CHAPTER

25 Management of Ophthalmic Tumors—Role of Chemotherapy and Radiation therapy

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INTRODUCTION

Ocular Oncology deals with the diagnosis, surgical and non-surgical management of tumors involving the eyelids, external ocular surfaces, intraocular structures and the orbit. Ocular tumors invariably are managed by multidisciplinary team of ocular surgeon and an oncologist experienced in the treatment of such tumors.

Radiation Oncology is the clinical and scientific discipline devoted to the management of patients with cancer and other diseases with ionizing radiation alone or combined with other modalities like surgery and chemotherapy. The aim of radiation therapy is to deliver a precisely measured dose of radiation to a defined tumor volume with minimal damage to surrounding healthy tissue.

Radiation used for cancer treatment is called ionizing radiation because it forms ions in the cells of the tissues it passes through, as it dislodges electrons from atoms. Ions are atoms that have acquired an electric charge through the gain or loss of an electron. This can kill cells or change genes. Other forms of radiation, such as radio waves, microwaves, and light waves are called non-ionizing. They have lower energy and hence can not ionize cells.

Ionizing radiation is of two major types

a. Non-particle Photons (X-rays and γ rays), which are most widely used.
b. Particle radiation (electrons, protons, neutrons).

The common types of radiation used for cancer treatment are:

1. High-energy photons come from radioactive sources such as cobalt, cesium, or a machine called a linear accelerator. This is by far the most common type of radiation treatment in use today.
2. Electron beams produced by a linear accelerator or beta particle emitting radioactive source like Strontium and Ruthenium. They are used for tumors close to a body surface e.g. skin, conjunctiva and sclera.
3. Protons are a newer form of treatment. Protons are parts of atoms that cause little damage to tissues they pass through but have maximum effect at the end of their path. This means that proton beams may be able to deliver more radiation to the cancer while causing fewer side effects to normal tissues nearby. Although it is used routinely for certain types of ocular and brain tumors, it still needs more study in others.
4. Neutrons are used for some cancers of the head, neck, and prostate. They can sometimes be helpful when other forms of radiation therapy do not work especially when the tumor has anoxic zones.

Radiation therapy delivery methods are as follows:

1. **External Beam Radiation (Teletherapy)** - It is the most widely used type of radiation therapy. The radiation is focused from machine outside the body onto the area affected by the cancer. This type of radiation is most often given by either radioactive source like cobalt or cesium or with linear accelerators (Figure 25.1). The

radiation is aimed at the tumor, but also affects the normal tissue it passes through on its way into and out of the body. External beam radiation allows large areas of the body to be treated and allows treatment of more than one area such as the primary tumor and nearby lymph nodes. External radiation is usually given in daily treatments, 5 days per week over several weeks.

2. **Internal Radiation Therapy (Brachytherapy) -** It is also known as brachytherapy, which means short-distance therapy. With this method, radioactive sources are placed directly into the tumor or into a cavity close to the tumor. The advantage of brachytherapy is the ability to deliver a high dose of radiation to a small area. It is useful in situations that require a high dose of radiation. The main types of internal radiation are:
   a. *Interstitial radiation*: The radiation source is placed directly into or next to the tumor using small pellets, wires, tubes, or containers. For example Carcinoma Tongue (Figures 25.2A and B)
   b. *Intracavitary radiation*: A container of radioactive material is placed in a cavity of the body such as the vagina, nasopharynx.
   c. *Surface (mould):* Radiation sources are placed over the tissue to be treated, e.g. Ca Hard palate.
   d. *Plaque Brachytherapy:* Concave shaped radioactive plaque is placed over the sclera for ocular melanomas, retinoblastoma, etc (Figure 25.3A).
   e. *Intraluminal:* Sources are placed in a lumen, e.g. Carcinoma esophagus.
   f. *Intravascular:* A single source is placed into small or large arteries such as coronary artery for prevention of stent restenosis.

Based on the duration of treatment, brachytherapy is classified as:

a. *Permanent (low dose rate) Brach therapy:* dose is delivered over the lifetime of the source until complete decay
b. *Temporary (high dose rate):* Dose is delivered over a short period of time and the sources are removed after the prescribed dose has been reached

Figure 25.1: Teletherapy machine for external beam radiation therapy

Figure 25.2A and B: Interstitial brachytherapy

Radiation therapy may be used alone or in combination with other cancer treatments, such as chemotherapy or surgery. In some cases, a patient may receive more than one type of radiation therapy.

External Radiotherapy in Ocular Tumors

Linear accelerators equipped with both photon and electron facility and multileaf collimators (MLC) are mainly used for the external radiation therapy of orbital tumors where multiple radiation beams are focused on the tumor. Simulator with all the parameters similar to linear accelerator but capable of only diagnostic X-rays is used for radiation therapy planning. It simulates the beams of the external radiotherapy machines before the patient is being taken for the actual treatment.

Conventionally radiation therapy planning is carried out by immobilizing the patient in treatment position and a CT scan is done in the treatment position with the immobilization in place. The images are transferred to the computerized treatment planning system. The tumor volume and the critical structures are delineated by the radiation oncologist and then the medical physicist plans the various beam angles and energies and gives various treatment options. The optimal plan is selected by the radiation oncologist and the patient is simulated according to bony landmarks visible under fluoroscopy and the data given by the treatment planning system. The computerized scan is invariably being used in all orbital tumors and the 3-dimensional conformal radiation therapy (3D-CRT) is planned.

All the efforts in the development of radiation therapy techniques are directed towards proper inclusion of tumor in the target volume and to spare the surrounding normal tissues. Intensity modulated radiation therapy (IMRT) is newer form of external radiation therapy that is capable of obtaining desired dose distribution in irregular and concave shapes sparing the adjoining critical organs like optic chiasm and pituitary gland.

Plaque Radiotherapy

A radioactive plaque is a device that can be used to deliver a high dose of radiation precisely and selectively to a tumor and negligible dose to the surrounding structures. It is made with radioactive Cobalt, Ruthenium, Iridium, Palladium or Iodine sealed within. Plaques come in various shapes and sizes ranging from 10 mm to 25 mm in diameter (Figure 25.3B).

The procedure is done under anesthesia. Preoperative assessment of the lesion: location, size and thickness are measured by means of ultrasound B-scan and the details are given to the ocular radiation oncologist. The radiation oncologist along with the radiation medical physicist plans the treatment with the help of computerized automated dosimetry software. An appropriate plaque, the radiation dose, dose rate and treatment time is selected. The treatment time may vary from 24 to 96 hours based on type and size of tumor. This process needs expertise of a radiation therapist and a radiation physicist well versed in brachytherapy.

Figure 25.3A: Radioactive plaques for intraocular tumors

Figure 25.3B: Ruthenium 106 plaque being placed on the eye for a choroidal melanoma

After obtaining a proper consent the patient is taken for the operative procedure. The concave shaped dummy plaque similar to the radioactive plaque is placed and checked and then the radioactive placed is placed and sutured in place (Figure 25.4). Patient is placed in isolation till the entire period of radiotherapy. The plaque is removed under anesthesia after the required dose of radiation is delivered.

Indications of plaque brachytherapy are as follows:

1. Retinoblastoma measuring < 16mm in basal diameter and < 8mm in thickness a primary treatment, as an adjuvant to chemoreduction, and for failure of focal therapy.
2. Primary treatment for most medium-sized and some large choroidal and ciliary body melanomas in an eye with salvageable vision.
3. Choroidal hemangioma.
4. Choroidal metastasis.
5. Extensive retinal capillary hemangioma.

Cell Cycle and the Principles of Anti-neoplastic Therapy

It is important to understand the growth pattern of tumor cells that affect the overall biological behavior of tumor and response to anti-neoplastic therapy, either radiation or cytotoxic chemotherapy. Cell cycle is composed of four distinct phases. The G1 phase consists of cells that have recently completed division and are committed to continued proliferation. After a variable period of time, these cells begin to synthesize DNA, marking the beginning of the S phase. After DNA synthesis is complete, the end of the S-phase is followed by the premitotic rest interval called the G2 phase. Finally, chromosome condensation occurs and the cells divide during the mitotic M phase. Resting diploid cells that are not actively dividing are described as being in the G0 phase.

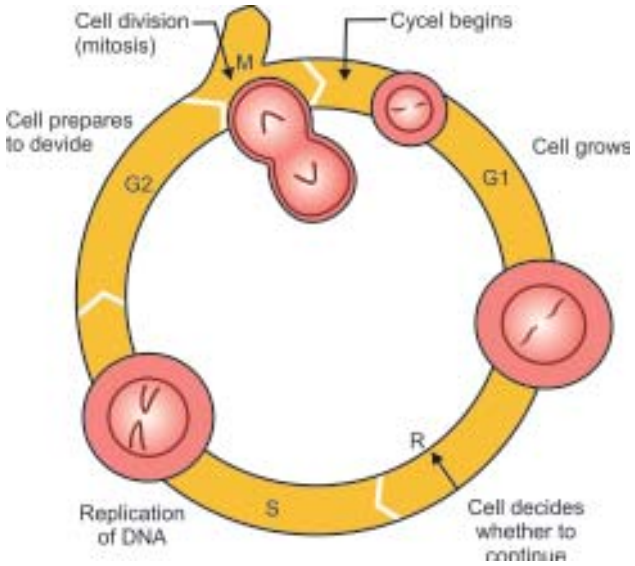

Fig. 25.4: Cell cycle

Ionizing radiation generally affects the neoplastic cells those are in synthetic and mitotic phase where the DNA of the cell is damaged either temporarily or permanently, causing subsequent cell death. Radiation therapy is usually delivered in multiple fractions to target the tumor cells which were in resting phase during earlier fraction of radiation.

Similarly, some anticancer agents induce their cytotoxic effects during specific phases of the cell cycle. Chemotherapeutic agents are used either as single agent or in the combination of different agents. Combination chemotherapy agents are selected according to different mechanism of action to have synergistic effect and with different toxicity profile. Cumulative doses of individual drugs are typically low in combination chemotherapy regimens, potentially minimizing the long-term toxicity and improving the therapeutic ratio.

Management of Ophthalmic Tumors

Ocular tumors with proptosis as the first symptom arise from eyelid and lacrimal gland, orbital soft tissues, optic nerve and orbital bones. Prominent ones among those are squamous and basal cell carcinoma of eyelid, rhabdomyosarcoma, non-hodgkin's lymphoma, optic nerve glioma, meningioma and orbital pseudotumor. Occasionally, retinoblastoma in advanced stage could present with proptosis of eye.

Tumors of the Eyelid

Most eyelid masses are benign tumors such as skin squamous cell papilloma, melanocytic nevus or congenital and acquired cysts. Common malignant tumors of eyelid include basal cell and squamous cell carcinoma.

Capillary hemangioma

It is the most common pediatric eyelid tumor. It may be a component of Hippel-Lindau syndrome or Surge-Weber syndrome. The natural history of lesion is spontaneous regression over 3 to 4 years, therefore usually these lesions are observed. Indications of treatment are obstruction of the vision, amblyopia, ulceration of the eyelid due to vascular compression. Steroids are the first line of treatment. Radiation therapy is reserved until other treatment methods have failed. Low energy photons or electrons are used in dose of 500 to 750 cGy in 2-3 fractions or fractionated low dose to a total of 1600 to 2000 cGy.[1]

Basal cell and Squamous cell carcinoma

Basal cell carcinoma (BCC) represents 90% of malignant eyelid tumors. Its four morphological types are the nodular, ulcerative, pigmented and the morpheaform tumor. It mostly involves the lower eyelid. More likely to affect fair skinned persons with high solar exposure. It may be mistaken for a chalazion or chronic blepharitis. Complete excision with frozen section control of tumor margins using cryostat is the standard treatment for localized tumors. Larger lesions are treated with definitive surgery and appropriate reconstruction.

Squamous cell carcinoma (SCC) is the second most common malignancy of the eyelids. Sun exposure is the most important factor in developing SCC of the skin. It may occur in previously normal appearing skin or more commonly arises from a pre-existing lesions like actinic keratoses, skin damaged by ionizing radiation or xeroderma pigmentosum. Unlike BCC of the eyelid, SCC can be an aggressive tumor and has the potential to invade the orbit, metastasize to lymph nodes and distant sites.

Primary excision is curative for small lesions in basal cell and squamous cell carcinoma of eyelid. Irradiation could be used for unresectable and recurrent basal cell carcinoma. It also could be used as an alternative to surgery with more than 90% of cure rate if patient prefers radiation therapy over surgery. Cryotherapy could be used for recurrent lesions; usually in medial canthus. Orbital exenteration is reserved for deep invasive lesions. Radiation dose of 50 to 60 Gy should be delivered with low energy X-rays or electrons with appropriate shielding of lens.[2]

Sebaceous Carcinoma

Ocular sebaceous carcinoma is a very rare but aggressive tumor, most commonly occurs in patients 60 to 80 years of age although the range is from early childhood through the nineties. It usually arises from the meibomian glands followed by glands of Zeiss and caruncle. It may be multicentric resulting in local recurrences. The incidence appears to be somewhat greater in women and in Asian population.[3]

General principle of treatment is wide excision (with 5 to 6 mm surgical margins) with either frozen section or permanent section control as primary management of sebaceous carcinoma.[4] Map biopsies of eyelids and conjunctiva should be carried out. Radiotherapy provides acceptable cosmesis both for primary treatment and for treatment of recurrent disease. Somewhat higher irradiation dosages in the range of 60 to 65 Gy in six to seven weeks are recommended, and the control rates are in the range of 80 to 90% or better.[5]

Tumors of Lacrimal gland

Epithelial tumors of lacrimal gland could be benign, e.g. pleomorphic adenoma (benign mixed tumor) or malignant, e.g. adenoid cystic carcinoma or pleomorphic adenocarcinoma (malignant mixed tumor). On imaging, pleomorphic adenoma appears as round to ovoid superotemporal orbital mass which may cause bony indentation, without bone erosion. Malignant tumors have irregular margin, often with adjoining bone destruction.

Complete excision of mass (excisional biopsy) is curative for pleomorphic adenoma. Incomplete excision can lead to recurrence and malignant transformation.

Malignant tumors should be completely excised if possible. Routinely postoperative radiation therapy to a dose of 5000 to 6000 cGy is delivered. In locally advanced lacrimal gland carcinoma, neoadjuvant chemotherapy with cisplatin and 5-fluorouracil followed by surgery and postoperative radiation therapy is given. Results of intra-carotid chemotherapy with Cisplatin and Doxorubicin followed by surgery and radiation therapy are encouraging[6,7]

Malignant Conjunctival tumors

Squamous cell carcinoma is the most common primary malignant tumor of conjunctiva, manifests usually as a fleshy vascularized mass at the limbus. Conjunctival tumors are treated by complete excision biopsy with frozen section control of tumor margins and cryotherapy of the tumor bed. Reconstruction can be done then by simple closure, conjunctival grafting or amniotic membrane transplant.

Primary or adjunctive use of local treatment with some chemotherapeutic agents such as Mitomycin-C, 5- Flourouracil and Interferon alpha 2-b have been reported. In some diffuse radiosensitive tumors such as lymphoma, fractionated external beam radiotherapy or application of a radioactive plaque may be employed.

Intraocular tumors

Intraocular tumors arise from iris, choroid, retina or optic nerve head. Iris masses could be melanocytic as nevus and melanoma, granuloma, hemangioma, leiomyoma, lymphoma, metastases, and extension from a ciliary body tumor. Choroidal melanoma is the most common intraocular tumor in adults. Other common intraocular pigmented tumors include optic nerve head melanocytoma, retinal pigment epithelium adenoma and combined hamartoma of retina and retinal pigment epithelium. Choroidal non-pigmented masses include amelanotic melanoma, uveal granuloma, lymphoma, osteoma and choroidal metastases. Retinal non-pigmented masses include retinoblastoma and toxocara granuloma.

Choroidal Melanomas

Small Lesions <1.5 mm height without high risk factors like juxta papillary location, presence of subretinal hemorrhage, presence of orange pigment are closely observed. Lesions of 1.5 to 10 mm height are treated according to its location. Peripheral lesions are locally excised. Central and mid peripheral lesions with size < 4 mm are treated with trans-pupillary thermotherapy (TTT). Lesions with > 4 mm of size are treated with plaque therapy or external radiation therapy with photons or protons. Lesions of >10 mm in height are treated with enucleation or external radiation therapy.

Ruthenium-106 is currently the most commonly used isotope for plaque radiotherapy of choroidal melanomas, although cobalt-60, Iodine-125, iridium-192, strontium-90, and palladium-103 have also been used. Modern techniques for plaque brachytherapy involve suturing a shielded plaque containing seeds of the radioactive isotope to the sclera.[8,9] This remains in place for a specified number of days in order to deliver the proper dose of radiation. Most melanomas are treated with a calculated apex dose of 70 to 85 Gy.[10]

Intraocular Lymphoma

This is a rare variety of non-Hodgkin's lymphoma, large cell lymphoma being the most common histology. Uveal tract, retina, vitreous or optic nerves are usually involved. Vitreoretinal involvement is usually associated with central nervous system lymphoma. Diagnosis is usyually done by vitreous biopsy. Usually they do not have systemic manifestation. Recommended treatment is external radiation therapy to a dose of 3600 to 4000 cGy at 1.8-2 Gy fractions.[11]

Retinoblastoma

For over 100 years or longer the treatment of intraocular retinoblastoma has been enucleation. Various forms of radiation treatment have been used in the management of retinoblastoma since World War II. The goal of radiation has been to destroy the tumour, save the eye, and maximise visual potential. Since the radiation in the paediatric age group has its potential long-term side effects newer modalities like chemotherapy has been attempted. Since the introduction of platinum and etoposide based chemotherapy there has been tremendous improvement in tumor control and survival.

Current standard teatment options for retinoblastoma include the following:

1. Cryotherapy: used in addition to radiation or in place of photocoagulation for lesions smaller than 4 disc diameters in the anterior portion of the retina.
2. Photocoagulation: occasionally used alone with small tumors. It is used for posteriorly located tumors that are smaller than 4 disc diameters, distinct from the optic nerve head and macula, and without involvement of large nutrient vessels or choroid involvement in patients with early-stage disease (in addition to radiation

therapy) or when there is limited recurrence following radiation therapy. Thermotherapy delivered via infrared radiation is an alternative to laser photocoagulation.[12]

3. Chemoreduction: Systemic chemotherapy is used to reduce tumor volume with intraocular tumors making them suitable for treatment with cryotherapy or photocoagulation.[13,14] Factors such as tumor location (macula), patient age, and tumor size correlate with responsiveness to chemotherapy.[15,16] Most tumors are treated with combination chemotherapy, Inj.Vincristine, Inj. Etoposide and Inj. Carboplatin. The dose of these drugs depends on the age, stage and the intention of treatment, either chemoreduction or adjuvant chemotherapy (Table 1). They also require additional local therapy. Overall, the response rate is highest for tumors that are unilateral or unifocal and without vitreous seeding.
4. Subtenon (subconjunctival) chemotherapy: Carboplatin is administered by the treating ophthalmologist into the subconjunctival space. This modality is undergoing testing in phase I and II trials and is generally used in conjunction with systemic chemotherapy and local ophthalmic therapies for retinoblastoma with vitreous seeding. This approach offers some promise in this group of patients.[17,18]
5. Surgery (enucleation) is usually undertaken when unilateral disease is massive and there is no expectation that useful vision can be preserved. Careful examination of the enucleated specimen by an experienced pathologist is necessary to determine whether high-risk features for metastatic disease are present. Postoperative external radiation therapy is indicated in the presence of optic nerve extension to transection, scleral infiltration and extrascleral extension. Systemic standard chemotherapy for six cycles is indicated for anterior chamber seeding, infiltration of iris, ciliary body infiltration, massive choroidal infiltration or optic nerve extension beyond lamina cribrosa. High dose chemotherapy for 6 cycles is used in patients with combined choroidal infiltration and optic nerve extension beyond lamina cribrosa or with scleral infiltration. High dose chemotherapy for 12 cycles is used in patients with extrascleral extension and optic nerve extension to transection. Vincristine, doxorubicin, and cyclophosphamide, or vincristine, carboplatin, and etoposide are the drugs in different dose schedules as described in (Tables 2 and 3). Intrathecal methotrexate is given if CSF is positive or there is radiological evidence of intracranial extension.
6. External Beam Radiotherapy: Retinoblastoma is generally a radiosensitive tumor. Presently, with effective chemotherapy drugs the indications for radiotherapy are minimized to avoid the late effects of radiotherapy, like facial deformities and second malignancies. External beam radiotherapy is a method of delivering whole eye irradiation to treat advanced retinoblastoma, particularly when there is diffuse vitreous seeding. Presently, the indications of external radiotherapy are residual disease after

Table 1: Chemoreduction regimen

Standard dose regimen		
Inj. Vincristine 1.5 mg/m^2	(0.05 mg/kg for children </= 36 months of age; max 2 mg)	Day 1
Inj. Etoposide 150 mg/m^2	(5 mg/kg for children </= 36 months of age)	Day 1+2
Inj. Carboplatin 560 mg/m^2	(18.6 mg/kg for children </= 36 months of age)	Day 1
High dose chemotherapy		
Inj. Vincristine 1.5 mg/m^2	(0.05 mg/kg for children </= 36 months of age; max 2 mg)	Day 1
Inj. Etoposide 250 mg/m^2	(12 mg/kg for children </= 36 months of age)	Day 1+2
Inj. Carboplatin 750 mg/m^2	(28 mg/kg for children </= 36 months of age	Day 1

Table 2: Management of intraocular retinoblastoma group I to IV-B

a. Focal therapy alone when appropriate
b. Standard chemoreduction x 6 cycles + appropriate sequential focal therapy
c. Chemocryotherapy at each cycle
d. Standard chemoreduction x 12 cycles, when suboptimal regression with chemotherapy at 6 cycles and RT is not feasible (e.g. age < 1year)
e. Alternative chemotherapy regimen or RT when there is no regression after 3 cycles of standard chemotherapy or recurrence during chemotherapy.

Table 3: Management of intraocular retinoblastoma group V-A and V-B

a Unilateral – Primary enucleation
b. Bilateral–High dose chemotherapy x 6 cycles + appropriate sequential focal therapy
c. Chemocryotherapy at each cycle
d. Periocular Carboplatin augmentation for group V-B
e. High dose chemoreduction x 12 cycles when suboptimal regression with chemotherapy at 6 cycles and RT is not feasible (e.g. age < 1year)

chemotherapy and local therapy, diffuse vitreous seeds, recurrent after chemotherapy, post enucleation (Scleral involvement, extraocular extension, optic nerve involvement). External-beam radiation with dose ranges from 3,500 to 4,600 cGy. Special expertise is very essential to treat pediatric ocular and orbital tumors. Newer methods of delivering external-beam radiation are being used in an attempt to reduce adverse long-term effects. This includes intensity-modulated radiation therapy (IMRT), stereotactic radiation therapy, and proton-beam radiation therapy.[19]

7. Brachytherapy with radioactive plaques. These are radioactive plaques in concave shapes, either beta or gamma emitting. The commonly used radioactive sources are Iodine125, Gold, Iridium192 and Ruthenium106. Ruthenium and 125I plaque therapy is preferred because of its favorable physical properties.[20,21] They are used for either focal unilateral presentations or recurrent disease following previous external-beam radiation. Indications of brachytherapy are lesion < 16 mm in basal diameter, < 8 mm in thickness, adjuvant to chemo reduction, failure of local therapy.

Extraocular disease may be localized to the soft tissues surrounding the eye or to the optic nerve beyond the margin of resection. However, further extension may occur into the brain and meninges with subsequent seeding of the spinal fluid, as well as distant metastatic disease involving the lungs, bones, and bone marrow. High dose chemotherapy for 3 to 6 cycles are given and disease is reassessed. Enucleation is performed followed by orbital external beam radiation therapy. Further, high dose chemotherapy is continued for total 12 cycles. In extraorbital retinoblastoma, palliative therapy with radiation (including craniospinal irradiation when there is meningeal involvement) and/or intrathecal chemotherapy with methotrexate, cytarabine, and hydrocortisone, plus supportive care have been used (Tables 4 and 5).

Table 4 Management of extraocular retinoblastoma

a. Baselins CT scan or MRI; bone marrow and CSF cytology
b. Intrathecal methotrexate if CSF is positive or there is radiological evidence of intracranial extension
c. High dose chemotherapy for minimum three cycles and reassess
d. Enucleation and continue high dose chemotherapy for 6-12 cycles and external beam radiation therapy (see post-enucleation protocol)
e. If systemic metastasis at the time of presentation, modify timing of local therapy depending on the extent of tumor.

Table 5: Post-enucleation adjuvant treatment protocol

a. Systemic standard chemotherapy for 6 cycles for
1. anterior chamber seeding,
2. infiltration of iris,
3. ciliary body infiltration,
4. massive choroidal infiltration
5. optic nerve extension beyond lamina cribrosa.
b. High dose chemotherapy for 6 cycles in patients with
1. combined choroidal infiltration
2. optic nerve extension beyond lamina cribrosa or
3. with scleral infiltration. High dose chemotherapy for 12 cycles is used in patients with extrascleral extension and optic nerve extension to transection.
c. High dose chemotherapy for 12 cycles in patients with
1. extrascleral extension
2. optic nerve extension to transection.

With emerging dose-intensive chemotherapy regimens and the use of high-dose chemotherapy with autologous stem cell rescue, clinical trials are ongoing to improve the dismal outcome for this relatively small group of patients. The agents used in the past included vincristine, cyclophosphamide, and doxorubicin; although they produce an initial response, overall survival has been less than optimal. Carboplatin, ifosfamide, and etoposide have shown more promise for remission and may be used in conjunction with high-dose chemotherapy followed by stem cell rescue. Patients presenting with extensive non-CNS metastases have been treated successfully with myeloablative chemotherapy with stem cell rescue.

Ocular Metastasis

Intraocular metastasis is now considered the most common malignancy of the eye. The frequency of ocular metastasis varies significantly among primary sites. Ocular metastasis, and particularly choroidal metastasis, can precede the diagnosis of the primary malignancy. Lung cancer is the most common primary tumor (35 and 41%) detected in patients with no neoplasm at the time of ocular diagnosis followed by breast cancer, leukemia, lymphoma, multiple myeloma and sarcoma. Rarely metastases from malignancies of prostate, cervix, thyroid, skin, GI tract and kidney can occur.

A number of options are available for the therapy of ocular metastasis, including observation, chemotherapy, photocoagulation, cryosurgery, surgical resection, or radiotherapy. The specific therapy chosen for a patient is an individualized process that considers the clinical condition of the patient. The most commonly applied treatment is external-beam radiotherapy. In general, 30 to 40 Gy in 10 to 20 fractions could be considered a standard course of radiotherapy. For patients with a long life expectancy, a higher total dose with lower dose per fraction can be considered.

Orbital tumors

Pediatric primary orbital masses include dermoid cyst, capillary hemangioma and lymphangioma, inflammatory lesions, lymphocytic and leukemic infiltrates, and pilocytic astrocytoma of the optic nerve, rhabdomyosarcoma and primary neuro-ectodermal tumor or Ewing's sarcoma. In adults, the most common localized tumors of the orbit include cavernous hemangioma, fibrous histiocytoma, schwannoma, orbital pseudotumor, Grave's ophthalmopathy and hemangiopericytoma. The most common lacrimal gland tumors include pleomorphic adenoma and adenoid cystic carcinoma.

Rhabdomyosarcoma

Orbital rhabdomyosarcoma is treated with combination of chemotherapy and radiation therapy after local excision or biopsy. Chemotherapy is usually given for 2 to 3 cycles prior to the initiation of radiation therapy, with the exception of patients with parameningeal disease and evidence of meningeal extension in whom radiation therapy generally begins as soon as possible. Vincristine, cyclophosphamide, doxorubicin, actinomycin-D, ifosfamide and etoposide are the drugs used for the treatment of RMS. Radiation therapy is effective for achieving local control of tumor for patients with microscopic or gross residual disease following biopsy, initial surgical resection, or chemotherapy. The radiation therapy dose depends predominantly on the extent of disease following the primary surgical resection. Patients with completely resected tumors (group I) of embryonal histology do well without radiation therapy but radiation therapy benefits patients with group I tumors with alveolar or undifferentiated histology.[22-24] In general, patients with microscopic residual disease (group II) receive radiation therapy to approximately 4,100 cGy.[25] Patients with gross residual disease (group III) should receive radiation dose of 5,040 cGy. The treated volume should be determined by the extent of tumor at diagnosis prior to surgical resection and prior to chemotherapy. A margin of 2 cm is generally used, including clinically involved nodes. Precautions should be taken to limit the dose to the lens, cornea, lacrimal gland, and optic chiasm.

Orbital Lymphoma

Most of the orbital lymphomas are confined to the orbit and are of low grade. Patient needs a staging workup (CBP, chest X-ray, USG abdomen, or CT scan of chest and abdomen, serum LDH, Bone marrow biopsy and CSF cytology) to rule out systemic lymphoma. Radiotherapy is a well-established treatment modality for orbital lymphoma. Primary chemotherapy has minimal efficacy in localized low-

grade orbital lymphoma and thus is not advocated as a first-line treatment. There have been numerous series advocating low dose radiation for treatment of orbital lymphomas. In general, radiation dose of 3000 cGy is recommended for low grade lymphomas and 4000-4500cgy for intermediate grade lymphomas.[26,27] If it is associated with systemic disease, it is treated with chemotherapy constituting cyclophosphamide, doxorubicin, vincristine and prednisolone for 6 cycles followed by local radiation therapy.

If associated with systemic lymphoma, it is treated with chemotherapy constituting cyclophosphamide, doxorubicin, vincristine and prednisolone for 6 cycles followed by local radiation therapy.

Orbital Pseudotumor

Orbital psuedotumor could be inflammatory, reactive lymphoid hyperplasia or atypical lymphoid hyperplasia. Corticosteroids have been the recommended initial drug (prednisone 1 mg/kg/d), Recently, antimetabolites (azathioprine, methotrexate, and leflunomide), T-cell inhibitors (cyclosporine and tacrolimus), and alkylating agents (cyclophosphamide and chlorambucil) were shown to be useful in the management of NSOI in different series.[28] Use of low-dose external beam radiation 2000 cGy demonstrated a 50 to 80% efficacy in a previous series.[29]

Grave's Ophthalmopathy

Severe exophthalmos may occur in some patients with thyrotoxicosis with involvement of intraocular muscles. Indications for therapy are corneal exposure which may cause corneal ulceration that progress to scarring, optic nerve compression. CT scan shows thickened introrbital muscles. Steroids and diuretics are the first-line treatment, administered for 2 weeks. Radiation dose of 2000 cGy in 10 fractions provides good symptomatic relief avoiding the need for further steroid therapy or surgical decompression.[30]

Optic nerve Meningioma

The diagnosis of optic nerve meningioma is usually presumptive and based on the appropriate clinical picture supported by appropriate neuroimaging. Biopsy is not routinely advocated, as surgical intervention carries significant morbidity and mortality. Patients often undergo reimaging at 3 months, and they are followed radiographically at 6 to 12 month intervals after the disease has stabilized. Treatment strategy should be individualized. Radiation therapy is recommended as soon as serial examination documents a new decline in acuity and/or visual field. Tumor enlargement without loss of visual function, as determined by serial imaging, may also provide an indication for radiotherapy. Recommended dose of radiation therapy is 5400cGy.[31] It should preferably be delivered via fractionated, 3-dimensional stereotactic and IMRT techniques that provide the most precise conformal application of the dose to affected tissues. Theoretically, this approach should reduce the risk of side effects to surrounding radiosensitive ocular and neural tissues.

Optic nerve Glioma

Chemotherapy is the first-line treatment, followed by radiation if chemotherapy fails. Standard chemotherapy for optic-pathway gliomas consists of vincristine and carboplatin, whereas second-line therapy is often thioguanine, procarbazine, and vincristine.[32] When these fail, chemotherapeutic agents used in other progressive low-grade gliomas can be considered. These include cyclophosphamide, topotecan, and oral VP-16.Stabilization or improvement in visual function and tumor size is considered a response to treatment. Surgery has a limited role. Biopsies are performed when clinical and radiologic features are atypical. Radiation therapy dose above 5000 cGy is required for tumor control. Optic-nerve gliomas should be operated upon only when grossly proptotic and the eye is blind or near blind. In large series from the Mayo Clinic with a median follow-up time of 10 years, patients with glioma confined to the optic nerve survived almost twice as long as those with involvement of optic chiasm.[33]

Sequelae of Radiation Therapy[34-38]

Postradiotherapy complications can be classified as acute (usually occurring within 3 months of treatment) or late (occurring many months to years after completion of treatment). Acute lesions generally affect rapidly proliferating cells, and most can be reversed by appropriate medical management. Such acute effects involving the ocular anterior segment

include blepharitis, conjunctivitis, and keratitis. However, residual stromal lesions and interstitial fibrosis may follow. Late effects are primarily caused by permanent vascular damage and resultant ischemia. Retinopathy, cataract, and optic neuropathy are examples of such late effects. (Table 6) Keratoconjunctivitis sicca, another late sequela to radiotherapy, may often be clinically nonmanifest or insignificant but can result in ulcerative thinning and corneal perforation.

Eyelid and periorbital skin radiation effects can be acutely controlled with topical corticosteroids, wound debridement, and antibiotic therapy. Occasionally, reconstructive surgery is indicated to treat lid deformities. Patients should be encouraged to wear ultraviolet protective sunscreens and avoid using harsh soaps and lotions.

Nasolacrimal duct occlusion may require silicone intubation or dacrycryocysto-rhinostomy, whereas severe lacrimal punctal stenosis may necessitate a conjunctivo-dacryocystorhinostomy.

Table 6: Radiation effects on the eye and orbital tissues

Eye lashes and Eyelid		Spared by megavoltage (Cobalt, LA) Becomes thinner; function not altered Lash loss at 40–60 Gy Telangiectasia at 55 Gy
Lacrimal sytem		Dryness in 8-25% pts at 30 to 45 Gy Dryness in all pts over 4-8 yrs at >55 Gy Atrophy at 50–60 Gy Stenosis at 65–75 Gy
Lens	EBRT	Single dose 2 Gy -Cataract Fractionated 8 Gy Cataract in 33% of pts > 11 Gy – Cataract in 100% of pts < 50 Gy – Cataract; vision not impaired > 60 Gy – Vision impairing cataracts
	Plaque	50 Gy at limbus 33% cataracts
Conjunctiva		Conjunctivitis at 55–75Gy Telangiectasia at 30 Gy
Cornea		Superficial keratitis- edema, epithelial defects at 30–50Gy Severe keratitis – Ulcer, scarring, perforation > 60Gy
Retina		40-60 Gy – retinopathy 10% > 60 Gy – retinopathy 30% CRA thrombosis may lead to edema and pallor of optic disc, retinal hemorrhages, blindness in 2-3 yrs
Optic nerve		Neuropathy at >55 Gy

Severe noninfectious inflammation may require a short course of corticosteroid therapy, but indiscriminate use of steroids should be avoided because it can promote extracellular matrix breakdown. Prolonged ocular surface inflammation or ulceration frequently requires prophylactic antibiotics. Artificial tears and ointments are indicated for dry eye relief. It is important to recognize that the irradiated cornea often has a poor capacity to heal, despite neovascularization, because of the degree of epithelial toxicity. Mild punctate keratopathy needs aggressive lubrication. Tear replacement therapy with nonpreserved artificial tears and ointments facilitates epithelial wound healing.

Infected corneal ulcers require prompt diagnostic and therapeutic measures, with initiation of broad-spectrum antibiotics modified as needed on culture and susceptibility results. Although hydrophilic soft contact lenses can be used as protective bandaging to promote corneal healing, they may not be well tolerated in severe dry eyes; furthermore, they may increase the risk of an infection in patients who are often additionally immunosuppressed by chemotherapy. Gas-permeable glued-on contact lenses have been used to treat radiation-induced keratitis effectively, but experience with this is limited. If necessary, a conjunctival flap can control severe pain caused by persistent corneal defects.

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