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Adenoid cystic carcinoma of the lacrimal gland: role of nuclear survivin (BIRC5) as a prognostic marker

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Adenoid cystic carcinoma of the lacrimal gland: role of nuclear survivin (BIRC5) as a prognostic marker

Aims: This study aimed to evaluate the expression of nuclear survivin in adenoid cystic carcinoma (ACC) of the lacrimal gland and to determine if this expression is associated with histopathological features, markers of apoptosis and proliferation or clinical outcomes.

Methods and results: Immunohistochemical staining for survivin, p53, Ki-67 and Bcl-2 was analyzed in 55 cases of ACC of lacrimal gland. Thirty-one cases (56.3%) expressed nuclear survivin. All cases expressed p53, Ki-67 and Bcl-2. Eleven cases (35.5%) had a high nuclear survivin score (NS-SCORE) and 20 cases (64.5%) had a low NS-SCORE. Cases with a high NS-SCORE had a shorter progression-free survival (PFS) ($P < 0.0001$), higher expression of Ki-67 ($P < 0.005$) and a solid tumour pattern >30% ($P < 0.005$).

Conclusion: Nuclear expression of survivin impacts prognosis significantly and is thus a promising prognostic marker in ACC of the lacrimal gland.

Keywords: adenoid cystic carcinoma, lacrimal gland, survivin (BIRC5)

Introduction

Tumours of the lacrimal gland are uncommon in clinical practice. They constitute approximately 7–9% of orbital tumours.[1–3] Traditionally, it has been said that 50% of lacrimal masses are epithelial and 50% are non-epithelial.[4] Epithelial tumours of the lacrimal gland account for 5–8% of all tumours at this site.[5,6] Adenoid cystic carcinoma (ACC) is the most common malignant epithelial tumour of the lacrimal gland, with a deceptively benign histological appearance characterized by indolent, locally invasive growth with a high propensity for local recurrence and distant metastases. ACC accounts for 1.6% of all orbital tumours and 3.8% of all primary orbital tumours.[5] Several clinicopathological features, such as advanced stage, solid histological subtype, high grade, the presence of perineurial invasion or a positive surgical margin, have been associated with recurrence or poor survival in ACC of the salivary gland.[7–10] The primary treatment for ACC of the lacrimal gland has been *en-bloc* surgical excision, which is usually followed by postoperative radiotherapy.[11,12] Neoadjuvant chemotherapy carries a risk of substantial toxicity.[13]

Cytotoxic agents have been associated with dismal antitumour activity in metastatic ACC of the salivary glands; this uniform lack of efficacy has prompted the evaluation of molecularly targeted therapies in these tumours. Unfortunately, their theoretical promise has yet to be fulfilled.[13] Several biomarkers have been studied for their possible role as prognostic indicators of ACC in the lacrimal and salivary glands and as potential targets of molecular therapy.[14–24] No validated protocols exist for ACC of the lacrimal glands.

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Survivin, also called baculoviral inhibitor of apoptosis repeat-containing 5 (BIRC5), is a member of the inhibitor of apoptosis (IAP) family. Survivin has been studied extensively in various human cancers for its potential role as a prognostic marker. Studies have associated survivin expression with poor clinical outcome.[25–28] It has also been evaluated for its prognostic role in ACC of the head and neck region.[12] However, its role in ACC of the lacrimal glands remains largely unknown. The purpose of this study was to determine whether nuclear survivin is expressed in ACC of the lacrimal gland and whether such expression has any association with various histopathological features, clinical outcomes of the disease, or markers of proliferation and apoptosis.

Materials and methods

We retrieved 65 cases of ACC involving the lacrimal gland diagnosed in the Ocular Pathology Service from 1995 to 2011. Ten cases were excluded from the study due to lack of follow-up information. Medical records were reviewed to evaluate clinical outcomes. All patients were assigned a pathological grade and a TNM stage according to the 7th edition of the American Joint Committee on Cancer (AJCC) staging system. A trained pathologist reviewed tumour tissue slides for histological pattern, histological grade, volume of solid component, perineurial invasion and status of the resected surgical margins. ACC was classified into three types based on the morphological growth pattern: cribriform, tubular and solid. The surgical resection margin was considered positive when residual tumour cells were found at the margin. The follow-up period ranged from 3 to 196 months (mean 51.8).

IMMUNOHISTOCHEMISTRY AND ANALYSIS

Serial 5-μm-thick tissue sections cut from paraffin blocks were mounted individually onto gelatine-coated glass slides. Sections were deparaffinized and rehydrated. Endogenous peroxidase activity was blocked by incubating the slides in 0.3% solution of hydrogen peroxide in methanol for 30 min. Microwave antigen retrieval was performed, for which tissues were immersed in Coplin jars containing 0.01 M phosphate-buffered saline, pH 7.4, and subjected to intermittent heating for three cycles of 5 min each in a 625W microwave oven to maintain the temperature of the buffer at approximately 95°C. After cooling the slides to room temperature, non-specific immunoreactivity was blocked by incubation with normal horse serum for 15 min (three cycles of 5 min each) at room temperature. Sections were rinsed in running tap water and phosphate-buffered saline (2 min each) at room temperature, and then stained immunohistochemically using commercially available monoclonal antibodies, with diaminobenzidine as the chromogen.

The following primary antibodies were used in the study: Ki-67 (clone Ki88), p53 (clone BP53-12-1), survivin (clone EP2880Y) and Bcl-2 (clone 100) (all from BioGenex, Fremont, CA, USA). Positive and negative controls were run simultaneously with every batch. Positive immunostaining for Ki-67, survivin and p53 was defined as brown staining confined to the nucleus, and for Bcl-2 as cytoplasmic/membranous staining (Figure 1).

NUCLEAR SURVIVIN SCORE (NS-SCORE)

Nuclear expression for survivin was scored in terms of intensity and percentage expression. Intensity was scored as zero (no staining), 1 (weak), 2 (mild), 3 (moderate) and 4 (strong). Percentage of staining was scored as 0 (0%), 1 (1–25%), 2 (26–50%), 3 (51–75%) and 4 (76–100%). Intensity and percentage scores were then summed to calculate the NS-SCORE. Tumours with NS-SCORES of 0–4 were grouped as low-score tumours, while those with NS-SCORES of 5–8 were scored as high-score tumours. NS-SCORES were correlated with histopathological features, clinical outcomes and expression of other markers.

STATISTICAL ANALYSIS

R (version 2.14.1) software was used for the statistical analysis. Progression-free survival (PFS) was calculated from the date of diagnosis to the date when the tumour recurred or the patient died. Survival was derived using the Kaplan–Meier method. The log-rank test was used to evaluate the statistical differences in the cumulative survival scores. The Cox model was used for the multivariate analysis. A 95% confidence interval (CI) was used for survival rates and hazard ratio.

ETHICS STATEMENT

This study was reviewed by the ethics committee of L.V.Prasad Eye Institute, Hyderabad, and was performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki. Informed consent was obtained from the patients.

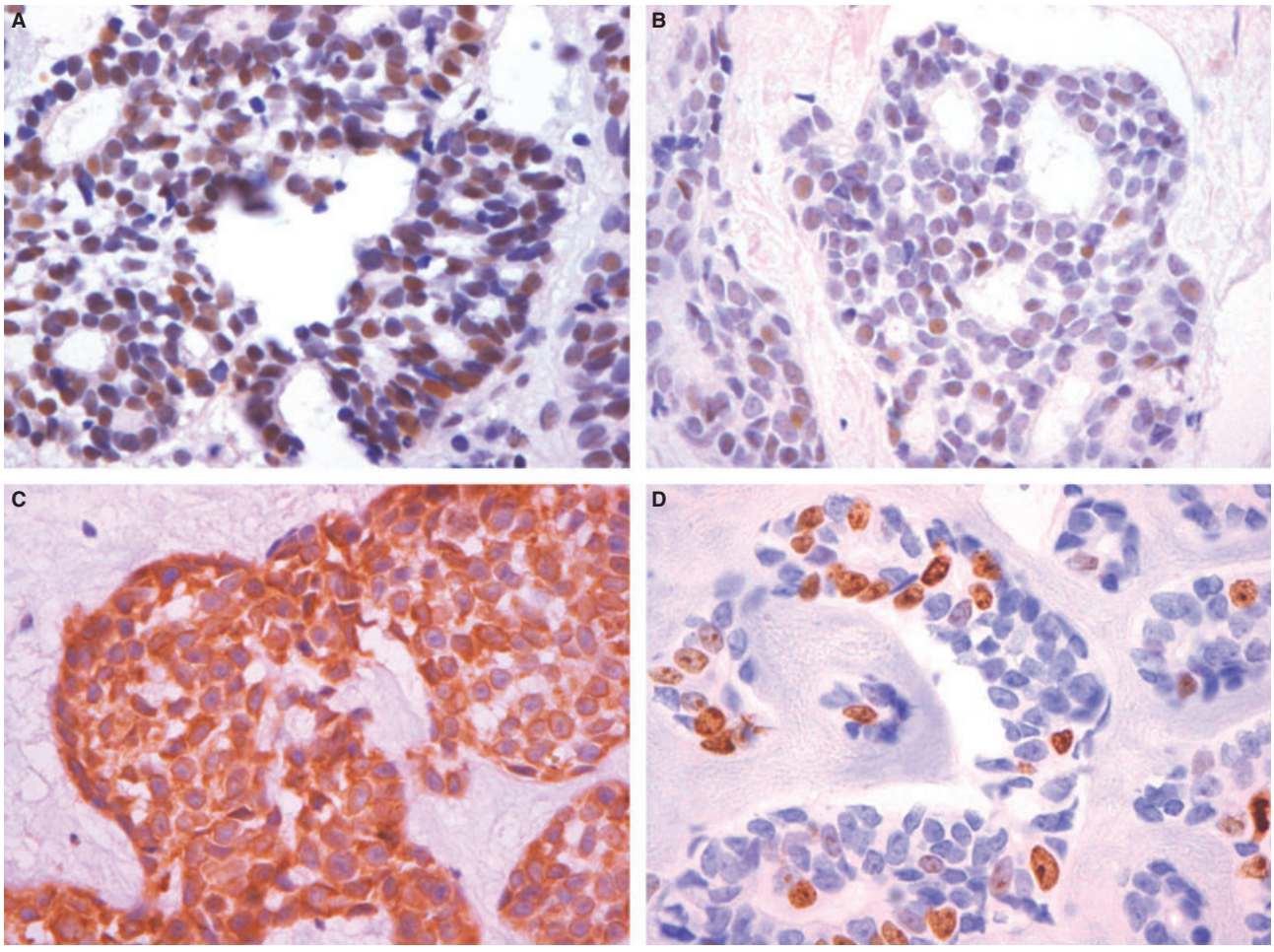

Figure 1. Immunohistochemical analysis of adenoid cystic carcinoma. Nuclear immunoreactivity for p53 (**A**), nuclear immunoreactivity for survivin (**B**), membranous/cytoplasmic immunoreactivity for Bcl-2) (**C**) and nuclear immunoreactivity for Ki-67 (**D**).

Results

CLINICOPATHOLOGICAL FEATURES

Table 1 depicts the clinicopathological features of the 55 cases of ACC of the lacrimal gland.

EXPRESSION OF KI-67, P53 AND BCL-2

All cases expressed p53, Ki-67 and Bcl-2. The proportion of tumour cells expressing Bcl-2, Ki-67 and p53 varied from 54% to 99%, 3.2% to 32% and 51% to 88%, respectively.

EXPRESSION OF SURVIVIN

We categorized the tumours into two groups: the 'nuclear' group, which included all tumours where survivin was expressed in the nucleus of tumour cells with/without cytoplasmic immunoreactivity for surviving, and the 'non-nuclear' group, where survivin expression was limited only to the cytoplasm or the tumour cells failed to express survivin either in the cytoplasm or the nucleus. Of the 55 cases, 31 cases (56.4%) expressed survivin in the nucleus of tumour cells. Table 2 shows the comparative analysis of the nuclear and non-nuclear groups. Tumours expressing nuclear survivin had a higher Ki-67 index ($P < 0.0001$), greater p53 expression ($P < 0.0001$), a greater volume showing a solid pattern ($P = 0.0015$) and were larger ($P < 0.0001$). Also, the recurrence rate was significantly higher ($P < 0.001$) and the PFS shorter ($P < 0.0001$) for patients whose tumours expressed nuclear survivin compared to those whose tumours did not. No significant association was seen between Bcl-2 expression and nuclear expression of survivin.

Table 1. Clinicopathological features of Adenoid Cystic Carcinoma of the lacrimal gland

Feature	No. of patients	Percentage (%)
Total	55	
Age in years, median (range)	35 (11–77)	
Gender		
Male	24	43.63
Female	31	56.36
Lymph node involvement	01	1.81
Tumour size		
≤2cm	31	56.36
>2cm	24	43.63
Histological growth pattern (Predominant)		
Cribriform	40	72.7
Tubular	09	16.36
Solid	06	10.9
Solid component		
≤30%	42	76.36
>30%	13	23.63
Histological grade		
Gx	0	0
G1	33	60.0
G2	9	16.36
G3	7	12.72
G4	6	10.9
Perineurial invasion		
Present	47	85.45
Absent	08	14.54
Resected surgical margins		
Involved	04	7.27
Not involved	51	92.72

EVALUATION OF THE NS-SCORES

Eleven cases (35.4%) had a high NS-SCORE, while 20 cases (65.4%) had a low NS-SCORE. Table 3 shows the comparative analysis of the high and low NS-SCORE groups. Cases with a high NS-SCORE had a shorter PFS ($P < 0.0001$), higher expression of Ki-67 ($P < 0.005$) and a greater proportion of solid tumour pattern ($P < 0.005$).

Figure 2 shows the Kaplan–Meier plots for survival analysis between the nuclear/non-nuclear and the high/low NS-SCORE groups. The reproducibility of the study was acceptable, with least-square regression analysis resulting in an R^2-value of 0.93.

Discussion

Adenoid cystic carcinoma (ACC) is a rare epithelial tumour of the lacrimal gland, most common in the 5th and 6th decades of life, but can appear at virtually any age ranging from 6.5 to 79 years.[29,30] In the present study, the age at presentation ranged from 11 to 77 years. Gender predisposition is an inconsistent feature in the literature, with authors variedly reporting male preponderance, female preponderance, and no gender predilection.[31,32] In the present study, the male:female ratio was 1:1.29. However, this difference was not statistically significant. Studies in the literature have correlated tumour size with prognosis.[12,33] A study on ACC of the head and neck found that all tumours >4 cm had an unfavourable prognosis.[33] In the present study, tumours >2 cm showed a trend for a shorter PFS but this difference was not statistically significant.

ACC can be classified morphologically into three prognostically significant patterns: cribriform, tubular and solid.[34] The presence of a solid component has been a consistent predictor of poor prognosis in several series.[7,35–37] In the present study, we found that cases with a solid pattern involving >30% of the tumour had a shorter PFS ($P < 0.0001$). The AJCC tumour stage is more predictive of prognosis and distant metastasis.[7,31] Wright *et al.* [29] have reported a greater frequency of recurrence in patients with ACC with a solid pattern accounting for more than half the tumour, compared to those where this pattern was not evident. Although we did not find a statistically significant association between solid tumour pattern and recurrence, such tumours showed a trend for a greater recurrence rate. In a recent review of ACC, 74.3% of patients showed advanced disease at the time of initial evaluation.[38] Despite this, cervical node metastases are a rare event. Lung, bone and liver are common metastatic sites.[32,39] Two patients in the present study had lung metastases in the follow-up period.

Survivin, or BIRC5, is a protein encoded by the *BIRC5* gene[40] and is a member of the IAP family. The survivin protein functions to inhibit caspase

Table 2. Comparative analysis between nuclear and non-nuclear groups for survivin

Feature	Nuclear group	Non-nuclear group	*P*-value
Age at presentation (years)	11–77 (Median 35)	11–72 (Median 35.5)	0.388
Predominant solid morphologic pattern	16.1% (5/31)	4.16% (1/24)	0.216
Solid component >30%	41.9% (13/31)	4.16% (1/24)	0.0015
p53 (% expression)	65–87 (Median 82)	51–88 (Median 67)	<0.0001
Bcl-2 (% expression)	54–99 (Median 92)	72–98 (Median 95)	0.353
Ki 67 index	5.2–32.0 (Median 25.2)	3.2–26.3 (Median 5.75)	<0.0001
Recurrence	74.2 (23/31)	4.2 (1/24)	<0.001
PFS (Months)	3–120 (31)	40–196 (Median 91.5)	<0.0001
Size (>2 cm)	87.09% (27/31)	16.6% (4/24)	<0.0001

Table 3. Comparative analysis of low and high NS-SCORE groups

Feature	High SSCORE	Low SSCORE	*P*-value
Age at presentation (years)	11–55 (Median 32)	11–77 (Median 36.5)	0.342
Predominant solid morphologic pattern	9.09% (1/11)	20% (4/20)	0.624
Solid component >30%	90.9% (10/11)	15% (3/20)	<0.005
p53 (% expression)	73–87 (Median 83)	85–87 (Median 82)	0.451
Bcl-2 (% expression)	54–99 (Median 93)	73–99 (Median 92)	0.408
Ki 67 index	23.4–32.0 (Median 29.1)	5.2–26.7 (Median 24.05)	<0.005
Recurrence	100% (11/11)	60% (12/20)	0.265
PFS (Months)	3–20 (Median 13)	12–120 (Median 40)	<0.0001
Size (>2 cm)	100% (11/11)	80% (16/20)	0.269

activation, thereby leading to negative regulation of apoptosis or programmed cell death. It is expressed highly in most human tumours and fetal tissue, but is completely absent in terminally differentiated cells.[41] The single survivin gene can give rise to four different alternatively spliced transcripts: survivin-2A, survivin-2B, survivin-delta-ex-3 and survivin-3B.[42] Survivin-2A and survivin-3B are predicted to be truncated forms of 120 and 128 amino acids, respectively, while survivin-2B and survivin-delta-ex-3 result from alternative splicing at the interface between exons 2 and 3.[43] The presence of transcripts of survivin has been correlated with cancer progression with differing conclusions.[42,44–46] Reports of the localization of survivin and its relationship with prognosis are also conflicting. Survivin-2B by itself is localized to both nuclear and cytoplasmic compartments, whereas survivin-delta-ex-3 is localized only to the nucleus. The localization of these three variants (survivin-2A, survivin-2B, and survivin-delta-ex-3) differ, however, when co-transfected together rather than individually.[42] A Western blot and immunocytochemistry analysis has confirmed that survivin could be detected both in the nucleus and the cytoplasm. Ponnelle *et al.*[47] detected survivin both in the cytoplasm and the nucleus of colorectal carcinoma, and also found a significant association between cytoplasmic expression and better prognosis. In a recent study, PSORT II analysis predicted a preferential cytoplasmic localization of survivin-2A and survivin-2B, but a preferential nuclear localization of survivin-delta-ex-3.[44] Liao *et al.*[48] found survivin expression in ACC of the lacrimal gland to be localized to the cytoplasm exclusively, and its expression was related to

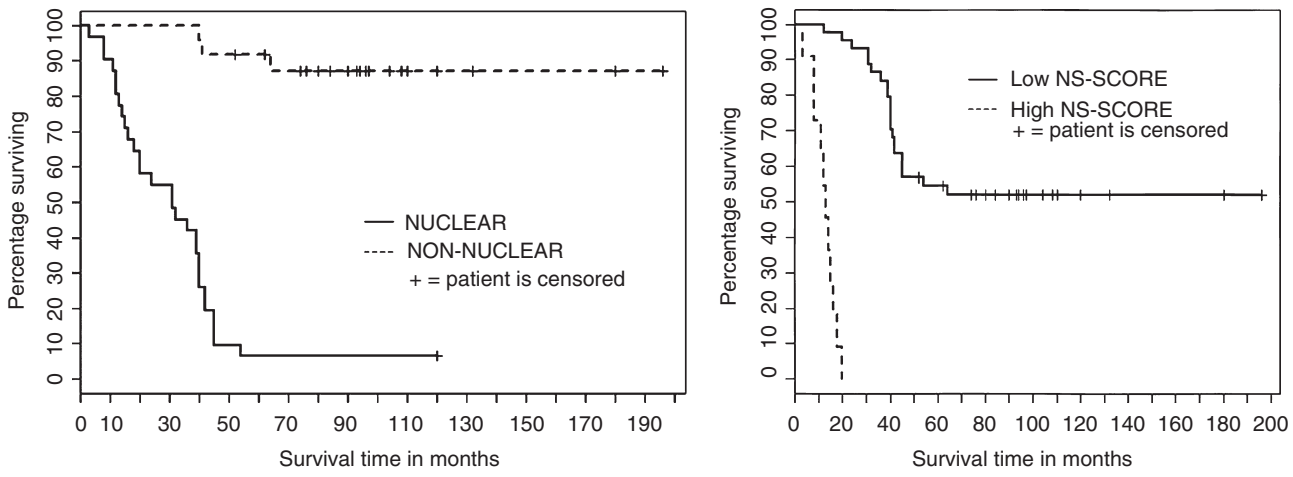

Figure 2. Kaplan–Meier survival plots for progression-free survival of patients with adenoid cystic carcinoma according to location of survivin expression (left) and nuclear survivin score (NS-SCORE) (right).

the T stage and proliferative index. They also documented that, of all the IAP proteins included in their study, survivin was the only factor that could predict prognosis independently. Ko *et al.*[12] concluded that expression of nuclear survivin has clinicopathological implications in patients with ACC of the head and neck region. In the present study, nuclear expression of survivin was associated with an increased recurrence rate, shorter PFS, higher Ki-67 index and higher p53 expression (Table 2). Also, tumours expressing nuclear survivin were larger, and had a greater proportion showing a solid tumour pattern, thus relating nuclear survivin to histological grade (G) and stage (T) of the tumour.

In the present study we scored the expression of nuclear survivin. This, to our knowledge, is the first time that a scoring system has been used to evaluate the expression of survivin in ACC of the lacrimal glands. Patients with tumours having a high NS-SCORE had a shorter PFS, and these tumours were more likely to show higher Ki-67 expression and a solid pattern involving >30% (Table 3).

Conclusion

Nuclear expression of survivin in ACC of the lacrimal gland correlates with histopathological indicators of poor outcome, such as the proportion of the solid component and tumour stage. It also correlates with high expression of markers of apoptosis and proliferation. Overall, nuclear expression of survivin impacts prognosis significantly and is thus a promising prognostic marker in ACC of the lacrimal gland. The novel concepts incorporated within our study may provide newer directions for further research into the management of ACC of the lacrimal gland.

Conflicts of interest

None.

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