radiotherapy approach reflects this biology and current 'gold-standard' involves irradiation of the entire craniospinal axis (CSI) with a boost to posterior fossa and tumour bed. Ependymoma's are rare tumours arising from glial cells (primary gliomas). In children they tend to occur intracranially, in the region of the fourth ventricle whereas in adults they are more frequently spinal. Radiotherapy is used, but in contrast to medulloblastoma it is usually delivered focally only to the tumour bed, depending on factors such as histological characteristics and extent of resection on postoperative MRI.[8] Where it does occur, over 90% of recurrences are local.[9-12] CSI is used only for confirmed CSF dissemination.[13]

Techniques for delivering CSI have evolved significantly over recent decades. The classical approach is to use parallel-opposed lateral cranial fields matched to a direct posterior field. The subsequent development of 3-D conformal and intensity modulated radiotherapy (IMRT) has seen these solutions increasingly used to deliver CSI and boost the posterior fossa,[14-17] and there is increasing interest in proton radiotherapy for both conditions, not least as reduced integral doses to normal structures may improve toxicity and second malignancy rates.[18]

Although minimising toxicity is important, the primary treatment objective must remain cure. Studies report the risk of cribiform plate recurrence in patients undergoing CSI in the era before this was considered to be part of the target volume, or when it was underdosed due either to inadequate technique or to deliberate shielding of the eyes.[4,19-21] The same technical errors also resulted in recurrences inferiorly in the frontal and temporal lobes,[21] and there is now a general consensus that these structures should be included in the target volume, however radiotherapy is planned and delivered.

An unresolved issue is the CSF contained within the dural reflections of the posterior fossa nerves (CN's, VII-XII) as they exit their respective skull base foramen. We suspect that a conventional field-based CSI technique for medulloblastoma will adequately cover these structures and their meningeal surfaces.[22] However, there is no consensus about how to approach this problem when planning volume-based radiotherapy, delivered either with photons or protons. A similar question is posed for ependymoma treatment and we suggest that the internal acoustic meatus (IAM), jugular foramen (JF), and hypoglossal canal (HC) may provide a breach in the natural barrier to local spread provided by the internal table of the skull.

The purpose of this study was therefore to investigate the anatomy of CSF extension into the IAM, JF, and HC and specifically how far CSF travels down these structures and away from the natural line of the internal aspect of the skull and a putative Clinical Target Volume (CTV).

MRI of posterior fossa cranial nerves

MRI has been used to assess the anatomy of the CNS and CSF for 30 years.[23,24] Much work has gone into establishing the optimal protocol for imaging cranial nerves. Sequences such as 3D Fourier transform (3DFT) and constructive interference in steady state (CISS) have been used to investigate trigeminal neuralgia, hemifacial spasm, and acoustic neuroma.[25] Subsequent work concluded that the 3D CISS sequence (with a 1.5T magnet) gave the best resolution for cranial nerves surrounded by CSF.[26] One of the difficulties of imaging CSF spaces with MRI is the artefact generated by natural fluid flow. Thus techniques that reduce scanning time should give better image quality. Ciftci et al described the addition of a driven equilibrium radio frequency reset (DRIVE) pulse to a T2 weighted turbo spin-echo (TSE) sequence.[27] The DRIVE sequences provided better image quality and performed slightly better than the T2-weighted 3D TSE sequences in identifying individual nerves. The scan times were also 25% shorter.

FIESTA MRI uses ultra-short repetition time (TR) and echo time (ET) to obtain very fast acquisition times. There is high signal to noise ratio with strong signal from fluid and suppression of background tissue which gives good contrast and, importantly, anatomical detail of small structures. One study looked to map the cisternal segments of cranial nerves IX-XI, using 3D balanced fast-field echo imaging (3D-bFFE) – the Phillips equivalent of FIESTA - to acquire detailed images of these structures and to measure both the length and angle of their intra-cisternal courses.[28] They concluded that the quality of the images obtained permitted very detailed and accurate anatomical information to be recorded. More recently, cranial nerve imaging data from a 7T magnet concluded that true-FISP sequences – another FIESTA equivalent – gave the best spatial resolution and contrast[29] and FIESTA MRI has been successfully used to identify the glossopharyngeal (CNIX), vagus (CNX) and accessory (CNXI) nerves within the JF,[30] although no measurements of CSF extension were made in this study. FIESTA images were therefore selected as the tool to address this anatomical question.

Methods

This project was registered as a service evaluation (Proposal No. 193) with the Addenbrooke's Cancer Division & Haematology Directorate and Audit department and constituted part of an MSc thesis project with the Institute of Cancer Research (ICR). It was a retrospective analysis of images for service evaluation where all imaging had been performed for clinical purposes and no further ethical approval was required or sought.

Patients

An automated search of the Addenbrooke's Radiology department archive for patients undergoing MRI which included the word 'FIESTA' was done. This produced 96 FIESTA MRI examinations of the posterior fossa. Patients were predominantly adults (median age 49 years, range 1-90). Ten patients in our study were under the age of ten, the remainder were adults. The three most common imaging indications were hearing loss (19%), hemifacial pain (19%) and headache (14%). A full list of indications (some patients had more than one) is given in supplementary figures and tables.

Imaging

Imaging was performed on 1.5T MR units (GE Signa Excite, GE Discovery MR450). Imaging parameters were TR 6.5 msec, TE 1.05 msec, field of view 22 cm, slice thickness 0.8 mm, overlap 0.4 mm, matrix 256 x 256. Example FIESTA images demonstrating the internal acoustic meatus, jugular foramen, and hypoglossal canal CSF and relevant cranial nerves are shown in Figure 1. Examinations were excluded from analysis for the following reasons; abnormal anatomy, sagittal reconstructions only, poor image quality, limited number of slices and no FIESTA images available. This left the following number of scans for analysis for each foramen respectively; 86 for left IAM, 84 for right IAM, 83 for left JF, 85 for right JF, 42 for left HC and 45 for right HC.

Measurement

The procedure for measuring CSF extension into relevant foramen is described below, with a sample image shown in Figure 2.

1. By careful visual inspection, identify the axial slice with the furthest extension of CSF along the meatus.
2. Measure the distance between the most prominent bony landmarks either side of the meatus (Fig 2A).
3. Measure half of that distance (Fig 2B).
4. Measure distance from this mid-point to the furthest CSF extent along the meatus (Fig 2C).

This protocol was used by 2 independent observers to assess reproducibility of the measurements made. Both observer 1 (a consultant neuro-radiologist) and observer 2 (a senior radiation oncology trainee) measured distances for the first 5 patients on the database. Measurements of the HC were excluded from analysis for reasons that will be described in results, leaving 20 data points for comparison. Observer 2 subsequently assessed the remaining 91 cases.

Statistics

Statistical analyses were performed using Microsoft Office Excel 2010™. Inter-observer variability was assessed with Pearson product moment coefficient and a Bland-Altmann analysis.[31] Data for the full cohort were plotted as histograms and described with mean values and standard deviation.

Results

Anatomy - Agreement

Inter-observer data for the first 5 patients are shown in Table 1. There were only 2 data points where the 2 measurements differed by more than 1mm. There appears to be good agreement. A scatter plot (Figure 3) shows excellent correlation (r = 0.987) but does not assess agreement so a Bland-Altmann analysis was undertaken. The difference between each data point was first calculated and from this both mean difference and standard deviation of those differences within the sample were computed (supplementary – Table 1). Differences between measurements were then plotted against the mean measurement for each data point (Figure 4).

The mean of the differences (d) of observer 1 measurements versus observer 2 was -0.275mm and the standard deviation of differences was 0.557. Further aspects of the Bland-Altmann analysis depend upon the distribution of the differences between measurements. A histogram of these differences (supplementary – Figure 1) demonstrates a convincing normal distribution, despite the small sample size.

If the assumption of normality is accepted then 95% of the measurements would be expected to lie in a range described by the mean difference (bias) and 1.96 standard deviations either side of this;

$$-0.275 - (1.96 \times 0.557) = -1.36$$

$$-0.275 + (1.96 \times 0.557) = 0.81$$

This suggests that the limits of agreement for measuring the IAM and JF on FIESTA MRI images with this protocol are -1.36 to 0.81mm. Therefore 95% of the measurements made by 2 independent observers using this technique were within 2.2mm of each other.

Anatomy – Internal Acoustic Meatus (IAM)

Eighty-six left and 84 right IAM's were measured giving 170 in total. The data were normally distributed (Figure 5A). The mean distance of CSF extension into the IAM was 12.2mm, the standard deviation was 1.75. It can therefore be inferred that in 95% of cases CSF extension into this structure will be 12.2 +/- (1.96 x 1.75) i.e. 8.8 to 15.6mm.

Anatomy – Jugular Foramen

Eighty-three left and 85 right jugular foramen were analysed giving 168 measurements in total. A normal distribution was assumed (Figure 5B).The mean distance of CSF extension into the jugular foramen was 7.3mm. The standard deviation was 1.67. Using the same argument as seen for IAM, 7.3 +/- (1.96 x 1.67), it can be concluded that in this population CSF extension into the JF will be between 4.0 and 10.6mm in 95% of cases.

Anatomy – Hypoglossal Canal (HC)

The HC was hard to identify and measure on many images. This was largely due to the structure being at the inferior extent of the scan. However, this was not universal and for some examinations the structure was clearly visible with a crisp interface between bone and CSF. An image of each circumstance is shown in Figure 6. Forty-two left and 45 right HC's were measured and the data were bimodally distributed (Figure 5C). The mean of these data is 4.9mm but given the distribution this is meaningless. Taking only data from scans where the structure was clearly visible we suggest that the 'true' figure is in the region of 9-10mm. This is a tentative conclusion and will be considered further in the discussion section.

Relevance for RT planning

This data is relevant for oncologists planning both CSI and focal RT for ependymoma. Figure 7 is the radiotherapy planning CT of a patient who underwent CSI at our centre, and demonstrates that these structures are well visualised on RT planning scans.

Discussion

MRI techniques have been shown to accurately identify and visualise cranial nerves and their passage into respective foramen. The detail achievable allows the precise anatomy of CSF evaginating into Dorello's canal with the abducent nerve to be seen and measured.[32] FIESTA MRI gives excellent images and permits detailed analysis of the cisternal segments of posterior fossa cranial nerves.[33-35] Our study is the first using FIESTA MRI to measure CSF extension into the dural cuffs of posterior fossa cranial nerves as they exit the skull base. Inter-observer variability shows good agreement, with 95% of measurements within 2.2mm of each other. A Bland-Altmann approach has been used to assess inter-observer variability of MRI parameters across a range of conditions and anatomical regions as varied as head and neck cancer, evaluation of normal breast tissue, and cerebral blood flow.[36-38] To the best of our knowledge, it has not been used previously in this context. One group have quantified inter-observer variability of cross sectional measurements of the cochlear and facial nerves.[39] They report correlation coefficients (0.974 and 0.987) very similar to that which we report (0.987), but did not measurement agreement with a Bland-Altmann analysis. We conclude that the method described gives an accurate assessment of meningeal and CSF extension into the relevant CN foramen.

The IAM data show that 97.5% of patients would be expected to have CSF extension into this structure no further than 15.6mm from the internal table of the skull. It is known that dura covers the bony surfaces of the IAM and that the neurovascular contents of this structure are surrounded by circulating CSF up to its fundus.[40] It is therefore reasonable to suggest that the internal aspect of the bone wall of the canal provides an excellent surrogate for CSF and meningeal extension. As shown in figure 7A, the bone wall of the IAM is well visualised on a radiotherapy planning CT, and the IAM should be specifically drawn as part of the CTV if all CSF and meningeal surfaces are to be included. Many RT planning software platforms permit fusion of the planning CT and MR images; accurate fusion in this context may facilitate precise measurement and optimise contouring.

For the JF the mean distance is 7.3mm (95% CI 4.0 – 10.6). By similar logic only 2.5% of people would be expected to have CSF extension into this structure beyond10.6mm. The JF has been described by one author as having 3 compartments; a neural compartment containing cranial nerves IX – XI, a larger venous compartment containing the sigmoid sinus (sigmoid part) and a smaller petrosal part containing the inferior petrosal sinus (which drains the cavernous sinus into the internal jugular vein).[41] Others describe a division into two parts by a fibrous or osseous bridge, with the antero-medial compartment, the pars nervosa, containing the glossopharyngeal nerve (IX) and the inferior petrosal sinus and the postero-lateral pars vascularis containing the vagus (X) and accessory (XI) nerves and the jugular bulb.[42]

However, radiological and surgical cadaveric studies agree that the anatomy of the JF is complex and varies significantly between individuals.[43-45] Thus, whilst CT images demonstrate the bony anatomy of the JF well,[43,44] and as seen with the planning CT example in figure 7B, this data may be extremely useful to an oncologist wishing to account for CSF in the structure and be guided as to the likely extent of CSF extension. Again it also makes the more straightforward point that CSF is found beyond the internal table of the skull in the JF and should be contoured as part of the CTV if the intention is to treat all meninges and CSF.

As described, fewer images permitted satisfactory measurement of the HC and the data that was generated is less clear. Other authors have successfully identified CN XII and the HC using MRI but concede that visualising different segments of nerve segments depends upon using the right sequences.[46-48] The main reason for the difficulty we found is that the HC was often at the inferior border of the scan and image quality was poor. Another possible reason is the angle at which slices of the structure were taken. Our impression, from the images reviewed in this study, is that the HC runs antero-laterally but also cranially across the occipital bone, as shown in Figure 8. This observation has not been quantified in our work, or elsewhere in the literature. If this assertion is true, a true axial image would not be parallel to the plane of the HC, which would therefore be harder to identify. However, as FIESTA is a 3D sequence with no gap, it would be possible to reconstruct imaging sequences with an adequate field of view in the oblique plane to better visualise this structure. It is also worth noting that the bony canal of the HC is well shown on a radiotherapy planning CT as shown in Figure 7C.

The most apparent weakness of this study is the fact that the radiological data was derived from a predominantly adult population, whilst the tumour types of interest are most common in children. It is known that the head grows less over childhood than torso and limbs and that adult body proportions are brought about by differential growth of body segments.[49] At birth, head length is a quarter of total body length; at 25 years of age it is one-eighth.[50] It must therefore be assumed that these structures in young children will be smaller than they are adults, although precise ratios may be difficult to quantify. In many ways however this is reassuring as the CSF data presented may be a slight overestimate of the reality in a paediatric population. Provided the data is taken in context and interpreted correctly, it can still act as a useful guide when planning radiotherapy for paediatric cases.

This study has not addressed issues around how to manage cranial nerves I-VI. It is reasonable to assume that the olfactory nerve will be contained within a CTV that includes the cribiform plate, and this has already been discussed.[4,19-21] We know that the optic nerves are surrounded by CSF to the back of the globe and that some radiotherapy planning techniques (TomoTherapy) underdose this area unless it is specifically contoured as part of the CTV.[51] Neither our work nor the literature investigates whether there are meningeal reflections and CSF through the middle cranial fossa foramen, superior orbital fissure, ovale, rotundum and spinosum and this would be an interesting topic for further research.

Conclusions & Implications for Radiotherapy Planning

This study has clearly shown that balanced fast-field echo MRI sequences can accurately describe the microanatomy of the foramen of cranial nerves VII-XII. Specifically, there is clear evidence that CSF flows beyond the internal table of the skull base. This has implications for RT delivery for both medulloblastoma and ependymoma, which can spread to local meningeal surfaces within the posterior fossa. We intend to use the data generated in this study to pursue further work, which will examine whether or not the CSF and meningeal surfaces within these structures are adequately treated with both photon and proton radiotherapy solutions.

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