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Review Article

A Review of Retinoblastoma and its Current Management

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Abstract:

Retinoblastoma is a malignant tumor of the eyeball commonly seen in small children. Its management is becoming complex as it is becoming necessary to rely on International Classification of Retinoblastoma (ICRB). The treatment also depends upon germline mutation, available institutional resources and psychosocial factors of the family. Pub Med was used to make the write up of this review article from 1945 to 1996. The keywords used for this search were retinoblastoma, germline mutations, family history, EBRT, Chemotherapy, Intra-arterial chemotherapy and chemotherapy, intravenous chemotherapy, and chemo reduction. The hypotheses for the origin and spread of Retinoblastoma were discussed, followed by the current treatment since 2020 which included intravenous chemotherapy (IVC), intra-arterial chemotherapy (IAC), intra-vitreal chemotherapy (IvitC), radiation-based therapies (external beam radiotherapy [EBRT] and plaque radiotherapy), and Enucleation. An overall consensus treatment options practiced in India were discussed in detail.

Keywords: Eye, Retinoblastoma, children, treatment and EBRT.

Introduction

Definition of Retinoblastoma

Retinoblastoma is considered primarily as a primitive neuroectodermal malignancy occurring in the orbit affecting young children presenting with Lekocoria.

Incidence and Epidemiology

Review of literature showed shows prevalence of Retinoblastoma varies in different countries; according to their census reports in all the continents of the world. Retinoblastoma is a commonly occurring malignant tumor in the orbits of children. [1] The prevalence of Retinoblastoma reported as from 03.4 to 42.6/ million live births varying from country to country. [2] In North America it was shown to occur in 11.8 cases/ million live births in children aged below 05 years. [3] Retinoblastoma malignancy accounts for 06.1% of all cancers occurring in this age group. Every year 350 new patients are reported with Retinoblastoma in North America. [4] There are approximately 350 new cases annually in the United States. India has a prevalence rate of 21/million live births and 2000 new cases are reported per year. [5] This is double the incidence of China and 6 times the incidence of USA. [6] The median age at which the diagnosis is made is 18 months. [7] Two thirds of these cases were found to be unilateral and 1/3rd of the cases are bilateral. [8] Retinoblastoma is categorized as germline (present in all cells of the body) and somatic (germline present in only the tumor). [9] Unilateral or bilateral Retinoblastoma is not predicted accurately by the germline theory; but one can say that bilateral disease

occurs in 15% and unilateral disease in the remaining explained by germline mutation. [10] Both the genders are equally affected. [11] Racial predilection for retinoblastoma is not common. [12]. Leukocoria (a white pupillary reflex; Fig 1) is present in all the children with Retinoblastoma; sometimes strabismus (a lazy eye) is evident.

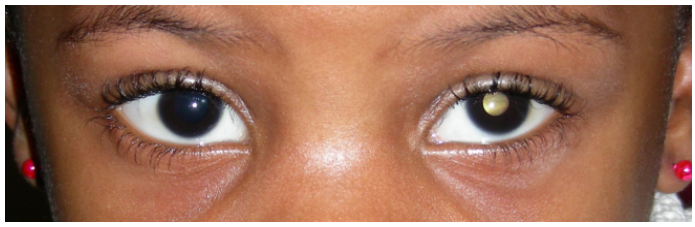

Figure 1: white pupillary reflex

Genetics

As Retinoblastoma was observed in families, it was presumed that a genetic background was the reason for the development of some type's forms of this cancer. [12] The genetic background was recently proved by Knudson [13]described the mechanism known as "two-hit" programme for tumor genesis for Retinoblastoma in 1971. It proves that there should be mutation in both the active copies of the gene required for normal retinal development and for the origin of Retinoblastoma. As the mutation starts it causes inactivation of one copy of the gene occurring either in somatic or germline cells; as the second mutation happens in the somatic cells of the developing retina. [14] That explains the development of inheritable form of retinoblastoma when the mutation occurs first in the germline cells. In 90% or more cases of Retinoblastoma occurs due to new mutation rather than with a family history. When mutation occurs causing Retinoblastoma, it occurs in very early age because all the somatic as well as germline cells undergo the "first hit." The age of occurrence of retinoblastoma in Retinoblastoma heritable and non-heritable retinoblastoma are the main clue for the Knudson's hypothesis. [15] Murphree [16] in 1984 via linkage studies mapped and concluded that the gene for the origin of Retinoblastoma was on a single locus due to the association between 13q- syndrome and retinoblastoma. The locus was located on sub-band 13q14.2. Friend in 1986 discovered the Retinoblastoma gene and called it as RB1. [17] Incidentally that was the first tumor suppressor gene that was discovered; it was called tumor suppressor gene because it causes restriction of the gene passing through the cell cycle. In comparison the classic oncogene promotes cell growth. Because RB1 is a tumor suppressor gene, it requires that the both alleles should be inactivated for tumor development. [18] In Germline patients who represent 40% of the retinoblastoma patients, all the cells carry one mutated copy of the retinoblastoma gene. [17] Such patients develop bilateral Retinoblastoma with multifocal tumors, risk for secondary tumors, including primitive neuroectodermal tumors in the brain (so-called "trilateral retinoblastoma"). Their off springs also tend to develop retinoblastoma in 45% of the cases; this gene acts as an autosomal dominant type and has 90% penetrance. [19] It will not be inheritable if both the RB genes' mutation occurs in a somatic cell of the developing retina. But it would likely cause a sporadic unilateral retinoblastoma. [20] Even among the unilateral Retinoblastoma which were sporadic and nonhereditary, almost 15% of the patients may have germline mutations. [17] It was also observed that though the tumor starts unilaterally, it may turn to bilateral disease over a time [17] Hence serum genetic testing is considered crucial to find out if the initial mutation was

germline or not which helps in the management of these patients clinically. [18]

Classification Systems

There are many classification systems developed in staging the Retinoblastoma tumors but for practical purposes to determine the best treatment options ophthalmologists all over the world use dividing Retinoblastoma tumors into 2 main groups: intraocular and extra ocular. Extra ocular Retinoblastoma tumors are further divided in to orbital retinoblastoma tumors, which spread locally only within the bony eye ball and others renamed metastatic type and they spread to distant parts of the body like bone marrow and brain. [20]

Reese-Ellsworth classified intraocular retinoblastoma tumors[21] in 1950 which helped in the assessment of prognosis of eye globe salvage after radiation. According to this classification Intraocular Retinoblastoma patients are grouped in to 5 groups. Very favorable: 1. Less than 4 disc diameter (DD) of Solitary tumor, at equator or behind it. 2. Not more than 4 DD Multiple tumors at equator or behind it. Favorable: 1. 4 to 10 DD in size, Solitary tumor at equator or behind it. 2. 4 to 10 DD in size, multiple tumors behind equator. Doubtful: 1. Tumor in front of equator, Solitary > 10 DD or behind the equator. Unfavorable: 1. Larger than 10 DD in size, multiple tumors. 2. Tumors extending in front of Ora serrata. : 1. Very large tumors more than 50% of the retina. 2. Seedlings in Vitreous. Nowadays chemotherapy has replaced the EBRT by many surgeons as the later was causing secondary tumors. Hence the classification of Reese-Ellsworth has become obsolete in predicting and assessing the prognosis after treatment with chemotherapy. Now International Classification of Intraocular Retinoblastoma (ICRB) [22] is being used to assess the prognosis of post chemotherapy intraocular retinoblastoma patients in much a better way: 1. Predicting cure 2. Saving the eye ball and by not removing it; avoiding EBRT. The ICRB classifies tumors from A to E:

A. 3 mm or less in size tumors; across; located only in the retina, > 3 mm from foveola, > 1.5 mm from the disc.
B. >3 mm tumors in a macular or juxtapapillary location. With a cuff of sub-retinal fluid < 3 mm from the tumor and no sub-retinal seeding.
C. Tumor with, < 3 mm localized sub-retinal or vitreous seeding; one quadrant of sub-retinal fluid
D. Tumors with wide area of sub-retinal or vitreous seeding > 3 mm from tumor; extensive sub-retinal fluid
E. Large Retinoblastoma with neo-vascular glaucoma, tumor anterior to the vitreous face (Figure 2), widely infiltrating Retinoblastoma; with phthisis bulbi; aseptic orbital cellulitis; or opaque media from diffuse vitreous hemorrhage.

The ICRB was successful in predicting the prognosis of globe saving methods after the starting of chemo-radiation era. [23] The success met with Group D eyes of Retinoblastoma cured with Intravenous chemotherapy was supported by Berry and colleagues. (24) However, Group E eyes had a very low success rate. [23] Invasion of choroid; the sclera; and/or the optic nerve are the points suggest the extra ocular spread of Retinoblastoma. Whether to use chemotherapy after enucleation of eye ball in children following treatment of Retinoblastoma is not yet clear. [23]

Diagnosis

Screening: As per the guidelines of the "American Academy of Pediatrics" a policy to conduct Examinations of the eyes for Red Reflex in all Neonates/ Infants/ Children before discharge from the Hospital. In addition there should be routine health supervision in neonatal nursery on all subsequent visits. [24] The examination in a dark room is preferable with

ophthalmoscope or a retinoscope. 1–1.5 feet distance should be maintained to observe for Leukocoria which is a common sign of retinoblastoma. Red reflex positive children should be subjected to thorough ophthalmic examination for other signs. In those infants with positive family history of Retinoblastoma must be examined carefully. Genetic counseling for the family members with children with Retinoblastoma is a must as it is a risk factor.

Clinical Presentation

Like with other diseases early diagnosis helps in maximizing the chances of preserving the vision of the children. All the children presenting with strabismus or Lekocoria, cellulitis or red eye like features must be screened for Retinoblastoma. Leukocoria is the absence of red reflex which occurs normally due to the tumor filling the eye globe. The second common presentation is strabismus; hence all children with strabismus must be searched for and Retinoblastoma to be excluded; Strabismus evaluation should include a total dilated ophthalmic examination. The other less common symptoms of Retinoblastoma are pain which is present in many eye diseases also such as end-ophthalmitis, uveitis, vitreous hemorrhage, orbital cellulitis and preseptal cellulitis. Extra global spread of necrosed Retinoblastoma is associated with periorbital inflammation; a poor prognostic sign. Spread of the Retinoblastoma occurs into the choroid or sclera or spread along the optic nerve directly into the orbit. Hematogenous spread causes widespread metastases to the bone, liver, the central nerve system (CNS), and other organs.

History

For a prompt diagnosis of Retinoblastoma careful history taking for the presenting complaints, family history, ophthalmic examination and appropriate ancillary laboratory studies are critical and essential. Elicitation of family history should be around asking leading questions like diminished vision, swellings of the eye, malignant tumors of childhood, and history of removal of the eye balls. Family history of sarcomas should be asked for. The parents should be encouraged to answer questions like whether leukocoria or strabismus were present observed, and their duration.

Physical Examination

A red reflex test must be done to confirm the presence of leukocoria. Age appropriate ophthalmic examination for visual acuity together with pupillary reflex response must be done. Anterior chamber examination to assess the presence of proptosis, ciliary injection, pseudo-hypopyon, and signs of secondary glaucoma should be undertaken. Pupillary dilatation examinations like search for retinal masses. A- and B-scan to look for retinal based masses with intra-lesional calcification is also critical. Children should be examined under General Anesthesia if all the tests of ophthalmic examination could not be undertaken completely to know the site, and extent of the tumor. Photographic documentation of the signs in the operating room is recommended. [25]

Fundus Examination

The common clinical presentation of the Retinoblastoma is either solitary or plenty nodular, white/ cream-colored masses most commonly presenting with prominent blood vessels coursing on the mass. The three types of presentations are: 1. Endophytic (Figure 2); Tumor grows from the retina and projecting into the vitreous cavity. 2. Exophytic (Figure 3); tumor expands in the sub-retinal space to cause exudative retinal detachments. 3. Diffuse infiltrating (Fig 4); Tumor infiltrates throughout the retina.

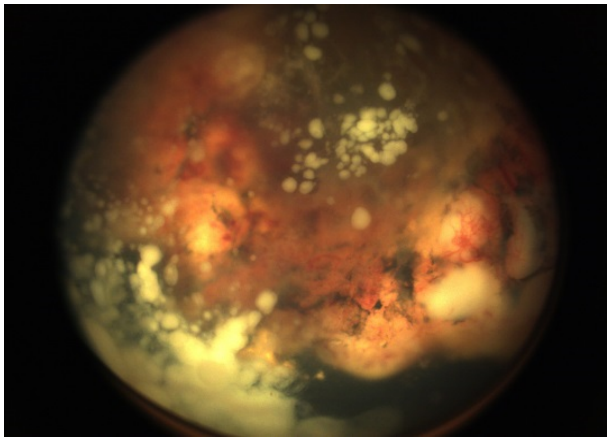

Figure 2: Endophytic tumor type

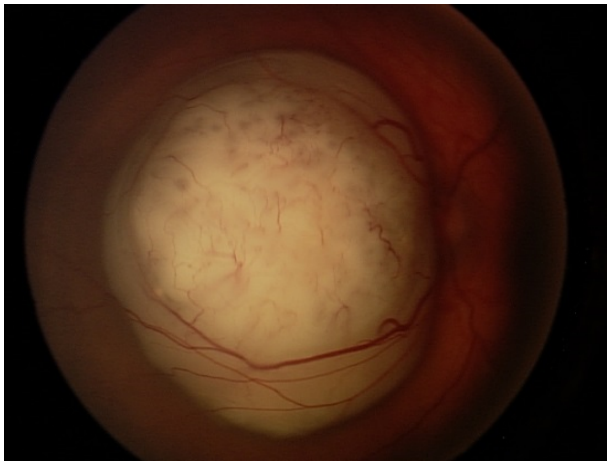

Fig 3: Endo and exophytic tumor type

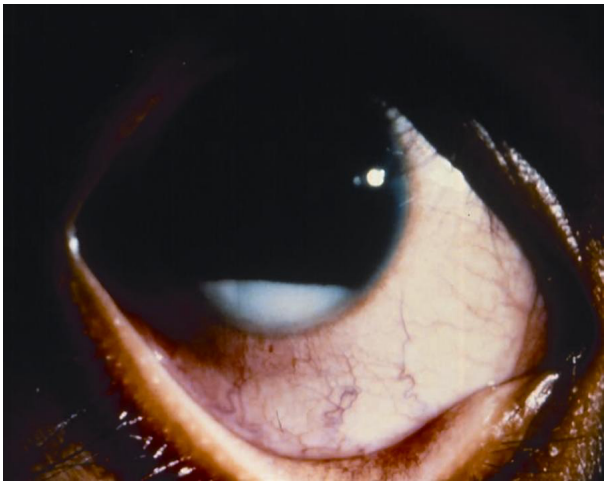

Fig 4: Pseudo hypopyon tumor type

Figure 4: Endophytic (left), mixed Endophytic and Exophytic (right), and pseudo-hypopyon.

Ancillary Diagnostic Tests

B- Scan ultrasound examination of the eye ball determines the height and thickness of the tumor and confirms its association with retinal detachment and diffuse intra-lesional calcification; pathognomonic for retinoblastoma. (Fig 5)

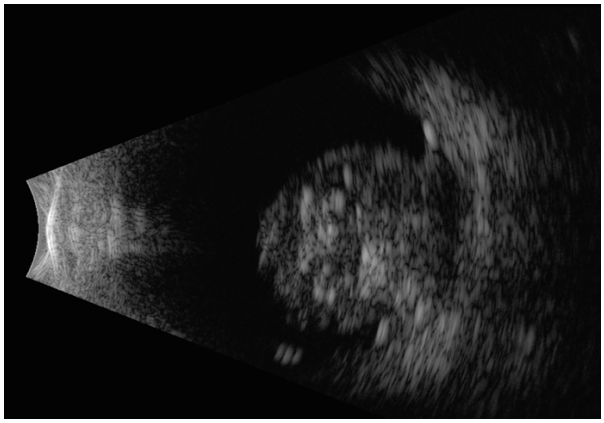

Figure 5: B-scan of retinoblastoma arising from the retina with calcifications within the tumor mass.

Radiological Investigations:

CT scan helps in delineating the size and type of Retinoblastoma but usually avoided in younger subjects due to a possible occurrence of genetic cancer syndrome. The MRI imaging was found more beneficial in assessing the optic nerve damage and tumor spreading to extra ocular regions. It also helps in diagnosing the possible neuroectodermal tumor (trilateral retinoblastoma, Figure 6).

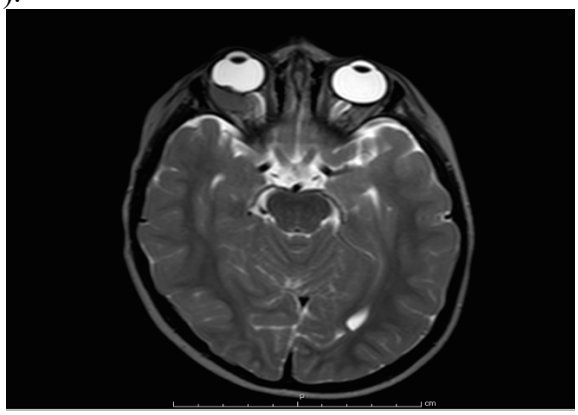

Figure 6: shows the MRI scan of intraconal orbital mass hypointense to the vitreous on right side.

Differential Diagnosis

The differential diagnosis of Retinoblastoma includes those diseases that resemble with absent red reflex; benign entities such as a lens opacities, Coats disease, premature retinopathy, retinal detachment, persistent fetal vessels (PFV), toxocariasis, choroidal coloboma, vitreous hemorrhage, myelinated retinal nerve fibers, and astrocytic hamartoma. Large corneal opacities sometimes white reflex, But easily differentiated from leukocoria on ophthalmic clinical examination. PFV, Coats disease, and toxocariasis pose a clinical challenge to differentiate from retinoblastoma. Ocular toxocariasis produces a white, peripheral retinal mass resembling Retinoblastoma; which is usually unilateral. If the tumor is in acute stage; signs of inflammation like injection, pain, photophobia, and anterior chamber or vitreous cells are present. Patients with peripheral larva migrans present with fever, eosinophilia, pneumonitis, or hepatosplenomegaly. Their Serum titers will be positive for *Toxocaracanis* which helps in the diagnosis. Among the congenital conditions, PFV presents with leukocoria very early in life especially after birth. It is usually occurs unilaterally with micro-ophthalmic eyes. Cataract will be present and presences of an elongated ciliary process are diagnostic of PFV. A

stalk between the retina and the optic nerve on USG also observed. These features differentiate PFV from Retinoblastoma. Coats disease is also unilateral disease of the orbit with abnormally dilated, tortuous vessels with significant exudation, causing lipid-laden mass with associated telangiectatic neovascularization. The exudates are much yellower than white as they contain cholesterol. It affects boys between the ages of 6 and 8 years unlike Retinoblastoma. B-scan USG helps to differentiating Retinoblastoma from Coats disease. Presence of diffuse intralesional calcification with solid mass favors the diagnosis of Retinoblastoma unlike non-calcified retro-lental mass favors a diagnosis of PFV. Fluorescein angiography (FA) helps to differentiate Coats disease from the Retinoblastoma tumor; the blood vessels are dilated and torturous in both. Micro aneurysms, intra-retinal micro vascular anomalies, and areas of retinal non-perfusion are found in Retinoblastoma. Coats disease presents with focal vasculatity made of small or medium sized vessels with "light-bulb" aneurysms. Profuse leakage of exudates into the sub retinal space in later stages of the FA is found. In exophytic tumors vascular abnormalities at multiple levels are found on FA and are characteristic of retinoblastoma. The explanation is that the vessels represent both of the tumor and the retina; which is not seen in Coats disease. [26]

Management

General treatment

Fundamental principles of the management of retinoblastoma in the order of priority are: 1. save the life, 2. save the eye globe, and 3. save the vision. In the process of treatment to minimize the complications and side effects are utmost importance especially in small children. The definitive management in Retinoblastoma is removal of the eye ball. This is especially in children who present in an advanced form of the disease. Systemic chemotherapy helps in salvaging the eye globe especially by consolidating the tumor focally also by and chemotherapy given intra-arterially. Focal consolidation therapy is useful in small tumors and it is effective. It is achieved by cryotherapy, photocoagulation by laser, and plaque irradiation. [27] In children aged below 12 years EBRT is avoided nowadays to restrict the associated side effects, but its role is to limit the local recurrences and seedlings. Chemotherapy given by Intra-vitreal route which is an advanced treatment added with a concept to supplement EBRT to control the seedlings and prevent vitreal extensions. [27]

Medical Treatment of Intraocular Retinoblastoma

Chemo reduction

Before 1990s, EBRT was the main stay of treatment of Retinoblastoma children. Chemotherapy was limited only to cases of recurrences and metastatic cases. In patients with germline mutations, EBRT had a prevalence of causing secondary tumors when followed over a long time by the clinicians who realized that using chemotherapy initially was significant was ideal. They found that almost 38.2% of patients with hereditary Retinoblastoma developed secondary malignancy. The mortality rate among such patients was 26%. [28, 29] It was also observed that the recurrence rate was as high as high as three times after EBRT, more so in children of under one year in age. (30) Non-use of EBRT was matched with the advent of newer and efficient chemotherapeutic agents with lesser toxic effects and side effects against Retinoblastoma. Chemotherapy in the treatment of Retinoblastoma was called as Chemo reduction because it helps in reducing the mass of the tumor and permits further treatment with therapy to consolidate the tumor focally (Figure 7). Reduced total mass of the Retinoblastoma improves the success rate of focal therapies, which are

less efficient with larger tumors. [31] Focal therapies help in later stages of the disease to destroy tumor cells directly and breaking down the blood-ocular barrier to promote better penetration of chemotherapeutic agents into the eye. [32]Currently medical management of Retinoblastoma consists of systemic chemo-reduction and local therapy; with a major eye ball salvaging options in Retinoblastoma treatment. [33]

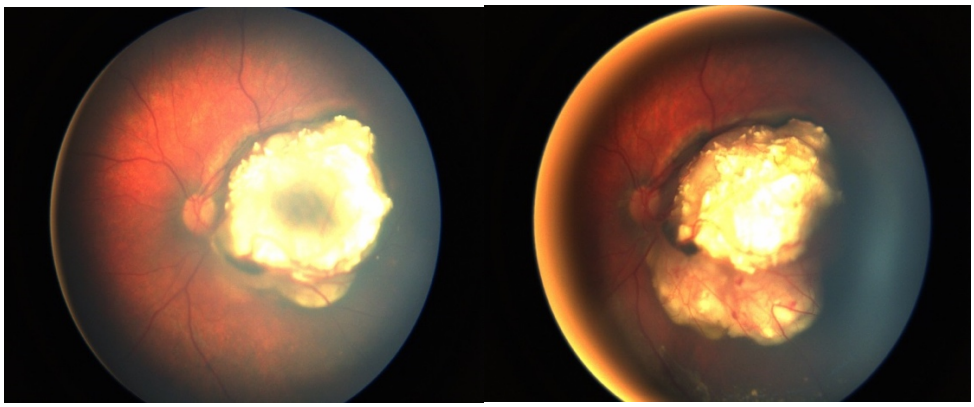

Figure 7: Retinoblastoma after chemo-reduction and local consolidation (above) showing a tumor recurrence below the tumor. 02 months post chemotherapy (below).

Intra-Arterial Chemotherapy

With the discovery of Intra-arterial Chemotherapy to improve the intraocular drug penetration at the same time lessening the systemic toxicity was possible. It had replaced the other modes of administration of chemotherapeutic agents like intravitreal injection and sub-conjunctival injections to advanced drug delivery methods using fibrin sealant. [34] Abramson and colleagues from Japan modified and used canula in carotid artery and delivered chemotherapeutic drugs to the eye; [35]. It was named after him as supra-selective intra-arterial chemotherapy and intra-arterial Inj. Melphalan was used and found to be having superior response for tumor reduction with fewer complications and toxic effects more so as they were used as primary treatment and salvage treatment. The Whole-body radiation with total dose given using multiple fluoroscopies also remained undefined.

Intravitreal Chemotherapy

In the treatment of Retinoblastoma the most challenging aspect is to attain control over the seedlings in the vitreous humor. Intra-arterial route of administration of anti-malignancy drugs have no control over these vitreous seedlings. Hence Kaneko and colleagues initially and later modified by Munier and colleagues recommended and showed that intra- vitreous administration of the drugs to the eye ball. [36] This method extra ocular spread or metastases with a median follow-up of 22 months were prevented. Among the side effects, the most common was salt and pepper retinopathy at the periphery of the retina around the injection site. This may be due to higher concentration of Inj. Melphalan deposition which further increased the protection against tumor spread.

Surgical Treatment of Intraocular Retinoblastoma

In Retinoblastoma Enucleation is indicated in the children belonging to group D and E tumor burden progressing in spite of conservative treatments. [37] Total eye ball enucleation consists of removal of at optic nerve by one centimeter at least making sure that the Optic nerve does not harbor tumor seedlings at its free end. [38] It reduces the chances of relapse in the orbit and obviates the need for adjuvant therapy? [39] At the time of enucleation harvesting the tissue for storage and genetic studies is undertaken. [40] The tissue harvesting is

usually done carefully, avoiding alteration of anatomy of the eye ball and creating artifacts that would jeopardize further pathologic evaluation.

Medical Treatment of Extra ocular Retinoblastoma

Prognostically extra ocular retinoblastoma is almost usually fatal. In the cases where the Retinoblastoma is limited to the orbit the chances of survival is only 10%. In children with metastatic Retinoblastoma the survival rate is only anecdotal. [41] After the invention of advanced chemotherapeutic regimens, the prognosis has significantly improved. Neo-adjuvant chemotherapy improves the success rate in intra-orbital Retinoblastoma. Such cases could be further treated using surgical de-bulking and supplemented by radiation wherever necessary. [42] In patients with systemic metastases mostly to CNS a suitable treatment with higher dosage chemotherapy (HDC) in combination with autologous stem cell rescue (ASCR) is recommended. [43] This would help in bypassing the tumor resistance and helps in routing out neoplastic cells totally. HDC is used with an aim to prevent further seedlings and tumor spread. It has a disadvantage that it would result in myelosuppression. To reduce the incidence of side effects of HDC, simultaneous ASCR should be started which helps in future restitution of the bone marrow. [44] Children's Oncology Group In 2008 used the ARET0321 trial to evaluate intensive multimodal therapy: It included high-dose systemic chemotherapy. In this induction chemotherapy cycles with vincristine, cisplatin, cyclophosphamide, radiation, and autologous stem-cell rescue were used for extra ocular disease.

Trilateral Retinoblastoma

Primitive neuroectodermal tumor (PNET) may arise in children with Retinoblastoma subsequent to the distant metastases to brain, and spinal cord. Such a situation is called as Trilateral retinoblastoma (Figure 8) in a similar terminology as bilateral retinoblastoma. PNET is rare and occurs in those with a germline etiology. [45] The outcome is poor in spite of similar treatment as used for Retinoblastoma. To enforce early diagnosis of PNET MRI scans are performed in children with Retinoblastoma in all the centers of the world. [45] However its incidence is lowered since the usage of HDC. [46] But few authors consider such lowered incidence is due to prophylactic effect of systemic chemotherapy or due to fewer patients being treated with EBRT. [47]

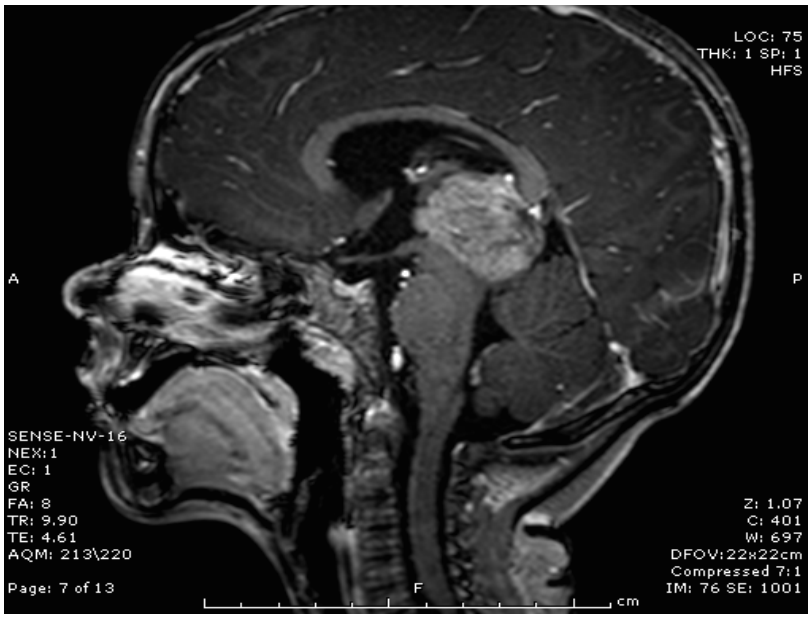

Figure 8: Shows a MRI with irregular, poorly defined mass consistent with a PNET

Follow-Up

All the children with Retinoblastoma require a prolonged follow up whether they are treated by any form of salvaging treatment (external beam radiation, chemo-reduction) with examination under anesthesia to monitor for recurrence. The follow up should be to monitor the tumor regression in terms of its appearance, size, location, and number of tumors documented during each examination. The tumor appears white after the treatment when it regresses but can also appear calcified mass or sometimes as translucent compared to as fish flesh. The children should be examined under anesthesia every 4 to 6 weeks till they reach the age of 3 years and which is very common. Hereditary retinoblastoma children should be followed up for very long periods and a consultation with systemic oncologists should be maintained as these children are likely to develop secondary malignancies throughout their life. One such malignancy is Osteosarcoma. [48] The other tumors are PNETs, fibrosarcoma, and melanoma. This predisposition for secondary malignancies is EBRT especially in the areas of exposure. [48] Both Ophthalmic and oncologic follow-up of all retinoblastoma children is compulsory with special vigilance for patients who have germline mutations.

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