**Abstract**

Tumors of the lacrimal sac are rare but their recognition and early management are imperative as they are locally invasive and potentially life-threatening. Because of their rarity, large clinical studies with statistically significant data on the natural course, management and prognosis of these neoplasms are unavailable. Current practices are therefore based on a few case series and a small number of isolated case reports. Most tumors are primary and of epithelial origin (60-94%), of which 55% are malignant. Lacrimal sac tumors typically present with epiphora and a palpable mass over the medial canthus; thus often erroneously diagnosed as chronic dacryocystitis. A full history, clinical and diagnostic workup is essential in order to plan treatment – which is often multidisciplinary. Statistically significant associations have been shown with higher tumor staging and size with increased metastatic risk and lower survival rates. Management usually involves complete surgical resection with adjuvant radiotherapy and/or chemotherapy for malignant lesions. Long term follow up is required as recurrences and metastases can occur may years after initial treatment.**Introduction**

Tumors of the lacrimal sac are uncommon but potentially life-threatening. Only 73 cases had been published up to 1950 but with recognition and improved diagnostic modalities approximately 775 cases have been reported in the literature worldwide from 1930s to present day. Overall more than 55% (range 55-100%) of tumors are malignant, tend to be locally invasive and have a high recurrence rate.1-19 Local recurrence and mortality rates vary but correlate to tumor stage and size.20 Lacrimal sac tumors may be broadly classified into 4 categories: epithelial, lymphoproliferative, melanocytic and mesenchymal; with each category being further subdivided into benign and malignant. A handful of neural neoplasms have also been reported. The vast majority of tumors are, however, primary and epithelial.1-10, 13,15,17-18 Of the malignant tumors, close to 90% are of epithelial origin. In order of frequency, the benign lacrimal sac tumors include: squamous papilloma, transitional papilloma, fibrous histiocytoma, oncocytoma and hemangiopericytoma. The latter, however, can also exhibit borderline malignant features. Malignant tumors include: squamous cell carcinoma, lymphoma, melanoma, transitional cell carcinoma, mucoepidermoid carcinoma and adenocarcinoma; with melanoma and transitional cell carcinoma being associated with high fatality rates.3-10, 13, 15-18

The majority of lacrimal sac neoplasms present with symptoms typical of secondary acquired nasolacrimal obstruction, including epiphora with a medial canthal mass and thus often misdiagnosed as dacryocystitis. During dacryocystorhinostomy (DCR), an incisional biopsy of the lacrimal sac is essential for confirming the diagnosis, and may therefore guide adjuvant treatment.4-20

**Clinical features, assessment and diagnostic evaluation**

Benign epithelial and mesenchymal tumors tend to present in younger adults whereas malignant tumors typically occur in the fifth decade with age ranges quoted from 22 to 94 years.2-20 Although there is no significant race or gender predilection for lacrimal sac tumors, 3 case series have reported a female preponderance of >70%.

Most lacrimal tumors insidiously present with signs and symptoms associated with chronic dacryostenosis or dacryocystitis. Hence, the initial diagnosis is often erroneous and patients’ tumors are diagnosed on lacrimal sac biopsy taken after a recurrence of their ‘dacrocystitis.’ Most commonly patients complain of unilateral epiphora (though bilateral involvement has also been noted) and a palpable mass in the lacrimal sac area. Tears may also be blood-stained. However, cardinal signs that would flag malignancy ‘until proven otherwise’ include: palpable, firm, incompressible, immobile mass above the medial canthal tendon; chronic dacyrocystitis which irrigates or partially irrigates; and sanguineous reflux on irrigation. Other features may include: epistaxis; non tender mass (whereby the benign tumors may still freely allow irrigation whereas carcinomas usually cause complete obstruction); proptosis or non-axial globe displacement occurs late with lacrimal sac tumors that have invaded the orbit; telangiectasia or overlying skin ulceration; and/or regional lymphadenopathy (preauricular, submandibular or cervical). Distant metastases are rare (reported range, 1-22%). 2-20

In all cases of lacrimal sac mass with epiphora, a complete workup comprising: a detailed history, full ophthalmic exam with lacrimal probing, irrigation and examination of the nose. It is appreciable, however, that a definite tumor mass may not be palpable in the early stages, and hence it is clinically difficult to differentiate from chronic dacryocystitis. Imaging is therefore essential in diagnostic evaluation of lacrimal sac tumors and chronic inflammatory conditions, which can masquerade neoplasms.3-18

Computerised tomography (CT) of orbits and sinuses would show a lacrimal sac mass and the extent of bony erosion and/or invasion into surrounding structures, including the paranasal sinuses. T1-and T2-weighted magnetic resonance imaging (MRI) sequences with gadolinium contrast would provide a superior tumor definition by delineating between a cystic/inflammatory or solid mass and also better definition of neighbouring soft tissue structures, including orbital fatty tissue. CT dacryocystography of the lacrimal drainage system would reveal a possible lacrimal sac filling defect due to a space-occupying lesion or delayed disappearance of contrast and show extent of obstruction. Radiological imaging is also valuable in postoperative follow up.5-10, 13, 15, 18

Fine needle biopsy and cytological assessment.

The role of fine needle aspiration biopsy (FNAB) in lacrimal sac tumors, and indeed lacrimal gland or orbital lesions, is controversial. In general, FNAB are reserved for particular suspected diagnoses – e.g. lymphomas –; to confirm malignancies that are unlikely to be completely excisable; or in cases where neither incisional or excisional biopsy is not possible. Interpretation of these FNAB can be difficult, and requires considerable experience in both ophthalmic pathology and cytology, and additional immunocytology or molecular diagnostics in some cases. Possible complications of FNAB include haemorrhage, infection, inadequate biopsy requiring additional incisional biopsy, and tumor seeding along the FNAB route.

If a lacrimal malignancy is suspected a full systemic workup is required, including further physical examination, hematological tests (complete blood count, routine biochemistry, lactate dehydrogenase, carcinoembryonic antigen) and CT chest and abdomen.

**Pathological features**

Lacrimal sac tumors can be simplified into epithelial and non epithelial subtypes. Epithelial tumors account for 60–94% of lacrimal sac tumors. Non epithelial tumors, as mentioned above, include: mesenchymal, lymphoproliferative, melanocytic and neural.2-19

*Epithelial tumors*: The lacrimal sac wall is lined by pseudostratified columnar epithelium containing goblet cells and cilia, i.e. the same as the upper respiratory tract. Epithelial neoplasms of the lacrimal sac are hence similar to those found in the upper respiratory system including the nasal and paranasal sinuses.1-4, 6-8, 15, 18 It has therefore been suggested that study of the natural history of nasal tumors, which are less rare than lacrimal sac tumors, would help ascertain the malignant potentials of their lacrimal sac counterparts where it is much harder to fully draw conclusions due their rarity.2 The histopathological classification of epithelial tumors has been summarised in Table 1.

Benign tumors are: papillomas (squamous, inverted, transitional cell or mixed/adenomatous), oncocytomas (~ 4% of all epithelial tumors; arise from oncocytes forming nests, chords or tubules), adenomas (~ 2%; glandular epithelium) and cylindromas (<1%).3-8, 10, 13-18, 21

Papillomas are the most common benign epithelial lesions reported (around 36% of all epithelial tumors), whilst the others are rare. They are believed to arise from pre-existing inflammation and their hyperplastic growth pattern may be exophytic (facing sac lumen) or endophytic (toward stroma of sac wall). Squamous papillomas show acanthotic, stratified squamous epithelium with dyskeratosis on a thickened basement membrane (Fig. 1A & 1B). They may arise from persistent irritation and thus cause squamous metaplasia. Transitional cell papillomas are polypoid lesions retaining their stratified columnar epithelium with goblet cells and cilia (Fig. 1C & 1D), whereas mixed cell papillomas exhibit features of both types. Papillomas have a tendency to recur (10-40%) particularly the endophytic or ‘inverted’ type, which also have a higher rate of malignant transformation. As cells undergo further de-differentiation/malignant degeneration they lose their cilia and ability to secrete mucus.1-8, 10-15, 18

Malignant epithelial lesions or carcinomas are thought to mainly arise *de novo* but can also arise from a pre-existing papilloma. Squamous cell carcinomas (well-differentiated with keratin pearls or poorly differentiated) are most frequently seen followed by transitional cell carcinomas (papillary growth pattern of cylindrical epithelial cells) and show cells with pleomorphic nuclei, prominent nucleoli, mitotic figures, inflammatory cell infiltrate and invasion/breach of the basement membrane. Other malignancies include: adenocarcinomas; oncocytic adenocarcinomas (large oncocytic cells, with nuclear atypia, arranged in an infiltrative pseudoglandular pattern); mucoepidermoid carcinomas (both epidermoid and mucus-secreting cells with mucin-filled spaces); poorly differentiated adenocarcinomas; cystic adenoid carcinomas (cribriform or basaloid pattern with aggregates of densely packed small malignant cells with hyperchromatic nuclei, and round cystic foci); and rarely basal cell carcinoma (Fig. 2). 1-8, 10-15, 18, 20-29

Carcinomas have been quoted to have a recurrence rate of around 50% and mortality of 37-100% (up to 100% in transitional cell carcinomas) despite treatment, with mortality increasing with recurrence. Lacrimal sac tumors most frequently spread by infiltration into neighboring structures. Spread via the lymphatics to the preauricular, submandibular or cervical lymph nodes has been demonstrated in less than a third of malignant cases and distant hematogenous metastases to lung and oesophagus in advanced cases. Metastases to the bone and skin have also been reported. 2-8, 10-15, 18, 20 Development of metastases was found to be associated with higher tumor staging and larger tumor size.19

The human *Papillomavirus* (HPV), notably low risk HPV-6, and-11, has been found associated with squamous cell papillomas whereas infection with high risk HPV-16 and-18 has been demonstrated in squamous cell carcinomas of the lacrimal sac. Hence HPV has been implicated as a cause of epithelial lacrimal sac neoplasms similar to cervical neoplasia.30-31

|  |
| --- |
| Benign: |
| Papilloma (squamous, transitional or mixed)  Oncocytoma  Adenoma (mixed tumor)  Cylindroma |
| Malignant: |
| Squamous cell carcinoma  Transitional cell carcinoma  Adenocarcinoma  Oncocytic adenocarcinoma  Mucoepidermoid carcinoma  Poorly differentiated adenocarcinoma  Adenoid cystic carcinoma  Basal cell carcinoma |

Table 1: Histopathological classification of epithelial tumors of the lacrimal sac.

*Non epithelial tumors:* These tumors are rare and constitute up to 25% of lacrimal sac tumors. Approximately 12-14% are mesenchymal tumors, such as: fibrous histiocytoma (most common type, mean age of patients 34 years; spindle-shaped fibroblasts and plump histiocytes); fibroma; hemangioma; hemangiopericytoma (10 cases reported in literature so far with unpredictable malignant potential; spindle-shaped pericytes surrounding prominent vascular channels with sinusoidal spaces); angiofibroma; lipoma (1 case; mature adipocytes separated by thin fibrovascular septae); juvenile xanthogranuloma (1 case); leiomyoma and osteoma. Malignant mesenchymal tumors include: Kaposi’s sarcoma and rhabdomyosarcoma (3 case reports).32-39

Lymphomas account for ~2-8% of lacrimal sac tumours, present in generally older patients (median age 71 years), may be primary but are mainly secondary due to systemic spread and should be suspected in leukemia (Fig. 3) or lymphoma patients presenting with epiphora and dacryocystitis. There are <70 primary cases and few case reports/series of secondary involvement.4, 7, 9-10, 13, 15, 18, 40-47 From the EORTC study of 15 primary lacrimal sac lymphoma cases, 33% of cases were classified as diffuse large B cell lymphoma (DLBCL; non-Hodgkin’s lymphoma), 33% as extranodal marginal zone B cell lymphoma of mucosa associated lymphoid tissue (MALT lymphoma), 20% were classified as transitional MALT lymphoma with features between MALT lymphoma and DLBCL, and 13% as unclassified B cell lymphomas.46 Other rarer malignant lymphoproliferative are granulocytic sarcoma and plasmacytoma. Benign reactive hyperplasia is also relatively uncommon.13, 15, 18

Malignant melanomas are very rare, exhibit similar features to mucosal melanomas and carry a poor prognosis, with metastatic potential, despite aggressive treatment measures (extensive surgical resection, radiotherapy and/or chemotherapy). They account for approximately 4-5% of lacrimal sac tumors. Melanomas arise from melanocytes in and below the epidermal lining of the lacrimal sac, and most are of epithelioid cell type. They can also represent secondary manifestations of conjunctival melanomas that have ‘seeded’ along the lacrimal drainage duct to the sac; hence, review of the ipsilateral conjunctiva is recommended in these patients. Only one case of a benign lacrimal sac nevus has been previously reported.4, 7, 9-10, 13, 15, 18, 48-49

Neural tumors of the lacrimal sac, such as: neurofibromas and neurolemmomas, are extremely rare (1%) with only 5 cases being reported in the literature.5, 9-10, 50

The major series of primary lacrimal sac tumors are summarized are in Table 2.

Secondary tumors of the lacrimal sac may arise by invasion from local structures including: the nose, paranasal sinuses, orbit, conjunctiva, skin; or as metastases. Metastases from cutaneous melanoma, hepatocellular carcinoma and even renal cell carcinoma have been described.51-54

Table 2: A review of the major case series of lacrimal sac tumors.

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | **Ashton et al. (1951)** | **Radnot et al. (1966)** | **Schenck**  **et al. (1972)** | **Ryan et al. (1973)** | **Flanagan et al. (1978)** | **Ni et al. (1982)** | **Stefanyszyn**  **et al.**  **(1994)** | **Yip**  **et al. (2002)** | **Anderson**  **et al.**  **2003** | **Parmar et al. (2003)** | **Jordan et al. (2004)** | **Sjo**  **et al. (2006; 2007)** | **Bi**  **et al. (2007)** | **Montalban et al. (2010)** | **Total** |
| **Epithelial benign** | 11 | 22 | 4 | 11 | 1 | 6 | 38 | 0 | 4 | 1 | 6 | 5 | 0 | 0 | 109 |
| **Epithelial malignant** | 27 | 64 | 14 | 16 | 2 | 71 | 44 | 0 | 4 | 8 | 4 | 6 | 83 | 6 | 349 |
| **Mesenchymal benign** | 30 | 5 | 1 | 0 | 0 | 1 | 15 | 0 | 0 | 1 | 0 | 0 | 3 | 0 | 56 |
| **Mesenchymal malignant** | 0 | 26 | 2 | 0 | 1 | 2 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 31 |
| **Lymphoid benign** | 0 | 1 | 0 | 0 | 1 | 0 | 2 | 0 | 4 | 0 | 4 | 0 | 0 | 0 | 12 |
| **Lymphoid malignant** | 5 | 14 | 0 | 0 | 0 | 1 | 9 | 11 | 10 | 5 | 9 | 15 | 5 | 1 | 85 |
| **Melanocytic benign** | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 |
| **Melanocytic malignant** | 0 | 5 | 3 | 0 | 0 | 0 | 6 | 0 | 0 | 0 | 0 | 0 | 3 | 0 | 17 |
| **Neural** | 0 | 0 | 1 | 0 | 0 | 1 | 1 | 0 | 0 | 0 | 0 | 0 | 2 | 0 | 5 |
| **Total**  (% malignant) | 73  (44) | 138  (79) | 25  (76) | 27  (59) | 5  (60) | 82  (90) | 115  (51) | 11  (100) | 22  (64) | 15  (87) | 23  (57) | 26  (81) | 96  (95) | 7  (100) | 665 |

**Management**

Treatment of lacrimal sac tumors depends on tumor type, malignancy, size, extension and the patient’s general health. The aim of treatment is complete tumor removal. Careful histopathological assessment is central in all cases to confirm diagnosis, tumor type and thus plan further treatment.2, 7, 9, 13, 15, 18, 51, 55-56

In cases where preoperatively unsuspected tumor is inadvertently found during routine dacryocystorhinostomy (DCR), which has been shown to be as high as 37%, a deep incisional biopsy is important to actually adequately sample tumor as peripheral/superficial chronic inflammation can masquerade underlying tumor. Where intraoperative frozen section or Mohs confirms tumor, then a dacryocystectomy without osteotomy (avoid spread of tumor cells into sinuses) is recommended. Frozen section assessment can confirm tumor type and help evaluate margin clearance. However, definitive therapy should be based on formalin-fixed paraffin embedded tissue rather than frozen section analysis alone. The patients should hence be informed that planned DCR (if no histological evidence of tumor) or reconstruction will take place on a later date. For benign epithelial or mesenchymal tumors confined to the lacrimal sac, a dacryocystectomy may suffice. In the case of malignancy, intact/*en bloc* tumor excision together with the periosteum of the lacrimal sac and nasolacrimal duct is advocated. Extension of premalignant and malignant lesions down the nasolacrimal duct is strongly believed to account for recurrences and treatment failure. For more advanced tumors, resection of the lacrimal drainage system with adjacent orbital and lateral nasal walls may also be required. However, if there is radiological evidence of tumor extension beyond the lacrimal drainage apparatus then more radical surgery, such as orbital exenteration, lateral rhinotomy/paranasal sinus resection and/or cervical lymph node dissection may be necessary. Eyelid sparing extensive surgical resection with postoperative radiotherapy has also been described for small epithelial malignancies and found to achieve similar survival outcomes to those treated with orbital exenteration.2, 7, 9, 13, 15, 18-20, 51, 55-56

Postoperative radiotherapy (especially if bony and/or lymphatic invasion, or neoplastic cells at surgical margins) or chemotherapy may be indicated for tumor clearance and minimise recurrence risk. Irradiation at 50-60 Gy is recommended for malignant epithelial tumors. Recurrent lesions may require further surgery and radiotherapy. In certain cases, radiotherapy may be palliative.7, 9, 13, 15, 18, 51

Lacrimal sac lymphoma or leukemic infiltration should be suspected in any patient with systemic lymphoma or leukemia presenting with epiphora and/or mass above the medial canthal tendon. Treatment is usually a combination of surgery, irradiation and /or chemotherapy (notably regimens involving chlorambucil and rituximab), but no commonly agreed treatment regimen for periocular lymphoma exists because of the limited number of cases seen.40-47

In summary, successful management of lacrimal sac tumors requires: 1) a high index of suspicion as these potentially fatal tumors are rare and often misdiagnosed as dacryocystitis until the lesion progresses and/or detected by histopathological or cytological assessment; 2) early and appropriately aggressive intervention, and 3) careful long-term monitoring. Although previous investigators have advocated lacrimal sac biopsy routinely in all DCRs performed, it is important for the surgeon to carefully inspect the sac intraoperatively to prevent missing a neoplasm. For lacrimal sac malignancies, a multidisciplinary approach is imperative for treatment planning and approach. Patients need to be carefully counselled about possible post-surgical scarring, disfigurement and risks of radiotherapy and/or chemotherapy toxicity. Long term, even lifetime, follow up is required as recurrence and/or metastases can still occur many years after primary management.

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**Figure legends:**

Fig.1: Histological examination of lacrimal sac papillomas.

A) Squamous cell papilloma (H&E x4, black lines indicating area of interest); B) Higher magnification of area of interest showing squamous cell papilloma (H&E x20); C) Transitional cell papilloma (H&E x2); D) Transitional cell papilloma (H&E x10).

Fig. 2: Basal cell carcinoma (BCC) of the lacrimal sac.

A) H&E x10; B) H&E x20 with black arrows showing a BCC with a nodular growth pattern.

Fig. 3: Chronic lymphocytic leukemia infiltration of the lacrimal sac.

A) Diffuse lymphocytic infiltrate showing intermediate-sized cells with prominent nucleoli (H&E x20); Immunohistochemistry (3,3'-Diaminobenzidine [DAB] x20) showing B cells with positive staining for: B) CD5; C) CD20 and D) CD23.