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Expression of inhibitors of apoptosis proteins in salivary gland adenoid cystic carcinoma: XIAP is an independent marker of impaired cause-specific survival

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Abstract

Objectives: Inhibitors of apoptosis proteins are crucial to carcinogenesis since their expression results in evasion of apoptosis. Overexpression of inhibitors of apoptosis has repeatedly been associated with resistance to treatment and poor prognosis in various cancers. The role of inhibitors of apoptosis in adenoid cystic carcinoma of the salivary gland is still unclear. The aim of this study was to investigate the expression of inhibitors of apoptosis and their potential prognostic value in adenoid cystic carcinoma.

Design, setting and participants: Forty-nine patients, diagnosed with adenoid cystic carcinoma of the salivary gland between 1996 and 2016, were retrospectively included in this study. The expression of cIAP1, cIAP2, XIAP, Birc6, Livin and Survivin was assessed using immunohistochemistry, and their association of survival and prognosis was evaluated during a median follow-up of 6.4 years.

Main outcome measure: Cause-specific survival and recurrence-free survival rates.

Results: XIAP, cIAP2, Livin and nuclear Survivin showed high expression levels in adenoid cystic carcinoma in most patients. There was no significant association of cIAP1, cIAP2, Livin, Birc6 and Survivin with outcome. However, high XIAP expression was associated with worse cause-specific survival and worse response to radiotherapy and proved to be an independent marker in multivariable analysis.

Conclusion: Our data indicate that high expression of XIAP may be used as a prognosticator for poor survival and poor response to radiotherapy in adenoid cystic carcinoma patients.

Lukas Kenner, Gregor Heiduschka contributed equally to this work.

1 | INTRODUCTION

Adenoid cystic carcinomas (ACCs) amount up to ten per cent of all salivary gland malignancies and are one of the most common salivary gland carcinomas, alongside mucoepidermoid carcinoma and adenocarcinoma. However, they represent less than one per cent of all head and neck tumours and are generally an uncommon malignancy.[1] The survival rates at 5 and 10 years vary between 68%-80% and 52%-65%, respectively.[2-4] Treatment options include surgical resection, adjuvant radiotherapy or radiotherapy alone in case of unresectable spread.[1,5] Recently, the application of heavy-ion therapy has shown promising results in unresectable cases. In particular, primary tumours located near the skull base may be treated with this kind of radiotherapy.[6,7] However, current therapeutic options are limited. Thus, the investigation of the underlying mechanisms of carcinogenesis and prognostic markers in ACC is needed to identify new treatment options and to select patients who require intensified therapy.

Hanahan and Weinberg initially defined the six hallmarks of cancer in 2000 and 2011.[8] One of those hallmarks is evasion of cell death. Apoptosis, a physiologic process for execution of programmed cell death, is a highly regulated process that can be activated or inhibited through extrinsic or intrinsic mechanisms. The inhibitor of apoptosis proteins (IAPs) inhibits apoptosis via suppression of initiator and effector caspases. This is achieved through binding of the active site of caspases, inhibition of pro-caspases, ubiquitination and degradation or activation of anti-apoptotic proteins. There are eight members in the IAP family: X-linked inhibitor of apoptosis protein (XIAP), cellular IAP1 (cIAP1), cellular IAP2 (cIAP2), IAP-like protein 2, baculoviral IAP repeat-containing protein 6 (Birc6), Livin, Survivin and neuronal apoptosis inhibitory protein (NAIP). Since apoptosis is a strictly regulated process among IAPs, their antagonists and caspases, imbalance due to upregulation of IAPs can lead to carcinogenesis as a result of decreased cell death. Naturally, IAPs are overexpressed in many malignancies and overexpression is associated with resistance to treatment and shorter survival.[9] Therefore, IAPs are currently under investigation as possible therapeutic targets, using synthetic mimetics of the second mitochondria-derived activator of caspase (SMAC), a natural inhibitor of IAPs.[10]

Data on the molecular mechanisms of ACCs are still limited, and to date, there are only little data available on the expression of IAPs in ACC of the salivary gland. Therefore, the aim of this study was to investigate the expression of IAPs and their clinical relevance in ACCs.

Keypoints

- Overexpression of inhibitors of apoptosis has repeatedly been associated with resistance to treatment and poor prognosis in various cancers.
- The expression of cIAP1, cIAP2, XIAP, Birc6, Livin and Survivin was assessed in patients with adenoid cystic carcinoma of the salivary gland using immunohistochemistry.
- XIAP, cIAP2, Livin and nuclear Survivin showed high expression levels in adenoid cystic carcinoma in most patients.
- High XIAP expression was associated with worse cause-specific survival and worse response to radiotherapy.
- Our data indicate that high expression of XIAP may be used as a prognosticator for poor survival and poor response to radiotherapy in adenoid cystic carcinoma patients.

2 | PATIENTS AND METHODS

2.1 | Patients

This retrospective, single-institution study included patients with histologically verified ACC of the major or minor salivary glands treated between 1996 and 2016 at the Departments of Otolaryngology and Head and Neck Surgery of the Medical University of Vienna. Exclusion criteria were age under 18 years, diagnosis of a second malignant disease or incomplete patient records. Data were obtained by medical chart review. Collected data included date of birth, time of initial diagnosis, recurrence, tumour grading, histology and date of death or date of last follow-up. This study was approved by the ethics committee of the Medical University of Vienna (EK 1517/2018).

2.2 | Tissue microarray

A tissue microarray (TMA) was constructed using a Galileo TMA CK Series—HTS Tissue Computer-assisted TMA Microarray Platform (Integrated Systems Engineering Srl). Cylindrical samples, measuring 2 mm in diameter and 4-6 mm in length, were taken from pre-selected formalin-fixed paraffin-embedded ACC tissue. Their histology was confirmed by H&E staining. The tissue samples were analysed by a pathologist for histologic pattern, grading according to Perzin/Szanto,[11,12] or Spiro,[13] perineural and lymphatic invasion. The pathohistological procedures at the Department of Pathology of the Medical University of Vienna are standardised and comply strictly with the certified requirements of ISO: 9001. These standards are maintained by regular audits from an official quality management system (Quality Austria). All pathohistological procedures were established with great care and quality controls defined in standards of practice (SOPs).

2.3 | Immunohistochemistry

Immunohistochemical staining was performed using a Lab Vision Ultra Kit (Thermo Scientific) according to the manufacturer's

protocol. The ideal antibody dilution and retrieval buffer was assessed prior to analysis. The TMAs were dewaxed and rehydrated. Antigen retrieval was performed using either EDTA or citrate buffer (pH 6.0) in a microwave (600 W). Subsequently, endogenous peroxidase activity was blocked in three per cent H_2O_2 for 15 minutes. After the application of Ultra V Block for 5 minutes, the tissue was incubated for 1 hour with the primary antibodies against cIAP1 1:200, cIAP2 1:100, Livin 1:100, XIAP 1:200, Birc6 1:1000 or Survivin 1:1000 (all Abcam) at room temperature. Next, the primary antibody enhancer and horseradish peroxidase enhancer were applied for 10 and 15 minutes, respectively. Staining was visualised by the application of UltraVision Plus Detection System DAB Plus Substrate System (Thermo Scientific). Counterstaining was performed with haematoxylin Gill III (Merck). The tissues were analysed using an Olympus BH-2 microscope (Olympus). The samples were assigned according to their staining intensity (0: negative, 1: weak, 2: moderate, 3: strong) and percentage of stained cells (0:0%-10%, 1:11%-30%, 2:31%-70%, 3:71%-100%). Scores were calculated by addition of staining intensity and percentage to dichotomise the expression level into low and high. A score <4 points was defined as low, and a score 4-6 points was defined as high expression. Notably, due to the overall low expression, Birc6 was categorised into negative (0 points) or positive (≥1) staining.

2.4 | Statistical analysis

Continuous data were reported as median and 25th and 75th percentiles and categorical data as absolute frequencies (%). Associations between the expression of IAPs and clinical data were analysed by either Fisher's exact test or chi-squared test. Time to event was calculated from the date of diagnosis to the date of cancer-associated death or tumour recurrence. Cause-specific survival (CSS) and recurrence-free survival (RFS) rates were visualised using Kaplan-Meier curves and analysed for statistical significance using log-rank test. The Cox proportional hazard model was used for uni- and multivariable regression analyses. The multivariable model for XIAP was corrected for staging and perineural invasion, and the subgroup that received postoperative radiotherapy was corrected for staging. Median follow-up was calculated based on the method published by Schemper et al[14] Statistical analysis was performed using Prism GraphPad software (GraphPad Software, Inc) and SPSS (Statistical Program of Social Sciences, version 23.0; Inc).

3 | RESULTS

3.1 | Analysis at baseline

A total of 49 patients with ACC who underwent surgical resection were included in this study (Table 1). The median observation period was 77.1 months (49.6-173.2). Nine patients were observed

TABLE 1 Basic data and descriptive statistics of salivary ACC patients

	Number of patients	Percentage (%)
Gender		
Male	23	46.9
Female	26	53.1
T stage		
1	5	10.2
2	6	12.2
3	8	16.3
4	24	49.0
X	6	12.2
N stage		
0	34	69.4
1	4	8.2
2	6	12.2
X	5	10.2
M stage		
0	41	83.7
1	3	6.1
X	5	10.2
Stage		
I	5	10.2
II	7	14.3
III	5	10.2
IV	25	51.0
X	7	14.3
Grading—Spiro		
1	28	57.1
2	12	24.5
3	3	6.1
X	6	12.2
Grading—Perzin/Szanto		
1	8	16.3
2	24	49.0
3	11	22.4
X	6	12.2
Localisation		
Minor	31	63.3
Major	16	32.7
Other	1	2.0
Perineural invasion		
Yes	23	46.9
No	25	51.0
X	1	2.0
Lymphovascular invasion		
Yes	6	12.2
No	42	85.7
X	1	2.0

for 10 years or more. The mean age at diagnosis was 58.6 years (47.0-70.4). Most patients presented with advanced stage (Stage IV in 51%), advanced tumour size (T4 in 49%) and absent lymph node metastasis (N0 in 69%). Distant metastases were found in three patients (6.3%). Perineural invasion was found in 23 patients (47%), and lymphovascular invasion was found in six patients (12%). Most ACCs were localised in the minor salivary glands (63%). Overall, 53% of the patients were female. The median CSS was 121.3 months, and the median RFS was 48.4 months. The 5-year and 10-year CSS was 72% and 53%, respectively. As for RFS, 43% and 24% were recurrence-free after 5 and 10 years, respectively. Most patients were treated with primary resection of the tumour (n = 43, 88%). Forty-three per cent (n = 21) received postoperative radiotherapy, 18% (n = 9) received postoperative radiochemotherapy and 4% (n = 2) were treated with adjuvant proton therapy.

3.2 | Expression of IAPs

Protein expression of XIAP, cIAP1, cIAP2, Livin, Birc6, nuclear Survivin (N-Survivin) and cellular Survivin (C-Survivin) was assessed by immunohistochemistry and stratified into high or low expression. High expression of IAPs was observed as follows (Figure 1G): N-Survivin (89.4%, n = 42/47), Livin (75.6%, n = 34/45), cIAP2 (74.5%, n = 35/47), XIAP (61.2%, n = 30/47), cIAP1 (47.8%, n = 22/46), C-Survivin (38.3%, n = 18/47) and Birc6 (0%, n = 0/36). The expression of Birc6 was therefore further divided into negative and positive expression (50%, n = 18/38).

3.3 | Analysis of clinicopathological data and expression of IAPs

The expression of various IAPs was analysed for their association of staging and grading using Fisher's exact test or chi-squared test. High XIAP expression was more frequently found in women (P = .003, corr. P = .021). There were no other interrelations between clinicopathological factors and the expression of IAPs (Table S1).

3.4 | Analysis of cause-specific survival and recurrence-free survival

The median CSS was decreased in case of high expression levels of XIAP (not reached vs 96 months, log-rank P = .043, corr. P = .301, Figure 2). Expression of all other members of the IAP family was not associated with survival. RFS was not associated with the expression of any IAP in our cohort. Kaplan-Meier curves for CSS and RFS were calculated as shown in Figure S1.

Subsequently, uni- and multivariable analyses were performed to further investigate the impact of XIAP expression on CSS. In univariable analysis, higher expression of XIAP was associated with worse CSS (HR = 1.52, 95% CI: 1.08-2.15, P = .016). Furthermore, multivariable analysis, adjusted for staging and perineural invasion status, revealed an increased risk of cause-specific death in the group with high expression of XIAP (HR = 1.53, 95% CI: 1.05-2.24, P = .028). Since low expression of XIAP was associated with better sensitivity to radio- and chemotherapy in other cancer entities, we further analysed the subgroup of patients who received postoperative radiotherapy (43%, n = 21). Univariable analysis revealed an increased risk of death in patients with a high XIAP score (HR = 1.89, 95% CI: 1.09-3.18, P = .024). This result prevailed after correction for staging in multivariable analysis (HR = 2.09, 95% CI: 1.22-3.56, P = .007). The subgroup that received chemotherapy could not be analysed separately due to the small number of patients (n = 9).

4 | DISCUSSION

Adenoid cystic carcinoma is among the three most common salivary gland malignancies. While short-term survival rates are favourable, long-term survival rates are rather poor. Currently, clinicopathological risk factors, such as perineural invasion, serve to guide therapeutic decisions.[3] However, outcomes of current therapeutic options are limited; therefore, it is necessary to investigate possible therapy targets and biomarkers.[1-4] In this study, we showed for the first time that high expression of the IAP XIAP is associated with poor prognosis and poor response to radiotherapy.

Upregulation and overexpression of various IAPs have been described in many tumours. They are partly responsible for tumour promotion and progression due to reduced apoptotic rates, which leads to enhanced survival and proliferation.[9] In ACC of the lacrimal gland, high nuclear expression of Survivin was described in 35.5%.[15] In pancreatic cancer, Lopes et al found the enhanced expression of XIAP, Livin, cIAP2 and Survivin.[16] According to Zhang et al, cIAP1, XIAP, Birc6, Survivin and Livin are overexpressed in oesophageal cancer.[17] In this study, the expression of cIAP1, cIAP2, Livin, XIAP, Birc6 and Survivin was assessed by immunohistochemistry. Most patients showed high expression of N-Survivin (89.4%), Livin (75.6%), cIAP2 (74.5%) and XIAP (61.2%), while cIAP1 (47.83%), C-Survivin (38.3%) and Birc6 (0%) expression was mostly low. These data indicate that N-Survivin, Livin, cIAP2 and XIAP may play a role in salivary gland ACCs.

Correlation of clinicopathological data revealed a significant association of high XIAP expression with female gender. However, there was no further association of IAPs with other clinicopathological characteristics. This finding is in concordance with other reports in the literature.[17-19] In contrast, expression of cIAP1 significantly correlated with lymph node metastasis and advanced clinical stage in head and neck squamous cell carcinoma,[20] and high expression of XIAP was associated with venous invasion, tumour differentiation and staging in colorectal cancer.[21]

Next, the expression of IAPs was analysed for its impact on survival and recurrence-free survival. In our cohort, CSS was significantly worse in case of high XIAP expression. Additionally, multivariable analysis showed that patients with high expression of

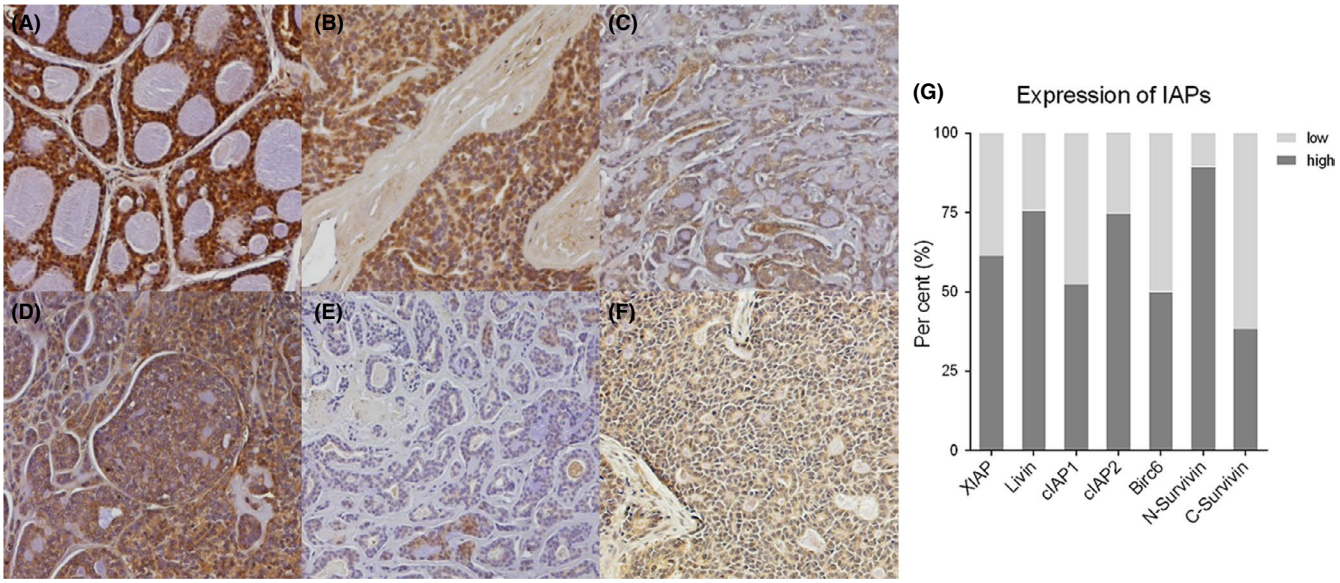

FIGURE 1 Images of high expression of immunohistochemical staining of XIAP (A), Livin (B), cIAP1 (C), cIAP2 (D), Birc6 (E), and N- and C-Survivin (F). (G) shows the percentage of patients with high and low IAP expression in immunohistochemical analysis. Expression of Birc6 was separated in positive and negative expression due to the overall low expression

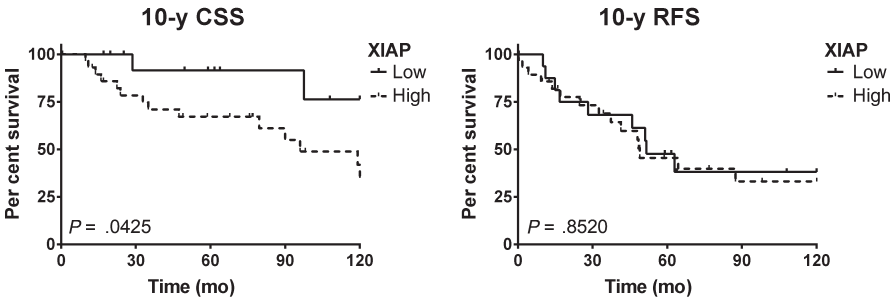

FIGURE 2 Kaplan-Meier curves of 10-y CSS and 10-y RFS for high and low staining intensity of XIAP. Survival was analysed using log-rank test. CSS, cause-specific survival; RFS, recurrence-free survival; *P*, log-rank *P* value

XIAP had a 53% increased risk of cause-specific death. All the other examined IAPs showed no association of CSS. Moreover, none of our tested IAP members had an impact on RFS. Interestingly, other studies showed decreased sensitivity to radio- and chemotherapy in patients diagnosed with oesophageal and ovarian cancer when XIAP was upregulated.[18,22,23] Therefore, we hypothesised that the decreased 10-year CSS rate for the high expression of XIAP might be due to the increased sensitivity to postoperative radiotherapy. In this study, the group with high XIAP expression that received radiotherapy showed a doubled risk of cause-specific death compared to the group with low XIAP expression. The subgroup that received chemotherapy was not analysed due to the small number of patients.

Altogether, our data indicate that XIAP might be a suitable candidate as a prognostic marker for cause-specific survival and response to radiotherapy in ACC. To date, several phase I and phase II studies have investigated XIAP as therapeutic target using SMAC mimetics in ovarian cancer, non-small cell lung cancer and solid tumours.[10] Since XIAP is expressed in most patients with ACC and associated with a more aggressive course of disease, our results warrant further in vitro studies investigating the effects of XIAP inhibition in ACC cells.

Limitations of this study are the small case number due to the retrospective, single-centre study design and limited observation period. Survival rates of ACC continuously drop with elapsed time.[1,4] The median observation period was 77.1 months (49.6-173.2); thus, late recurrence or death might not be recorded in this study. Furthermore, due to the retrospective design of this study, immunohistochemistry was performed on formalin-fixed tissue. Hence, some protein might be lost compared with fresh tissue. However, pathohistological procedures comply with strict standardisations at the Department of Pathology of the Medical University of Vienna. Therefore, it is assumable that the used grading system is valid and reliable. To validate our finding, they should be verified by an external validation cohort.

In conclusion, this retrospective study has shown that the IAPs XIAP, cIAP2, Livin and N-Survivin are highly expressed in salivary ACC. While there was no significant association of cIAP1, cIAP2, Livin, Birc6 and Survivin with outcome, high expression of XIAP was associated with worse CSS and worse response to postoperative radiotherapy. These data merit further investigation of XIAP expression and its potential use as prognostic marker for disease outcome. Furthermore, XIAP might be a suitable candidate for targeted therapy in ACC of the salivary gland.

CONFLICT OF INTEREST

None to declare.

AUTHORS' CONTRIBUTIONS

JS and L.Ka. contributed to the study design, data collection, statistical analysis and manuscript writing. BJJ, FO, FB, EG, JC, RS, L.Ke. and GH contributed to the study design, data collection and manuscript revision. All authors critically reviewed and revised the manuscript. All authors read and approved the final manuscript. All authors have neither financial nor ethical conflict of interests.

ETHICAL APPROVAL

This study was approved by the ethics committee of the Medical University of Vienna (EK 1517/2018).

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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