

Recent Trends in Management of Thalamic Tumours in Pediatric Age Group

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Abstract

Background: Tumors of the thalamic origin represent about 2-5% of pediatric brain tumors. They are considered a challenging subset of brain tumors to both neurosurgeons and radiotherapists due to their critical anatomical position and the proximity of functionally significant structures especially in children.

Aim of Study: Is to present the authors' experience in the management of 33 cases of pediatric thalamic brain tumors.

Patients and Methods: Medical records of 33 pediatric patients with thalamic brain tumors admitted to CCHE during the period from July, 2007 till December, 2014 have been reviewed as regard surgical inter-ference, chemotherapy and radiation therapy in relevance to different histo-pathological subtypes, tumor size, patients' age and patients' presenting symptoms.

Conclusion: Pediatric thalamic brain tumors are highly challenging tumors with significant level of morbidity and mortality that require integrated analysis of further studies to achieve better outcome.

Key Words: *Thalamic tumours – Pediatric age group.*

Introduction

ABOUT 2-5% percent of pediatric brain tumors arise in the thalamic region [1,2]. The existing literature that discuss the management of thalamic brain tumors is sparse and usually includes both adult and pediatric cases which make it difficult to focus on the pediatric subset of the tumors arising in this anatomic region [3,4].

Another limitation of the existing literature is that there was no clear distinction between tumors arising in the thalamic region and those arising from other diencephalic structures and basal ganglia nuclei [5,6].

Since that time, management of pediatric thalamic brain tumors was mainly based on their

anatomical origin. Tumors were classified into two major groups: Unilateral thalamic and bithalamic tumors [7].

Here, we are presenting our experience in management of 33 cases of thalamic brain tumor in pediatric age group of different histopathological types where the plan of management is based mainly on the histological grading of the tumor [8].

Aim of work:

Reviewing the different modalities used in the management of patients with thalamic tumours. Stating and clarifying that based on clinical presentation, MRI characteristics and understanding surgical anatomy with pathology, it will be possible to assess the most appropriate group of patients in whom different forms of surgery, radiotherapy or chemotherapy would be beneficial. Following the different management plans applied for the included studied cases.

Patients and Methods

Thirty-three patients with thalamic tumors were included in this study (13 were retrospective and 20 patients were prospective). These patients were admitted and managed in Children Cancer Hospital of Egypt. An informed consent for every procedure or line of management was signed by patient's relatives.

Inclusion criteria:

Patients included are those patients who:

- Were below 18 years.
- Were presenting with tumors along the thalamus (intrinsic or extrinsic).

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Exclusion criteria:

- Above 18 years of age.
- Patients with lesions not arising primarily from the thalamus.
- Patients with previous management (whether surgical or non surgical).

All patients were managed as follows:

- History Taking
- Full Examination
- Investigations
- Initial Management:
- All patients with increased intracranial pressure secondary to hydrocephalus had ventriculo-peritoneal shunt inserted.
- Patients with small unilateral or bilateral thalamic tumors for stereotactic biopsy.
- Patients with large tumors diffusely infiltrating the surroundings for direct surgical intervention.

Surgical techniques:

- Stereotactic biopsies were taken using the frameless brain lab guided navigation system. A small linear incision and burr hole were done after localization was done by the navigation system.
- Thalamic tumours were approached via transcortical approaches (through the middle temporal gyrus or posterior parietal lobule).
- Inverted U shaped incision was located by the navigation with wide base. The scalp flap was reflected as a single layer and then free bone flap was done, opening the dura then cortisectomy was done, then removal of the tumor, and hemostasis then closure of all layers.

Chemotherapy regimen:

- The chemotherapy regimen included Induction phase (carboplatin/vincristine for 10 weeks - Except for week 5 and week 6 which contains vincristine only). This was followed by Maintenance phase after 2 weeks rest. The later phase consisted of 8 cycles of weekly vincristine / carboplatin for three weeks followed by carboplatin at week 4 with 2 weeks rest between each cycle.
- This chemotherapy used with low grade protocol for low grade tumors after stereotactic biopsy.

Radiotherapy regimen:

- For patients with high grade glioma.
- From 30 to 33 session with 3D radiotherapy.

Follow-up and serial evaluation of the patients:

- Each patient was followed by serial neurological examination, visual acuity assessment and fundus examination for the assessment of neurological outcomes, development of any new neurological deficits, seizures, behavioral changes, or any complications.
- MRI brain with contrast was done every 3 to 6 months for every patient for detection of any progression or regression of size of the tumors, and for any complications.

Statistical analysis:

Statistical analysis was performed using SPSS software (version 20) and values are expressed in the form of mean \pm standard deviation. Progression free survival was also calculated for low grade tumors (WHO grade I and II) and high grade tumors (WHO grade III and IV) individually.

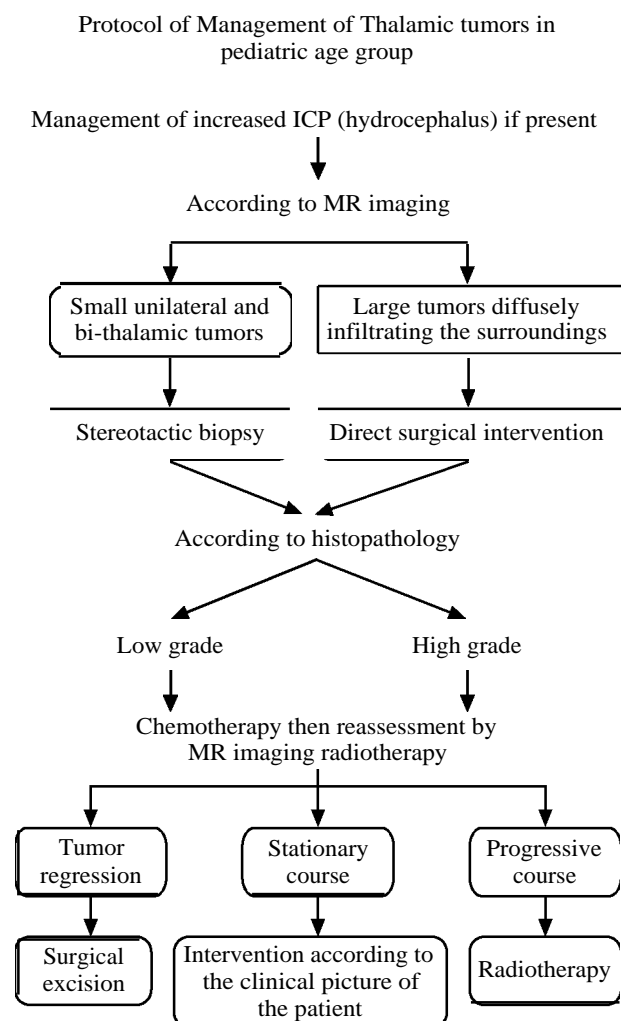


Fig. (1): Algorithm show protocol of management of thalamic tumors in pediatric age group.

Results

By reviewing the medical records of pediatric patients (below 18 years) presented to CCHE with thalamic tumors, we found that 33 patients had thalamic brain tumor. Among whom 17 were males and the remaining 16 were females with a percent of 51.5% and 48.5% respectively. The patients' ages at presentation range from (1-15 years) with average age 7.5 years.

25 patients (76%) presented by manifestations of increased intra-cranial tension (headache, vomiting, and blurring of vision). Five patients (15%) presented by contra-lateral weakness. Two other patients (6%) presented by seizures. The last patient presented by involuntary movements. Thirteen (52%) of the patients who were presented by manifestations of increased intra-cranial tension developed contralateral weakness later on during the course of the disease. The two patients with bithalamic tumors presented by symptoms of increased intracranial tension as shown in Table (1) which summarizes both the clinical features and the anatomical origin of the tumors.

Table (1): The anatomical position and clinical features of 33 pediatric patients with thalamic brain tumor.

Presenting symptom	Anatomical site of the tumor		
	Unilateral	Bithalamic	Thalamo-peduncular
Total	28	2	3
Manifestations of increased tension	25	2	2
Contra-lateral weakness	22	1	3
Visual problems	2	1	0
Seizures	2	0	1
Involuntary movements	1	0	0

All patients with manifestations of increased tension secondary to hydrocephalus underwent ventriculo-peritoneal shunt on the same side of the thalamic lesion (except with few exceptions) in an attempt to relieve the symptoms and decrease the mid-line shift.

MR imaging showed that 31 (94%) of the patients had unilateral thalamic tumors while only two patients (6%) had bithalamic tumors. Three of the patients with unilateral thalamic tumors had thalamo-peduncular tumors which is a subset of unilateral thalamic tumors which arises at the junction between the thalamus and cerebral peduncles. 17 (54.8%) of the patients with unilateral tumors had their lesions on the left side. One of the two patients with bithalamic tumors had intra-ventricular extension and was presented mainly

by manifestations of increased intra-cranial tension and developed also weakness later on during the course of the disease. The other patient had supra-sellar extension and was presented mainly by symptoms of increased ICP but in contrast to the previous patient, he did not develop weakness. However he had in addition to the previous symptoms left eye proptosis and squint and diminished visual acuity up to counting fingers on right eye and no perception of light on the left eye.

Stereotactic biopsy was performed in 31 (94%) of the patients as a primary diagnostic procedure, whereas the remaining 2 (6%) patients had direct attack of de-bulking surgery because of the rapidly deteriorating conscious level and severe midline shift on initial MR imaging. The management strategy for the 33 patients is shown in Table (2).

Table (2): Different histopathological findings in the 33 pediatric patients with thalamic brain tumors.

Histopathological type	No. of patients with the tumor type	%
<i>Astrocytoma:</i>		
- Pilocytic	10	30.3
- Pilomyxoid	1	3.03
- Low grade	2	6.06
- Anaplastic (malignant)	3	9.09
- Astroblastoma (well differentiated)	1	3.03
- Ependymoma	3	9.09
- Primitive neuroectodermal tumor (malignant)	4	12.12
Gangliocytoma	1	3.03
Ganglioglioma	6	18.18
Glioblastoma multiform (malignant)	1	3.03
Yolk sac tumor (malignant)	1	3.03
Total	33	100

NOS = Not otherwise specified.

According to the histopathological findings obtained through the previous procedures the patients were classified into two main groups: 24 (73%) patients with low grade tumors, and 9 (27%) patients with high grade tumors.

Low grade tumors:

Twenty-four (73%) patients were found to have low grade tumors on histopathology. Twenty-two (66.5%) of those patients with low grade tumors received chemotherapy according to their histopathological findings as an initial line of treatment in an attempt to decrease the tumor size, create plane of cleavage, change the tumor consistency and make it succable during surgery.

The mean age of those patients at presentation was 7.5 years and the mean volume of the lesions at initial MR imaging was 96.5ml. seven patients out of 22 ones (after excluding the two patients who had low grade tumors and underwent direct de-bulking surgeries without stereotactic biopsy sampling) became candidates for surgical interference. Among those seven patients, five patients underwent total excision and the remaining two underwent subtotal excision as indicated by post-operative MR imaging.

All five patients who underwent total excision had completely recovered as regard both clinical features (neurological findings) and radiologic findings with no residual tumor nor recurrences through the period of follow-up (mean follow-up duration 3 years and the median 2.25 years). Those five patients had not received any chemotherapy or radiation therapy during the post-operative period and were only followed up by MR imaging every 3 months during the first year and every six months during the second year of the follow-up period.

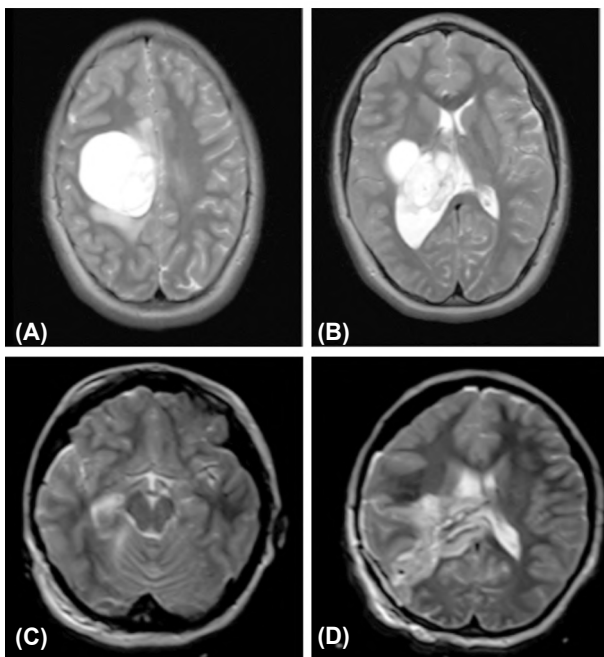


Fig. (2): Right thalamic ganglioglioma demonstrated in MR imaging obtained in a 10 years old girl before and after total excision. (A & B): Pre-operative axial T2 weighted images demonstrating large lobulated right thalamic SOL partially solid and partially cystic with mild degree of perifocal edema. (C & D): Early post-operative axial T2 weighted images demonstrating total excision of the tumor with no evidence of residual enhancing lesions. Parenchymal distortion with hemorrhagic components and subdural and intraventricular air are also noted. Right parietal shunt tube is also noted with no hydrocephalic changes.

The two patients who underwent subtotal excision with removal of more than 90% of the tumor had a stationary course of their residuals during the period of follow-up (mean follow-up duration 2.2 years). Histological results confirmed that both patients had pilocytic astrocytoma. They had not received any chemo or radiotherapy exactly as patients with total excision and the residual tumors showed stationary course with no progression during the follow-up period. The pre and post-operative MR imaging of a patient who underwent sub-total excision.

As an exception to our protocol, two patients were subjected to direct de-bulking surgeries because of the rapidly deteriorating conscious level with severe midline shift on MR imaging. These two patients underwent subtotal excision as indicated by post-operative MR imaging with no neo-adjuvant chemotherapy. The histological results revealed that both cases were pilocytic astrocytoma. The two patient received adjuvant chemotherapy with no radiation therapy. One of the patients had a stationary course while the other surprisingly had regressive course of the residual during the period of follow-up (mean follow-up duration was 2.25 years).

The remaining fifteen patients with low grade tumors who found not to be candidates for surgical interference after receiving neo-adjuvant chemotherapy had been followed-up for a mean follow up duration of 4 years. Two of them had regressive course of the tumor while being on chemotherapy alone with no need for radiation therapy. One of these two patients had pilocytic and the other had pilomyxoid astrocytomas.

Another six patients had stationary course of the tumors. Two of them had ependymoma and were on both chemo and radiotherapy, whereas the other four patients were only on chemotherapy and had astrocytomas and gangliogliomas. The last seven patients with low grade tumors had progressive course of their lesions despite receiving both chemotherapy and radiotherapy. Their histopathologic findings showed great variability. Three of them had ganglioglioma, another two patients had pilocytic astrocytoma, while the remaining two patients: One had ependymoma and the other had well differentiated astroblastoma.

High grade tumors:

Nine patients (27%) were found to have high grade tumors on histo-pathological findings obtained by stereotactic biopsy sampling. The mean age of those patients at presentation was 7.5 years,

similar to patients with low grade tumors. They all were unilateral thalamic tumors and six of them were on left side. The mean volume of the lesions at initial MR imaging was 126ml and the median was 99ml with lesions ranging (42-131.5ml) (an outlier was a patient with tumor size of 406.5ml who was found to be a yolk sac tumor on histopathology and was excluded from the previous range).

Four patients were subjected to sub-total excision as indicated by early post-operative MR imaging then they received adjuvant chemotherapy according to their histopathological findings. Only one patient (who had the yolk sac tumor) received radiotherapy in addition to chemotherapy.

Three of those four patients had disease progression and the remaining patient showed surprisingly regression of the residual tumor during the follow-up period (mean follow-up duration was 2.1 years).

The other five patients who were not subjected to surgical excision, had received both chemo and radiotherapy. All the five patients had rapid disease progression during their follow-up period (mean follow-up duration was 1.6 years) and one patient had died. Fig. (2) shows an example of a patient with high grade tumor who has disease progression.

Table (3): Summary of different treatment modalities received by the 33 patients with low and high grade thalamic tumors according to CCHE management protocol of pediatric thalamic tumors.

<ul style="list-style-type: none"> • Treatment of hydrocephalus by VP shunt in 25 (76%) patients • Stereotactic biopsy sampling in 31 (94%) patients & direct de-bulking surgery in 2 (6%) patients 	
Low grade tumors 24 (73%) patients	High grade tumors 9 (27%) patients
Neo-adjuvant chemotherapy 22 (66.5%) patients	
Total excision in 5 (15%) patients	
Sub-total excision in 2 (6%) patients	Sub-total excision in 4 (12%) patients
<ul style="list-style-type: none"> • Overall treatment 	
Chemo only in 8 (24%) patients	Chemo only in 0 (0%) patients
Chemo and radio without excision in 7 (21%) patients	Chemo and radio without excision in 0 (0%) patients
Excision and chemo in 9 (27%) patients	Excision and chemo in 3 (9%) patients
Excision, chemo and radio in (0%) patients	Excision, chemo and radio in 6 (18%) patients

There was no correlation between patient age at presentation and tumor size and disease outcome. Whereas statistically significant correlation was found between histological findings and degree of excision from one side and disease outcome from the other side.

Postoperative complications:

- Four patients (12.1%) experienced postoperative complications.
- Two patients had postoperative deterioration of their conscious level that was improved later one spontaneously with medication and the other with further debulking of the tumor.
- Postoperative seizures occurred in one patient.
- Intracerebral hematoma at tumor bed occurred in one patient which need another surgery for evacuation.
- During the period of the follow-up five patients need VP shunt revision four proximal and one distal revision.
- Another two patients complicated with shunt infection which need EVD and after then reinsertion of the VP shunt.

Neurological outcome:

- During the follow-up period four patients had seizures, one of them in the immediate postoperative period and two of them presented initially by fits.
- Patient with contralateral weakness improved in five patients, and stationary course in other patients.
- Other neurological manifestations record including deterioration of level of conscious in one.

Survival outcome:

Event survival rate at 6 months, 1 and 2 years were 100%, 100%, 96,9% respectively. The two-years over all survival rate was 98.9%. One patient died from the progression of the disease.

Discussion

Thalamic tumors in pediatric age group account for about 4% of all intracranial tumors [1]. The management of thalamic tumors in existing literature is mainly based on the anatomical origin of the tumors being classified into three main groups: Unilateral, bithalamic tumors and thalamopeduncular tumors [8].

In this study, we are presenting another approach in the management of thalamic brain tumors in pediatric age group according to the management protocol adopted by our hospital shown in Fig. (1),

which is mainly based on the histological grading of the tumors being classified into 2 main categories: Low grade and high grade tumors.

The main presentation of the patients in this study was the manifestations of increased ICP followed by contra-lateral weakness. Very few patients were presented by seizures and visual problems which is coinciding with previous literature [7,8].

All patients with thalamo-peduncular tumors had contra-lateral weakness either as the presenting symptom or developed later on during the course of the disease due to involvement of the corticospinal tract which is also consistent with existing literature [9].

On MR imaging, the tumors were found to be either confined to one thalamus (unilateral) or bithalamic. A subset of unilateral tumors is thalamo-peduncular tumors that arise at the junction between the thalamus and cerebral peduncles and usually exert stretch and compression on the descending pyramidal tract fibers in the cerebral peduncles leading to contralateral weakness [9]. Most of the tumors were found to be extending to the nearby structures like: The basal nuclei, third ventricle, optic chiasma and midbrain.

It is also important to note that not all thalamic lesions are neoplastic especially bilateral thalamic lesions which could be either encephalitis or metabolic diseases [10]. This necessities to confirm the neoplastic nature of these thalamic lesions before administering any harmful adjuvant therapy which is performed by MR spectroscopy. If the lesions were found to be neoplastic in nature, stereotactic biopsy was then performed to confirm the diagnosis and to identify the pathology.

Stereotactic biopsy (three biopsy bits) was used as a primary diagnostic procedure in nearly all cases (with exception of the two cases who were subjected to direct de-bulking surgeries as a result of rapid deterioration of the conscious level of the patients with severe midline shift on neuroimaging), as a safe procedure (associated with low morbidities and very low mortality) with high diagnostic yield [11,12,13].

According to histopathological findings obtained by stereotactic and open biopsies, the patients were classified into low and high grade tumors.

Low grade tumors:

Low grade tumors accounted for 73% in this series. The most common subtypes were pilocytic astrocytoma (27%) and ganglio-glioma (18%).

High grade tumors:

High grade tumors accounted for 27% in this series. The most common subtypes were PNET (12%) and anaplastic astrocytoma (9%).

It is strongly suggested from the previous results of the patients with high grade tumors that surgical excision has nothing to do in preventing disease progression but certainly it can prolong patients' survival. Surgical excision for high grade tumors does not affect the outcome compared to low grade tumors where it significantly affects the outcome. Also, it is clearly obvious that adjuvant therapy by its 2-types; chemo and radiotherapy has no benefit in halting the progression of high grade tumors.

Again irradiation therapy is found to be strongly correlated with progression of high grade tumors supporting the allegation of "radiation therapy inducing tumor transformation".

There are few data in the literature on the clinical outcome of patients undergoing resective surgery for thalamic tumors after resective surgery because these tumors are uncommon and are rarely operated on. For that reason, all series are retrospective, with a variety of different histopathological diagnoses.

The approach to thalamic tumors needs to be planned according to the location of critical neural structures.

GTR of thalamic tumors in children bears acceptable morbidity and may even improve preoperative deficits. Surgery alone can be curative in low-grade tumors; in high-grade or infiltrating tumors, GTR is only part of the overall.

Conclusion:

Thalamic brain tumors in pediatric age group are mostly low grade pilocytic astrocytoma. They usually present by manifestations of increased intracranial tension and/or contralateral weakness. According to their anatomical origin in the thalamus indicated by MR imaging they can be classified into three types; thalamo-peduncular, bithalamic and unilateral tumors.

Thalamo-peduncular tumors usually present by contralateral weakness due to compression and stretching of pyramidal tract fibers in the cerebral peduncles.

Bithalamic tumors should be established and confirmed first by means of MR spectroscopy and stereotactic biopsy before starting any harmful

adjuvant therapy. Surgery has limited role in management of bithalamic tumors.

Unilateral tumors diagnosed by stereotactic biopsy as a primary minimally invasive diagnostic procedure.

Tumors that were found to be of low grade on stereotactic biopsy, were managed by neo-adjuvant chemotherapy in an attempt to reduce the tumor size and vascularity. This markedly participated in reducing perioperative morbidity and mortality.

On the other hand, all patients with high grade tumors, whether operated only by stereotactic biopsy or debulking received adjuvant therapy either chemotherapy alone or both chemo- and radiotherapy. This adjuvant therapy was found not to be very effective in preventing disease progression but generally overall survival was prolonged.

Two factors were found to affect the patients' outcome; histological grading of the tumor and radicality of surgery. Surgical excision for high grade tumors does not that much affect the outcome compared to low grade tumors where it significantly affects the outcome.

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الوسائل الحديثة لعلاج أورام المهاد عند الأطفال

تمثل أورام المهاد عند الأطفال نسبة من أورام المخ، وعادة ما تكون هذه الأورام من الأورام الحميدة. يأتي المريض عادة بأعراض زيادة ضغط المخ مثل الصداع المستمر، عدم وضوح الرؤية، الترجيع المستمر. وذلك نتيجة وجود استسقاء بالمخ نتيجة ضغط الورم على البطين الثالث بالمخ ويحتاج المريض لتثبيت صمام مخى بريتنوى وذلك لتقليل ضغط المخ.

بالإضافة إلى الأعراض الأخرى مثل ضعف الأطراف وخصوصاً بالجهة العكسية بالجسم من الورم. هذه الأورام إما أن تكون على ناحية واحدة من المخ، أو على الناحيتين، أو تكون لها اتصال بدعامات المخ. هذه الأورام التي لها اتصال بدعامات المخ عادة ما يكون هناك ضعف بالأطراف عند المرضى وذلك نتيجة الشد على مجموعة الألياف العصبية الهرمية بالمخ.

تشخيص الأورام المتواجدة على الناحيتين عادة عن طريق الرنين المغناطيسى الطائفى، أو عن طريق أخذ عينة بالجهاز الملاحي وذلك قبل ما نبدأ العلاج المساعد من العلاج الكيماوى أو العلاج الإشعاعى. أما تشخيص الأورام المتواجدة على ناحية واحدة عادة ما سيكون عن طريق أخذ عينة عن طريق الجهاز الملاحي. معظم الأورام تكون أورام حميدة ويتم علاجها على حسب حجمها لو صغيرة وداخل المهاد تعالج بالعلاج الكيماوى المخصص للأورام الحميدة وذلك لتقليل حجم الورم وتقليل الأوعية الدموية المغذية له. ثم يعاد تقييم المريض للتدخل الجراحى. أما لو كان هذه الأورام الحميدة كبيرة وخارج المهاد ويتم التدخل الجراحى المباشر للاستئصال ثم العلاج المساعد من العلاج الكيماوى والعلاج الإشعاعى.

الأورام الخبيثة تحتاج للعلاج الإشعاعى والعلاج الكيماوى لتقليل التطور المرضى ومضاعفاته للمرضى. هناك عاملان يتحكمان فى حالة المريض وتطوره المرضى وهما درجة الورم الباثولوجى ومدى الاستئصال أثناء الجراحة. وجد أن التدخل الجراحى للمرضى ذات الأورام الخبيثة غير مفيد مثل الأورام الحميدة. قد يحتاج بعض مرضى الأورام الحميدة للعلاج الإشعاعى فى حالة أنها أورام حميدة نشطة.

هذا البروتوكول فى العلاج أدى بشكل كبير إلى تقليل المضاعفات المرضية، والوفيات بشكل ملحوظ وخصوصاً عن الأبحاث الأخرى. يمثل مرض أورام المهاد لسنوات تحدى لجراحى المخ والأعصاب ولكن فى السنوات الأخيرة وفرت الوسائل التشخيصية والجراحية والعلاجية الحديثة لعلاج تلك الأورام نتائج أفضل للمرضى من حيث زيادة فائدة العلاج أو الإقلال من مضاعفاته.

وهدف الدراسة: هو تحديد تلك الوسائل العلاجية وطرق استخدامها وتأكيد فائدتها وإلقاء الضوء على استخدامها فى مصر.