Orbital metastases: diagnosis and course

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Abstract

***Aims*—Three issues were investigated in adult outpatients with orbital metastases. One, how accurate are current diagnostic methods? Two, what is the survival associated with orbital metastases? Three, did any clinical factors correlate with prognosis in this patient cohort?**

***Methods*—Retrospective analysis of patients with orbital metastases managed in an ocular oncology unit.**

***Results*—11 of 31 (35%) patients had no known primary malignancy at the time of orbital diagnosis. In eight of 31 (26%) computed tomography and/or magnetic resonance imaging data did not yield the diagnosis of metastases. In 15 of 17 (88%) cases a fine needle aspiration biopsy was diagnostic. Several types of therapy were used. The median survival was 1.3 years.**

***Conclusion*—Orbital metastases, even with newer diagnostic techniques can be difficult to diagnose. Management was based on location and extent of both orbital and systemic disease as well as vision. In most cases, orbital symptoms were palliated; however, survival was dismal. No clinical factor correlated with prognosis.**

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Orbital metastases are an infrequent aetiology of adult proptosis; approximately 3–7% of orbital biopsies have domonstrated a metastatic tumour, and this diagnosis is often unexpected.[1–5] Metastatic orbital deposits are less common than uveal metastases; in several series the relative incidence was approximately one to eight.[4 6 7] In both sites, a metastatic tumour may present with ophthalmic symptons before the discovery of the primary neoplasm; this more common with lung, gastrointestinal, thyroid, and renal carcinomas.[4 5] In contrast, as many as 90% of breast cancers that metastasise to ocular structures have had treatment for the primary tumour.[1 5 8]

A number of advances have occurred in the evaluation of patients with possible metastatic disease including newer imaging strategies, increased use of fine needle aspiration biopsies (FNAB), serological studies, and the application of molecular biology techniques to detect tumour.[9] Despite these advances, several investigators have pointed out limitations of extensive medical evaluations for patients with a tumour metastatic from an unknown primary site.[10] Patients who present with systemic metastases, before detection of a primary lesion, are uncommon. In one series, patients with an unknown primary tumour accounted for approximately 2% of all oncology referrals; in other reports the incidence was between 2% and 15%.[10] The identification of a primary site does not significantly alter either therapy or prognosis, with the exception of lymphoma and possibly breast and uterine carcinoma.[10] Similarly, while in a few isolated malignancies alteration in metastatic management has markedly improved survival, this is not the case for most metastatic orbital tumours.[11]

Methods

We retrospectively reviewed the ocular oncology database at the University of California, San Francisco, for outpatients managed from 1976 to 1995 in whom the diagnosis of orbital metastases was established. Hospitalised patients with widespread disease, noted to have incidental orbital metastases, were excluded from this analysis. Records from 36 adult outpatients with metastatic orbital tumours were found; however, adequate data were only available in 31 cases. All charts, radiological scans, pathological materials, and death certificates were reviewed. All patients had either computed tomography (CT), magnetic resonance (MR), or both types of imaging studies.

Results

There were 15 males and 16 females, with a median age of 57 years (range 37 to 77 years). The racial distribution was five black, one Asian, and 25 white patients.

In these adult outpatients, 11 of 31 (35%) patients had no known primary lesion at the time of ocular diagnosis (Table 1). After either cytological or histological orbital diagnosis, five of these 11 patients had a presumptive primary site retrospectively established (one each of renal, lung, probable breast, and contralateral salivary gland carcinoma, and one cutaneous melanoma <0.05 mm thick). In the latter two cases, history established the primary site; both had had systemic tumours in the distant past with a low likelihood of metastases. In two other cases, medical evaluation was able to establish a primary site (renal cell carcinoma and lung cancer). One patient with breast cancer had that tentative diagnosis established on the basis of special histological stains. In six patients (19%), the primary site was not identified.

The predominant orbital symptoms at presentation are shown in Table 2. Most commonly, patients presented with diplopia (48%); less frequently proptosis (26%) and decreased vision (16%). Pain was also noted in six cases. Three patients had a secondary complaint of ptosis.

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Table 1 History of systemic malignancy at orbital diagnosis

Unknown	11
Breast carcinoma	8 (1 male)
Cutaneous melanoma	5
Uveal melanoma	2
Prostate cancer	2
Carcinoid	1
Liposarcoma	1
Stomach	1

Table 2 Predominant symptom at presentation

Diplopia	15
Proptosis	8
Decreased vision	5
Red eye	1
Photophobia	1
Multiple simultaneous	1

*Six patients also complained of headache or pain

Table 3 Imaging patterns

Intraconal diffuse	6
Muscle only	7
Intraconal focal	6
Extraconal	4
Bone plus mass	4
Other	4

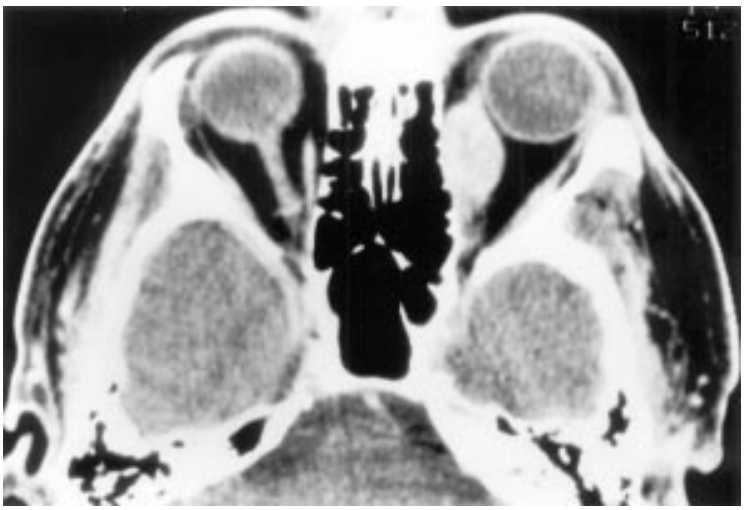

Figure 1 Focal area of muscle enlargement is a typical radiological finding in some orbital metastases. This is noted on axial computed tomography.

Figure 2 Bony destruction contiguous to an orbital mass is a finding often seen orbital metastases in contrast with most benign orbital tumours. This is shown on a parasagittal computed tomography reconstruction.

Imaging studies (CT, MRI, or both) combined with subjective data were not diagnostic in eight cases (26%). In these cases metastases were not on a short list of differential diagnoses. Thus, even with modern non-invasive diagnostic tests there was a significant false negative diagnostic rate for the detection of a metastatic aetiology of these orbital lesions. In the other 23 cases the diagnosis of a metastasis, based on both subjective and objective data, was high on the differential diagnosis, although not always the primary thought. We did not find a single instance in which MR data were superior to CT to establish the diagnosis of metastases. While a number of these cases were not studied with a complete panoply of CT and MRI techniques, seven diagnostically difficult cases have been investigated in that manner without obtaining a more definitive diagnosis using high quality MR technology. The imaging patterns are listed in Table 3. Several patterns were thought to be very typical for orbital metastases, especially with a history of a systemic malignancy. These included intramuscular focal masses (Fig 1), bone destruction plus contiguous mass (Fig 2), and diffuse intraconal lesions (Fig 3). An atypical pattern for an orbital metastasis, a focal, discrete, solitary tumour, is shown in Figure 4. While metastases can produce this pattern, on a statistical basis this imaging picture is much more commonly the result of a benign mesenchymal tumour. No symptomatology or imaging pattern of orbital metastases was associated with prognosis.

The diagnosis was established in 15 cases by FNAB. In two of the 15 cases (13%) FNAB was negative (one scirrhous carcinoma and one small, fibrotic lung cancer at the orbital apex). In 11 cases an open biopsy was performed as the initial procedure. Usually an open biopsy was performed if the correct diagnosis was not suspected when a focal mass was present or if metastasis was to be therapeutically debulked regardless of the histology. Five patients had a sufficiently diagnostic pattern or, in one case, a previous biopsy at another institution obviating the need to obtain orbital histology.

In two cases there was simultaneous detection of intraocular metastatic disease; one had a combined intraocular and orbital metastasis while the other patient had bilateral choroidal lesions and a solitary orbital mass. No patient had bilateral orbital disease detected at diagnosis.

In three of the seven women with breast carcinoma the orbital disease was the first sign of dissemination; all three had high risk malignancies. In two of the three, concurrent simultaneous other metastases were noted as a result of medical evaluation for the orbital findings.

Several therapeutic options were used. Tumour debulking was used in four settings: (1) in patients who were thought to have a primary orbital tumour; (2) in two patients who refused FNABs; (3) in a few patients with decreased vision as a result of optic nerve compression, a debulking procedure was used to decompress the nerve with good temporary results; (4) in a few other cases where there appeared to be

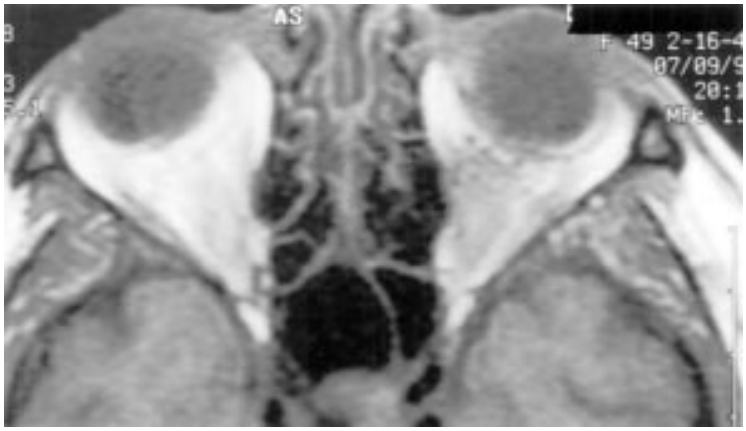

Figure 3 In an older patient, diffuse intraconal lesions are commonly due to metastases. This axial magnetic resonance scan demonstrates diffuse infiltration of the intraconal area.

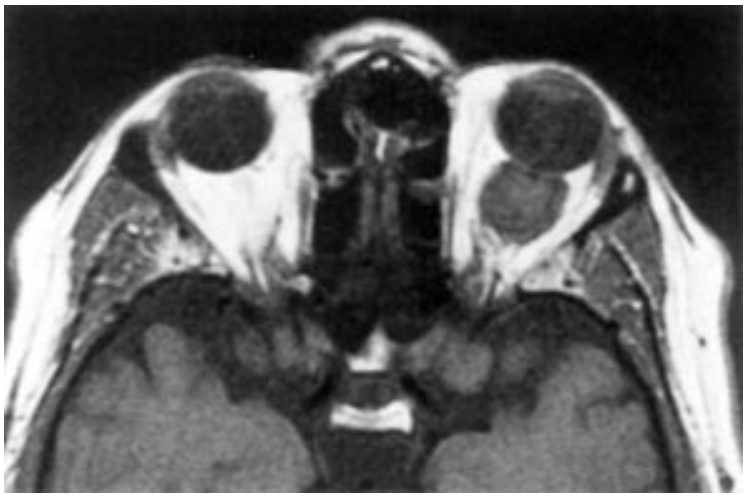

Figure 4 This axial T1 weighted magnetic resonance scan demonstrates a focal intraconal mass.

solitary metastases, the tumour was removed. Several patients were treated with either photon or (for metastatic cutaneous melanoma cases) heavy charged particle irradiation. These irradiated patients either had solitary orbital disease or had progression while on chemotherapy. Patients with widespread systemic disease were treated with chemotherapy.

The median survival was 1.3 years; the 2 year survival rate was 27% (Fig 5). There was no significant difference in survival duration between patients with and without a known primary tumour at the time the orbital metastases were diagnosed. Patients with breast cancer had a longer survival, on average, than patients with other primary malignancies, however the difference was not statistically significant (2.4 years versus 1 year).

Discussion

Orbital metastases are relatively uncommon. In our experience 36 of 612 orbital biopsies for suspected neoplasm (6%) were metastatic in origin; this incidence is similar to that reported in other series.[1–5] In this outpatient series, almost one third of cases did not have a history of a primary malignancy, and in 26% imaging studies were more consistent with a primary orbital tumefaction. Font and Ferry, in a series

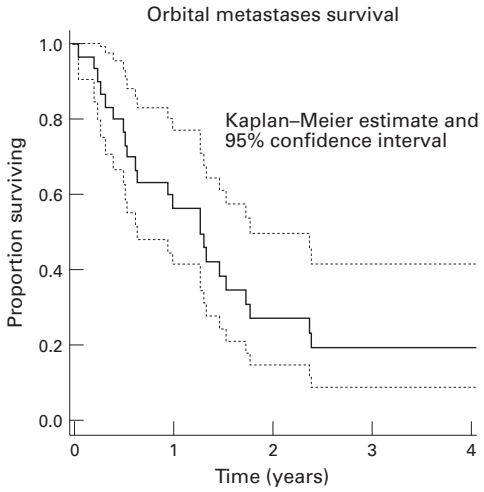

Figure 5 Kaplan–Meier curve of survival of patients with orbital metastases. The mean survival of patients with orbital metastases was 1.3 years; the 2 year survival rate was 27% (31 cases).

reported from a national pathology registry, noted that 17 of 28 patients (61%) presented with orbital metastases before the detection of the primary tumour.[4] As others have noted, breast carcinoma, followed by lung carcinoma, is the most common source of orbital metastases, although the prevalence varies in different series, contingent on referral patterns.[1–6] As an example, in our tertiary referral practice, the pattern of orbital metastases is at variance with many other series.

Diplopia was the most common presenting symptom in patients with metastatic tumours, in contrast with most other orbital neoplasms, where either proptosis or visual loss was more frequent.[1 5 9] Unfortunately, this symptom array is not diagnostic; in an older patient with mild proptosis and diplopia and no systemic thyroid signs or symptoms, the possibility of a metastatic orbital tumour should be considered in the differential diagnosis.

Altered extraocular muscle function was first described for orbital metastases by Horner in 1864.[12] The aetiology of the motility disturbance can be multifactorial; usually diplopia is due to either direct tumour infiltration of the muscle (Fig 1[1]) or mass effect; however, rarely it develops as part of a paraneoplastic phenomenon, mainly with lung carcinoma.[13 14] Other common causes of diplopia and proptosis in older adults include thyroid orbitopathy and idiopathic orbital inflammation.[9] As others have pointed out, most commonly the muscle and contiguous orbital structures are involved with metastatic foci; involvement of the muscle or muscles alone is less common.[15–23] It is estimated that approximately 5% of orbital metastases involve only extraocular muscles.[22]

While some authors have stressed that pain is very typical for metastatic orbital lesions, any primary malignancy that has perineural invasion and some benign processes will present with pain.[9 24] In our series no patient presented with bilateral orbital involvement. In as many as 25% of choroidal metastases, multiple or bilateral tumours were present; bilaterality is much less frequent in orbital metastases.[4 5 20 25–27]

In a series reported by Tijl and colleagues, four of 34 patients had bilateral orbital metastases and all of these bilateral cases had breast carcinomas.[28]

FNAB was used diagnostically in 17 cases, with positive results obtained in 15 cases (88%). We were unable to establish the diagnosis with this approach in two patients, both of whom illustrate some of the problems with this orbital technique. One false negative result was in a patient with scirrhous carcinoma metastatic to the orbit. The second patient had a small focus of tumour at the apex in the superior rectus muscle. In neither case could we satisfactorily obtain a sample with CT controlled FNAB. In the first case this was due to a fibrous matrix incorporating the tumour cells, while the other illustrates the point that with a small tumour contiguous to visually vital structures at the orbital apex, sometimes insufficient material is obtained. No false positive results were obtained, and we had no significant morbidity associated with this diagnostic procedure. In cases that could be diagnosed by FNAB, this obviated the need for an open orbital procedure under general anaesthesia. In a few patients with palpable lesions we have just done a FNAB in the office. In a few additional cases, we performed FNABs in the operating room when the area of interest was exposed (data not shown.) The advantage of the latter approach is twofold. (1) In our centre we can have data within 2 minutes, while a frozen section report often takes as long as 30 minutes to obtain. (2) An open FNAB allows sampling in one or multiple areas, with less damage to normal structures than removal of conventional biopsy samples. Several other series have reported orbital FNAB techniques for both primary and metastatic orbital tumours.[28–34] There are a number of potential disadvantages with an open FNAB approach. The major caveat is that it is necessary for a skilled cytopathologist to be available in the operating room. If this service is not present in an institution, the usefulness of this technique is markedly diminished.[35]

Therapy was based on establishing a correct diagnosis, the systemic status of the patient, and whether optic nerve compression was present. This was an outpatient series, with mobile, active patients, hence more treatment was performed than would be indicated in terminally ill patients with widespread disease. In our experience, in patients with suddenly decreased vision due to a mass compressing the optic nerve, surgical debulking of the tumour is the optimum treatment and we have been able to restore vision in such patients. In a few patients with focal tumours that produce symptoms from a mass effect, surgical extirpation of the lesion was locally effective.

In patients with a solitary orbital metastasis that was either diffuse or involved an important structure, such as the muscle, globe, or nerve, almost 80% of patients will obtain symptomatic relief with a total dose of 30 to 40 Gy of photon radiation. It is imperative to obtain a brain MR scan with gadolinium before irradiating a metastatic orbital tumour. Not infrequently, patients will have silent brain lesions when they present with orbital disease. In one series of ocular and orbital breast metastases, 10 of 32 had central nervous system lesions, and if such lesions involve the contiguous brain they should be included in the treatment field.[36] Failure to obtain these imaging studies can result in patients having the same anatomical area re-irradiated when the contiguous metastatic deposit is, only later, discovered, with resultant increased morbidity.

In patients who have both widespread metastases and chemotherapeutically sensitive tumours, chemotherapy is the treatment of choice. Finally, we have managed a few patients with either asymptomatic orbital metastases or with minor symptoms and far advanced disease, by serial observation alone.

As other series have shown, prognosis is usually dismal in these patients; however, a few have had long term remissions and are alive 10 years after the orbital disease was diagnosed.[4 5 37] The median survival was a little over 1 year, and only 27% had 2 year survival. In this small series, patients with breast cancer had a slightly longer survival than did patients with other malignancies.[5 8] The variability of survival in different series is best shown by contrasting our breast carcinoma patients with a series reported by Ratanatharathorn and colleagues in which the median survival of 11 patients with orbital breast metastases was only two months (range 0 to 29 months).[35–37] In that study survival with orbital compared with intraocular metastases was shorter; however, in a report by Font and Ferry and others, the opposite was noted.[4 29 36 37] The disparities point out probable differences in referral, selection, or inclusion criteria in different reports. Survival differences with choroidal versus orbital metastases, and different histological types of orbital metastases that have been described must be interpreted cautiously with the above caveats. Surprisingly, there was no difference in our study in survival between those who presented with orbital lesions with or without a known primary neoplasm. In some tumours, such as renal carcinoma, cases have been reported with long term survival after removal of a solitary orbital metastasis.[38]

In as many as one quarter of outpatients with orbital metastases, the correct diagnosis is not suspected with non-invasive techniques. If a fine needle aspiration biopsy was performed, it was diagnostic in almost 90% of the cases. Orbital therapy was usually effective for local palliation; however, long term survival was rare.

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1 Henderson JW, Campbell RJ, Farrow GM, Garrity JA. *Orbital tumors*. 3rd ed. New York: Raven Press, 1994:361–76.
2 Moss HM. Expanding lesions of the orbit: a clinical study of 230 consecutive cases. *Am J Ophthalmol* 1962;**54**:761–70.
3 Silva D. Orbital tumors. *Am J Ophthalmol* 1968;**65**:318–39.
4 Font RL, Ferry AP. Carcinoma metastatic to the eye and orbit. III A clinicopathologic study of 28 cases metastatic to the orbit. *Cancer* 1976;**38**:1326–35.

5 Goldberg RA, Rootman J, Cline RA. Tumors metastatic to the orbit. *Surv Ophthamol* 1990;**35**:1–24.
6 Reese AB. *Tumors of the eye*. 2nd ed. New York: Harper and Row, 1963:426–32.
7 Jones IS, Jakobiec FA. *Diseases of the orbit*. Hagerstown: Harper and Row, 1979:554–69.
8 Burmeister BH, Benjamin CS, Childs WJ. The management of metastases to eye and orbit from carcinoma of the breast. *Aust NZ J Ophthalmol* 1990;**18**:187–90.
9 Char DH. *Clinical ocular oncology*. 2nd ed. Philadelphia: Raven-Lippincott, 1996:390–7.
10 Abbruzzese JL, Abbruzzese MC, Lenzi R, Hess KR, Raber MN. Analysis of a diagnostic strategy for patients with suspected tumors of unknown origin. *J Clin Oncol* 1995;**13**: 2094–103.
11 Doz F, Neuenschwander S, Plantaz D, Courbon B, Gentet JC, Bouffet E, *et al.* Etoposide and carboplatin in extraocular retinoblastoma: a study by the Societe Francaise d'Oncologie Pediatrique. *J Clin Oncol* 1995;**13**:902–9.
12 Horner F. Case report: *Klin Monatsbl Augenheilkd* 1864;**2**: 186–92.
13 Kuntzer T, Steck AJ, Fiorini E, Mirimanoff RO, Regli F. [Lambert-Eaton myasthenic syndrome. Physiopathological aspects and therapeutic modalities.] *Rev Neurol* 1991;**147**: 819–24.
14 Lowe BA, Mershon C, Mangalik A. Paraneoplastic neurological syndrome in transitional cell carcinoma of the bladder. *J Urol* 1992;**147**:462–4.
15 Wintersteiner H. Fzin Fall von Augenmuskelmetastasen nach Carcinoma mammal. *Klin Monatsbl Augenheilkd* 1889;**37**:331–8.
16 Bedford PD, Daniel PM. Discrete carcinomatous metastases in the extrinsic ocular muscles. *Am J Ophthalmol* 1960;**49**:723–6.
17 Thomas A, Oommen MM, Sudarsanam D, Singh AD. Metastatic carcinoma breast in lateral rectus muscle. *Ind J Ophthalmol* 1979;**27**:23–4.
18 Adelstein, FE, Schmidt, W. Sobre una metastasis tumeral en los musculos extrinsecos del ojo. *Arch Soc Oftal Hisp-Am* 1968;**28**:752–6.
19 Ashton N, Morgan G. Discrete carcinomatous metastases in the extraocular muscles. *Br J Ophthalmol* 1974;**58**:112–7.
20 Fred W, van Gelderen C. Gastric carcinoma metastases to the extraocular muscles. *J Comp Assist Tomogr* 1993;**17**: 499–501.
21 Divine RD, Anderson RL. Metastatic small cell carcinoma masquerading as orbital myositis. *Ophthalmic Surg* 1982; **13**:483–7.
22 Arnold RW, Adams BA, Camoriano JK, Dyer JA. Acquired divergent strabismus: presumed metastatic gastric carcinoma to the medial rectus muscle. *J Pediatr Ophthalmol Strabismus* 1989;**26**:50–1.
23 Orcutt JC, Char DH. Melanoma metastatic to the orbit. *Ophthalmology* 1988;**95**:1033–7.
24 Boldt HC, Nerad JA. Orbital metastases from prostate carcinoma. *Arch Ophthalmol* 1988;**106**:1403–8.
25 Carriere VM, Karcioglu ZA, Apple DJ, Insler MS. A case of prostate carcinoma with bilateral orbital metastases and the review of the literature. *Ophthalmology* 1982;**89**:402–6.
26 Hugkulstone CE, Winder S, Sokal M. Bilateral orbital metastases from transitional cell carcinoma of the bladder. *Eye* 1994;**8**:580–2.
27 Green S, Som PM, Lavagnini PG. Bilateral orbital metastases from prostate carcinoma: case presentation and CT findings. *Am J NeuroRadiol* 1995;**16**:417–9.
28 Tijl J, Koornneef L, Eijpe A, Thomas L, Gonzales DG, Beenhof C. Metastatic tumors to the orbit—management and prognosis. *Graefes Arch Clin Exp Ophthalmol* 1992;**230**: 527–30.
29 Westman-Naeser P. Tumours of the orbit diagnosed by fine-needle biopsy. *Acta Ophthalmol* 1978;**56**:969–76.
30 Czerniak D, Woyke S, Daniel B, Krzysztolik Z, Koss LG. Diagnosis of orbital tumors by aspiration biopsy guided by computerized tomography. *Cancer* 1984;**54**:2385–9.
31 Berquist TH, Bailey PB, Cortese D, Miller WE. Transthoracic needle biopsy. Accuracy and complications in relation to location and type of lesion. *Mayo Clin Proc* 1980;**55**:475–81.
32 Tijl JWM, Koornneef L. Fine needle aspiration biopsy in orbital tumours. *Br J Ophthalmol* 1991;**75**:491–2.
33 Zadjela A, Vielh P, Schlienger P, Haye C. Fine-needle cytology of 292 palpebral orbital and eyelid tumors. *Am J Clin Pathol* 1990;**93**:100–4.
34 Dresner SC, Kennerdell JS, Dekker A. Fine needle aspiration biopsy of metastatic orbital tumors. *Surv Ophthalmol* 1983;**27**:397–8.
35 Liu D. Complications of fine needle aspiration biopsy of the orbit. *Ophthalmology* 1985;**92**:1768–71.
36 Ratanatharathorn V, Powers WE, Grimm J, Steverson N, Han I, Ahmad K, *et al.* Eye metastasis from carcinoma of the breast: diagnosis, radiation treatment and results. *Cancer Treat Rev* 1991;**18**:261–76.
37 Goldberg RA, Rootman J. Clinical characteristics of metastatic orbital tumors. *Ophthalmology* 1990;**97**:620–1.
38 Bersani TA, Costello JJ Jr., Mango CA, Streeten BW. Benign approach to a malignant orbital tumor: metastatic renal cell carcinoma. *Ophthal Plast Reconstr Surg* 1994;**10**:42–4.