

**Original article:**

## **Preinvasive and invasive malignant lesions and nonmalignant-SOL of eye and its adnexa**

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### **ABSTRACT**

**Introduction:** Our aim was to describe and compare the epidemiological characteristics, morphology and clinico-pathological correlation of patients with preinvasive and invasive malignant lesions and nonmalignant space occupying lesions (nonmalignant-SOL) of eye and its adnexa as seen in Ahmedabad, India from 2008 to 2010.

**Materials and methods:** We analysed 144 surgical specimens of the eye and its adnexa lesions seen over a three year period. Of these 144 cases, 110 histologically proved cases of preinvasive and invasive malignant lesions and nonmalignant-SOL were included in the study.

**Results:** This study included 110 patients of which 51.86% were male and 48.2% were female. Bimodal peaks in incidence of ophthalmic lesions was seen; one peak in below 10 years age and another after 40 years age. Eyelid (47%) was the most commonly affected site. Lympho-vascular hamartomas (12.7%) were most frequent nonmalignant-SOL. Ocular surface squamous neoplasia (OSSN) was the commonest group of neoplastic lesions (13.4%). Malignant and non malignant cases were (38.2%) and (62.8%) respectively. Incidence of cases with malignant lesions was sharply increased after 40 years of age. The most common cancer was meibomian gland carcinoma (9.1%), followed by squamous cell carcinoma (8.2%).

**Conclusion:** Multiple factors such as location of eye affected by the lesion, age and sex of patient, geographical, racial and environmental conditions determine the frequency and variability of eye lesions; and awareness to these factors can augment clinical and histology diagnosis correlation. Histopathological examinations of excised or incised orbital or ocular lesions are absolutely mandatory to come to a definitive diagnosis.

**Keywords:** Eye lesions, malignant lesions, OSSN.

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### **INTRODUCTION**

Ophthalmic tumours and other space occupying lesions (SOL) consist mainly of epithelial cysts, developmental and hamartomatous conditions, granulomatous and inflammatory pseudo tumours, parasitic infestation, benign neoplasms, preinvasive and invasive malignant lesions. Ophthalmic malignancies are rare and clinically and radiologically may

mimic other space occupying lesions<sup>1</sup>. A clinico-pathological diagnosis correlation has been low and documented to 30-49% of cases in different studies<sup>2</sup><sup>3</sup>. Histopathological examinations of excised or incised orbital or ocular lesions are absolutely mandatory for each case to come to a definitive diagnosis and for patient management. The detailed study correlating the clinical presentation and

histomorphological features of preinvasive and invasive malignant lesions and nonmalignant-SOL of eye and its adnexa will be helpful in better understanding of the overlaps of ophthalmic malignancies and other SOL and minimize the errors of diagnosis. The goal of the present study is to describe and compare the epidemiological characteristics, histomorphological features, and clinicopathological correlation of preinvasive and invasive malignant lesions and nonmalignant-SOL of eye and its adnexa.

### **MATERIALS AND METHODS**

We analysed 144 cases of ophthalmic surgical specimens and biopsies that were sent to Rushabh Pathology and Endocrine centre, Ahmedabad, India, during November 2008 to September 2010. Of the initial 144 cases, 110 histologically proved cases of preinvasive and invasive malignant lesions and nonmalignant-SOL were entered for the study. Eyeball excisions for non malignant lesions other than SOL, such as sympathetic ophthalmitis, injury, phthisis bulbi, acute inflammation were omitted from the study. Cases whose biopsy evaluation did not lead to any definite conclusion were excluded from the study.

Clinical information collected included patient age, sex, chief complaints and its duration, and radiological findings. In an attempt to obtain better convenience to analyse the distribution of the ophthalmic lesions across the age span, patients were grouped as progressive decades of age such as, 1 - 10, 11 - 20, 21 - 30, and so forth. Pattern and characteristics of ophthalmic lesions affecting different age groups was recorded and analysed. The surgically resected specimens and biopsies were fixed in the 10% formalin. Gross examination

findings of specimen recorded and representative areas of tissue were subjected to routine tissue processing, paraffin embedding and 5-7 um thick tissue sections stained with haematoxylin & eosin were prepared and were examined for histomorphological features. Based on the histological interpretation, to obtain better understanding of the disease pattern in relation to gross appearance, histogenesis and behaviour pattern, lesions were grouped as epithelial cysts, benign tumours, preinvasive and invasive malignancies, parasite infestations and a miscellaneous group of nonmalignant-SOL of hamartomas, developmental and congenital lesions, reactive non-neoplastic proliferations and inflammatory lesions.

### **RESULTS**

In this study of 110 cases of preinvasive and invasive malignant lesions and nonmalignant-SOL of eye and its adnexa, 38.2% cases were malignant and 62.8% were nonmalignant-SOL [Table1].

The gap between proportion of male and female patients was narrow in the group of 110 patients, 51.8% and 48.2% respectively. However in the cohort of patients with preinvasive and invasive malignant lesions, majority of the affected patients were male (57.1%).

Age details of 106 patients were available [Table2]. The youngest and the eldest patient were of one year and ninety years age respectively. Two peaks in incidence of ophthalmic lesions were seen, one in less than ten years of age (15.1% cases) and the other between 41 and 50 years (17% cases) was observed. However, the incidence of malignant lesions showed only one peak which was observed in 41-60 years age group with occurrence of 8 cases in each decade. Though absolute number of malignant cases were

high in 41-60 years age, but it is important to note, that proportion of cases with malignant lesions over nonmalignant-SOL was highest in age group 70 years and above; 6 out of 7 cases (85.7%) in 71 - 80 years age group were malignant, whereas, only one case was recorded in 81 – 90 years age and that was of Non Hodgkin lymphoma. All malignant lesions in age group below ten years were retinoblastoma and all lesions in age group 11- 20 were nonmalignant-SOL.

Location wise distribution of ophthalmic lesion indicates eyelid as the most common site being affected (47.7%), followed in order by conjunctiva (21.1%) and orbit (15.6%). Cornea was least affected (0.9%) [Table3]. Though number of malignant lesions of conjunctiva (n=13) was less than eyelid cancers (n=18) but proportion of malignant lesions over nonmalignant-SOL was higher in conjunctiva (54.2%) than the eyelid lesions (34.6%) [Table4,5]. All intraocular tumours were malignant, four cases were of retinoblastoma and two cases were of choroid melanoma. Two cases of hydatid cyst (*Echinococcus granulosus*) presented as orbital SOL [Table6]. Of the ten cases affecting lacrimal apparatus (lacrimal gland, lacrimal sac and lacrimal duct), one case of lacrimal gland malignancy, adenocarcinoma, was recorded [Table7].

Histological analysis reveals hamartomas of lymphatic and vascular malformations (capillary haemangioma, cavernous haemangioma, arterio-venous malformation and lymphangioma) were the most frequent nonmalignant-SOL of eye and its adnexa (12.7%). Eyelid was most common site involved by hamartomas, followed by orbit and conjunctiva. Meibomian carcinoma was the commonest invasive malignancy forming 9.09% of

110 study group cases, and 23.8% of the malignant lesions [Table8]. Eyelid was seat of occurrence of all meibomian carcinomas.

OSSN cases, which include squamous papilloma, preinvasive lesions (CIN), and verrucous carcinoma and squamous cell carcinoma, were the commonest group of neoplastic lesions, comprising of 15 cases (13.4%) of the total 110 study cases [Table9].

## DISCUSSION

Ophthalmic malignancies are uncommon and clinically and radiologically mimic other SOL resulting into poor clinico-pathological correlation. In this study we analysed and compared characteristics of preinvasive and invasive malignant lesions and nonmalignant-SOL so as to identify features which can improve clinical prediction of the lesion. Considering histology diagnosis as the gold standard, our approach was a comprehensive analysis of the ophthalmic lesions in relation to location, age, histogenesis and gross appearance of the lesion so as to produce meaningful data so as to facilitate clinical and histological diagnosis correlation.

In our study of 110 histologically proved ophthalmic cases of preinvasive and invasive malignant lesions and nonmalignant-SOL lesions, 38.2% cases were malignant and 62.8% were nonmalignant-SOL. Compared to previous reports by Sanjay et al<sup>3</sup> (30 % malignant and 70% benign) and Ud-Din N et al<sup>4</sup> (32.5 % malignant and 61.5% benign) the proportion of malignant lesions was high in our study due to the specific criteria of including only the SOL of nonmalignant lesions and omitting the other lesions which did not presented as SOL. In group of patients with malignant lesions, males (57.1%) were affected more often than females (42.9%). Other studies have

reported 51.2% to 56 % males and 44% to 48.8% females<sup>3, 5, 6</sup>.

The number of malignant lesions peaked in 41-60 years age group which was contrary to most of the previous studies which reported two peaks, one below ten years of age and another after forty years of age<sup>6, 7</sup>. The first peak observed in previous studies was due to high number of retinoblastoma cases. Only four cases (3.6%) have been recorded in our study of 110 cases. For better insight in the pattern of disease distribution across the age span, authors attempted to analyse the proportion of malignant and nonmalignant-SOL cases affecting each age decade. In patients above 70 years of age, 87.5% cases were malignant. This is the first report highlighting the high proportion of malignant lesions over nonmalignant lesions in age group 70 years and above, because, unlike previous studies, we compared the frequency of malignant lesions and nonmalignant-SOL in different age groups, and nonmalignant lesions other than SOL were omitted from the study. Thus any SOL of eye and its adnexa occurring in patients above 70 years of age has high likelihood to be of malignant behaviour.

Our report of most frequent eyelid malignant lesions (n=18), followed by conjunctival malignant cases (n=13) was in congruence with previous studies. Authors will like to emphasis that though number of eyelid malignant lesions was high, but, proportion of conjunctival malignant lesions among all the lesions affecting the conjunctiva was 54.2%, higher than the corresponding proportion of malignant lesions in eyelid (34.6%). This was contrary to Sanjay et al<sup>3</sup> and to Japanese study by Obata H et al<sup>8</sup> because geographical<sup>9</sup>, racial<sup>1</sup> and environmental factors such as humidity<sup>6</sup> affect frequency of eye tumours. Thus

conjunctiva when affected by an SOL, relative chances of malignancy are fairly high than any other extraocular location.

OSSN cases, which include squamous papilloma, preinvasive (CIN) lesions, verrucous carcinoma and squamous cell carcinoma, were the commonest group of lesions, comprising of 15 cases (13.6%) of the total 110 study cases. In regard to prevalence of OSSN, there has been conflicting reports of frequency of OSSN cases due to geographical variations; tropical countries have higher incidence of OSSN than United Kingdom<sup>9</sup>. Of the 15 OSSN cases, the site of origin for 14 cases was conjunctiva. From histogenesis point of view, high frequency of OSSN cases suggests that conjunctival squamous epithelium is more prone to neoplastic proliferation and is seat of majority of neoplastic proliferations of eye. The OSSN lesions are usually asymptomatic and often go unsuspected; Hirst et al<sup>10</sup> have reported 9.8% of OSSN in 533 pterygium specimens, thus true incidence of OSSN may be much higher. OSSN needs to be picked up early, as prompt treatment in early stages is usually curative and mutilating surgery of advanced invasive lesions can be prevented.

Meibomian carcinoma is the commonest malignancy in our study. There has been great variability in previous reports in regard to frequency of various malignant lesions, as various studies has claimed retinoblastoma<sup>6</sup> or squamous cell carcinoma<sup>2</sup> or melanoma<sup>11</sup> as the commonest malignancy. The relative frequencies of these histological types vary widely in different countries<sup>1</sup>. It has been observed that most frequent eye cancers are either melanoma or retinoblastoma in white populations<sup>12</sup>. Kale et al have suggested that there is an increase in incidence of meibomian carcinoma in Asian countries<sup>13</sup>.

Authors of the study conducted in Chennai reported high frequency of meibomian carcinoma and have suggested that climatic factors such as humidity is cause for increase number of meibomian carcinoma<sup>6</sup>. Results of our study indicate that awareness of pattern of occurrence of malignant lesions and nonmalignant-SOL in different locations of eye and its adnexa, and understanding the relation of the lesion with age and sex of patient can help to

augment clinical and histology diagnosis correlation. Geographical, racial and environmental factors significantly affect the frequency of ophthalmic lesions. Variability in frequency of eye lesions reported in various studies highlight the importance of histopathological examination of excised or incised eye lesions for definitive diagnosis and patient management.

Table 1: Characteristics of patients of 110 study cases.

		Malignant n=42 (38.2%)	Nonmalignant-SOL n=68 (62.8%)	Total n=110
SEX	Male	24 (57.1%)	33 (48.5%)	57 (51.8%)
	Female	18 (42.9%)	35 (51.5%)	53 (48.2%)
	TOTAL	42	68	110

Table 2: Incidence ratio of malignant and nonmalignant-SOL cases in different age groups. Age details were available in 106 cases.

AGE GROUPS	Malignant	Nonmalignant-SOL	Total
0 - 10	04 (23.5%)	12 (76.5%)	16 (15.1%)
11 – 20	00	14 (100%)	14 (13.2%)
21 – 30	01 (9.1%)	10 (90.9%)	11 (10.3%)
31 – 40	04 (28.6%)	9 (71.4%)	13 (12.3%)
41 – 50	08 (55.5%)	10 (44.5%)	18 (17%)
51 – 60	08 (61.5%)	07 (38.5%)	13 (12.3%)
61 – 70	07 (53.8%)	05 (46.2%)	13 (12.3%)
71 - 80	06 (85.7%)	01 (14.6%)	07 (6.6%)
81 - 90	01 (100%)	00	01 (0.9%)
TOTAL	39	67	106 (100%)

Table 3: Location wise distribution of ophthalmic lesions (N=110).

	No.	%
Eyelid	52	47.7
Conjunctiva	24	21.1
Orbit	17	15.6
Lacrimal gland, sac and duct	10	9.2
Retina	4	3.7
Choroid	2	1.8
Cornea	1	0.9

Table 4: Histology of different Eyelid lesions (N=52).

<i>Eyelid lesions n (%)</i>	<i>Histology</i>	<i>No</i>	<i>%</i>
Epithelial Cysts 8 (14.4%)	Simple duct cyst	4	7.7
	Epidermal keratinous cyst	4	7.7
Miscellaneous 9 (17.3%) (Congenital, developmental, hamartomatous, reactive, and inflammatory lesions)	Dermoid cyst	3	5.8
	Capillary haemangioma	3	5.8
	Cavernous haemangioma	3	5.8
	Arterio-venous malformation	1	1.9
	Lymphangioma	1	1.9
	Reactive lymphoid hyperplasia	1	1.9
Benign neoplasms 14 (26.9%)	Intradermal nevus	5	9.6
	Eccrine adenomas of sweat gland	3	5.8
	Mesenchymal tumours	3	5.8
	Squamous papilloma	3	5.8
Preinvasive and Malignant lesions 18 (34.6%)	Meibomian carcinoma	10	19.2
	Basal cell carcinoma	4	7.7
	Squamous cell carcinoma	2	3.8
	Melanoma	1	1.9
	Non Hodgkins Lymphoma	1	1.9

Table 5: Histology of different Conjunctival lesions (N=24).

<i>Conjunctival lesions n (%)</i>	<i>Histology</i>	<i>No</i>	<i>%</i>
Epithelial Cysts 1 (4.2%)	Inclusion cyst	1	4.2
Miscellaneous 8 (33.3%) (Congenital, developmental, hamartomas, reactive and inflammatory lesions)	Dermoid	3	12.5
	Capillary haemangioma	1	4.2
	Reactive lymphoid hyperplasia	2	8.3
	Pyogenic granulomum	1	4.2
	Lymphangioma	1	4.2

Benign neoplasms 2 (8.3%)	Nevus	1	4.2
	Collagenous Fibroma	1	4.2
Preinvasive and invasive malignant lesions 13 (54.2%)	Squamous cell carcinoma	7	29.2
	Preinvasive OSSN (CIN)	4	16.4
	Verrucous carcinoma	1	4.2
	Non Hodgkin Lymphoma	1	4.2

Table 6: Histology of different orbital lesions (N=17).

<i>Orbital lesions n (%)</i>	<i>Histology</i>	<i>No.</i>	<i>%</i>
Parasite Cysts 2 (11.8%)	Hydatid cyst	2	11.8
Miscellaneous 9 (53%) (Congenital, developmental, hamartomatous, reactive, and inflammatory lesions)	Reactive lymphoid hyperplasia	3	17.6
	Cavernous haemangioma	2	11.8
	Inflammatory pseudotumour	2	11.8
	Capillary haemangioma	1	5.9
	Lymphangioma	1	5.9
Benign neoplasms 3 (17.6%)	Pilocytic Astrocytoma	1	5.9
	Neurofibroma	2	11.8
Pre malignant and Malignant lesions (17.6%)	Leiomyosarcoma	1	5.9
	Epithelioid Haemangioendothelioma	1	5.9
	Non Hodgkin Lymphoma	1	5.9

Table 7: Histology of different lesions of Lacrimal gland sac and duct (N=10).

<i>Lacrimal lesions n (%)</i>	<i>Histology</i>	<i>No</i>	<i>%</i>
Epithelial Cysts	Lacrimal duct cyst	2	20
Inflammatory lesions	Chronic Dacryoadenitis	2	20
	Sarcoidosis	1	10
Benign neoplasms	Pleomorphic adenoma	4	40
Malignant lesions	Adenocarcinoma	1	10

Table 8: Histology of malignant eye lesions.

<i>Histology</i>	<i>No</i>	<i>%</i>
Meibomian carcinoma	10	23.8
Squamous cell carcinoma	9	21.5
Basal cell carcinoma	4	9.5
Melanoma	3	7.1
Retinoblastoma	4	9.5
Non Hodgkin Lymphoma	3	7.1
Preinvasive OSSN (CIN)	5	11.9
Verrucous Carcinoma	1	2.4
Adenocarcinoma of lacrimal gland	1	2.4
Leiomyosarcoma	1	2.4
Epithelioid haemangioendothelioma	1	2.4
Total cases	42	100

Table 9: Ocular Surface Squamous Neoplasia (OSSN).

	<i>Squamous Papilloma</i>	<i>Preinvasive OSSN</i>	<i>Verrucous carcinoma</i>	<i>Squamous cell carcinoma</i>	<i>TOTAL</i>
Conjunctiva	0	4	1	7	12
Cornea	0	1	0	0	1
					13

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