

# Adjuvant radiation therapy for malignant tumours of the eyelid: Experience from a tertiary cancer centre in India

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## ABSTRACT

**Background.** Tumours of the eyelid are a rare subgroup of neoplasms with varied histology and inherent differences in clinical behaviour. Surgery is the standard of care, and adjuvant radiation therapy (RT) is given in the presence of features suggesting a high risk of local recurrence. The treatment of lymph nodes in the neck is debatable. We reviewed the utility of RT for lymph nodes in the neck in patients with malignant tumours of the eyelid.

**Methods.** We reviewed medical records of all patients with tumours of the eyelid treated at our centre from July 2006 to December 2014 for their demographic, clinical profile, treatment details and outcome.

**Results.** The records of 37 patients were included for analysis, of these 34 underwent surgery and 21 received adjuvant RT. Their median age was 60 (range 30–85) years. Sebaceous cell carcinoma was the most common (50.4%). The median disease-free survival (DFS) was 35 months (95% CI 17.9–52.0). The 1- and 3-year DFS were 82.7% and 45%, respectively. Univariate analysis showed a superior outcome with early stage (T1) tumours ( $p=0.01$ ), RT dose of  $\geq 60$  Gy and those underwent lymph node dissection ( $p=0.03$ ). The presence of high-risk factors including close or positive margin had an inferior outcome with a trend towards statistical significance ( $p=0.06$ ).

**Conclusion.** We found a favourable outcome with early T stage, RT dose of  $\geq 60$  Gy and lymph node dissection. High-risk histopathological features including close margins and positive lymph nodes merit adjuvant RT including regional lymph nodes.

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## INTRODUCTION

Primary carcinoma of the eyelid is an uncommon malignancy and accounts for 5%–10% of all head-and-neck skin cancers. This includes a rare subgroup of neoplasms with varied histology and inherent differences in clinical behaviour. The incidence of tumours of the eyelid differs worldwide with a higher incidence

in the USA (15.7 cases/100 000) compared to Asia (5.1/100 000). Basal cell carcinoma is the most common and is reported to be the predominant tumour (80%–90%) among Caucasians. Squamous cell carcinoma represents 3.4%–12.6% and sebaceous cell carcinoma represents 0.6%–10.2% of all head-and-neck skin cancers.<sup>1</sup> In the Indian population, sebaceous histology is common accounting for 2.4%–30.2% of malignant tumours of the eyelid.<sup>2,3</sup> Compared to basal cell carcinoma, which is slow-growing and insidious, squamous and sebaceous cell carcinoma are more aggressive with a risk of metastasis.<sup>4</sup> Squamous cell carcinomas may masquerade benign clinical conditions such as blepharitis, are often misdiagnosed clinically and present with advanced disease. In addition to being locally aggressive, they are also associated with cranial neuropathy and orbital invasion and a high rate of involvement of regional lymph nodes (24%). Local recurrence rates after surgical resection have been reported to be 2.4%–36.9% at 5 years.<sup>4</sup> Sebaceous cell carcinomas are aggressive with increased metastases to regional lymph nodes (8%–18%) and distant sites (3%–8%). Lymph node involvement has a dismal prognosis.<sup>5–7</sup>

Surgical excision is the gold standard for curative treatment of primary tumours of the eyelid; however, it can be technically difficult and may result in functional and cosmetic impairment. Radiation therapy (RT) is used either as definitive therapy or in the adjuvant setting in the presence of high-risk features including close/positive margins, invasion of lymphovascular space and involvement of lymph nodes.

Studies on treatment outcomes and optimal treatment strategy are limited due to rarity of the disease. Sebaceous histology is a locoregionally aggressive histology and merits further adjuvant therapy.<sup>8</sup> We analysed our data of tumours of the eyelid and identified the association of various factors in patients treated with surgery with/without RT for tumour response and pattern of failure.

## METHODS

We reviewed the records of all patients ( $n=57$ ) with tumours of the eyelid attending the Department of Radiation Oncology from July 2006 to December 2014. We extracted information related to demographic and clinical details, pathological characteristics, RT and outcome of patients with tumours of the eyelid. We excluded 11 patients whose details were incomplete and 9 patients who did not complete their treatment. A total of 37 patients with complete treatment and demographic details were included in the study.

Patients were evaluated and were treated as per the institutional protocol with multimodal therapy. The evaluation protocol involves complete physical examination with visual

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acuity, laboratory investigations with complete blood count, liver function tests, kidney function tests and computed tomography (CT) of the orbit. The work-up for distant metastasis included chest X-ray and ultrasound of the abdomen. This study was approved by the institute's ethics committee.

#### *Clinical outcome end-points and statistics*

The following demographic data were extracted: sex, age, date of diagnosis, baseline radiological imaging, site of disease, T- and N-stage depending on the histopathology report of the surgical specimen, the number of lymph nodes dissected and positive for tumour deposit.

Disease-free survival (DFS) was calculated from the date of histopathological diagnosis of malignancy till the date of relapse. Relapse was defined as either locoregional recurrence or appearance of new distant metastatic lesion. Patients not having any event at the time of the last follow-up were censored. DFS was estimated using the Kaplan–Meier method. Cox regression was used for univariate analysis for predicting the impact of prognostic factors in DFS. Prognostic variable analysis included histology (sebaceous *v.* non-sebaceous), size of lesion (<2 *v.* ≥2 cm), pathological lymph nodal status, RT dose (<60 *v.* ≥60 Gy) and presence of high-risk features such as close/positive margin. *p*<0.05 was considered statistically significant. The data were analysed using STATA software version 11.2.

#### *Surgery*

Surgery was considered in patients with acceptable oncological and cosmetic outcome and good Eastern Cooperative Oncology Group performance status 0–2. Surgical intervention was based on the size of lesion, visual function and local extent of the disease. Extent of surgery varied from wide local excision in early-stage tumours to orbital exenteration in locally advanced tumours. Soft-tissue reconstruction was done using temporalis muscle flap and local rotation advancement flaps to achieve skin closure. In patients with clinically positive lymph nodes or sebaceous cell carcinoma, a modified neck dissection was done including periparotid lymph nodes and anterolateral group of lymph nodes (level 1 to level 4 lymph nodes). The extent of lymph node dissection was based on intraoperative findings and the clinical judgement of the operating surgeon.

#### *Radiation therapy*

Patients with a tumour >2 cm (T3), lymph node-positive disease, close or positive margins, recurrent tumour and/or lympho-vascular space invasion were offered adjuvant RT. Radiation planning was done using two-dimensional simulations with bony landmarks, if treatment was done for the primary alone. Patients were treated in the supine position. A lead piece, 5.5 mm thick with a square window for diseases of the eyelid was made. Eye shield made of tungsten material was placed to protect the cornea after instillation of local anaesthesia. Adjuvant RT consisted of 60–64 Gy in conventional fractionation delivered to the primary site with 9 MeV electrons in CL-2300 linear accelerator (Varian Medical System, Palo Alto, California, United States). If the neck lymph node was positive, it was included in the primary postoperative tumour bed. For conformal planning, gross and clinical target volumes were generated as per the clinical and radiological extent of the disease. Planning target volume was generated with 5 mm margin for daily set-up variation. Based on the reports of lymph nodal metastasis, we adopted a uniform policy in RT planning.

Level 1b, II and intraparotid groups of lymph nodes were contoured according to the RTOG contouring guidelines. Conformal radiation planning was done in Eclipse Planning System (version 6.5) and treatment was delivered with 6-MV photon beam in CL-2300.

#### *Evaluation of treatment response*

Patients were monitored during RT with clinical examination and haematological investigations for acute radiation reactions.

Acute adverse events of the skin, conjunctiva and cornea were recorded as per the RTOG guidelines. At our centre, we did a clinical examination every 3 months with CT imaging of the face and neck every 6 months for the first 2 years. Subsequently, clinical examination was done every 6 months with imaging annually or in the presence of clinical suspicion of local recurrence or lymph nodal disease.

#### RESULTS

Our patients had a median age of 60 years (range 30–85 years). The duration of symptoms ranged from 3 to 60 months with a median of 12 months. There were 20 males and the same number had disease in the right eye (Table I).

#### *Treatment details*

Surgical resection was done in 34 patients, of which 18 underwent wide local excision. Exenteration was performed in 16 patients due to locally advanced disease and 13 patients also had a neck dissection. Twelve patients with sebaceous histology had an upfront neck dissection and 9 had a positive lymph node on histopathology. The remaining 8 patients with sebaceous cell carcinoma underwent wide excision of the primary lesion only. Adjuvant RT was given to 21 patients. Two patients received

TABLE I. Demographic profile and clinical presentation of patients

Characteristic	Frequency (%)
<i>Gender</i>	
Male	20 (54)
Female	17 (36)
<i>Presenting complaint</i>	
Swelling	28 (75.7)
Discharge	2 (5.4)
Ulcer	7 (18.9)
<i>Laterality</i>	
Right	20 (54)
Left	17 (36)
<i>Location</i>	
Upper	19 (51.4)
Lower	18 (48.6)
<i>Histology</i>	
Squamous cell carcinoma	4 (10.8)
Basal cell carcinoma	8 (21.6)
Sebaceous cell carcinoma	20 (50.4)
Adenoid cystic carcinoma	1 (2.7)
Melanoma	1 (2.7)
Mucoepidermoid	1 (2.7)
Adenocarcinoma	2 (5.4)
<i>Comorbid conditions</i>	
Nil	32 (86.5)
Hypertension	3 (8.1)
Tuberculosis	2 (5.4)
Diabetes	1 (2.7)
Xeroderma pigmentosum	1 (2.7)

definitive RT, and 2 patients with advanced disease were treated with palliative RT. Eleven patients received salvage RT after local recurrence.

External beam RT was administered most commonly as adjuvant therapy after surgery. The median dose used for adjuvant RT was 60 Gy (range: 60–64 Gy) (Table II).

The median number of lymph nodes dissected was 10 (range 1–18). Median number of positive nodes was 1 with a range of 1–5.

*Survival outcome*

At a median follow-up of 25.3 months (range 1.3–108.7 months), median DFS was 35 months. One- and 3-year DFS were found to be 82.7% and 45%, respectively (Fig. 1a). Univariate analysis showed a superior outcome with T1 tumour, RT dose  $\geq$ 60 Gy and those undergoing lymph node dissection ( $p=0.01$ ,  $0.01$  and  $0.03$ , respectively; Table III and Figs 1b-d).

The presence of high-risk factors including close or positive margin had an inferior outcome with a trend towards statistical significance (3-year DFS 42.4% v. 87.5%;  $p=0.06$ ; Fig. 1e).

*Pattern of recurrence*

Eighteen patients had recurrence after initial therapy: 11 patients developed local recurrence and 7 had lymph nodal failure. A high rate of lymph nodal failure was observed in the sebaceous cell subgroup: 10 patients developed recurrence, 4 had local recurrence and 6 patients had lymph nodal failure. Four patients with basal cell carcinoma, 2 with squamous and 1 patient with adenocarcinoma had local recurrence (Table IV).

*Salvage treatment*

Surgical salvage alone was offered to 7 patients. Surgery and adjuvant RT were offered to 4 patients. Three patients were treated with RT alone (60 Gy) in 30 fractions over 6 weeks. Two patients had disease progression and were administered palliative RT (20 Gy) in 5 fractions in 1 week. Two patients

TABLE II. Treatment details of patients with tumour of the eyelid

Treatment	Frequency (%)
<i>Surgery</i>	34
Wide local excision	18 (52.9)
Exenteration	16 (47.1)
Neck dissection	13 (35.1)
Modified neck dissection type I	5 (13.5)
Modified neck dissection type II	2 (5.4)
Modified neck dissection type III	4 (1.8)
Extended neck dissection	1 (2.7)
Intraparotid	1 (2.7)
<i>Histopathology/risk factors</i>	12 (32.4)
Lymph node positive	11 (29.7)
Margin positive	1 (2.7)
Close margin	10 (27)
Lymphovascular space invasion	0
<i>Radiation therapy (RT)</i>	
Definitive	2 (5.4)
Postoperative	21 (56.7)
Preoperative	1 (2.7)
Palliative	2 (5.4)
Salvage	11 (29.7)

TABLE III. Impact of different prognostic variables on disease-free survival in univariate analysis

Variable	Survival in months (median)	95% CI	DFS (12 months) (%)	DFS (36 months) (%)	p value
<i>Gender</i>					
Male	35.0	23.5–46.5	89.4	40.9	0.99
Female	28.0	0–58.93	73.9	49.9	
<i>Site of lesion</i>					
Upper	35.0	10.1–59.8	51.2	49.9	0.14
Lower	29.0	5.6–52.3	70.8	44.2	
<i>Histology</i>					
Sebaceous	46.0	21.4–70.6	88.24	49.16	0.11
Non-sebaceous	29.0	15.6–42.4	67.19	50.4	
<i>T stage</i>					
T1	45	–	100	100	0.01
T2	16	0–33.2	60	NR	
T3	35	16.2–53.8	87.8	49.5	
T4	3	–	50	50	
<i>Lymph node</i>					
Negative	29	16.0–42.0	76.1	39	0.11
Positive	NR	–	100	68.6	
<i>Radiation therapy dose</i>					
$\geq$ 60 Gy	46	30.9–61.0	94.1	62.8	0.01
<60 Gy	8	0–21.2	50	NR	
<i>Type of surgery</i>					
Wide local excision	45.0	23.7–66.3	75.4	58.6	0.49
Exenteration	35.0	16.7–53.3	93.8	44.4	
<i>High-risk features</i>					
Yes	29	13.1–44.9	81.8	42.4	0.06
No	NR	–	87.5	87.5	
<i>Lymph node dissection</i>					
Yes	59.0	23.4–94.6	100	55.9	0.03
No	29.0	15.5–42.5	72.0	39.3	

DFS disease-free survival NR not recorded

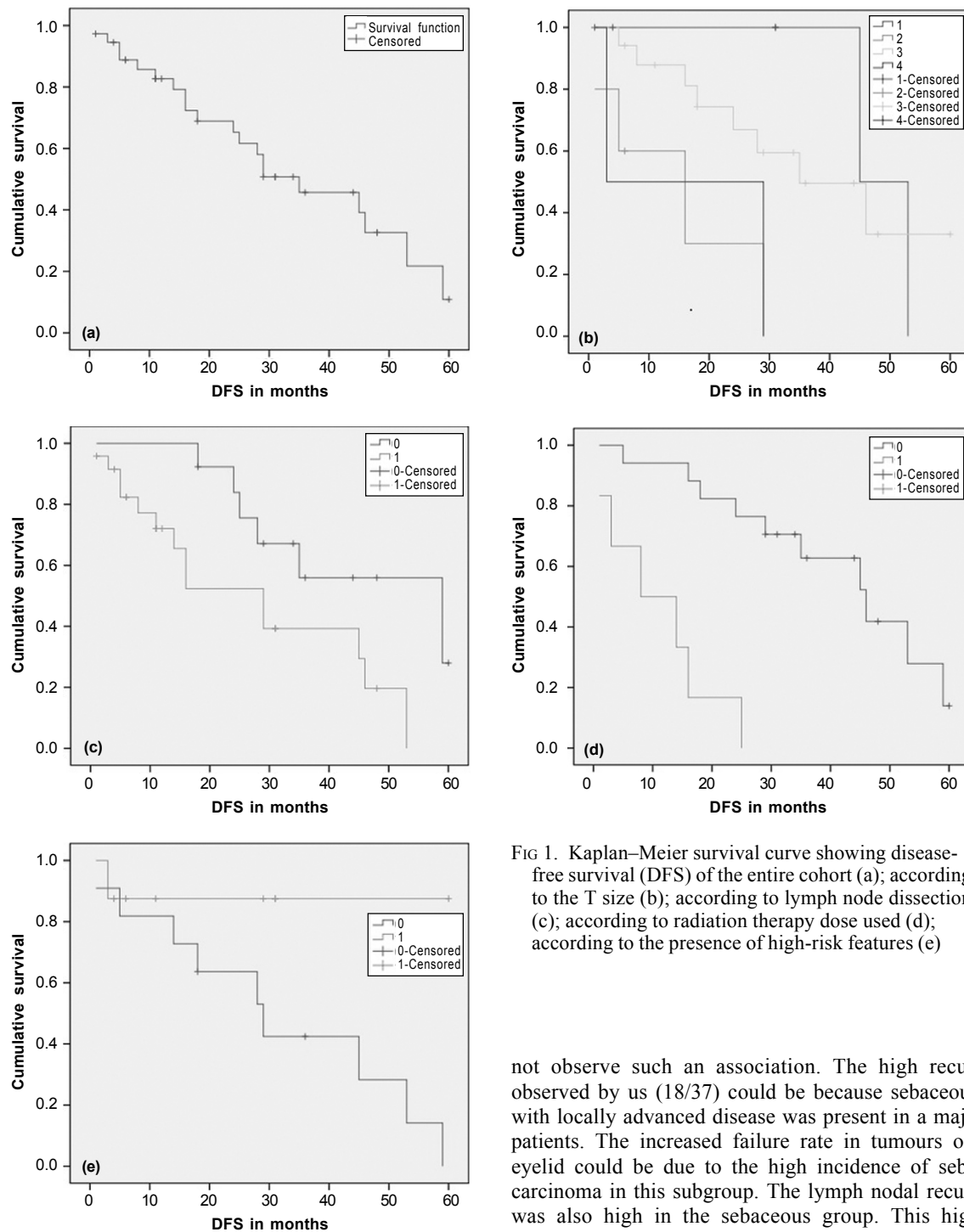


FIG 1. Kaplan–Meier survival curve showing disease-free survival (DFS) of the entire cohort (a); according to the T size (b); according to lymph node dissection (c); according to radiation therapy dose used (d); according to the presence of high-risk features (e)

received RT after second recurrence following salvage surgery.

#### DISCUSSION

Our study evaluated the role of adjuvant RT and the pattern of failure in patients with cancers of the eyelid, who received adjuvant RT. In agreement with earlier reports, we observed an increased incidence of sebaceous cell carcinoma (54%).<sup>6,9</sup> In our study, the mean age was 60 years, similar to that reported in the literature.<sup>7,10</sup>

The site of tumour (upper v. lower) and histology (sebaceous v. non-sebaceous) are predictors of survival. However, we did

not observe such an association. The high recurrence rate observed by us (18/37) could be because sebaceous histology with locally advanced disease was present in a majority of our patients. The increased failure rate in tumours of the upper eyelid could be due to the high incidence of sebaceous cell carcinoma in this subgroup. The lymph nodal recurrence (6/7) was also high in the sebaceous group. This highlights the aggressive course of sebaceous histology and the need for elective lymph nodal irradiation in the adjuvant setting. The T-category correlates with the risk of lymph nodal and distant metastases; with T2b and larger tumours associated with increased lymph nodal metastasis. Our study observed improved DFS in T1 (median DFS 45 months). However, the survival was superior in T3 than in T2 (median DFS 35 and 16 months, respectively).

Yoon *et al.* have emphasized the need for negative margins for adequate local control and prevention of recurrence. Our study also highlighted poor outcomes in patients with high-risk features (close/positive margin), with a trend towards statistical significance ( $p=0.06$ ).<sup>11</sup> The management of regional lymph

TABLE IV. Patterns of failure according to stage and histology

Histological type	n	Recurrence	Primary site	Lymph node
<i>Sebaceous carcinoma</i>				
Stage I	5	1	1	0
Stage II	2	1	0	1
Stage III-A	5	4	2	2
Stage III-B	6	4	1	3
Stage III-C	2	0	0	0
<i>Basal cell carcinoma</i>				
Stage I	6	3	3	0
Stage II	2	2	1	1
<i>Squamous cell carcinoma</i>				
Stage I	1	1	1	0
Stage III	3	1	1	0
<i>Others</i>				
Stage I	1	1	1	0
Stage III	3	0	0	0

node metastasis consists of complete dissection of cervical nodes I/II along with parotidectomy.<sup>9,12</sup>

Thirteen patients underwent lymph node dissection for T3 disease, sebaceous histology and lymph nodal failure/clinically significant lymphadenopathy.

Petsuksiri *et al.* also showed that primary RT for squamous cell carcinoma of the eyelid provided excellent local control and may be considered as an alternative to surgery.<sup>13</sup> A superior outcome was observed in our study with higher radiation dose in patients receiving  $\geq 60$  Gy. Inaba *et al.* suggested there was a tendency towards favourable outcomes in patients treated with  $\geq 56$  Gy and therefore preferred this dose for tumour control.<sup>14</sup> However, whether dose escalation is beneficial for advanced stages needs further larger studies.

Adjuvant RT has a crucial role in optimum locoregional control in the locally aggressive histology (sebaceous cell carcinoma) and presence of high-risk factors including positive margin and lymph node.<sup>15–17</sup> Currently, there are no consensus guidelines for elective lymph nodal irradiation, and the existing literature on the role of adjuvant RT is limited. In lymph node-positive patients, complete neck dissection followed by adjuvant RT is used for optimal local control. However, there are no data suggesting survival advantage with the addition of RT. Addressing the neck in RT for the eyelid is a debatable issue.

Basal cell carcinoma has an indolent course and is locally aggressive, whereas lymph nodal failure rates are high with sebaceous and squamous variants. Based on our observations in sebaceous and squamous histology and absence of clear high-risk factors to indicate neck irradiation, we suggest it is imperative to consider ipsilateral elective lymph nodal irradiation in locally advanced squamous and sebaceous cell carcinomas.

The median time to recurrence observed was 27.5 months. We suggest long-term surveillance for tumours of the eyelid with meticulous clinical examination and imaging to detect early locoregional failure.

Several factors including a small patient number, clinical heterogeneity and retrospective data are limitations of our study, which preclude us from making more definite conclusions.

Multicentric studies are needed to elucidate the efficacy of adjuvant RT for regional metastasis.

### Conclusion

Diagnosis and treatment of tumours of the eyelid pose a challenge due to their wide range of clinical presentations, often masquerading benign conditions. Each histological variant is unique in biological behaviour, thus requiring a tailored approach for management.

There is no consensus on RT and dose of regional lymph nodes in tumours of the eyelid, and management strategies are not standardized for regional failure. An RT dose of  $\geq 60$  Gy may be helpful, especially for patients with positive margins. Sebaceous and squamous cell carcinomas have an aggressive clinical behaviour and have an increased propensity to locoregional metastasis. Neck dissection and elective neck irradiation may be considered in this subgroup ( $\geq T3$  disease).

*Conflicts of interest.* None declared

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