Orbit and Oculoplasty - I
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Orbital Involvement in Periocular Sebaceous Gland Carcinoma: Clinical Profile and Outcomes

Dr. Anuradha Ayyar, Dr. Swathi Kaliki, Dr. Milind Naik

Sebaceous gland carcinoma is the most common eyelid malignancy in the South-east regions of Asia, as unlike the western world where basal cell carcinoma is most prevalent. The carcinoma is infamous for masquerading as a benign nodule such as a chalazion or a chronic inflammatory disease like blepharoconjunctivitis. Sebaceous gland carcinoma of the eyelid has been associated with a high mortality rate ranging from 18-30%. Failure of the treating doctor to recognise the carcinoma in time, inaccessibility to specialized eye care centres, incomplete treatment of initial lesion, recurrence or plain neglect contribute to the prevalence of orbital extension of this tumor.

Orbital involvement of the tumor is associated with poorer prognosis. In the past while the only option considered for orbital extension was exenteration, neoadjuvant chemotherapy has in the recent years proved to be an effective and efficient modality of treatment with a significant impact on disease prognosis and outcome. Orbital involvement in sebaceous gland carcinoma of the eyelid has not been represented in significant numbers in literature till date. The aim of this study is to review the clinical profile and outcomes of 30 patients with sebaceous gland carcinoma of the eyelid with orbital involvement.

MATERIALS AND METHODS

A retrospective chart analysis of 191 patients with SGC from April 1995 to April 30, 2014 was performed using the coding “Eyelid sebaceous gland carcinoma” at the Ocular Oncology Service, Institute for Eye Cancer, L V Prasad Eye Institute, Hyderabad, India. Thirty among these were diagnosed with orbital involvement of periocular SGC. Institutional Review Board approval was obtained. The demographic data such as the age at presentation (years), gender, laterality, symptoms were retrieved from medical records. Thorough ocular examination findings were noted. The periocular tumor
details including size (largest dimension), color, condition of eyelid margin, extent into surrounding structures, gland of origin were documented in detail. CT scan findings, thorough examination of regional lymph nodes and systemic investigations in the form of ultrasound of the abdomen, chest X-ray and liver function test were performed in all patients. Fine needle aspiration cytology (FNAC) was done to assess nodal metastasis in patients with suspicious lymph nodes. All patients underwent incision biopsy and histopathological examination of the specimen to confirm the diagnosis of SGC before initiation of any treatment modality. Specimens were sent in formalin for routine examination while fresh specimen was sent for Oil red O examination. All tumors were retrospectively classified by TNM staging (Tx, 0, is, 1, 2, 3, or 4; N0 or 1; M0 or 1) based on 7th edition of American Joint Cancer Committee Classification. The patients were followed up at close intervals. Intervention in the form of excision biopsy (with 4 mm margins) with eyelid reconstruction, orbital exenteration, systemic chemotherapy, external beam radiotherapy was performed in the patients depending on their stage. The main outcome measures were loco regional metastasis, systemic metastasis and death. Photographic documentation was done in all cases.

Neoadjuvant chemotherapy was the chosen primary modality of treatment in 15 patients. Chemotherapy was initiated only after analyzing the complete blood count, renal function examination and procuring fitness from an Internal medicine consultant as well as an experienced Oncologist. A combination of a platinum-based agents (cisplatin/carboplatin) and 5-fluorouracil was used in all cases. Details regarding chemotherapy drugs, cycles, dose, side effects were recorded.

Cases with good response to neoadjuvant systemic chemotherapy were advised eyelid excision biopsy with wide margins under frozen section control, and those with moderate/ poor response were advised orbital exenteration. Adjuvant or secondary treatment in the form of surgery (ocular/ radical neck dissection), radiotherapy, and chemotherapy were noted in detail.

Thorough histopathology examination was performed and recorded for all patients except one who was lost to follow up after the first visit. The final outcome at last follow up (alive with disease, alive with no evidence of disease, dead due to disease, dead due to other causes) was recorded. Patients who were lost to follow up were periodically called and updates regarding any treatment elsewhere were noted. In case of patients who had died, details of the circumstances leading to their death were procured from a reliable first degree relative.
RESULTS

According to the AJCC system, 30 patients were recognized to have periocular sebaceous gland carcinoma with orbital involvement (stage III and IV). The mean age of presentation was 60 years (range: 35-100) while mean follow up duration was 21 months (range :< 1-80). Nine patients had a clinical follow up of less than 20 weeks. There were 12 (40%) male and 18 (60%) female patients.

All patients presented with unilateral disease. The average duration of symptoms was 25 months (range: 1-260 months). Eyelid deformity (15/30, 50%) or mass (25/30, 83%) were the most common symptoms. The other symptoms included pain, decreased vision, discharge, bleeding, protrusion of the eyeball, watering and drooping of the eyelid. The tumor epicentre was the upper lid in 17 (57%) patients and lower lid in 13 (43%). The average tumor basal diameter was 32 mm (range: 4-80 mm). The gland of origin was the meibomian gland in 29 cases while it was the gland of Ziess in only 1. The tumor morphology was nodular (9/30, 30%) or noduloulcerative (10/30, 33%) in most cases. The other types of morphology being papillary (1/30, 3%), diffuse eyelid thickening (4/30, 13%) or a fungating mass (6/30, 20%). While all patients had orbital extension of tumor, 3 (10%) had paranasal sinus involvement and one (3%) patient had intracranial extension at the time of presentation. As per the AJCC TNM classification. There were 27 patients classified as stage III and 3 patients as stage IV.

Two patients had diabetes mellitus while three suffered from hypertension. There were no patients with immunosupression.

Neo-adjuvant chemotherapy was used as the primary treatment modality in 60% of patients (15/25), 28% (7/25) underwent orbital exenteration while excision biopsy was performed in 12% (3/25). Among the remaining five patients, three were lost to follow up (one patient died of systemic metastasis 14 months later). One 35 year old woman who presented with metastasis to the brain and liver and a 100 year old man with paranasal sinus involvement were offered palliative therapy.

Among the patients who underwent Neoadjuvant chemotherapy as the first treatment modality, 10 underwent 3-4 cycles of a combination of 5-Fluorouracil with a platinum based chemotherapeutic agent (Cisplatin/ Carboplatin). Two patients were given EBRT to the orbit and nodes after 3 cycles of chemotherapy and eyelid sparing exenteration. Excellent response to chemotherapy facilitated excision biopsy in 4 patients followed by radiotherapy to decrease risk of tumor recurrence. One among these patients was given 3 more cycles of adjuvant chemotherapy since the excised tumor margins were very close to the base.

Five patients did not adhere to the chemotherapy protocol for completing
all cycles. Each patient died of systemic metastasis from 13-27 months from last chemotherapy cycle. One patient had intracranial extension of SGC on presentation. He completed once chemotherapy cycle and died 12 months later.

Side effects related to chemotherapy such as nausea, gastritis, vomiting were managed with symptomatic medical treatment. Three patients needed granulocyte colony stimulating factor for pancytopenia. Chemotherapy induced anemia was treated with packed cell volume transfusions. Chemotherapy and related complications were handled by a team of an in–house Oncologist and an Internal medicine consultant.

A 55 year old woman with loco regional metastasis died due to chemotherapy related complications (septicaemia and azotaemia) after the first cycle of neoadjuvant chemotherapy.

One 70 year old male patient had developed an upper eyelid SGC with orbital invasion in his only seeing eye. His other eye was enucleated in the past after trauma. FNAC demonstrated regional nodal metastasis. Systemic investigations showed metastatic deposits in the liver. Considering his one eyed status, vision salvage was of priority. He completed 3 cycles of chemotherapy with regression of orbital tumor and liver metastasis. He refused to undergo EBRT, hence was advised a fourth cycle of chemotherapy following which he has remained tumor-free.

Seven patients (28%, 7/25) underwent exenteration as a primary treatment modality. One patient is alive and well without any evidence of recurrence or metastasis. Nodal involvement was detected in three patients. One amongst these three patients completed radiotherapy and remains cancer free. One patient died of systemic metastasis 20 months later. The third patient remains lost to follow up. Another patient who did not have any metastasis at presentation and had undergone an uneventful exenteration died of systemic metastasis 70 months later. A 60 year old woman with a prior history of excision biopsy and radiation twice elsewhere for eyelid SGC was referred to us for orbital recurrence of the tumor. She was detected with spinal and nodal metastasis. She underwent exenteration for the orbital mass while started chemotherapy locally. She died of generalize metastasis 28 months later. One 52 year old woman in our series unfortunately died during exenteration surgery secondary to uncontrolled arterial bleed.

An interesting scenario was presented by a 50 year old woman who was referred to us with a diagnosis of orbital inflammatory disease for which she had been on oral steroids for three months with no response. She presented with fever, vomiting and clinical and ocular signs of orbital cellulitis. CT imaging revealed a surperolateral orbital mass with superior rectus and lateral rectus thickening and dilated superior ophthalmic vein. Worsening
status while on intravenous antibiotics made us suspect a fungal granuloma. But the incision biopsy revealed histiocytes around the vessels and no fungal elements. A histopathological diagnosis of lipogranuloma was made. In view of the blind status of the eye, severe proptosis, chemosis, pain and the psychological affection on the patient, exenteration was proceeded with to relieve symptoms. To our surprise, the histopathological examination of the specimen revealed SGC. The patient was quiet relieved after surgery and refused to undergo further evaluation and adjuvant treatment in the form of EBRT/chemotherapy for micrometastasis and did not follow up after. She developed generalized systemic metastasis 4 years later and died.

One patient presented with orbital recurrence of tumor after a prior excision biopsy elsewhere few years ago. In the absence of any metastasis, patient underwent 3 cycles of neoadjuvant chemotherapy followed by exenteration. The inferior skin margin of specimen was positive for malignant cells. So patient was recommended 3 cycles of adjuvant chemotherapy and EBRT. The patient did not return after 2 cycles of adjuvant chemotherapy.

Secondary treatment was required in 7 patients in the form of wide excision biopsy in 3 (43%) patients and orbital exenteration in 4 (57%) patients. Adjuvant treatment in the form of external beam radiation was performed in 65% (13/20), systemic chemotherapy in 10% (2/20) and radical neck dissection in 5% (1/20) patients.

Among the surgically incised or excised lesions, histopathology examination (HPE) showed well-differentiated tumor in 8% (2/24) patients, moderately differentiated in 63% (15/24) and poorly differentiated in 29% (7/24) patients. The most common tumor growth pattern was mixed (9/21) followed by lobular (8/21), comedo (3/21) and papillary (1/5). The mitotic activity varied with 92% of the lesions having moderate to high grade activity. Pagetoid involvement of the conjunctiva was noted in 31% (8/26) of the cases. Perivascular and perineural invasion was noted in 13 (13/23) and 3 (3/25) of the specimens respectively.

At the conclusion of the study, 21% (6/28) patients were alive and well, 14% (4/28) had regional lymph nodal metastasis, 14% (4/28) showed evidence of systemic metastasis, 46% (13/28) died of SGC related systemic metastasis while one (4%) died of an unrelated cause. The duration from the first visit to our institute to their death by all causes varied from 1 to 88 months (average: 29 months).

**DISCUSSION**

Sebaceous gland carcinoma is more commonly seen in the Asian population as compared to the western population accounting for 28–60% cases of all eyelid malignancies.\(^1\) Due to the higher risk of recurrence and
systemic metastasis of this tumor (~30%), early diagnosis and treatment is crucial. The liver and lung are the most commonly involved sites for metastasis. Regional node metastasis (preauricular, submandibular and cervical nodes) is known to occur in 30% of cases. The tendency of this lesion to masquerade benign conditions such as a chalazion or blepharoconjunctivitis cannot be stressed upon enough. This accounts as the major cause for delayed diagnosis and subsequently accounting for the high mortality associated with this carcinoma. In any suspicious lesion such as a recurrent chalazion, a non resolving unilateral blepharoconjunctivitis, it is mandatory to obtain an incision biopsy/map biopsy in every patient especially those with South-East Asian origins.

In our series on orbital involvement of periocular SGC, the average age of presentation was 60 years (range: 35 to 100 years). This matches the average age group of 57-72 years where this tumor has been previously reported. Females constituted 60% of the total patients again proving the increased predisposition of the female gender for this carcinoma.

The clinical features predictive of poor prognosis in periocular SGC are duration of symptoms over 6 months, tumor diameter exceeding 10 mm, involvement of both upper and lower eyelids, and orbital invasion. Recently Kaliki et. al. found canthal involvement, larger tumor size (basal diameter >10mm) and perivascular invasion to be predictive for loco regional and systemic metastasis in their series of 191 patients with SGC of the eyelid.

Imaging is a pre-requisite in all cases with clinical or suspected orbital invasion. Examination of local lymph nodes and investigations for systemic metastasis is essential for staging the disease. An incision biopsy and histopathological examination is mandatory to confirm the diagnosis before proceeding for any surgical or chemotherapeutic modality.

Accurate and precise histopathological diagnosis plays a major role. As was evident in the case of the 50 year old woman diagnosed elsewhere with orbital inflammatory disease and whose initial biopsy revealed lipogranuloma while the exenterated specimen showed SGC. Misdiagnosis in SGC is reported to be as high in the eyes of an inexperienced pathologist.

Neoadjuvant chemotherapy has proven to be an effective modality as primary treatment. It allows significant tumor reduction, thereby enabling a lid sparing exenteration or even excision biopsy. Lid sparing exenteration allows faster healing and rehabilitation of the patient. Further neoadjuvant chemotherapy aids in dealing with the micrometastasis that is common with this tumor and also is the treatment modality of choice in the event of loco regional or systemic metastasis. Multiple reports on the use of neoadjuvant chemotherapy in the setting of pericocular SGC have been written extrapolating data from head and neck SGC.
Omega et al. reported complete recovery in a patient with recurrent SGC and loco regional metastasis with a single dose of chemotherapy. In our own series of 10 patients who underwent neoadjuvant chemotherapy for periocular SGC significant tumor volume reduction was achieved in all cases, making 6 patients suitable for eyelid excision biopsy and 4 cases for eyelid-sparing orbital exenteration.

In the present orbital SGC series, Neoadjuvant chemotherapy was preferred as the primary modality of treatment in 60% patients (15/25). The patients who completed the recommended 3-4 cycles of chemotherapy received adjuvant treatment in the form of an eyelid sparing exenteration (2 patients), EBRT (7 patients) or excision biopsy (4 patients).

Traditionally, exenteration was the choice of surgery for SGC with orbital involvement.

Shields et al. in their series of 60 patients with sebaceous carcinoma of the eyelids reported exenteration in 13% (8/60) cases. In our series 28% (7/25) patients underwent exenteration as the primary treatment modality. The reason for this difference might be attributed to the initial presentation of patients with orbital involvement, time of presentation before chemotherapy was utilized for SGC, lack of medical fitness for chemotherapy, larger bulk of patients with advanced localized orbital tumor in our setup, the refusal of a patient for chemotherapy. Zurcher et al. reported exenteration in 23% of patients in their case series of sebaceous carcinoma of the eyelid.

Shields et al. report a local recurrence rate of 18%. In our series 1 patient developed tumor recurrence after completion of treatment at our institute. One 60 years old woman had a sebaceous gland carcinoma of the upper eyelid excised followed by eyelid reconstruction 1.5 years ago. She returned with recurrence of tumor in the orbit. In the absence of loco regional and systemic metastasis, she underwent 3 cycles of Neoadjuvant chemotherapy for the orbital SGC. Eyelid sparing exenteration was performed. Histopathological examination showed involvement of the inferior skin margin. Hence 3 more cycles of chemotherapy were given. Patient was recommended EBRT to the orbit as the final treatment modality. Patient was alive and well as of last follow up at 62 months.

Over time neo-adjuvant chemotherapy has proven to be the agent of choice to reduce the size of the tumor such that lesser aggressive surgery is amenable. A high rate of death due to systemic metastasis could be due to undetected micro-metastasis. In our series one 60 year old male came to us with an orbital mass. He gave a history of excision biopsy of an eyelid mass followed by external beam radiotherapy elsewhere. Recurrence of the tumor occurred for which a second excision biopsy, radical neck dissection and EBRT was performed. Incision biopsy of the orbital mass confirmed SGC.
Systemic investigations revealed metastasis to the spine. He underwent exenteration for the orbital carcinoma and started chemotherapy for the spinal metastasis with an Oncologist. He died 28 months after start of treatment due to generalized metastasis. We believe that timely initiation of Neoadjuvant chemotherapy at the first recurrence and thorough systemic investigations may have dealt with micrometastasis and prevented the progress of the disease.

It is beneficial to remember the goals of management as described by Shields et. al. in the order of importance while dealing with this carcinoma 3:

1. Tumor control to save the patient’s life
2. Globe salvage
3. Vision salvage
4. Patient comfort
5. Acceptable cosmetic appearance

In the final outcomes, it is important to note that among the patients who are alive and well, 5 out of 6 patients received neoadjuvant chemotherapy followed by adjuvant treatment in the form or surgery and/or radiotherapy. While among the seven who underwent exenteration, 3 patients with locoregional metastasis died of systemic spread of the cancer over the next few years (range: 18-70 months) on refusing to comply with further treatment in the form of radiation after the exenteration. One patient died due to surgical complication.

In their study of 60 patients with SGC of the eyelid, Shields et. al. reported a final outcome which was quite favourable with 88% patients being alive and well, 2% alive with metastasis, 2% with nodal metastasis (death due to unrelated cause), 6% dead due to metastasis and finally 6% dead due to other cause. Of the five patients with clinical evidence of metastasis, 3 with lymph nodal metastasis (1 at presentation, 2 developed later) died of systemic metastasis over a range of 15 to 39 months 11. Zucher et. al. reported death in 9% of their patients 15.

While in the recently published series on 191 patients with SGC of the eyelid by our group, 75% (136/181) patients were alive and well, 23% (41/181) showed regional lymph nodal metastasis, 14% (26/181) displayed systemic metastasis at the final outcome. Nineteen patients (10%) died due to systemic metastasis while 4 (2%) died of an unrelated cause. The overall 5-year KM estimate was 17% for regional lymph node metastasis, 10% for systemic metastasis, and 2% for metastasis-related death 16.

In contrast in the presence of orbital involvement in SGC as in our study, the final outcome was dismal wherein 21% (6/28) patients were alive and
well, 14% (4/28) had regional lymph nodal metastasis, 14% (4/28) showed evidence of systemic metastasis, 46% (13/28) died of SGC related systemic metastasis while one (4%) died of an unrelated cause. The duration from the first visit to our institute to their death by all causes varied from 1 to 88 months (average: 29 months).

Our series has 30 patients with orbital involvement of periocular SGC. This is the largest series of such as per our literature search. Through our series of orbital invasion of periocular SGC, we wish to emphasize the poor prognosis associated with orbital involvement. Delayed presentations due to delayed diagnosis or patient hesitation in procuring treatment are prominent factors to consider. Elderly age group and those with immuno compromised status have added disadvantages due to their lower threshold for chemotherapy/ radiation / surgery/ anesthesia tolerance as well as difficulties with treatment compliance and follow up, thus bringing in new challenges to treat this category of patients. The purpose of this study has not been to redefine treatment protocols since 15 patients had been referred to us for SGC after undergoing some intervention elsewhere in the form of surgery and/or radiotherapy. This series is for assessing the clinical features and outcomes in general. Multi modal treatment, good patient compliance and educating the patient and first of kin on the disease and prognosis plays a paramount role in long term outcomes.

The limitations of this study include the shorter follow up of some patients with 9 patients having a follow up of less than 20 weeks. Nevertheless over time we have managed to contact all patients or their first of kin except for one to find out the whereabouts and health status of the patients in the study. We continue to follow up the surviving patients with periodic evaluation for orbital recurrence and systemic metastasis and send reminder calls and notes to those who require evaluation.

There are many unanswered questions in respect to this tumor. Is there any role of sentinel lymph node biopsy? What is the ideal screening protocol for detecting metastasis? What are the factors that predispose certain races to this carcinoma more than others? What is the best modality of treatment? What should be the follow up protocol? Considering the large number of patients with SGC in our population, we believe that the answers to these questions lie in our subcontinent.

CONCLUSION

Orbital involvement in periocular SGC (stage III and stage IV) is an ominous sign that signifies poor prognosis and a high incidence of recurrence. Thorough evaluation in the form of imaging, incision biopsy, lymph node examination and search for systemic metastasis is necessary. Patient is to
be closely followed up for recurrence and signs of metastasis. The systemic co-morbidities that are commonplace in the elderly population are to be considered while planning treatment. Neo-adjuvant chemotherapy is the modality of choice in case of lymph node involvement and systemic metastasis and it also aids in a less extensive surgery such as lid sparing exenteration or even excision biopsy. Multi-modal treatment with a combination of neoadjuvant chemotherapy, surgery and radiotherapy achieves the best possible result. Close follow up is crucial and is a game changer when it comes to timely detection of metastasis. It is important to create heightened awareness on eyelid/periocular tumors among the general public and also sensitize the general ophthalmologist and practitioneers in allied branches on these carcinomas. It is only a high level of suspicion that will enable early diagnosis, referral and treatment which shall decrease the burden of advanced cases and improve the prognosis of this carcinoma.

REFERENCES

Intra-Orbital Foreign Bodies (IOFB): A Study on 27 Cases

Dr. Syeed Mehbub Ul Kadir, Dr. Md Gulam Haider, Dr. Mukti Rani Mitra, Dr. Mohammed Moinul Hoque

An intra orbital foreign body is an important cause of ocular morbidity usually in the younger age group than in older patients. The term of intra orbital foreign body is foreign body within the orbit but outside the globe.\(^1\)\(^2\) It usually occurs after a high velocity injury such as a Road traffic accident, fall over objects, physical assault, gunshot injuries, political and social violation but even relatively trivial trauma can cause orbital trauma and foreign body may retained in the orbit. Loss of vision is usually a result of the initial trauma. Orbital foreign bodies are more commonly observed in males than in females.\(^2\)\(^3\) They can be classified according to their composition into a) metallic inorganic such as steel, pellet, iron, lead b) nonmetallic inorganic such as glass, silicone, plastic and concrete; c) organic such as wood or vegetable matter. In general, metal and glass are well tolerated, and if not causing any symptoms or signs, may be left...
in situ, while organic matter like wood and vegetable matters are poorly tolerated, elicits an intense inflammatory reaction, and need to be removed urgently.\textsuperscript{1,3} Surgery is planned based on certain aspects that include the nature of the intra orbital foreign body (poorly tolerated organic objects such as wood and vegetable matter, or well tolerated objects such as stone, glass, plastic, iron, steel and aluminum); location of the foreign body (anterior or posterior orbit), and presence of other injuries or foreign body related complications (such as optic nerve compression, infections, and extra ocular muscle involvement).\textsuperscript{4,5} We attempt to describe the pattern of foreign bodies, types of injuries, different types of clinical presentations, radiological appearance, visual improvement following management, and management strategies of intra orbital foreign bodies.

**MATERIALS AND METHODS**

An observational case series study was done in department of oculoplasty in National institute of ophthalmology and hospital between 2007 and 2013. Patients with different types of presentations of retained intra orbital foreign body had been treated. Details of ocular history including age, gender, nature of injury and location of intra orbital foreign bodies, imaging studies obtained, preoperative ocular examination, initial and final visual acuity, length of follow up period, treatment modalities, surgical procedure and subsequent management, related adverse reactions and or complications were recorded. We preferred computed tomography scan of the orbit to identify the types and location of intra orbital foreign bodies. Magnetic Resonance Imaging is contraindicated in suspected ferromagnetic foreign body. Conservative treatment including broad spectrum antibiotic were given prior to surgery. Surgeries were planned based on the nature, location of foreign bodies, and presence of other injuries or foreign body-related complications. Appropriate test of significance was done.

**RESULTS**

We evaluated twenty seven cases involving twenty three male and four female patients ranging in age from one to through fifty nine years. Male patients were twenty three (85.2\%) highest in this study than female patients (14.8\%). The age of the twenty two cases were...
below forty years that was 81.5% of all patients. Male patients were usually young but most of the female patients (75%) were more than forty years of age. The Mean age of all patients was 26.68 years. Orbital foreign bodies were commonly found in pediatric and younger age group. The common cause of intra orbital foreign bodies were accidental injuries like as fall from height, road traffic accident, occupational injury and sport injury. The accidental injury was found in eleven numbers of cases (40.7%). Seven cases (26%) were the result of political unrest. We found six (22.2%) retained foreign bodies in the orbit due to social clash. Three cases (11.1%) were from iatrogenic cause (default surgery). Eighteen cases had CT scans to assess the injury, seven cases had MRI and two patients had plain radiographs. Left orbit was frequently involved that was 80% in compared to involvement of right orbit (16%). Both orbits were involved in one case (4%). The mean duration of presentation to us was 28.16 days. The range of the duration was 1 to 240 days. The median days of duration were fifteen. We assessed associated injuries like as fracture of the orbit (18.5%), Face injury (15%), Head injury (11%) and chest injury (7.4%) along with intra orbital foreign bodies. Common presenting features were chronic discharging sinus (37.3%), entry wound 926%), non healing ulcer/infection (22.2%), loss of vision (22.2%), proptosis (15%), ptosis (11.1%) and periocular ecchymosed (11.1%). Among the 22 cases with no ocular involvement, only three (11.1%)
patients had ruptured globe, two patients had retinal detachment, 3 patients had both retinal hemorrhage and optic neuropathy, and three patients had restricted ocular movement. IOFBs were located in the extraconal space in 40% of cases, 32% were involved both extraconal and intraconal space and 28% cases only involved the intraconal space of the orbit. Surgeries were performed in 92.6% patients of IOFB. Only conservative management was given in only two cases (7.4%) because metallic foreign body (pellet) was in the posterior orbit near to orbital apex. Foreign bodies were extracted from twenty five cases. The surgical approaches were Orbitotomy in twenty one cases (84%), evisceration (8%), enucleation (4%) and exenteration (4%). The metallic foreign bodies and vegetative foreign bodies were found in the same number of cases (12) which was (44.4%).

Gauze piece in 2 cases (7.4%) and 1 case (3.7%) was of silicone material (retained DCR tube). Intra orbital foreign bodies were more than single foreign body in 22.2% cases. Initial visual acuity ranged from 20/20 to no light perception. Six patients had no light perception at initial vision of presentation, as did final visual acuity. Improving of vision was statistically very highly significant following management of the patients.

DISCUSSION

27 cases of intra orbital foreign body involving 12 (44.4%) metallic, 3 (11.1%) nonmetallic inorganic and 12 (44.4%) organic (wood or vegetative material). A retained foreign body can result to devastating complications, the most serious of which is loss of the eye. Mean age of all patients was 26.68 years, median age was 24 years and the age of 81.5% cases were less than 40 years. Assessment through radiological images assists in the proper localization of the foreign body, estimation of its consistency and size, and evaluation of the response of surrounding orbital tissue. Additionally, it is useful in determining the integrity of the globe.

The choice of imaging modality usually depends on the pattern of the suspected foreign body. We ordered CT scans of the orbit in eighteen cases to assess the all types of injury, MRI in seven cases to clear cut outlined the
Figure 1-4: 11 years girl presented chronic discharging sinus, coronal CT image shows hypodensity foreign body in the left orbit, removing the wooden IOFB, extracted wooden foreign body.

Figure 5-7: 34 years old male patient presented chronic discharging sinus from medial aspect of left upper eyelid, Axial CT image showing the longitudinal hypodensity IOFB between medial rectus muscle and medial wall of the orbit with surrounding inflammatory change, Extracted wooden foreign body from the left orbit through orbitotomy.

Figure 8-11: 19 years old young patient presented an entry wound with swollen and tender left upper eyelid, 3-D X-ray shows radio-opaque rounded IOFB in the superomedial quadrant of the left orbit, metallic IOFB is extracting from the orbit, removed round, smooth, medium sized pellet.

organic vegetative foreign bodies and only plain radiographs were done in 2 cases due to patient’s economic condition. Plain X-ray is useful to localize radiopaque objects. However, plain x-ray is to sufficient demonstrating the object details, their actual location in relation to surrounding structures and tissue response or damage. CT scan of the orbit is the imaging modality of choice in this situation. Ideally, thin axial and coronal views of 1.0-1.5 mm cuts of the orbit are extremely useful to delineate the shape and for determining the composition of the foreign body. However, despite being highly sensitivity and specific outlined for detection of foreign bodies, CT scans may produce false negative results, particularly if the size of the foreign body is less than 0.5 mm, and especially in the case of wooden objects. These are better seen with magnetic resonance imaging (MRI).
However, an MRI is contraindicated if the suspected foreign body is ferromagnetic. Wooden foreign bodies can remain entrapped in the orbit for long time and lead to complications like orbital cellulites, abscess formation, chronic discharging sinus, noninfectious inflammation, and fibrosis. They can migrate intra cranially leading to chronic brain abscess or undergo spontaneous extrusion.\textsuperscript{9,10} We were tried to find out the cause of the intra orbital foreign bodies. Political and social unrest was significant for orbital trauma. Accidental injury was 40.7%, injury due to Political clash was 26%, social injury was 22.2%, and iatrogenic cause found in 11.1% cases. The iatrogenic cause was default surgery, 2 cases were gauze piece in the orbit with history of previous DCR surgery in one case and Orbitotomy for lacrimal gland tumor in one case. Another one case had metallic DCR tube introducer. Meticulous surgery should be done at every case that will be reduced the rate IOFBs. 21 cases had stable or improved vision following management. Visual improvement was statistically significant. 6 patients had no light perception at initial vision of presentation. 93% of IOFBs were extracted from the orbit. Foreign bodies removed from the orbit in 25 cases and we managed conservatively only in 2 cases who had pellet (metallic IOFB) with history of gunshot injuries in posterior orbit near to orbital apex.

Fulcher et al. studied on 40 retrospective consecutive case series conducted over 10 years, foreign body composition were classified as metallic, organic (wood) and non-metallic inorganic (glass, plastic, fiberglass, concrete). Most common associated ocular morbidities were perforating eye injury, occurring in 25% (10 of 40) of patients. Others included infection (orbital cellulites, orbital abscess, and cerebral abscess), ophthalmoplegia, ptosis, optic neuropathy and orbital fracture. 85% (34 of 40) of patients underwent surgical removal. All 6 cases that did not had posterior located IOFBs. In reviewing the surgical indications, the most important factors were foreign body location and composition.\textsuperscript{2}

Finkelstein et al. reviewed 27 consecutive patients over 7 years. All cases involved metallic foreign bodies, the majority of which were BB gun injuries (20 of 27). 13 of the foreign bodies were located in the anterior orbit, 4 epibulbar and 10 posterior. Practically all (94%, 16 of 17) anterior and epibulbar foreign bodies were surgically removed, whereas only
20% (2 of 10) of those located posterior were extricated (which occurred during ruptured globe repair). Most common associated ocular morbidities included local trauma (subconjunctival hemorrhage, corneal abrasion, chemosis), ophthalmoplegia, retinal or vitreous hemorrhage, traumatic optic neuropathy, orbital fracture, retinal detachment, retinal tear and choroidal rupture. Final visual acuity correlated to location of foreign body. 85% (11 of 13) of patients with anterior IOFBs retained final visual acuity greater than 20/40, compared to only 30% (3 of 10) of patients with posterior IOFBs. Additionally, of the 3 patients who developed NLP vision, all had posterior IOFBs. It was deemed that management of each case was dependent on location of the projectile, and foreign bodies not readily surgically accessible may be left safely in place.

If inflammatory signs persist and limited of ocular movement after a patient presented with a history of an ocular injury caused by organic material such as wood, the possibility of a retained orbital foreign body must be considered.

Peralt R.J et. al. presented a case report a 20 year old male presented to one day after a high velocity projectile injury (BB pellet) to the right orbit. Clinical examination revealed an entrance wound 10 mm inferior to the right medial canthus but no exit wound, mild pain and limitation of extra ocular movements, mild relative afferent pupillary defect (APD) and complete loss of color vision on Ishihara testing in right eye. CT scan showed a metallic foreign body deep in the posterior orbit near the orbital apex and right optic nerve. They managed the case with an inert, well tolerated metallic foreign body located deep in the posterior orbit conservatively with observation and appropriate supportive care, thus avoiding potential iatrogenic injury to vital structures adjacent to the orbital apex.

**CONCLUSION**

Management of intra orbital foreign bodies should include an accurate and detailed history as well as a CT scan of the orbit, which is the best initial mode of imaging. Early diagnosis, management and extraction of the foreign body if indicated, greatly influence the final outcome. All patients should have antibiotic therapy because of the high incidence of secondary orbital infections. Surgical removal is indicated for all organic IOFBs. Posterior located inorganic inert IOFBs should be left alone, unless they are causing significant orbital complication.

**REFERENCES**

Intraoperative Cytology in Eyelid and Orbital Tumors: An Alternative or Adjunct to Frozen Section?

Dr. Kaustubh Mulay, Dr. Ekta Aggarwal, Dr. Santosh G Honavar

Diagnosis of orbital and eyelid tumors requires correlation of clinical, radiologic and histologic assessment and knowledge of clinicopathologic entities and their common locations. Advances in imaging and surgical techniques have dramatically revolutionized the diagnosis and treatment of these tumors. Both, excision and incision biopsies are regularly
performed and the volume of tissue available to a pathologist may vary. Intraoperative pathologic evaluation is crucial in many of these tumors to achieve optimal management outcomes. Traditionally, frozen sections (FSs) have been used for rapid intraoperative diagnosis (IOD). Since Patrick and Dudgeon first introduced cytology as a method for IOD of tumors, this technique has been evaluated by several authors and is now widely used. Although Intraoperative cytology (IOC) is popularly and regularly used in central nervous system tumors, it has also been successfully used in tumors at other anatomical locations of the human body. Studies on the role of IOC in ophthalmic oncology are sparse. The main objective of our study was to evaluate the accuracy of IOC diagnoses of eyelid and orbital tumors.

**MATERIALS AND METHODS**

This was a prospective study of 89 fresh, unfixed intraoperative specimens submitted during eyelid and orbital surgeries from Jan’12 to May’15. Of these, 15 cases where a cytologic diagnosis could not be rendered due to inadequate sample volume (n=2), nature of the specimen (fibrous tissue, 2; resected margins, 9) which was non-conducive for cytologic preparation, sub-optimal quality of cytologic preparation (n=1) or poor cellularity (n=1) were excluded. Seventy-four specimens (eyelid, 25; orbit, 49) included in the study were interpreted with both, IOC and FS.

The tissues were thoroughly and carefully examined grossly. Excess blood or saline water was gently blotted using a tissue paper or gauze.

**Cytology**

The fresh tissue submitted for intraoperative consultation was first used for IOC. A squash preparation was made by placing tiny bits of the tissue between 2 clean, glass slides and gently drawing the glass slides apart. At least 2 slides were prepared of which 1 was fixed in alcohol for 5 minutes and 1 was air-dried. While the alcohol-fixed slide was stained by a rapid hematoxylin and eosin (H&E) technique, the air-dried smear was stained by Diff-quick technique.

**Frozen Section**

After preparation of smears for IOC, the specimen in entirety (if small) or representative sections were embedded in Optimal Cutting Temperature Compound (OCTC). The tissues were then frozen in a cryostat at -35°Celsius. The sections were cut 4-6 mm thick and stained by H&E technique.

Both, the squash preparation and frozen section slides were examined by a pathologist (KM) and a diagnosis made on each of them separately, first on the squash preparation followed by the frozen section slides. After correlating with the clinical and radiologic data, a diagnosis was offered. Remainder
of the tissue was fixed in 10% neutral buffered formalin and processed as routine. Special histochemical stains and Immunohistochemistry were performed as required. The IOC and FS diagnoses were compared with the final histopathologic diagnosis.

**Diagnostic Accuracy Assessment**

Each of the IOC and FS diagnoses were scored using the system suggested by Khalid *et al.* as follows:

**Score 0:** The diagnosis was incorrect with respect to benign or malignant.

**Score 1:** Diagnosis was correct with respect to benign or malignant but incorrect with respect to final specific diagnosis (*i.e.* carcinoma or sarcoma or lymphoma) or the diagnosis was deferred to assessment of permanent sections.

**Score 2:** The diagnosis was essentially correct *i.e.* correct regarding benign or malignant and in terms of a broad categorization (*e.g.* carcinoma or sarcoma) but not absolutely specific (*e.g.* carcinoma instead of sebaceous carcinoma or sarcoma instead of fibrosarcoma) OR the correct diagnosis was included in the differential diagnoses.

**Score 3:** The diagnosis was correct and specific (*e.g.*: rhabdomyosarcoma, pleomorphic adenoma *etc.*)

**Statistical Analysis**

Percentage accuracy, sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) were calculated for both, IOC and FS using permanent histopathologic diagnosis as the gold standard.

**RESULTS**

This study included 34 eyelid and 40 orbital lesions. Overall, 17 were benign (neoplastic and non-neoplastic) and 57 were malignant cases (Table 1). Age ranged from 1.5 to 75 (mean 54) years. The study included 31 males and 43 females (M:F=1.17). Among eyelid lesions, lipogranulomatous reaction (5/7) and sebaceous carcinoma (18/27) were the most frequent benign and malignant diagnoses respectively. The most frequent benign and malignant orbital lesions were idiopathic orbital inflammation (IOI, 4/10) and non Hodgkin’s lymphoma (10/30) respectively. In 2 (2.7%) cases, the diagnosis was deferred till permanent sections. As shown in table 2, the overall diagnostic accuracy for distinguishing benign from malignant by IOC and FS was 95.9% (71/74) and 97.3% (72/74) respectively but improved to 100% when a combination of both methods was used. For the diagnosis of malignancy, use of IOC alone resulted in 2 false-positives and 3 false-negative results while FS, when used alone, had 1 false-negative and false-
positive case each. FS had better positive- and negative predictive values for malignancy (98.2% and 94.1% respectively) as compared to IOC (97.3% and 85% respectively). Both these values improved to 100% when IOC and FS were used together for the diagnosis.

**Scores for Accuracy of Diagnosis**

**Score 0:** There were 5 such cases for IOC, 2 for FS and none for a combined diagnosis.

**Score 1:** There were 4 such cases, 3 on IOC and 1 on FS. Two of these were deferred till permanent sections. The 3 cases where the IOC diagnosis carried score 1 had a score of 2 on FS. In the remaining case where the FS diagnosis had score 1, the IOC was diagnostic with a score of 3. This was a case of primary orbital a typical teratoid rhabdoid tumor where the rhabdoid morphology was distinctly appreciated in cytologic preparations.

**Score 2:** There were 10 such cases. Among these IOC had 8 while FS had 2. All 8 cases which were scored 2 on IOC were those of eyelid carcinoma (sebaceous carcinoma, 6 and squamous cell carcinoma, 2) which were diagnosed as poorly differentiated carcinoma. Their morphologies were appreciated better on FS slides.

**Score 3:** 55/74 cases earned a score of 3. Of these 50 had a score 3 on both, IOC and FS. In the remaining 5 cases, 2 FS rated a score of 2 while IOC rated a score of 2 in 3.

**DISCUSSION**

There are several reports in the world literature confirming the efficacy and utility of IOC for intraoperative consultation. Lie et al. investigated the utility of intraoperative touch preparation and comparison of FS in 122 cases. The rate of correct diagnosis for touch preparation was 88.5% as compared to 86.1% for FS. The rate of incorrect diagnosis for touch preparation was 4.1% as compared to 2.5% for frozen section while the undetermined diagnosis were 7.4% for touch preparation and 11.6% for frozen section. For pathologists, with considerable experience of cytology, both touch and frozen section diagnostic accuracy rates were similar. The pathologist who lacked this experience had lower touch diagnostic accuracy. All pathologists who had cytological experience requested a frozen section only for cases with an undetermined touch preparation. In correct TIC diagnosis a frozen section was requested in 46.3% cases. Therefore touch and frozen section were complementary and both provided accurate diagnosis. Some pathologists consider that touch preparation may replace frozen section completely in over 50% of cases.

It is well recognized, however, that the freezing and sectioning techniques
of frozen section results in unavoidable distortions and artifacts, rendering diagnosis difficult in many instances. The greatest advantage of cytology examination is of not having such artifacts, resulting in excellent nuclear and cytological details. Minimal tissue is needed for cytology examination. The diagnosis of very small lesions is therefore facilitated and tissue is saved for permanent section. Certain tissues that cannot be studied by frozen section i.e. bone, necrotic tissue and fat etc. give accurate results on touch preparations.

Scucchi et. al. compared 2,250 intraoperative cytology with frozen section with the final diagnosis achieved on paraffin sections.\textsuperscript{19} In 18 cases the diagnosis were deferred until the paraffin section at the time of Intraoperative consultations. The diagnostic accuracy in distinguishing benign from malignant lesions by combined intraoperative cytology and frozen section was 99.2%. The accuracy rate is higher than reported in large series based on frozen section alone. Sensitivity and specificity were respectively 98.2% and 100%. The diagnostic accuracy of each technique alone was 94.9%. For FS, the sensitivity was 89.9% and specificity 97.9% as compared to the touch cytology, which had a sensitivity of 94.9%, and specificity of 96.8%. Guarda carried out a comparative study of the two techniques and found the accuracy of cytology and frozen section 98.4% and 99.2% respectively.\textsuperscript{20} The cytology was found to be more valuable in the field of neuro-pathology, lymph node and most of the epithelial tumors. It also provided better morphological preservation and details than frozen sections. Mair et. al.\textsuperscript{21} studied 206 cases from various body sites and found the accuracy of cytological examination comparable to that of frozen section analysis. The quality of cytological preparation was significantly superior to that of frozen section. The combination of the techniques provided 99.5% accuracy rate. Ieesab and Haque\textsuperscript{22} also confirmed the utility of touch imprint cytology and its diagnostic accuracy comparable to frozen section. In our study the sensitivities of both methods were comparable. The diagnostic accuracy of IOC and FS were 95.9% and 97.3% respectively. IOC provided better cellular details and fewer artifacts. The diagnostic accuracy in distinguishing benign from malignant lesion by combined IOC and FS was 100%. Both these methods complemented each other. As FS gives good architectural details, cytology provides excellent cellular details. The experience of the pathologist in interpretation of the touch preparations is the mainstay in improving the diagnostic accuracy when both techniques are combined. Two cases were deferred and these were both lymphoproliferative lesions in which both IOC and FS were not able to make the definitive diagnosis.

The usefulness of IOC is not limited to simple differentiation between benign and malignant lesions. IOC has been found quite reliable and useful in determination of surgical resection margins\textsuperscript{23,24}, sentinel lymph nodes\textsuperscript{25},
adenomatous goiter\textsuperscript{26,27} and confirmation of parathyroid tissue.\textsuperscript{8,28,29} IOC has special role in brain and spinal cord lesions as these tissues are quite soft and various types of gliomas, meningiomas and other lesions yield cellular smears.\textsuperscript{30-32} In gynecology and obstetrics, IOC is quite useful in differential diagnosis of ovarian tumors.\textsuperscript{33,34} In basal carcinomas of skin where a lot of frozen sections were needed to evaluate margins heavily taxing the time and energy of pathologist, IOC has provided satisfactory results without that much pain and sweat.\textsuperscript{35}

IOC has also been shown to be quite reliable in diagnosis of various soft tissue tumors. Its utility and accuracy, for instance has been reported in alveolar soft part sarcoma.\textsuperscript{36} Lymph nodes are very difficult to interpret by FS, however IOC provide much more crispier and preserved cellular details enabling to render a confidant diagnosis of lymphomas in most cases.\textsuperscript{37} Finally in cases of ophthalmic tumors, IOC provides accurate diagnosis.\textsuperscript{13-16}

In conclusion both FS and IOC provide accurate diagnoses. The accuracy is quite high in both, particularly in differentiating benign from malignant lesions. IOC reveals crisper cytological details and has further advantage of being inexpensive, simple and quicker than FS. Considering the few yet significant drawbacks, IOC may be used to complement frozen section and be an useful adjunct to it in providing a highly accurate rapid intraoperative consultation diagnosis.

Rhinoorbitalcerebral Mucormycosis – Our Experience

Dr. Shaloo Bageja, Dr. Ashok Kumar Grover

Rhino-orbito- cerebral mucormycosis (ROCM) is an acute, often fatal fungal infection occurring in immunocompromised patients including diabetics and occasionally in healthy individuals. The disease process originates in the sinuses and extends rapidly into adjacent structures like orbit and central nervous system. Fungus invades the internal elastic membrane of the vessels and hyphae are responsible for vascular occlusion. ROCM consisting of involvement of sinuses with or without brain/orbits, has accounted for up to half of all cases of mucormycosis.\textsuperscript{1,2} Rhino-cerebral involvement is usually the most common (21%), followed by sino-orbital (8%) and sinusitis (8%).\textsuperscript{3}
MATERIALS AND METHODS

Fourteen consecutive patients with histologically confirmed diagnosis of Rhinoorbital mucormycosis who presented to Sir Ganga Ram Hospital, New Delhi from March’2010 to March’ 2015 were reviewed. All patients were evaluated with detailed history and clinical examination including ENT and neurologic examination.

Investigations included complete blood count, blood glucose levels, kidney function tests. Endoscopically nasal swab, preferably from middle meattus was collected in all cases and was sent for microbiology for KOH preparation and histopathological evaluation. Imaging (CT scan / MRI) of orbit, sinuses and brain was done to assess the extent of the disease.

Management of deranged metabolic status was initiated immediately under supervision of physician. Intravenous Amphotericin B was started after confirmation of diagnosis. After a test dose of 1 mg of Ampoterincin B in 100 ml of Normal saline, 0.5-0.75 mg/kg/day of Amp B was started. Kidney function tests were performed on alternate days to rule out any drug induced side effects. The dosage was increased by 25 mg/day to a maximum of 150-200 mg/day till a cumulative dose of 2 gm. Liposomal Amp B was preferred especially in individuals with chronic renal failure. It was started at a dose of 3-5 mg/kg/day to a cumulative dose of 3gm-5gm.

RESULTS

Among Fourteen patients of Rhino-orbito-cerbral mucormycosis, there were 12 males and 2 females with age ranging from 22-74 year (mean 47 years).

Predisposing Conditions

Diabetes was the commonest underlying disease. 10/14 patients had uncontrolled diabetes. 6/10 diabetics had ketoacidosis (Table 1).

Clinical features

Presenting ophthalmic and non-ophthalmic symptoms (Figure 1a-c) and signs are listed in Table 2.

Diagnosis

On Imaging (Contast enhanced CT Scan/MRI) all patients had evidence of involvement of paranasal sinuses. The ethmoid and maxillary sinuses were most commonly involved.

Orbital changes in imaging showed altered signal of retrocular tissue, thickening of extraocular muscles and optic nerve and bony destruction.

Confirmation was carried out by isolation of organism either by nasal swab
Table 1

<table>
<thead>
<tr>
<th>Condition</th>
<th>N</th>
</tr>
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<tbody>
<tr>
<td>Diabetes</td>
<td>10</td>
</tr>
<tr>
<td>Chronic renal disease</td>
<td>3 (2 were diabetic also)</td>
</tr>
<tr>
<td>CLL</td>
<td>2</td>
</tr>
<tr>
<td>Non Hodgkin Lymphoma</td>
<td>1</td>
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</tbody>
</table>

Table 2: Non-Ophthalmic symptoms and signs

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
<td>9</td>
</tr>
<tr>
<td>Facial pain and swelling</td>
<td>5</td>
</tr>
<tr>
<td>Nasal blockage</td>
<td>5</td>
</tr>
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</table>

<table>
<thead>
<tr>
<th>Signs</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sinusitis</td>
<td>14</td>
</tr>
<tr>
<td>Altered sensorium</td>
<td>1</td>
</tr>
<tr>
<td>Cavernous sinus thrombosis</td>
<td>2</td>
</tr>
<tr>
<td>Facial nerve palsy</td>
<td>2</td>
</tr>
<tr>
<td>Palate necrosis</td>
<td>2</td>
</tr>
</tbody>
</table>

Table 3: Ophthalmic symptoms and signs

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diplopia</td>
<td>2</td>
</tr>
<tr>
<td>Loss of vision</td>
<td>8</td>
</tr>
<tr>
<td>Eyelid and skin necrosis</td>
<td>2</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Signs</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proptosis</td>
<td>7</td>
</tr>
<tr>
<td>Ptosis and ophthalmoplegia</td>
<td>9</td>
</tr>
<tr>
<td>CRAO</td>
<td>7</td>
</tr>
</tbody>
</table>

Figure 1A: 57 yr old male with left eye proptosis and ophthalmoplegia

Figure 1B: showing facial nerve palsy
or biopsy for histopathological examination and culture. KOH preparation was also helpful in identification of organism. Appearance of aseptate hyphae with right angled branching was pathognomonic for the morphology of mucor.

**Management**

All patient received intravenous Amphotericin B. Two patient died within 5-8 days of start of treatment due to rapid intracranial progression. All patients underwent endoscopic debridement of all necrotic tissue from sinuses and nasal cavity. 12 patients underwent exenteration. Two patient received intraorbital amphotericin (1 mg/ml/day) for 2 weeks.

**Outcome**

10/14 patients with Rhino-orbital disease survived following combined medical and surgical therapy. 2/4 patients of cerebral involvement survived.

**DISCUSSION**

Rhino-orbito-cerebral mucormycosis infections are commonly seen in immunocompromised patients. Uncontrolled diabetes was one of the commonest cause in our study like in many other previous studies. Visual loss along with ptosis and ophthalmoplegia (72%) was the most common presenting symptom, compared with 80% reported by Bhansali *et al.* and 65% by Yohai *et al.*

On imaging, paranasal sinuses were involved in all cases with ethmoid and maxillary sinuses being the most common, while Ferry *et al.* reported sinus involvement in 69% of patients.

Endoscopic debridement of sinuses, resection of all affected tissues was essential in all cases as it improved the outcome. Orbital exenteration was mandatory in cases of orbital involvement except in case of bilateral involvement and rapid intracranial progression. Exenteration and extensive resection including muscle, skin of the nose, all involved sinus, infratemporal fossa, temporal area proves to be a life saving procedure in such eyes.

To conclude, A high index of suspicion in predisposed individual especially uncontrolled diabetics is essential for early diagnosis of ROCM.
Rapid management of metabolic imbalance along with Amphotericin B and surgical debridement of sinus, nasal tissue and exenteration gives a reasonable chance of survival. Early diagnosis therefore, becomes imperative.

REFERENCES

A Novel Technique of Fornix Reformation

Dr. Parvathi T Hari, Dr. Gupta Roshmi, Dr. Shetty Bhujang K

In an anophthalmic socket loss of inferior conjunctival fornix fixation leads to a shallow inferior fornix, often causing difficulty retaining the prosthesis, especially in up gaze. This has been routinely corrected using a fornix fixation. It consists of passing a suture from the lower fornicial conjunctiva, deep through the orbital rim peristemeum and out through the lower eyelid skin and fixed with bolsters. We found that with the use of bolsters the chances of infection increased due to poor hygiene and skin erosion under the bolsters. Hence we describe this modified technique of fornix formation.
**MATERIALS AND METHODS**

It was a randomized, interventional prospective study in a tertiary care centre.

All patients with anophthalmic socket underwent complete clinical evaluation. Shallowing of the fornices was noted on clinical evaluation. Presence of conjunctival shortening was not considered as no additional procedure was done for it. Any volume or surface deficit in the socket was noted. The indications for surgery included non-retention of prosthesis, poor cosmesis due to upward tilting of prosthesis, and enophthalmic appearance of prosthesis.

Patients with shallow fornix on clinical evaluation underwent fornix formation. In addition, volume deficit was treated with secondary orbital implant or dermis fat graft and surface deficit with mucous membrane graft or amniotic membrane graft. All surgeries were performed by a single trained oculoplasty surgeon.

**Alternate patients:** Patients were alternatively enrolled into 2 different groups when scheduled for surgery groups. In both the groups a silicone 240 band about 3 cm 3 cm/mm long was used on the conjunctival surface and three horizontal mattress sutures (4 0 poly glactin) passed through the silicone band and the conjunctiva at the maximum depth of the fornix. A bite is then taken through the orbital rim periosteum. In group A the sutures emerged through the lower eyelid skin were skin were secured on the lower eyelid skin surface with bolsters. In the new technique (group B), three 2 mm long incisions along the lower orbital rim were made, and the sutures were then brought out through the incision, secured and knot allowed to retract into depth of the incision. The skin incision was then closed with 6-0 polyglactin sutures, thus burying the knot.

Post operatively in both the groups, the sutures along with the bolsters and the silicone band was removed on the tenth post operative day.

At final visit the clinical outcome considered good in patients who retained the prosthesis well without tilting and had deep fornices clinically.

The complications during the post operative period like skin excoriation, infections, shallowing of the fornix, granuloma formation were documented.

**RESULTS**

We included 16 eyes of 16 patients with anophthalmic socket requiring fornix deepening.

The study was done between May-Dec 2014. Out of the 16 patients, 9 patients
were enrolled in group A (traditional external technique with bolsters) and 7 were included in Group B (internal technique with buried sutures. Three patients in group A underwent only fornix formation; another three had dermis fat graft along with fornix formation. One of them underwent both upper and lower fornix formation along with amniotic membrane grafting. Two patients had secondary implant with fornix deepening suture (FDS). In the group B four patients of them underwent fornix formation along with secondary implant insertion, one fornix formation with dermis fat graft, One patient had isolated fornix formation alone and another fornix formation with dermis fat graft, while one fornix formation alone, and one another patient has enucleation with+ implant and fornix formation, Table 1 compares the pre-operative characteristics of the two groups of patients.

Four of the patients had undergone radiation following enucleation for retinoblastoma, 3 of them in group A and one in group B and the rest were post traumatic. One of the patients in group A had undergone fornix formation twice earlier.

The mean follow up period was 12.2 weeks (range 6 weeks- 24 weeks).

All the patients had good anatomical and clinical outcome with well formed fornices, and good retention of the prosthesis without tilting. One patient of group A required a repeat procedure. He underwent the same external procedure with bolsters and was doing well at the final visit. Another patient of group B also underwent repeat FDS, but with the external technique.

Two patients in group A had suture granuloma, which was excised and two patients showed of them skin excoritiation and scarring below the bolsters. Both were treated with topical antibiotic ointment. All the patients in group A had trouble maintaining hygiene of the eyelids due to the difficulty cleaning around the bolsters and pain.

One patient in group B had a suture granuloma due to a retained fragment of suture, which was later excised. Another patient had suture site infection.

Table 1: Comparison of Pre-operative Characteristics of Group A and B

<table>
<thead>
<tr>
<th></th>
<th>Group A</th>
<th>Group B</th>
</tr>
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<tbody>
<tr>
<td>Conventional fornix formations sutures over bolsters N=9</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Additional orbital volume augmentation (dermis fat graft or secondary orbital implant)</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>Additional Surface augmentation (mucous membrane graft or amniotic membrane graft)</td>
<td>1</td>
<td>0</td>
</tr>
</tbody>
</table>

Table 1 compares the pre-operative characteristics of the two groups of patients.
DISCUSSION

Anophthalmic socket undergoes remodeling over the period of time. Socket contracture results from shortening and shrinkage of the orbital tissues, leading to shallowing of the fornices. In some cases there is a decrease or loss of space in the fornices, while an adequate amount of conjunctiva is present. This occurs due to the anterior migration of the inferior orbital fat and thinning and disruption of the suspensory ligaments of the inferior fornix (anophthalmic socket syndrome).\(^2\,^3\) reference -Tyers and Collins published in 1982, Smith and Koorneef 1991).

Various techniques of fornix formation have been described in literature. It is usually combined with a lateral canthal tendon procedure to improve the results.

Commonly performed is the external technique with bolsters on skin surface, as done in the group A patients.\(^1\,^2\,^11\) Smith and Nesi, collins.

Another alternative technique is to place a transverse conjunctival incision is placed around 10 mm inferior to the lower lid margin and then sutures passed through the ends of conjunctiva and the periosteum and tied in the fornix. With this there is no scar on the eyelid, but the risk of infection increases and irritation is more as the knot is in the fornix.\(^11\) Smith and nesi.

In a retrospective study, Neuhaus et. al. described direct fixation of the conjunctival cul-de-sac to the periosteum immediately posterior to the orbital rim, with no external sutures. They reported good outcome with retention of the prosthesis. Minimal lower lid retraction and mild entropion has been reported post surgery.

In our study we compared the outcome of the traditional external technique with the modified novel buried technique. We found that the clinical and anatomical outcome of both the techniques were comparable. Both techniques were equally effective even in contracted socket following radiation.

The cosmetic appearance and the maintenance in immediate post operative period are better in the buried technique. By improving the hygiene, it also reduces the risk of infection as the compared to the use of bolsters. The scar with skin incisions were faint and barely visible in all cases.

We found no difficulty removing the sutures from the fornix along with the silicone band. But, we found that even with the use of absorbable sutures, incomplete removal of sutures in case it is not removed completely suture related complications such as granuloma formation or infection can occur.

We hypothesise that the loss of fixation of conjunctiva in the fornix to the inferior retractor complex is possibly not the only mechanism that leads to shallowing of the fornix. There is also an inferior migration of the orbital

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socket fat and soft tissue. Hence, a firm fixation of the fornicial conjunctiva to the periosteum is essential and can be achieved only by passing the sutures through the skin over the orbital rim.

The limitations of the study include: effectiveness in case of upper fornix shortening not studied and needs a longer follow up period. In our study, we are unable to comment on the effectiveness of this technique for the superior fornix.

The novel buried technique is as effective as the traditional technique with the advantage of better post operative comfort and cosmesis. The maintenance of improved hygiene makes it more desirable in the post-operative period. The occasional risk of skin excoritation and residual scar on the lower lid, which is present with bolsters, is avoided in the buried suture technique.

REFERENCES


Orbital Rhabdomyosarcoma – Clinical Profile and Outcome Following Multimodal Management

Dr. Sonal Chaugule, Dr. Santosh G Honavar, Dr. Vijay Anand P Reddy, Dr. Kaustubh Mulay

Rhabdomyosarcoma is the most common soft tissue sarcoma in pediatric population. Orbital variant comprises of 25-30% of rhabdomyosarcoma of head and neck region. Intergroup Rhabdomyosarcoma Study Committee (IRSG). Four major trials- I to IV (1972-1991).
Staging and classification of rhabdomyosarcoma.
Dramatic advances have been made by IRS in the understanding of the behaviour and management of rhabdomyosarcoma.
Purpose of this study is to study the clinical presentation, histopathological features, and outcome following multimodal management in primary orbital rhabdomyosarcoma.

**MATERIALS AND METHODS**

**Study Design**
- Retrospective, non-comparative, interventional case series
- Study population:
  - 35 consecutive patients presenting with orbital rhabdomyosarcoma.

**Data was reviewed with respect to Demographics**
Age, gender, laterality

**Clinical Features**
- Symptoms, duration of symptoms, initial diagnosis
- Examination: Affected eye, visual acuity, ocular motility, proptosis
- Data regarding tumor: Referral diagnosis, prior management, tumor location, size, appearance on imaging

**Management**
- Modalities of tumor management:
  - Surgery, Chemotherapy, Radiotherapy
  - Histopathological analysis
  - Clinical response to treatment

**Outcome Measures**
- Final visual outcome
- Local tumor control
- Regional lymph node outcome
- Systemic outcome

**RESULTS**
(n=35)
1) Age: Mean 9 years; range 1 month -40 years
2) Sex distribution: Male: Female= 17:18
3) Laterality: 100% Unilateral

4) Clinical features at presentation:
   a. Proptosis 51%
   b. Palpable orbital mass 37%
   c. Pain 17%
   d. Diminution of vision 14%

5) Onset of symptoms
   a. Acute 40%
   b. Subacute 23%
   c. Chronic 20%

6) Visual acuity at presentation
   a. 20/20-20/40 = 40%
   b. 20/40-20/100 = 34%
   c. <20/200 = 23%
   d. No PL = 3%

7) Clinical signs
   a. Ocular motility restriction in 54%
   b. Proptosis in 51%
   c. RAPD in 23%

8) Management
   a. Surgery: Incison biopsy, Debulking, Excision biopsy
   b. Chemotherapy: 6 cycles of VAC (A) + IE (B) at 3 weekly interval
   c. Radiotherapy: Stereotactic radiotherapy sandwiched between 2 sets of 3 cycles of chemotherapy

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vincristin</td>
<td>1.5mg/m2</td>
<td>D1</td>
</tr>
<tr>
<td>Actinomycin D</td>
<td>500 microgm/m2</td>
<td>D1-5</td>
</tr>
<tr>
<td>Cyclophosphamide</td>
<td>1250mg/m2</td>
<td>D1</td>
</tr>
<tr>
<td>Ifosphamide</td>
<td>1500-2000mg/m2</td>
<td>D1-5</td>
</tr>
<tr>
<td>Etoposide</td>
<td>100mg/m2</td>
<td>D1-5</td>
</tr>
</tbody>
</table>
Table 1: IRSG Staging

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Completely resected localized disease implying both gross resection and microscopic confirmation of complete resection and absence of regional lymph node involvement</td>
</tr>
<tr>
<td>II</td>
<td>Residual disease, regional lymph node involvement, or both</td>
</tr>
<tr>
<td>III</td>
<td>Incomplete resection with biopsy or gross residual disease at site of origin or in regional lymph nodes</td>
</tr>
<tr>
<td>IV</td>
<td>Distant metastasis present at onset</td>
</tr>
</tbody>
</table>

Table 2: IRSG: IV- Current Recommendations for Treatment of Orbital Rhabdomyosarcoma

<table>
<thead>
<tr>
<th>Stage</th>
<th>Radiation therapy</th>
<th>Chemotherapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>None</td>
<td>VA for 32 weeks (regimen 44, VA)</td>
</tr>
<tr>
<td>2</td>
<td>4140 cGy CFI</td>
<td>VA</td>
</tr>
<tr>
<td>3</td>
<td>5040 cGy CFI or 5940 cGy HFI</td>
<td>VA + C for 52 weeks (regimen 41 VAC) or VA + I for 52 weeks (regimen 42 VAI) or VI + E for 52 weeks (regimen 43 VIE)</td>
</tr>
</tbody>
</table>

Radiotherapy
- No residual disease: 4500 cGy to 5000 cGy
- Residual disease: 5000 cGy to 5500 cGy
- Dose rate: @ 180-200 cGy/ fr

9) Histopathology:

<table>
<thead>
<tr>
<th>Type</th>
<th>Number</th>
<th>Percentage (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Embryonal</td>
<td>20</td>
<td>57</td>
</tr>
<tr>
<td>Alveolar</td>
<td>12</td>
<td>34</td>
</tr>
<tr>
<td>Anaplastic</td>
<td>2</td>
<td>6</td>
</tr>
<tr>
<td>Botryoid</td>
<td>3</td>
<td>3</td>
</tr>
</tbody>
</table>

10) Final visual outcome
- 20/20- 20/40 = 34%
- 20/40- 20/200 = 26%
- <20/200 = 40%

11) Local and systemic tumor outcome
- Local tumor regression was documented in 86%
- Regional lymph node metastasis was documented in 9% of cases.
c. Distant metastasis was documented in 3% of cases.

d. Overall survival was 97%.

**DISCUSSION**

- Rhabdomyosarcoma displays a strong tendency for local invasion, local recurrence, and hematogenous and lymphatic metastases
- Treatment protocols involving both chemotherapy and radiotherapy have shown good outcomes.
- Recurrent tumors in the orbit are usually treated with orbital exenteration, supplemented with chemotherapy and radiotherapy as needed.
- Our study describes the outcomes in cases of advanced rhabdomyosarcoma (IRSG stage III and IV).
- Embryonal being the most common subtype (57%) alveolar subtype was also found in 34%.
- Eye salvage was possible in 33 (94%) of cases.
- Life salvage at the end of mean follow up period of 3.3 years was 97%.

**CONCLUSION**

Orbital rhabdomyosarcoma commonly presents as proptosis in the first or second decade of life.

Presentation of advanced rhabdomyosarcoma was seen in majority of cases. Embryonal followed by alveolar variant was common subtype found in our series.
Multimodal treatment including initial surgery, followed by multi-drug chemotherapy and stereotactic radiotherapy provides excellent chance of local tumour control (86% primary control, 100% secondary control) and life salvage (97%) in cases of advanced rhabdomyosarcoma.

Retinoblastoma Presenting as Preseptal/Orbital Cellulitis: A Study of 40 Consecutive Cases

Dr. Prerana Tahiliani, Dr. Swathi Kaliki, Dr. Vijay Anand P Reddy, Dilip Kumar Mishra

Retinoblastoma (RB) commonly presents as leukocoria, strabismus, red eye or proptosis; rarely as glaucoma, phthisis bulbi or preseptal or orbital cellulitis. A manifestation resembling orbital cellulitis, though rare, has been previously reported by Shields et. al. in 1.3% of the 450 cases of retinoblastoma reviewed by them,1 Mullaney et. al. (4.8% in 292 cases),2 Agarwal et. al. and other authors. Sterile orbital cellulitis in RB is postulated to arise from an immune response to high grade necrotic tumours that outgrow their blood supply.

An orbital cellulitis-like presentation of retinoblastoma may be misdiagnosed to be an extraocular extension or due to an infective etiology, leading to improper medical treatment and delay in beginning appropriate treatment.

Purpose is to study the clinical and histopathological features, management, and outcomes of retinoblastoma (RB) presenting with preseptal/orbital cellulitis at a tertiary eye care centre in a 5 year period.

MATERIALS AND METHODS

A retrospective review of all cases that presented with retinoblastoma to the outpatient department between April 2009 and March 2014 was carried out. IRB approval was obtained. Patients that presented with preseptal cellulitis/orbital cellulitis were studied for demographic, clinical, radiological and histopathological features. Patients with definite clinical and radiological extraocular retinoblastoma were excluded.

All patients underwent evaluation under anaesthesia for anterior segment, IOP and examination of the retina (where possible) for 360° up to the periphery after which the tumour was graded according to the International Classification for Intraocular Retinoblastoma (ICIOR) where applicable. A computerised tomography (CT) scan of the orbits (2 mm cuts in coronal and
axial planes) was requested in all cases and tumour characteristics, specially optic nerve thickening or breach in the ocular coats was documented. Patients with severe orbital inflammation evidenced clinically or on CT scan were administered intravenous Dexamethasone prior to enucleation. Based on the presence of histopathological high risk features, adjuvant chemotherapy and radiotherapy was administered. Statistical analysis was carried out using the SPSS-12 software.

RESULTS

Out of the 551 patients with RB that were reviewed from April 2009 to March 2014, 51 eyes of 40 (7%) patients presented with preseptal/orbital cellulitis. Eleven cases had bilateral disease while 29 had features only in one eye. Majority of the cases were females (n=24, 60%) with a mean age at diagnosis of 33 months.

Of the 51 eyes analysed, 32 (63%) had advanced disease at presentation and belonged to Group E ICIOR. Most cases (14) were classified as cT3b using the TNM classification i.e. associated with the presence of tumour associated neovascular or angle closure glaucoma, tumour extension into the anterior segment or with hyphaema or vitreous haemorrhage.

On studying the CT/MRI films, orbital/optic nerve involvement was seen in 12 (24%). Patients with gross extraocular and intracranial extension of tumour i.e. 7(14%) eyes were excluded form being classified as those presenting with sterile cellulitis.

Twenty seven eyes underwent primary enucleation. Of these, 11 showed the presence of high risk features. Four enucleated eyes had post laminar or massive choroidal involvement thus falling under stage pT3a and 1 had evidence of both (pT3b). In 5 eyes with high risk factors, tumour invasion was present at the surgical resection line in the optic nerve.

One patient each had regional lymphadenopathy, single and multiple non CNS metastatic foci at the time of presentation.

A total of 37 (93%) patients received intravenous chemotherapy in the form of neoadjuvant, adjuvant therapy or both (n=5). Five of these cases with tumour upto surgical line of resection also received additional adjuvant radiotherapy. At a mean follow up of 25 months, 11 (28%) patients died due to the disease. All 24 eyes in which the globe could be salvaged retained some vision (> perception of light and projection of rays).

DISCUSSION

Retinoblastoma that most commonly presents with leucocoria may rarely present as orbital cellulitis. The pathogenesis of this response may be
multifactorial as has been proposed by various authors. Shields et al. have suggested that the inflammatory signs could be secondary to a necrotic tumor that outgrows its blood supply, or that the tumor in one eye induces an immune response, which may lead to necrosis of the tumor in the fellow eye. Meir et al. and Haik et al. have suggested anterior segment involvement with necrosis of the iris and ciliary body as a trigger for inflammation in adjacent orbital soft tissues. Tumor necrosis with leakage of necrotic products has been suggested as a mechanism by Mullaney et al. Prause et al. correlates the occurrence of orbital cellulitis in retinoblastoma without extraocular extension with the invasion of tumor cells into the subretinal pigment epithelial space and choroid; the retinoblastomas which fail to express a Fas receptor signal then result in marked invasion of cytotoxic T-cells causing marked uveal effusion and orbital cellulitis, while the retinoblastomas that express a strong Fas receptor signal induce apoptosis of the invading cytotoxic T-cells, resulting in B-cell driven low-grade inflammation.

Compared to previous studies, the present study consists of a large cohort of patients presenting with cellulitis. Of the 260 patients with retinoblastoma retrospectively reviewed at a tertiary eye care centre by Walinjkar et al., 14 presented with orbital cellulitis. Five out of the 9 patients that received systemic steroids prior to enucleation underwent prompt resolution of inflammation. The present study also documented the role of intravenous dexamethasone administered prior to enucleation in aiding the surgery. Post enucleation chemotherapy and EBRT was administered in 5 of 9 cases due to the presence of high risk histopathological characters. In our study, EBRT was administered in 5 patients that had tumour positivity at the surgical line of resection on histopathology.

The authors concluded that advanced tumours with anterior segment involvement may present as orbital cellulitis. This study also highlights the prompt resolution of inflammation aiding enucleation. On histopathological examination of 4 patients reported by Agarwal et al. that presented with orbital cellulitis, all eyes showed anterior segment involvement with extensive necrosis. This is in contrast with the current study. One case had a well differentiated tumor and one showed extraocular extension of the tumor. In our patients with orbital inflammation, MRI and CT scans showed periocular soft tissue swelling with indistinct fascial planes, which appear hyperintense on T2W images, consolidating the finding proposed by de Graaf and Chawla et al.

In a study by Mullaney et al., 12 RB patients of the 14 with preseptal cellulitis were alive without evidence of metastasis. The number of deaths due to
the tumour were higher in the present study. This could be attributed to a larger number of cases enrolled and also those with high risk features or metastasis. Compared to previous studies, a poorer prognosis was noted in the present study.

CONCLUSION
Preseptal/orbital cellulitis is a rare presenting feature and hence we propose that all children presenting with signs of orbital inflammation should have a complete ophthalmic examination including a fundus examination. In cases where the posterior segment is obscured, adequate and appropriate imaging should be carried out. Careful surgical dissection with administration of steroids prior to surgery can reduce the inflammation associated with the tumour. Since a poorer prognosis was observed, adequate adjuvant therapy as needed must be administered.

REFERENCES

Outcome and Histopathological High-Risk Features in Group D and Group E Retinoblastoma
Dr. Fairooz PM, Dr. Santosh G Honavar, Dr. Vemuganti Geeta Kashyap, Dr. Vijay Anand P Reddy
Retinoblastoma although a rare malignancy in general population, it is the most common childhood intraocular malignancy comprising of 4% of all pediatric cancers.1 The annual incidence of retinoblastoma is estimated
to be 1 in 20,000 population, 8000 reported cases/year. The main goal of retinoblastoma management is elimination of tumor locally and, prevent systemic spread. Outcome is encouraging in early disease with protocol-based management. Early diagnosis and treatment offers >98% survival. Survival depends on the clinical and histopathological risk factors present at the time of diagnosis. Eye salvage and outcome has been found to be poor in Group D eyes of International Classification of Intraocular Retinoblastoma (ICRB) and, dismal in Group E with associated risk of systemic metastasis. It is curable yet challenging. Recent paradigm shift in the management of RB has focussed on intraarterial chemotherapy. Histopathological risk factors in Group D and E eyes suggests that concurrent systemic chemotherapy may be indicated if eye salvage is considered in such eyes. It is estimated that 3001- 3376 children die annually due to this curable eye cancer. It is not uncommon in the developing countries where >50% of children presents with advanced retinoblastoma requiring enucleation. The indication of enucleation is, eyes belonging to group E; tumor occupying more than half of the globe, anterior chamber tumor seeding, secondary glaucoma, neovascular glaucoma and hyphema, necrotic tumor with secondary orbital inflammation, associated vitreous hemorrhage and hazy media precluding the visualization of the tumor.

**MATERIALS AND METHODS**

We retrospectively analyzed the records of all patients diagnosed as Retinoblastoma (RB) who were classified as Group D and Group E under International Classification of Intraocular Retinoblastoma (ICRB) at Ocular Oncology Services in a tertiary eye care center in India. Those patients less than 12 months of follow up were excluded form the study. The study was approved by the institutional review board and informed consent was taken from parents and guardians.

The data analyzed constituted demographic profile including patient age at diagnosis (in months), gender, hereditary pattern (familial/sporadic), laterality of involvement and the involved eye, symptoms and clinical manifestations. Metastatic work-up included cerebrospinal fluid (CSF) cytology and bone marrow (BM) biopsy. Computerized tomography (CT) and magnetic resonance imaging (MRI) reports were performed. All patients received 6 cycles of systemic intravenous chemotherapy where indicated. All group E eyes underwent minimal manipulation enucleation with implant including minimum 10 to 15 mm of optic nerve stump. Histopathological reports were evaluated for the presence of high risk factors including, anterior segment invasion, ciliary body invasion, massive choroidal invasion (≤ 3 mm), post laminar optic nerve invasion, combination of choroidal invasion with any degree of optic nerve invasion,
scleral invasion, extra scleral extension and, optic nerve transection involvement.

**Statistical analysis**

The clinical data was analyzed with respect to the main outcome measure—eye salvage and, systemic metastasis. The effect of each individual demographic factor, clinical variable and treatment modality on the final outcome was analyzed.

**RESULTS**

Of 1360 eyes of 929 patients evaluated, 743 (54%) were classified as Group D and, Group E eyes by the international classification. We included 642 eyes belonging to Group D (n=159, 12%) or Group E (n=483, 36%) in our study with a minimum follow up of 12 months. The mean age of presentation was 30 months (range, 2 months to 28 years; median, 24 months). Of which 60% were males and 40% females. The disease was unilateral in 317 eyes (49%) and bilateral RB in 319 (51%). Systemic chemotherapy was administered in 52% (n=82) in Group D and, 15% in Group E eyes as primary modality of management. Primary enucleation was performed in 64% (n= 307) in Group E and 45% (n=71) in Group E eyes. Neo adjuvant chemotherapy was done in 20% of Group E eyes prior to enucleation. Overall 80% (n=390) of Group E eyes underwent enucleation including those after failed systemic chemotherapy, compared to 53% (n=85) in Group D eyes. Eye salvage was 47% and 20% in Group E and Group D respectively.

Of the eyes that underwent enucleation, histopathological high-risk factors were present in 16% in Group D and, 35% in Group E (p<0.0001). The high risk factors identified in Group E and D eyes were compared as in Table 1. All the patients with high risk factors received 6 cycles of adjuvant chemotherapy. Seven patients developed orbital extension of intraocular

<table>
<thead>
<tr>
<th>Pathological high risk factors</th>
<th>Group E (%)</th>
<th>Group D (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Massive choroidal invasion</td>
<td>61 (45)</td>
<td>7 (50)</td>
</tr>
<tr>
<td>Retrolaminar optic nerve extension</td>
<td>41 (30)</td>
<td>3 (21)</td>
</tr>
<tr>
<td>Optic nerve transection</td>
<td>9 (7)</td>
<td>2 (14)</td>
</tr>
<tr>
<td>Extrascleral extension</td>
<td>10 (7.5)</td>
<td>1 (7)</td>
</tr>
<tr>
<td>Scleral invasion</td>
<td>17 (13)</td>
<td>1 (7)</td>
</tr>
<tr>
<td>Ciliary body invasion</td>
<td>18 (13)</td>
<td>11 (79)</td>
</tr>
<tr>
<td>Iris invasion</td>
<td>18 (13)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Angle invasion</td>
<td>14 (10)</td>
<td>0 (0)</td>
</tr>
</tbody>
</table>
retinoblastoma who were diagnosed to have Group D (n=1) and, Group E (n=6) who declined treatment and returned with advanced disease. Overall orbit retinoblastoma occurred 6% in both Group D (n=9) and Group E (n=28). Systemic metastasis occurred in 0.6% in Group D and 4.2% in Group E.

DISCUSSION
Despite the advances in the management of retinoblastoma, access to care and late diagnosis has been the major challenges. Although life salvage has been the primary goal in the management of retinoblastoma, eye salvage and vision salvage has been attempted with recent advances. However, mortality has been reported as high as 60% in developing countries because often, disease is detected and treated in advanced stage.\(^1,3\) The major cause of death in retinoblastoma is systemic metastasis.\(^6\) We evaluated the outcome of retinoblastoma in Group D and Group E retinoblastoma according to the International Classification of Intraocular Retinoblastoma.\(^5,7\) Eye salvage in Group D eyes has always been difficult in majority of cases, which may undergo enucleation subsequently due to treatment failure and or recurrence. Shields et. al. reported eye salvage of 48% and 25% with Group D and Group E eyes respectively.\(^8,9\) Similarly, we found that eye salvage was 47% and 20% in Group D and Group E eyes respectively with chemoreduction. Recently, targeted techniques like intraarterial chemotherapy has paved way for better eye salvage rate.\(^10,11\) However, eye salvage in Group E eyes was always dismal.\(^10\) Various authors have reported the clinical and systemic risk factors for systemic metastasis. This warrants enucleation in clinically high-risk disease to salvage life especially in Group E eyes. Often, without treatment most of these eyes advance to orbital extension and systemic metastasis. Of the 28 Group E eyes that developed orbital retinoblastoma, 6 had previously declined enucleation later presenting with orbital extension. We found high-risk features in 35% Group E eyes undergoing enucleation as compared to 16% in Group D. massive choroidal invasion (45%) was the most common pathological high-risk feature identified followed by retrolaminar optic nerve extension (30%). Eagle et. al. found 18.5% eyes with high-risk features in 55 eyes undergoing enucleation.\(^12\) Kaliki et. al. evaluated 406 eyes and found 16.5% had pathological high-risk features.\(^13\) In the presence of histopathological high risk factors, there lies increased risk of systemic metastasis. Honavar et. al. reported metastasis in 24% patients with pathological risk factors without treatment. Addition of adjuvant chemotherapy in these patients reduces the mortality rate to < 4%.\(^6\) Despite treatment, systemic metastasis occurred in 0.6% in Group D and 4.2% in Group E in our series.
CONCLUSION

It is known that eye salvage in Group D and Group E retinoblastoma is low. Major challenge in the management of retinoblastoma is the advanced presentation leading to systemic metastasis and death. In advanced disease there is high risk of associated systemic metastasis and one third of enucleated Group E eyes have histopathological high-risk factors for metastasis.

REFERENCES

Adenoid Cystic Carcinoma of the Lacrimal Gland — Management and Outcome in 40 Patients

Dr. Fairooz PM, Dr. Santosh G Honavar, Dr. Kaustubh Mulay, Dr. Vemuganti Geeta Kashyap, Dr. Vijay Anand P Reddy

Henderson in his Mustarde’s lecture mentioned, “I fear adenoid cystic carcinoma of the lacrimal gland because I consider it the most evil of all primary neoplasms of the orbit”1. ACC of the lacrimal gland is an aggressive tumor with high mortality.1-17 Although relatively rare, it is the most common malignant epithelial tumor of the lacrimal gland accounting for about 2% of all orbital tumors, 5% of all primary orbital neoplasms and 29% of all epithelial tumors of the lacrimal gland.2,3,4,5

Several studies document local tumor recurrence ranging from 55-88% within 5 years after treatment of ACC with surgery coupled with external beam radiotherapy (EBRT).3-15 Complex regional anatomy and the proclivity for microscopic perineural, soft tissue, and bone infiltration makes it difficult to provide complete tumor clearance despite meticulous excision or orbital exenteration.17 Radical orbitectomy has been advocated by several authorities.18,19 This disfiguring surgery involves removal of orbital contents along with orbital bone. Comparison of survival rates for radical versus eye-sparing procedures has failed to demonstrate improved survival benefit.8,10,18,21-23 Because of these well-known limitations of surgical modalities, post-operative EBRT was advocated to reduce the risk of local tumor recurrence.17,23 However, the poor rate of local tumor control in these series suggests that EBRT is unable to favorably alter the course of the disease.3,5,17,23

Despite extensive surgery and EBRT, the systemic prognosis of these patients remains grim, with survival of less than 50% at 5 years and 20% at 10 years.1,3-6,21-25 The dismal systemic prognosis has been attributed to aggressive biological behaviour of this tumor and propensity to neural, hematologic and lymphatic invasion.1,3-6,14,26

ACC of the lacrimal gland has many similarities to malignant epithelial tumors of the parotid and salivary glands. They share common morphology, embryogenesis, and the biological potential for perineural invasion.17 Neoadjuvant chemotherapy with cisplatin for ACC of the salivary glands combined with surgical excision and EBRT has yielded some promising preliminary results.27,28 Meldrum et. al. reported the use of neoadjuvant intracarotid cisplatin and intravenous doxorubicin prior to exenteration followed by combined EBRT and chemotherapy and, noted improved survival in two patients.16 Recently, Tse et. al. reported the outcome of intra-arterial chemotherapy prior to exenteration and, followed by
Although the role of adjuvant chemotherapy in reducing the risk of systemic metastasis is not established.\(^5,16\)

The management of ACC of the lacrimal gland is still in evolution. It is apparent that there is no consensus yet on the relative role of various primary surgical procedures in providing local tumor control and adjuvant treatment modalities in improving patient survival. In this study, we analysed and compare the treatment outcome in 3 groups, Group 1 (surgery + radiotherapy), Group 2 (surgery + radiotherapy + adjuvant chemotherapy), Group 3 (neoadjuvant chemotherapy + surgery + radiotherapy + adjuvant chemotherapy).

**MATERIALS AND METHODS**

The study involved a retrospective review of medical records of all consecutive patients with adenoid cystic carcinoma (ACC) of the lacrimal gland managed at a tertiary care center in Southern India from January 1993 to December 2013. Of 1160 biopsy proven orbital tumors managed during the study period retrieved from the orbital tumor database, 40 consecutive cases of ACC were included. Cases with follow up less than 24 months were excluded.

The clinical variables studied included age, gender, presenting symptoms, duration of symptoms before diagnosis, presenting signs, radiological features, methods of treatment, local recurrence, interval to local recurrence, presence and location of systemic metastases, interval to systemic metastasis, and outcome at final follow up.

Management of ACC has evolved over time in our clinical practice. Initially, surgery (complete tumor excision or orbital exenteration) followed by EBRT was the primary management (Group 1). Complete excision was performed in case of well-defined tumors, if extensive and diffuse, an orbital exenteration was performed. If orbital exenteration was planned, a trans-septal incisional biopsy was first performed to confirm the diagnosis. Surgery was followed by EBRT 4-6 weeks later. Addition of adjuvant chemotherapy to surgery and EBRT was the next evolution in our clinical practice (Group 2). Typically, 6 cycles of chemotherapy was provided with a combination of Cisplatin + 5FU following surgery and EBRT. Use of neoadjuvant chemotherapy to achieve chemoreduction, followed by surgery, EBRT and adjuvant chemotherapy is our current practice (Group 3). Neoadjuvant chemotherapy included 3 to 4 cycles of Cisplatin + 5FU at 3 weekly interval. The decision to perform tumor excision or orbital exenteration was governed by the appearance of the tumor on computed tomography scan. Excision was performed in cases where the tumor appeared well defined on computed tomography scan without apparent
involvement of the contiguous orbital soft tissues or bone. Orbital exenteration was planned in patients with diffuse tumor involving contiguous orbital structures. Tumor excision was performed by the lateral orbitotomy approach, avoiding bone cut where possible. Tumor was excised en-bloc along with the overlying periorbita. Orbital exenteration was of the eyelid sparing type with transverse blepharorrhaphy to cover the exenterated orbit. In cases where the orbital bone was found clinically or radiologically involved, the involved portion of the bone was resected during tumor excision or orbital exenteration and the defect was reconstructed as appropriate.

Adjuvant EBRT was provided 4-6 weeks following tumor excision or orbital exenteration. Field of EBRT comprised the entire orbit, superior orbital fissure and the cavernous sinus in all cases and contiguous areas if involved, plus 10 mm margin all around. Fractionated dose of 4500 to 5000 cGy was administered.

Adjuvant chemotherapy was provided to minimise the risk of systemic metastasis. It included a combination of Cisplatin + 5FU for a total of 6 cycles (after adjusting for the cycles of neoadjuvant chemotherapy if received) administered at 3 weekly interval following completion of surgery and EBRT.

The histopathological features studied included the predominant histologic pattern (Swiss cheese [cribriform], sclerosing, basaloid [solid], comedocarcinomatous and tubular [ductal]), mitotic count per 20 high power fields (40x), and the presence of necrosis, hemorrhage, and neural, intraosseous, vascular, leptomeningeal or optic nerve invasion. The surgical specimens were formaldehyde fixed and paraffin embedded, and the preparations were stained with hematoxylin and eosin. The slides were re-evaluated by an experienced ophthalmic pathologist who was masked to the clinical details of the patient.

Local tumor recurrence and systemic metastasis were the main outcome measures. Kaplan Meier analysis was performed for cumulative probability of survival without local tumor recurrence and systemic metastasis at different time points until 10 years following primary treatment.

RESULTS

Of 1160 biopsy proven orbital tumors and 167 (14%) lacrimal gland tumors managed in the study period, we found 40 consecutive cases of adenoid cystic carcinoma comprising about 3% of all orbital tumors and 24% of all lacrimal gland tumors. The mean age at presentation was 36±35 (median= 13; range=11-72) years There were 4 patients under 16 years of age. There were 26 male (65%) and 14 female (35%) patients. None of the cases were bilateral.
Protrusion of the eye was the major symptom (36 patients, 90%) while 10 (25%) had diminution of vision, 7 (18%) reported pain and 4 (10%) had displacement of the eye. The mean duration of symptoms before presentation was 7.6 + 10.8 (range 0.3 –46.7) months.

The primary management was surgery with adjuvant EBRT in 12 (30%) patients (Group 1), surgery with adjuvant EBRT and chemotherapy in 8 (20%) patients (Group 2), and neoadjuvant chemotherapy followed by surgery, adjuvant EBRT and adjuvant chemotherapy in 20 (50%) patients (Group C). Overall, chemotherapy was used in 28 (70%) patients. Primary surgery comprised of en-bloc tumor excision in 36 (90%) or orbital exenteration in 4 (10%)

The predominant histologic pattern was cribriform in 27 (67.5%), tubular in 5 (12.5%), basaloid in 5 (12.5%), sclerosing in 3 (7.5%), and comedocarcinomatous in none. The median follow up after completion of treatment was 60 (mean, 58±26; range, 29 to 180) months. Local tumor recurrence occurred in 10 (25%) patients at a median of 23 (mean, XX±XX; range, XX to XX) months after primary treatment. On subgroup analysis, local tumor recurrence occurred in 5 (43%), 2 (25%), and 3 (15%) patients in Group 1, 2 and, 3 respectively. Local recurrence was managed by cranio-orbital resection + EBRT + chemotherapy in 3, excision + after-loaded brachytherapy + chemotherapy in 3, excision + chemotherapy 2, and, orbital exenteration + chemotherapy in 2. All of them remained regressed at the last follow up. Overall, 34 (85%) patients had eye salvage while 6 (15%) underwent orbital exenteration. Final visual acuity was >20/40 in 23 (58%).

In all, systemic metastases occurred in 10 (25%) patients at a median of 28 (mean, 43±52; range, 12 to 120) months following primary treatment, 6 to the brain and 3 to the lung. Nine patients with systemic metastasis had

<table>
<thead>
<tr>
<th>SI No.</th>
<th>Features</th>
<th>Median follow up (months)</th>
<th>Total no. of eyes (Group 1+ Group 2 + Group 3) n=40 (%)</th>
<th>Group 1 (Surgery + RT + Chemo) n=12 (%)</th>
<th>Group 2 (Surgery + RT) n=8 (%)</th>
<th>Group 3 (Chemo+ Surgery+ RT+ Chemo) n=20 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Exenteration</td>
<td>24</td>
<td>6 (16)</td>
<td>4 (33)</td>
<td>1 (13)</td>
<td>1 (5)</td>
</tr>
<tr>
<td>2</td>
<td>Eye salvage</td>
<td>60</td>
<td>34 (84)</td>
<td>8 (67)</td>
<td>7 (87)</td>
<td>19 (95)</td>
</tr>
<tr>
<td>3</td>
<td>Vision salvage</td>
<td>60</td>
<td>24 (60)</td>
<td>6 (50)</td>
<td>4 (50)</td>
<td>14 (70)</td>
</tr>
<tr>
<td>4</td>
<td>Local tumor recurrence</td>
<td>60</td>
<td>10 (25)</td>
<td>5 (43)</td>
<td>2 (25)</td>
<td>3 (15)</td>
</tr>
<tr>
<td>5</td>
<td>Systemic metastasis</td>
<td>30</td>
<td>10 (25)</td>
<td>8 (67)</td>
<td>1 (13)</td>
<td>1 (5)</td>
</tr>
<tr>
<td>6</td>
<td>Mortality</td>
<td>36</td>
<td>6 (15)</td>
<td>5 (42)</td>
<td>1 (13)</td>
<td>0 (0)</td>
</tr>
</tbody>
</table>
undergone primary tumor excision with EBRT, 2 of them had received adjuvant chemotherapy and one had received neoadjuvant chemotherapy. Seven patients with local recurrence developed systemic metastases.

Six patients with systemic metastasis were managed by palliative chemotherapy, five of whom died while one was alive with metastasis at the last follow up. Three patients with orbital and limited intracranial extension of the tumour underwent orbitocranial excision and stereotactic radiotherapy, two of whom were tumor free at the last follow up. One patient was managed with chemotherapy + EBRT, who was alive with metastasis at the last follow up. Death due to systemic metastasis occurred in 6 (15%) overall, 42% (5 of 12) in Group 1 and 13% (1 of 8) in Group 2.

**DISCUSSION**

ACC of the lacrimal gland is a rare tumor. Billroth gave an early detailed description of the tumor. 1 Complete surgical cure is difficult to achieve due to the infiltrative nature of the tumor, early perineural invasion, soft tissue infiltration, and bone involvement. 3,17,25 Not surprisingly, orbital exenteration, combined with radiation, and radical cranioorbital resection have not resulted in improved local tumor control or survival. 1-23 The tumor, considered a “treacherous neoplasm”, is characterised by high rates of local recurrence and systemic metastasis, and a dismal prognosis for survival.

Because of the relative rarity of ACC of the lacrimal gland, it is probably difficult to derive statistically significant conclusions from a single institutional cases series. Our series represents the pattern of presentation of ACC that is likely to be seen in a tertiary care referral centre. The mean age at presentation was 36 years in our study which is about a decade earlier than noted the literature. 8,9 Significantly, children comprised about 10% in our series. In a series by Esmaeli and associates, there was one patient under 16 years of age (5%)10 and in a series by Wright and associates there were 3 (7.9%). 8 There was a male preponderance in our study similar to a report by Wright and associates. 8 However Esmaeli and colleagues noted a female preponderance in their study.10

The mean duration of symptoms of about 9 months in our series is comparable to the data reported by Wright and associates 8 (7.6 months), and Lee and associates 9 (10.4 months in men and 9 months in women). The most common symptom was protrusion of the eye in 90% of our patients, similar to a report by Lee and associates who noted it in 92% of their patients. 9 The other common symptoms were diminution of vision in 10 (25%) and pain in 7 (18%) in our series. Pain has been cited as an important presenting feature of adenoid cystic carcinoma and may indicate perineural spread. 8 Wright and colleagues noted that pain was the most common
symptom\textsuperscript{8} while 58\% of patients in a series by Lee and associates reported pain as a major symptom.\textsuperscript{9} However in our study, pain was present in only 7 patients.

There is no established protocol for surgical management of ACC of the lacrimal gland. The primary management for these tumors for many years involved tumor excision alone. Removal of the adjacent bone was attempted in recurrent tumors.\textsuperscript{16,21} Reese and Jones proposed removal of the lateral orbital wall and the orbital rim along with orbital exenteration but this procedure did not significantly improve systemic prognosis.\textsuperscript{18} Radical surgery involving orbital bone resection was not routinely performed due to the high risk of meningitis and death.\textsuperscript{1} Murray and colleagues proposed cranio-orbital resection for primary orbital disease.\textsuperscript{19} We performed tumor excision for a majority of patients and orbital exenteration was reserved for massive infiltrative tumors. If there was clinical or radiological involvement of the bone, the involved portion was resected. All the patients with local recurrence had undergone tumour excision with adjuvant external beam radiotherapy and 5 of them had received adjuvant chemotherapy. Ten (25\%) of the patients had local recurrence, of whom seven developed systemic metastases. Of the 6 patients who underwent exenteration, only one (5\%) belonged to Group 3. This is in contrast to 4 (33\%) in Group 1 and 1 (13\%) in Group 2. Vision salvage (>20/40) was 50\% (6 of 12) in Group 1, 50\% (4 of 8)) in Group 2, and 70\% (14 of 10) in Group 3.

The role of adjuvant EBRT for microscopic residual tumor remains debatable. In our series 36 (90\%) patients received adjuvant EBRT of whom 7 (19\%) developed local tumor recurrence and 9 (25\%) developed systemic metastasis. Lee and associates reported that 88\% of their patients received adjuvant EBRT with apparently no beneficial effect on patient survival 9 Wright and associates treated 25 patients with extensive infiltration or tumors extending outside the orbit with EBRT with or without tumor resection. 8 They observed that tumor excision combined with EBRT significantly delayed local tumor recurrence and was associated with longer survival compared to the group that received EBRT alone. Esmaeli and associates used EBRT in 16 patients in their series, all of whom had perineural invasion. The median survival of these patients was lower (18 months) compared to the entire cohort (25 months). Neutron beam therapy may be potentially useful for these tumors but has several complications.\textsuperscript{22}

Chemotherapy has not been extensively used in the primary management of ACC of the lacrimal gland. However, chemotherapeutic agents like cisplatin and doxorubicin have been tried in the management of malignant epithelial tumors of the parotid and salivary glands.\textsuperscript{5,16,17,27,28} Systemic chemotherapy often fails to deliver therapeutic concentration to the target area. In contrast,
intra-arterial delivery achieves a higher drug concentration in the target area while minimizing systemic side effects. The new treatment protocol involving neo adjuvant preoperative intracarotid chemotherapy, orbital exenteration, post-operative radiation, and post-operative adjuvant chemotherapy has shown promising results. Meldrum and colleagues reported on the favourable outcome of neoadjuvant chemotherapy using cisplatin and doxorubicin in 2 patients in the treatment of advanced ACC of the lacrimal gland. Both the patients subsequently underwent orbital exenteration and achieved a long-term survival of 9.5 and 7.5 years respectively.

Theoretically, adjuvant chemotherapy following surgical management may have the potential to eradicate occult micrometastasis and help improve patient survival. Lee and associates reported the use of 5 fluorouracil in 1 patient. Font and Gamel reported on the use of an unspecified chemotherapy regimen in 5 patients, of whom 4 died within a year and the fifth survived 3 years before succumbing to the disease.

Of 28 patients who received adjuvant chemotherapy in our series, 2 (7%) developed local tumor recurrence and systemic metastasis and, three (11%) developed local tumor recurrence alone. Five (41%) out of 12 patients who did not receive adjuvant chemotherapy developed local tumor recurrence and 8 (67%) developed systemic metastasis. It is not clear if adjuvant chemotherapy has a protective role in preventing recurrence and metastasis. From the data available for our analysis, it does not appear that more advanced cases were preselected for adjuvant chemotherapy. Perhaps adjuvant therapy may have limited role in improving prognosis in patients with ACC of the lacrimal gland.

A detailed analysis of the histopathology was performed by an experienced ophthalmic pathologist who was masked from the clinical details of the patients. The cribriform pattern was predominant (65%). Four (13%) of these patients developed local recurrence. The presence of a basaloid pattern has been associated with a poor prognosis in ACC of the lacrimal gland and the salivary gland. Wright and associates noted that >50% basaloid differentiation was associated with local tumor recurrence and a reduction in the estimated disease free survival. However Lee and colleagues did not find any association between the basaloid pattern and survival. They found that lower tumor grade and a predominantly Swiss cheese pattern was associated with a longer survival. In our series, all 5 patients with > 50% basaloid pattern developed local recurrence, with 3 of them developing systemic metastasis. This may indicate a pattern of increased aggressiveness of the tumor in relation to the proportion of basaloid differentiation.

ACC of the lacrimal gland is characterised by a high rate of local tumor
recurrence. Our recurrence rate was 25% (Group 1, 50%; Group 2, 25%, Group 3, 10%) at a mean of 23 months following primary treatment. Esmaeli and colleagues noted that 25% had local tumor recurrence at a median of 24 months. Wright and associates noted local tumor recurrence in 47.3% with a mean interval of 26 months. Font and Gamel noted that all their patients had local tumor recurrences at a mean interval of 3.5 years.

Overall systemic metastasis occurred in 25% (Group 1, 67%, Group 2, 13%, Group 3, 5%) in our series at a median of 28 months following initial treatment. Metastasis occurred 7 to the brain and 3 to the lung. Font and Game and Lee and associates reported systemic metastasis in 50% of cases, most commonly to the lung and lymph nodes. Esmaeli and associates noted systemic metastasis in 80% of their cases, most commonly to the lung, bone, and liver, and at a mean interval of 51 months.

ACC of the lacrimal gland is reported to have a dismal prognosis for survival. Esmaeli and colleagues reported that 65% of patients in their series died of the disease and the 10 year survival rate was 49%. Font and Gamel noted that 60% of their patients died with a mean survival of 5 years. Henderson reported 11 patients, (81.8%) of whom died at a mean interval of 3 years and 7 months following initial diagnosis. Our mean follow up was 58 months. At the final visit, 32(80%) patients were alive and well, 2(5%) were alive with systemic metastasis, and 6(15%) were dead with systemic metastasis.

Our series reiterates the aggressive nature of ACC of the lacrimal gland, high incidence of local tumor recurrence and systemic metastasis following tumor excision. We observed beneficial effect of multimodal therapy including neoadjuvant systemic chemotherapy, surgical excision, adjuvant chemotherapy and external beam radiotherapy in this limited series. A reliable answer to this important question, as well as the role of primary orbital exenteration are outstanding and may need a large series and a collaborative multicentric effort.

REFERENCES
VA. Adenoid cystic carcinoma of the lacrimal gland: Role of nuclear survivin (BIRC5) as a prognostic marker. *Histopathology* 2013;840-6.


