Management of craniopharyngiomas: Role of conservative strategies

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ABSTRACT

Craniopharyngiomas are uncommon tumors and their management remains controversial. Despite gross total resection, recurrences can occur in 15-43% during long-term follow-up of more than 10 years. Furthermore, radical surgery can be associated with complications associated with hypothalamic damage, which can lead to a poor quality-of-life. Limited surgery followed by adjuvant radiotherapy (RT) can provide excellent long-term tumor control with minimum complications and good functional outcome. RT can however, produce insidious onset of hypopituitarism and vasculopathy. Secondary malignancies are a rare complication of RT. Modern radiation techniques and intracystic radiation can reduce these complications. Intracystic radiation is highly effective for cystic craniopharyngiomas. Intracystic bleomycin (ICB) and interferon alpha (IFN) are rarely curative, but can produce long lasting control of tumor cysts and this is very useful in very young children who may not tolerate radical surgery or RT. IFN has fewer toxicity issues compared to ICB.

Key words: Bleomycin, craniopharyngioma, interferon alpha, management, radiotherapy

INTRODUCTION

Craniopharyngiomas are uncommon tumors, which arise from the ectoblastic remnants of the craniopharyngeal or Rathke's duct. The incidence tends to peak in two age groups, children aged 5-14 years and adults more than 45 years. These tumors, by virtue of their location in the sella and suprasellar region are intimately associated with vital structures including, the hypothalamus, optic nerves and chiasm, pituitary stalk and gland and vessels of the circle of Willis.

The management of craniopharyngiomas has remained controversial and challenging. Harvey cushing considered them to be one of the most baffling tumors to confront a neurosurgeon.[1] Matson and Crigler as early as 1960 recommended complete excision of craniopharyngiomas, especially in children.[2] In that series, he reported complete excision in 12 of 16 children and in one of two adults, with nine children and both the adults doing well over a follow-up period of 1-10 years. Mortality was 22% and three of the children were significantly disabled while all required some form of hormonal replacement. Despite improvements in technology, radical surgery continues to be fraught with potential morbidity, even today. This has led to the evolution of more conservative strategies to deal with this complex tumor, including, limited surgery alone, limited surgery followed by radiotherapy (RT), RT alone and intracystic therapies involving instillation of the tumor cyst with drugs such as bleomycin, interferon alpha (IFN) or radioactive substances. The plethora of options is a reflection of the constant endeavor to improve the outcome of patients with craniopharyngioma and also an acknowledgement of our failure to achieve the perfect solution. The fight against this tumor is often akin to a long drawn out war consisting of intermittent battles and transient victories.

This review will first discuss the current status of surgery for craniopharyngiomas with respect to survival and morbidity and then compare it with more conservative strategies.

Access this article online	
Quick Response Code:	Website: www.ijns.in
	DOI: 10.4103/2277-9167.118114

CURRENT STATUS OF RADICAL SURGERY

Outcome

Craniopharyngioma is a benign tumor and ideally is best treated with total excision. Unfortunately, it is

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also an uncommon tumor and even large neurosurgical centers often see only three to five such patients in a year.[3] These numbers are not conducive to developing adequate surgical expertise and very few neurosurgeons can claim to have mastered the technique of consistently and safely excising these complex lesions. Yasargil, *et al.* in 1990 reported a gross total resection (GTR) in 90% of their 144 patients.[4] Van Effenterre and Boch could achieve only 59% GTR in their 122 patients.[5] Zuccaro used both magnetic resonance imaging (MRI) and computed tomography (CT) scans post-operatively to document GTR. They considered even a speck of residual calcification as evidence of incomplete resection despite an apparently complete resection on MRI. This rigorous criterion resulted in GTR of 69%.[6] Shi *et al.* in the largest series of craniopharyngiomas from a single center in China were able to achieve GTR in 89% of 309 patients with craniopharyngioma.[7] Elliott documented GTR in 100% of their 57 patients presenting with primary craniopharyngiomas, but only in 62% of 29 children with recurrent tumors. Elliott *et al.* identified four factors as being responsible for decreased overall survival (OS) and progression free survival (PFS), namely, presence of hydrocephalus or ventriculoperitoneal shunt, tumor size more than or equal to 5 cm and subtotal resection (STR) of the tumor.[8]

Recurrence

The recurrence rates following GTR have varied widely from zero to 43% in the modern era partly because the mean follow-up duration has not been uniformly reported and the frequency of recurrences increases the longer the follow-up despite radiologically documented GTR.[4-6,8-18] A meta-analysis involving 377 patients from 109 studies found the 1-year PFS and 5-year PFS to be 89% and 77%, respectively following GTR alone, whereas, following STR alone it was 76% and 43%, respectively.[19] In series with mean follow-up of more than 10 years, the recurrence rates following GTR have ranged from 15% to 43%.[8,18,20,21]

Complications

The tendency of this tumor to involve the hypothalamus and third ventricular region is the reason why many patients following radical surgery develop a hypothalamic dysfunction syndrome.[22,23] This consists of varying degrees of a constellation of symptoms including a morbid "hypothalamic obesity" associated with a pathological desire to constantly eat which leads patients to beg, borrow or steal food. Zuccaro found that 35% of their patients had significant obesity post-operatively compared with 25% pre-operatively.[6] De Vile *et al.* found that all, but 7 of 63 survivors of craniopharyngioma surgery had worsening of their body mass index (BMI) standard deviation during follow-up ranging from 1.5 to 19 years. This worsening was directly proportional to the extent of hypothalamic damage visible on MRI brain.[22] Sainte-Rose *et al.* found that 70% of 66 children had some degree of hyperphagia, with 18% being affected severely enough to cause morbid obesity and 15% had impaired neuropsychological function. The quality-of-life based on the Health Utility Index correlated with the BMI, neuropsychology and the hypothalamic involvement on pre- and post-operative MRI. The degree of hypothalamic damage in the post-operative scan depended on the extent of pre-operative hypothalamic involvement (worst for Type 2 or severe involvement) and the experience of the surgeon (worst for <3 cases/year).[13] With a more conservative operative strategy to avoid hypothalamic damage, Mallucci *et al.* found that none of their patients developed any significant changes in BMI.[24]

Impairment of memory or concentration, emotional labiality, thermoregulatory imbalance and daytime somnolence can play havoc with education and work. Metabolic crisis of hypothalamic origin can sometimes have fatal consequences. In the series by Elliott *et al.* 25% developed new or worsened hypothalamic disturbances following radical surgery. 10% of children had intelligence quotient (IQ) <80 or required assistance for all activities of daily living because of cognitive dysfunction.[8] On the other hand, Zuccaro found that all their children following surgery and GTR were able to go to normal school and were no more than 1 year behind expected grade, whereas, among those who underwent STR followed by RT 38% either required special assistance or were not able to attend school.[6] Predictors of increased hypothalamic morbidity according to De Vile *et al.* included symptoms of hypothalamic disturbance already established at diagnosis, greater height (≥3.5 cm) of the tumor in the midline and attempts to remove adherent tumor from the region of the hypothalamus at operation.[25]

Diabetes insipidus (DI), especially if accompanied by impaired thirst sensation, can result in difficult to manage fluctuations in serum sodium levels. DI occurred in 81% of patients post-operatively in the series by Zhang *et al.*[26] The Liverpool experience suggests that even a more conservative surgery will result in DI, but with preserved thirst mechanism which makes it much easier to manage the DI.[24] The intimate adherence of this tumor to the pituitary stalk and gland often leads to pan hypopituitarism following surgery.[8,24] Visual deterioration following surgery is another devastating complication.[8] The close relationship of the tumor to the vessels of the circle of Willis can lead to ischemic insults either from vasospasm or inadvertent vessel damage.[27]

Thus, although many patients with craniopharyngiomas can be successfully offered radical surgery in expert hands, treatment needs to be individualized to minimize the complications, especially those related to hypothalamic dysfunction.

ROLE OF CONSERVATIVE MANAGEMENT

In 2005, the United Kingdom children's cancer study group and the British Society for paediatric endocrinology and diabetes developed a consensus statement on the management of craniopharyngiomas. They recommended that radical surgery should only be considered in the "low risk group" of patients, namely, older children (a cut-off age was not identified, although 5 years was considered), with small tumors <2-4 cm in maximum dimension in the midline and absent hypothalamic syndrome, breach of 3rd ventricular floor or hydrocephalus. A more conservative approach with the aim of relieving raised intracranial pressure, decompressing visual and neural pathways and preserving existing hypothalamic function, even if it meant leaving behind residual tumor was advocated in the "poor risk group" consisting of younger children with tumors more than 2-4 cm in midline, hydrocephalus and hypothalamic dysfunction or breach of the 3rd ventricular floor. Residual tumor was to be treated by immediate (for older patients) or delayed (for younger patients <5 years) adjuvant external fractionated conformal radiotherapy (CRT). Patients with GTR were to be followed-up with repeat MRI scans of the brain every 6 months and any recurrent tumor could be treated either with repeat surgery if feasible or RT.[9]

In patients with cystic tumors, particularly those younger than 5 years, the cyst could be reduced in size to decrease its compressive effects using techniques such as repeated aspirations through an Ommaya reservoir or endoscopic fenestration and shrinkage of the cyst. The latter technique has been used by Mallucci *et al*. as the initial procedure prior to a second stage craniotomy in order to enable complete excision once the tumor cyst has decreased in size.[24] Cysts can also be controlled by instillation of the cyst with radioactive colloids or chemotherapeutic agents such as bleomycin and IFN.[28-33] Other techniques to deliver localized radiation to the craniopharyngioma while minimizing the damage to surrounding vital structures include stereotactic radiotherapy (SRT), stereotactic radiosurgery (SRS) and gamma knife radiosurgery.[34]

Sainte-Rose *et al*., based on their finding that quality-of-life was most severely affected when radical surgery was attempted in children having a pre-operative MRI showing invasion of the hypothalamus by the craniopharyngioma (Type 2), recommended conservative surgery preserving the hypothalamic region followed by RT in such patients.[13] Van Gompel *et al*. found that post-operative weight gain and increase in BMI can occur in adults too and this gain correlates with the extent of hypothalamic involvement pre-operatively. They also noted that involvement of the hypothalamus by the craniopharyngioma can be objectively classified based on the presence of hyper intensity of the hypothalamus on T2 weighted MRI scan of the brain and/or irregular hypothalamic enhancement.[35]

ROLE OF RT

RT as a treatment for craniopharyngiomas has come a long way from the first report by Kramer *et al*. in 1961 from the Royal Marsden Hospital. They treated six children with craniopharyngioma cyst aspiration followed by RT and at a follow-up of 6 years found good control of tumor in all.[36] Since then radiation delivery has evolved from Co^{60} to linear accelerator and imaging to guide the treatment has moved on from X-rays showing sella and suprasellar calcification to MRI and CT scan of the brain to precisely delineate tumor from surrounding normal brain. Rajan *et al*. from the same center published their cumulative experience from 1950 to 1992, which represents the largest series of craniopharyngioma patients ($n=188$) treated with conservative surgery followed by external beam RT. They found that 26 patients (14%) had an acute deterioration around the time of start of RT, most commonly because of hydrocephalus or cyst enlargement. Eighteen of them improved following immediate surgical intervention and 10 year PFS among them was 77%, whereas, six of seven who did not undergo surgical intervention died. The 10-year PFS among the 162 patients without deterioration was 86%.[37] Their experience suggested that survival and PFS were not influenced by the extent of surgical excision.[38]

Manaka *et al*. compared two groups of patients from among 125 who had undergone only partial excision of craniopharyngioma from 1950 to 1979. The 45 patients who had received RT had a median survival of more than 10 years, whereas, the 80 who had not (control group), had a median survival of 3.12 years. The 5- and 10-year survival rates were 88.9% and 76.0% for the irradiated group and 34.9% and 27.1% for the control group, respectively.[39]

Habrand *et al*. reviewed the outcome of 37 children following surgery and RT, either immediately following surgery or as a salvage procedure. The 10-year survival and event-free survival was 78% and 56.5%, respectively.

24% were dead due to the various causes. Functional outcome was impaired in all but five children out of 35 fully evaluable (86%) and related with their initial symptomatology and/or therapy.[40]

Pemberton *et al*. evaluated the outcome following surgery for craniopharyngioma combined with RT either adjuvantly (n=44) or at relapse (n=43) and found the PFS at 10 and 20 years was 78% and 66%, respectively. The outcomes were not different based on the timing of RT. The quality-of-life (QOL) did not worsen significantly over time except in those who relapsed following RT. Children had a worse QOL compared to adults.[41]

Flickinger *et al*. treated 21 patients with megavoltage external beam RT. They used a minimum tumor dose between 51.3 and 70.0 Gy prescribed to the 95% tumor volume resulting in a median total dose of 60.00 Gy and median dose per fraction of 1.83 Gy. Actuarial OS was 89% and 82% at 5 and 10 years. Actuarial local control was 95% at 5 and 10 years. Higher doses of radiation up to but not more than 60 Gy have led to better tumor control, but this puts surrounding vital structures particularly the optic nerves and chiasm at risk.[42] Other structures at risk include the pituitary gland and stalk, the hypothalamus and the vessels of the Circle of Willis and the carotid arteries. Thus most centers have over time limited radiation doses to 50-55 Gy, given in fractions of 1.5-2 Gy/day for 5 days a week for 6 weeks.

COMPLICATIONS OF RT

Visual complications

Visual deterioration during RT is most often due to cyst enlargement or hydrocephalus and usually resolves with cyst aspiration, which may need to be repeated.[37] Flickinger *et al*. reported that among 21 patients treated for craniopharyngioma the actuarial risk at 5 years for optic neuropathy was 30% and brain necrosis was 12.5% in the high dose group, which received more than 60 Gy at 1.8 cGy/fraction.[42] The vast experience at the Royal Marsden hospital of conservative surgery followed by RT demonstrates that visual field defect improved after RT in 36% of patients (38/106) and visual acuity in 30% (27/91). No patient developed radiation optic neuropathy.[38] The general consensus in the literature is that a dose of 54-55 Gy in fractions of 1.8 Gy is not associated with neuritis or necrosis of the optic apparatus.[43,44]

Endocrine dysfunction

The exact incidence of endocrine dysfunction following RT is hard to identify from the literature because patients often present with some degree of tumor induced hypopituitarism, which may be aggravated by surgery. Unlike the hypopituitarism that follows surgery and manifests in the immediate post-operative period, the endocrine dysfunction following RT manifests insidiously and unless closely monitored may be missed until a crisis erupts.[24,40,43] Kiehna and Merchant have needed to provide replacement of growth hormone (GH) in 70%, thyroid hormone in 90%, gonadotrophic hormones in 40% and cortisol in 75% of their patients with craniopharyngioma following RT. DI almost never occurs as a direct consequence of RT.[44]

Cognitive outcome

Serial measurements of IQ over a period of 5 years following CRT have demonstrated very little deterioration, although, worse outcome is predicted by factors such as age <7 years, treatment of hydrocephalus with shunt procedure, large cystic tumors requiring multiple aspirations, extensive surgery and DI.[43]

Vasculopathy

RT for craniopharyngiomas will inevitably result in the carotid arteries and the vessels of the circle of Willis receiving some of the radiation. This can lead to a progressive vasculopathy which can manifest in a variety of ways. Liu *et al*. reported vascular abnormalities in 6 out of 20 patients who underwent RT for the treatment of craniopharyngioma. One had bilateral temporal cavernomas, one had moyamoya syndrome, one had an aneurysm of the internal carotid artery and three children had decreases in the caliber of the carotid or cerebral arteries, but were asymptomatic.[45] Another large study evaluating the risk of development of moyamoya syndrome in children with brain tumors following RT found this to occur in 12/345 (3.5%) patients. Radiation dose above 50 Gy was identified as one of the important predisposing factors and the relative risk of developing moyamoya syndrome increased by 7% for every 100 cGy increase of radiation beyond 50 Gy.[46]

Secondary malignancies

RT particularly in young children is associated with a small but definite risk of secondary malignancies, although as the accuracy of RT delivery improves, this incidence is likely to fall. Rajan *et al*. among 173 patients with craniopharyngiomas treated with RT did not report a single case of secondary malignancy. Kiehna and Merchant in their review of the literature found four reports of secondary malignancies among 626 craniopharyngioma patients (0.6%).[44] Unfortunately, these secondary tumors were all malignant gliomas and invariably fatal. RT for other indications has also resulted in benign secondary malignancies such as meningioma.[47]

TIMING OF RT

The 2005 UK consensus statement recommended RT immediately following STR.[9] However, Mallucci *et al*. argue that in patients with near total resection, immediate RT is not required if they can be kept under regular follow-up because the natural history of such small residuals is still not fully understood. They report that they could reduce the number of patients who underwent RT to 45% from 65% by following this protocol.[24] Moon *et al*. compared early RT within 3 months of surgery with delayed RT following regrowth of tumor preceded by repeat surgery if required. They concluded that quality-of-life (QOL) was better following early adjuvant RT because regrowth and the associated need for surgery led to worsening of QOL.[48]

ADVANCES IN RADIATION DELIVERY

Use of stereotactic techniques has increased the precision of delivery of radiation to the tumor while minimizing the fall out on the surrounding normal structures. During 3D CRT using a thermoplastic mask for immobilization, the planning treatment volume incorporates a 1-2 cm margin beyond the limits of gross tumor volume (GTV). This additional margin beyond GTV can be reduced to 2-3 mm during planning for SRT which uses a re-locatable stereotactic frame or infrared camera guided frameless stereotactic robotic arms to help localize the tumor in space.[49] SRT usually involves delivery of 54 Gy in 30 fractions, although smaller doses have been tried and is usually effective with minimal complications and is within the tolerance limit of the optic apparatus.[50,51] Weekly imaging is advisable during treatment to identify changes in cyst size, which can cause marginal failure.[52]

Intensity modulated radiation therapy (IMRT) is an advanced form of 3D CRT in which delivery of conformal radiation is improved by inverse planning algorithms which adjust the radiation intensity by modifying multiple small beamlets. This results in reduced complications especially in children. However, experience with this technique in patients with craniopharyngioma is still limited.

Gamma knife radiosurgery involves delivery of a single fraction of high dose radiation to the tumor which is localized using the Leksell stereotactic frame, thus ensuring accuracy in the range of 1 mm and reducing radiation to surrounding normal tissue. It has certain limitations, since the craniopharyngioma has to be <2.5 cm in diameter and should be at least 3 mm away from the chiasm and is solid rather than cystic. Niranjan *et al*. treated 46 such patients with a median prescription dose to the tumor margin of 13 Gy (range, 9-20) and reported an OS rate of 97% at 5 years. The PFS for solid tumor control was 91% at 5 years and the overall local control rate for both solid tumor and cyst control was 91%, 81%, and 68% at 1, 3, and 5 years, respectively. Complete radiosurgical coverage was associated with better tumor control.[53]

Conformal proton beam therapy is ideal for a benign tumor such as craniopharyngioma because of the sharp fall in radiation delivery beyond the Bragg peak. The radiation toxicity for surrounding structures such as the optic chiasm and nerves, hypothalamus, pituitary gland and vessels of the circle of Willis are minimal. With the help of intermittent weekly or twice weekly imaging to monitor for cyst progression and intermittent cyst aspiration to regulate the cyst size, even cystic tumors have been treated using this technique.[52]

The relative rarity of craniopharyngiomas and the fact that these advances in radiation delivery are only recently being used for its treatment means that we still do not have adequate long term data to prove that they reduce complications while maintaining the benefits of conventional external beam RT. However, extrapolating data from other tumors like pituitary adenomas suggests that these newer modalities of RT will stand the test of time in the management of craniopharyngiomas.

ROLE OF INTRACYSTIC THERAPIES

Since the majority of craniopharyngiomas have cystic components, it was logical to try and control the tumor by instilling a variety of agents with the ability to destroy the epithelial lining of the cystic component. These agents included beta-emitting radionuclides, bleomycin and IFN.

Intra cavity irradiation

Intra cavity irradiation has evolved from the days of Leksell and Liden who introduced this technique in 1952 and most reports quote cyst control rates ranging from 66% to 100% at varying follow-up periods.[54] The ideal agent should be a beta-emitting radionuclide with high energy, short tissue penetrance, half-life of a few days and without a gamma component. Some of the agents which have been used include phosphorus-32 (P^{32}), yttrium-90 (^{90}Y), Rhenium-186 (^{186}Re) and Aurum-198 (^{198}Au). The latter two have their efficacy limited by their gamma component. ^{32}P has a half-life of 14.3 days, maximum beta energy emission of 1.71 MeV and a half value depth in soft tissue of 0.8 mm with a maximum range in soft-tissue of 7.9 mm. ^{90}Y on the other hand has a half-life of 2.67 days, maximum beta energy emission of 2.27 MeV

and a half value depth in soft tissue of 1.1 mm with a maximum range in soft-tissue of 11 mm.

Voges *et al*. treated 66 craniopharyngioma cysts with stereotactic guided ^{90}Y instillation into the cyst. The targeted beta delivery dose was 200 Gy. There was complete shrinkage in 32 of 66 cysts and partial remission in 23 of 66 cysts. Six patients required re-aspiration of the cyst because of increase in the size of the cyst 1 week after yttrium application and they subsequently had good cyst shrinkage. Once remission was achieved the cysts remained stable throughout the follow-up period (41 patients had more than 10 years follow-up). However, actuarial survival rates at 5 and 10 years were 55% and 45%, respectively, because solid components of the craniopharyngiomas did not respond to the treatment. Only one out of ten patients with a solitary cyst and treated exclusively with intracavity radionuclide died during follow-up. The 10-year survival of this latter group is the best among all their patients (90%). Visual deficits (38 of 62 patients) had improved in 23 patients and were stable in 15 patients. During the 6-12 months after treatment with ^{90}Y three patients became completely blind (2/3 had pre-operative severe optic nerve changes), one had worsening of visual field cuts, one developed a third nerve palsy and three patients developed DI and/or pan hypopituitarism. The authors postulated that if the cyst wall is very thin and is very close to the optic apparatus, then these structures can receive additional radiation and visual deterioration can occur as happened in one patient with normal pre-operative vision who had visual deterioration. In this respect, ^{32}P may be a better choice because of a shorter range in tissue and a longer half-life. There was no operative or perioperative morbidity or mortality. However, one patient died 9 months after ^{90}Y instillation probably as a result of radiation damage to the hypothalamus.[55]

Hasegawa *et al*. reported their 16-year experience of treating 49 patients, including 15 children, with stereotactic ^{32}P instillation into craniopharyngioma cysts either as primary treatment (25) or as adjuvant treatment following surgery, RT, aspiration or bleomycin treatment (24). The radiation dose varied from 189 to 250 Gy to the cyst wall during five half-lives of the isotope (mean, 224 Gy). The mean follow-up was 7 years from diagnosis and 4 years from treatment. The actuarial survival rates from the time of diagnosis were 90% at 5 years and 80% at 10 years. Among 15 patients with only cystic tumor (single or multiple), 80% decreased in size and 87% had tumor control, whereas, among the 26 patients with mixed solid and cystic tumor's, 73% of the cysts decreased in size and 88% had cyst control. The overall actuarial cystic tumor control rates were 76% at 5 years and 70% at 10 years. 25 solid tumor components in 26 patients with mixed solid-cystic tumors were evaluable. Only three (12%) decreased in size, while 14 (56%) remained unchanged. Eight (32%) tumors increased in size and during follow-up, six patients (13%) developed new cysts. Eventually, 12% of the patients required craniotomy for cyst decompression and five patients (12%) had SRS for treatment of the solid component. Four patients (10%) had repeat ^{32}P intracavity radiation to treat newly developed cysts. Post-operatively, there was improvement of the visual acuity in 48% and 47% and of the visual fields in 52% and 41% of the patients in the primary treatment group and adjuvant treatment groups, respectively. Three patients had new-onset visual abnormalities despite tumor regression and therefore these adverse effects were directly attributed to the effect of ^{32}P irradiation. New onset post-operative hypopituitarism was seen in 4% and 3% of the patients in the primary and adjuvant treatment groups, respectively. Three patients developed DI after treatment because of tumor progression.[56]

Pollock *et al*. reporting on thirty patients treated with intra cavity ^{32}P found that fourteen of 20 adult patients (70%) continued to perform at their pre-operative functional level and three of five children who were age appropriate at the time of treatment continued to develop normally.[57]

The above reports are some of the largest series of patients of intra cavity treatment of cystic craniopharyngiomas with radionuclides and have long follow-up periods to accurately assess outcome. They suggest that this form of treatment, especially with ^{32}P, is very effective for exclusively cystic tumors and has relatively few side-effects. However, the technical support and the radionuclides required to provide this form of treatment is not easily available at all centers.

Intracystic bleomycin therapy

Bleomycin is an anti-tumor antibiotic secreted by *Streptomyces verticillus*. It is cytotoxic and affects the G, M and S phases of the cell cycle. It can be used for intra cavity treatment of craniopharyngiomas both as primary treatment and following recurrence. Bleomycin is generally not considered as a curative therapy and is most often used as a temporizing measure, especially in children, until long-term tumor control can be achieved by either surgery or RT. However, Takahashi *et al*. consider this to have curative potential in cystic craniopharyngiomas.[58]

Takahashi *et al*. were the first to report on a management strategy involving minimal resection followed by an intensive regimen of serial injections of bleomycin into

the cyst cavity in seven children. Four patients had no recurrences at 5 years follow-up, but others who had more of a solid tumor component developed progression of the tumor and eventually died.[59] In 2005, Takahashi *et al.* reported on further follow-up, now ranging from 21 to 26 years, of these four patients. One patient had a cystic recurrence, which was treated with repeat injection of bleomycin and subsequently there was no further growth. The other three had an excellent outcome with no recurrence. Another group of 11 patients were also treated with ICB and followed-up for 3-16 years. Seven of these had excellent to good control of cyst growth and have achieved good school life while three needed additional SRS for solid and cystic regrowth and one patient died due to hypothalamo-pituitary insufficiency without cyst recurrence.[58] In contrast Steinbok and Hukin have noted tumor progression in 2 patients as long as 8 and 10 years after excellent responses to bleomycin.[33]

In general, ICB is delivered through a subgaleal Ommaya reservoir connected to a catheter, the tip of which with all its holes is positioned within the cyst cavity. Placement of the catheter is either through an open craniotomy under direct vision or endoscopic guided or stereotactic guided. Ultrasound is helpful in ensuring that the catheter is well-positioned within the cyst. Contrast injection into the cyst followed by a CT scan to detect a leak of contrast outside the cyst is essential prior to proceeding with ICB. This test is generally best done 4-6 weeks after insertion.[54] The dosage and duration of ICB have not been standardized and range from 1 to 10 mg/injection given on alternate days or daily until a total dose of 40-150 mg has been achieved or until the fluid becomes clear. Lactate dehydrogenase (LDH) was initially considered by Takahashi *et al.* to be a good marker of the fluid secreting ability of the cyst wall.[59] Subsequent reports have questioned the value of serial LDH measurements in this context.[33,54]

Hukin *et al.* reported the combined experience of the Canadian pediatric neurosurgical centers with the use of ICB. 17 patients completed this treatment. Five patients achieved a complete response, six achieved a partial response and five achieved a minor response to bleomycin. The median follow-up was 4 years (range, 0.5-10.2 years). One patient was stable for 2.8 years. At the time of last follow-up, 8 patients had not required further intervention. The median PFS was 1.8 years (range: 0.3-6.1 years). The biggest advantage was that radiation therapy could be delayed by a median of 43 months (range: 2-112 months) in these young children in whom the adverse effects of RT are most pernicious. Complications of ICB in this series included transient symptomatic peritumoral edema (two patients), precocious puberty (one patient) and panhypopituitarism (two patients).[60]

Mottolese *et al.* treated 24 patients (20 children and 4 adults) with ICB and during a follow-up period ranging from 2 to 10 years found nine patients had complete cyst regression, three had cyst reduction of at least 70%, five had cyst reduction between 50% and 70% and remaining also had some degree of reduction. Seven patients required surgery for tumor decompression. Injection of a toxic dose in one patient resulted in blindness.[32]

Headache, fever and vomiting along with transient fever are common minor symptoms during ICB administration. These occur in as many as 70% of patients and typically 24 h after each instillation and are self-limiting.[60] Delayed complications are varied and are related to high individual and cumulative dose. They include sensorineural hearing loss, peritumoural edema, visual loss, hypothalamic dysfunction resulting in hyper somnolence, personality changes, poor memory, cerebral ischemia, hemiparesis, progressive panhypopituitarism, precocious puberty, moyamoya disease and death.[33] The key to reducing complications according to Takahashi *et al.* is injecting a lesser dose (5 mg or less) every other day in the appropriate concentration (1-5 mg in 5 ml saline) immediately after aspirating about 10 ml of cystic fluid and follow this with injecting 2 ml saline to push out the bleomycin from the Ommaya device.[58]

Intra cystic IFN

IFN has been used as an alternative to bleomycin for intra cystic treatment of craniopharyngiomas. IFN destroys the tumor cells by activating Fas-mediated apoptosis.[30]

IFN is less toxic to neural tissues compared to bleomycin. In 2005, Cavalheiro *et al.* first reported on the use of IFN for treating nine children with craniopharyngiomas.[28] They were given one to three cycles of treatment with a total dose ranging from 36 to 108 million units of IFN. Seven patients had a complete response and two had a partial response. Fever was noted in the 1st week in six patients. Two patients developed eyelid erythema, which was transient. One patient developed arthralgia and chronic fatigue syndrome 45 days after the treatment.[28]

Other centers have tried this therapy but their patients have not had as much success as Cavalheiro's group.[33] Thus, IFN appears to be a good alternative to bleomycin, without its toxicity. It has role in achieving tumor control in young patients while waiting for them to grow until they are able to tolerate more definitive therapy such as surgery or RT. However, more clinical studies

need to be done before its place in the management of craniopharyngiomas becomes clear.

CONCLUSIONS

Radical excision of craniopharyngiomas can safely achieve a cure in older children and adults who harbor small tumors without hypothalamic involvement. However, limited surgery followed by adjuvant RT, SRT, IMRT or SRS are equally effective in this population especially in larger tumors with hypothalamic involvement. Cystic tumors can be effectively treated with Intra cavity radiation using ^{32}P. In very young children who cannot tolerate RT and in those seeking to avoid the potential long term effects of RT, ICB and IFN are valuable tools to buy time until more permanent solutions can be used. ICB and IFN by themselves can be very effective in purely cystic tumors.

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How to cite this article: Pillai S. Management of craniopharyngiomas: Role of conservative strategies. Indian J Neurosurg 2013;2:142-50.

Source of Support: Nil, **Conflict of Interest:** None declared.