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Title:

The role of early intra-operative MRI in partial resection of optic pathway/hypothalamic gliomas in children.

Running Title:

Intra-operative MRI and partial OPHG resection in children.

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Abstract:**Introduction:**

Optic Pathway/Hypothalamic Gliomas (OPHG) are generally benign but situated in an exquisitely sensitive brain region. They follow an unpredictable course and are usually impossible to completely resect. We present a case-series of 10 patients who underwent surgery for OPHGs with the aid of intra-operative MRI (ioMRI). The impact of ioMRI on OPHG resection is presented and a role for ioMRI in partial resection is discussed.

Methods:

10 patients with OPHGs managed surgically utilising ioMRI at Alder Hey Children's Hospital between 2010 and 2013 were retrospectively identified. Demographic and relevant clinical data were obtained.

MRI was used to estimate tumour volume pre-operatively and post-resection. If ioMRI demonstrated that further resection was possible, second look surgery, at the discretion of the operating surgeon was performed, followed by post-operative imaging to establish the final status of resection. Tumour volume was estimated for each MR image using the MRlcron software package.

Results:

Control of tumour progression was achieved in all patients. 7 patients had on table, second look surgery with significant further tumour resection following ioMRI without any surgically related mortality or morbidity. The median additional quantity of tumour removed following second look surgery, as a percentage of the initial total volume was 27.79% (range 11.2-59.2%). The final tumour volume remaining with second look surgery was 23.96% vs. 33.21% without ($p=0.1$).

Conclusions:

OPHG are technically difficult to resect due to their eloquent location, making them suitable for debulking resection only. IoMRI allows surgical goals to be reassessed intra-operatively following primary resection. Second look surgery can be performed if possible and necessary and allows significant quantities of extra tumour to be resected safely. Although the clinical significance of additional tumour resection is not yet clear, we suggest that ioMRI is a safe and useful additional tool, to be combined with advanced neuronavigation techniques for partial tumour resection.

Introduction:

Optic pathway/hypothalamic gliomas (OPHG) account for approximately 2-7% of intracranial tumours in the paediatric population, with 65% of these tumours found in children less than 5 years of age [2,11,16,24,28,33]. They comprise a broad spectrum of tumour sizes and localisations, and typically follow an unpredictable course. Presentation tends to be due to compression of the optic pathways and diencephalon, but obstructive hydrocephalus is also a common feature [2,24]. Histologically, OPHGs are nearly always low-grade tumours, with pilocystic astrocytomas (WHO grade I) accounting for the majority, along with a proportion of pilomyxoid astrocytomas (WHO grade II) [5,7,9,11,17,22,30]. A strong association with Neurofibromatosis Type 1 (NF1) is observed, which tends to correlate with a more benign course [6,10,11,13,17,24-25,28,34].

The management of OPHGs has been the topic of much debate. The role of surgery has traditionally been less favourable when compared to radiotherapy and chemotherapy due to the relatively benign nature of these tumours, their eloquent location to the visual pathways, and the impossibility of obtaining a complete resection. A recently published multidisciplinary consensus statement regarding surgery for these lesions stated “It was agreed that primary attempted surgical resection of HCLGG [hypothalamic chiasmatic low-grade glioma] is not the current recommended standard of care. However, it was acknowledged that selected cases were amenable to attempted resection or debulking with low risk” [35]. We have previously demonstrated that good functional outcomes and long-term survival can be achieved in children with OPHGs by using a tailored therapeutic approach that includes chemotherapy, radiotherapy, and surgery in selected cases. We believe that surgery has a clear role for diagnosis, tumour control, and relief of mass effect, and is safe and effective without adjuvant therapy [12]. By limiting radiotherapy use to older children in whom other therapies have failed, the well-described, devastating complications of midline cranial irradiation can be avoided [12].

Incorporating ioMRI with neuronavigation for tumour resection in the adult population has been shown to have a synergistic effect on resection because ioMRI allows the neuronavigation system to be updated intra-operatively, counteracting brainshift and allowing the surgical aim to be modified accordingly to safety considerations or new surgical goals [19,23,27,29]. There is limited evidence for the use of ioMRI in the paediatric population, and we have previously demonstrated that ioMRI has increased the rate of complete resections, with intraoperative surgical strategy being modified in 30% of procedures in our series of 40 cranial tumours [3,4,37]. Other groups have also demonstrated a modified surgical strategy ranging from 21% to 60% [8,14,20-21,27]. Although the clinical effectiveness of ioMRI has been demonstrated for total tumour resection [4,31], a role for ioMRI has yet to be demonstrated in partial and subtotal tumour resection.

In the present paper, we seek to add to the discussion about the role of ioMRI in partial and subtotal resection of OPHG tumours. As the goal of surgery in patients with OPHG tumours is inevitably debulking resection, these patients represent a suitable cohort by which to evaluate the role of ioMRI. We describe a series of 10 patients with Optic Pathway/Hypothalamic Gliomas, in which the initial tailored surgical aim was partial or subtotal resection with the aid of ioMRI and image analysis with MRICron.³⁸ We describe the medical and surgical management of these patients together with their

outcome and discuss the implications for this strategy on tumour resection. Within this series the major surgical interventions were performed by a single surgeon (C.M).

Methods:

Patient selection:

We identified all patients with OPHG tumours managed surgically with ioMRI at our centre between 2010 and 2013. 11 patients were initially identified. One patient was subsequently excluded as the aim of this patient's surgery was deemed to be total, rather than subtotal. This patient had an optic pathway Glioma that had caused an irreversible loss of vision. As preservation of the optic nerve to spare vision was futile, subtotal resection was not the surgical intent.

Data collection:

Medical records and relevant MR imaging was obtained for each patient. Demographics including sex and age at presentation were noted. Previous chemotherapy and radiotherapy history was recorded along with NF1 status. Tissue diagnosis, anatomical location, pre-operative endocrine dysfunction, and presenting symptoms were recorded. Operative approach +/- second look surgery, postoperative endocrine and hypothalamic dysfunction, and time to follow-up were also recorded.

Surgery & Imaging:

Pre-operative MRI included T1-weighted 1-mm isotropic 3-D gradient-echo with and/or without gadolinium, which provided the volumetric data for neuronavigation. Brainlab neuronavigation was used to perform MRI image fusion during surgery. All patients had an early limited ioMRI scan following maximal resection, as determined by the operating surgeon. In patients whose first ioMRI indicated that further resection was possible, neuronavigation was updated with the new T1 non-contrast volumetric data prior to further resection. The early scan was particularly useful thus to re-establish accurate and safe navigation after initial debulk and to evaluate in particular the extent of resection in terms of avoiding the floor of the third ventricle and hypothalamus. Following second look surgery; a new ioMRI was obtained to establish the final status of resection, and the satisfactory completion of the operation. The full ioMRI protocol has been discussed in our previous publication [1].

In the 3 patients where no further surgery was performed – the extent of the resection was already felt to be adequate and to have achieved the pre-operative goal and/or it was felt that further resection could damage the vital hypothalamic/optic pathway structures.

The surgical approach used was transcallosal in 7 patients, while 1 patient had a combined transcallosal and pterional approach, 1 had a cerebellopontine angle approach, and 1 had a pterional approach.

Semi-automated Delineation of Tumour Tissue:

In order to estimate the percentage of brain tumour resected between each MR image acquisition it was necessary to segment the tumour on each MR image. These regions were obtained using the software MRICron [38]. The semi-automated process was iterative, involving two main steps, namely seeded 3D region-growing followed by 3D Gaussian smoothing.

In region-growing a seed is manually placed at approximately the centre of mass of the tumour. A recursive process is then performed where neighbouring voxels which (a) are no further away from the seed voxel than “Radius (mm)”, (b) have grey-level no more than “Difference from origin” different to the grey-level of the seed voxel and (c) have grey-level no more than “Difference at edge” different to the grey-levels of its neighbours are included in the region. Due to the high contrast between grey-level intensity of tumour tissue and cystic areas within the tumour, voxels representing cystic fluid are not included by the region-growing. Several regions were therefore created to encompass the entire tumour and these were then consolidated into a single large region.

Using MRICron, the regions were then smoothed in order to in-fill gaps and blur any rough edges. This technique makes use of two parameters, namely the “FWHM (mm)” and the “Threshold”. [38] The first parameter, the full width half maximum, alters the width of the smoothing function. The second parameter determines the intensity threshold for including voxels into the region. This threshold was left constant for the entire dataset. Although the smoothing technique correctly discards groups of voxels that fall outside the tumour and in-fills gaps within the tumour, it also results in the deletion of voxels on the boundary of the region. It was therefore required to perform region growing and smoothing iteratively until a satisfactory result was achieved.

The regions were then reviewed and found to be sufficiently accurate by an expert neuroradiologist with experience in ioMRI interpretation. Tumour volumes were then independently calculated on pre and intra operative images and postoperative images when second look surgery had been performed with the stage of resection blinded to the operator. Student T test was used to compare the final resection status between groups.

This study was approved by the research department of our institution as a service evaluation, as defined by the United Kingdom National Patients Safety Agency.

Results:

A total of 10 patients (5 males, 5 females) with OPHGs undergoing surgical management at our centre with the aid of ioMRI were included in this series. 1 patient who underwent surgery with the aim of total resection due to existing damage to the optic pathways was excluded as previously described. Demographic and clinical data for all patients is summarised below (Table 1).

Average follow-up was 28 months (range 1-40). All patients were alive at follow-up without any surgically related morbidity.

1 patient was investigated due to an underlying diagnosis of NF1 (the only case in this series). 3 patients already had hypothalamic/pituitary deficits pre-op (including 1 with diabetes insipidus).

8 patients had a tissue diagnosis of pilocytic astrocytoma. 1 patient had a diagnosis of pilomyxoid astrocytoma. 1 patient had a high grade glioma.

Treatment history:

5 patients had surgery as their first mode of treatment at our centre. 3 of these patients ultimately received post-operative chemotherapy due to tumour progression and have remained stable since. In the remaining patients the tumour size remained stable at follow up. 5 'salvage' patients had received variable degrees of treatment at another centre and were subsequently referred to our centre for further management. All 5 patients had received at least one course of chemotherapy, with 4 having received radiotherapy in addition to chemotherapy. All 5 patients had received previous surgery for biopsy, debulking, or hydrocephalus management. Despite all of the previous treatments they continued to progress and thus were referred for further surgery.

Complications:

There were no neurological complications and no new neurological deficits recorded after surgery.

Postoperative endocrine and hypothalamic dysfunction and follow-up:

4 patients developed new transitory diabetes insipidus post operatively, however all resolved with no new permanent cases of DI.

Vision

4 patients initially presented with a disturbance in their vision. Post operatively, there were no cases of new visual deficits at follow-up although surgery resulted in no improvement either.

Surgical outcome:

7 patients underwent second look surgery and further tumour resection following ioMRI where the operating surgeon was able to safely establish new operative goals. Imaging of a typical case is illustrated with MRI images of patient 7 including pre, intra, and post-op (Figure 1).

Resection volumes:

Resection volumes for first look surgery (n=10), second look surgery (n=7), and remaining tumour volume, as a percentage of the original tumour volume are summarised graphically (Figure 2).

The median additional quantity of tumour removed following second look surgery, as a percentage of the initial total volume was 27.79% (range 11.2-59.2%). The final tumour volume remaining with second look surgery (n=7) was 23.96% vs. 33.21% without (n=3) (p=0.1) (Figure 3).

Figure 1 – MRI images of an illustrative case (Patient 8). A – Pre-op T1 Sag with Gad and B – Pre-op T1 Coronal with Gad, demonstrating a mainly posterior exophytic hypothalamic/third ventricle glioma. C – Intra-op T1 Sag without Gad and D – Intra-op T1 Coronal without Gad, surgeon felt it was possible to remove more of the posterior tumour and navigation was updated. E – Post-op T1 Sag with Gad and F – Post-op T1 Coronal with Gad, final intra-operative MR images. Surgeon satisfied with maximal safe debulk. A thin layer of tumour has been left safely on the floor of the third ventricle and chiasm. Images demonstrate the transcallosal interforaminal route that was taken in this case. No new deficits post-operatively.

Figure 2 – Tumour resection volumes expressed as a percentage of the total tumour volume for all 10 patients. Raw data was generated from the MRICron software package. Where only one phase of resection has been performed, one bar is shown to represent the resection volume, followed by a second bar to represent the remaining tumour volume (Patients 1-3). Where second look surgery has been performed, following iMRI, the first bar represents the initial resection volume; the second bar represents the second look surgery resection volume, while the final bar represents the remaining tumour volume (Patients 4-10).

Figure 3

No.	Sex	Age	Presentation	Pre-Op Endocrine Disturbance	Surgical approach	2 nd look	Histology	Nf1	New Post- Op Endocrine Disturbance	New Post-Op Hypothalamic Disturbance	Treatment Naive	Radio Tx	Chemo Tx	F/U (Months)
1	F	6Y	Brainstem compression Visual deterioration Ataxia	Pan-hypo	CP Angle	No	PA	No	DI (transitory)	None	No	+	+	40
2	F	2Y	Hydrocephalus	None	Pterional	No	PA	No	None	None	Yes	-	+	22
3	F	8Y	Visual loss Hydrocephalus	ACTH deficit	Transcallosal	No	PA	No	DI (transitory)	None	No	+	+	40
4	M	3M	Macrocephaly Seizures Hydrocephalus	None	Transcallosal	Yes	HGG	No	DI (transitory)	None	Yes	-	+	39
5	M	15Y	Bi-temporal hemianopia	None	Transcallosal + Pterional	Yes	PA	No	None	None	Yes	-	-	36
6	M	5Y	Left eye visual loss Hydrocephalus	None	Transcallosal	Yes	PA	No	DI (transitory)	None	No	+	+	40
7	F	10Y	Squint, Hydrocephalus	None	Transcallosal	Yes	PMIX	No	None	None	Yes	-	+	24
8	M	8Y	Ix of NF1	DI Precocious puberty	Transcallosal	Yes	PA	Yes	None	None	No	-	+	31
9	F	9Y	Growth delay Hydrocephalus	DI SIADH	Transcallosal	Yes	PA	No	None	None	No	+	+	5
10	M	2Y	Hydrocephalus	None	Transcallosal	Yes	PA	No	None	None	Yes	-	-	1

Table 1

Discussion:

High-field strength ioMRI in combination with state-of-the-art neuronavigation is becoming increasingly popular as a tool to facilitate the resection of both adult and paediatric brain tumours. The benefits of being able to reassess surgical goals, and update neuronavigation, thereby counteracting brainshift potentially allows for more accurate and more efficacious tumour resection in both adults and children [1,3,4,14,19,20,21,23,26,27,29].

The surgical management of OPHGs has historically caused much debate because the tumours themselves are low grade and tend to follow a benign course, are located in an eloquent area, and are near impossible to completely resect. Therefore, chemotherapy and radiotherapy have traditionally provided the primary management options. A large proportion of these tumours occur in children under the age of 5 years and the use of midline cranial radiotherapy below this age has well-described, devastating effects [12]. However, surgery is neither curative nor completely free of risk considering the eloquent location of these tumours to the optic pathways and diencephalon, and the risk of causing new, or worsening existing endocrine and/or hypothalamic disturbances.

However, a multidisciplinary consensus statement on the management of these tumours stated “It was agreed that primary attempted surgical resection of HCLGG [hypothalamic chiasmatic low-grade glioma] is not the current recommended standard of care. However, it was acknowledged that selected cases were amenable to attempted resection or debulking with low risk”[35]. It is clear that there is a role for surgery for the initial diagnosis, for gaining control of tumour progression, especially in those aged less than 5 years where secondary chemotherapy can avoid the need for radiation exposure [32], and for the relief of mass effect [24]. Additionally, it was stated that those tumours that are large, exophytic, cystic, or hypothalamic would be particularly amenable to surgical management [35].

The added benefit from the use of ioMRI for debulking of tumour has yet to be demonstrated. Here we present a small series of 10 patients with OPHG tumours that have been managed surgically at our centre, with the use of ioMRI. By utilising the MRICron software package for quantitative analysis of resection volumes, a reliable measure of surgical outcome was possible. 7 patients proceeded to have second look surgery following ioMRI with further significant tumour resection taking place. We observed that an additional median resection volume of 27.79% took place, which would otherwise have been left in situ. This resulted in the comparative final remaining tumour volumes of 23.96% with second look surgery compared to 33.21% without further resection ($p=0.1$). Although not statistically different, a trend towards a smaller residual tumour volume was observed in those patients having second look surgery following ioMRI.

More importantly, the added safety of a possible interim appraisal of the surgical goal and updated navigation led to no surgically related morbidity or mortality being observed in this series. This suggests that further, necessary resection can take place without any added surgically related morbidity or mortality. Although it is not clear from this series what the long-term benefit of further resection may be, or if there even is one, the impact of ioMRI on primary resection in this series allowed for on table evaluation of the intended surgical goals and further complication-free surgery, with comparable outcomes, and a trend to increased resection volumes.

The role for ioMRI in tumour resection in our series of 10 OPHGs is therefore quite different to that which has previously been described. As the surgical aim is not complete resection, as this is near on impossible to perform without deficit, ioMRI should be used to a) assess whether the surgical goals have been completed while the patient is still on the table, b) provide a postoperative MRI without requiring additional sedation at a later date, c) assess whether further operative goals are available, necessary,

and safe, and d) update neuronavigation, particularly in large tumours, where accuracy is compromised due to brainshift.

This small series demonstrates a new application of ioMRI in tumour surgery. The complex relationship of OPHGs to neighbouring eloquent structures poses a particular challenge to the operating surgeon. We believe that the ability to assess and modify surgical goals on table, update neuronavigation, and obtain a postoperative picture immediately, with no added morbidity or mortality, is advantageous regardless of whether extra tumour is removed, because this strategy potentially allows on table quality and safety assessment.

One of the challenges of assessing the extent to which ioMRI is responsible for greater tumour resection is determining the point at which the intra-operative scan is performed. We acknowledge that there is potentially a self-fulfilling effect when one knows that ioMRI is available at any point, and it is the operating surgeon who decides when to stop operating and perform the interim scan. Therefore, we anticipate that the significance of the extent of tumour resection in surgically managed OPHGs with the aid of ioMRI, will be better understood with a comparative study in the future.

Conclusions:

A role for the surgical management of OPHGs has been established, however these tumours are technically difficult to resect due to their eloquent location, making them suitable for limited resection only. ioMRI allows surgical goals to be reassessed intra-operatively following primary resection and its safety and efficacy has been previously established in relation to total tumour resection in the adult and paediatric population [3].

Second look surgery can be performed if possible, necessary and safe to do so. We suggest that ioMRI may be a safe and useful addition to aid the neurosurgeon when performing sub-total tumour resection. We observed an additional median resection volume of 27.79% and final remaining tumour volume of 23.96% with second look surgery compared to 33.21% without further resection ($p=0.1$) in this case-series of 10 OPHGs. Importantly, we did not observe any added surgically associated morbidity or mortality and propose that ioMRI has a useful role in this complex and delicate surgical area.

Disclosure:

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

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