Prognostic impact of HLA class I immunohistochemistry staining intensity with regard to the risk of recurrence of adenoid cystic carcinoma

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Received October 6, 2025; Accepted December 3, 2025

DOI: 10.3892/mco.2026.2926

Abstract. Adenoid cystic carcinoma (AdCC) evolves from the salivary glands and may arise in the head and neck region or outside of this area. The symptoms of AdCC are generally nonspecific, and its diagnosis is challenging due to its heterogeneous histopathology and indolent growth. Moreover, reliable prognostic markers are lacking. Therefore, the present study investigated the prognostic potential of immunohistochemical staining of the immune markers HLA class I, CD4, CD8 and FOXP3 in AdCC. In total, 72 patients diagnosed with AdCC between January 2000, and December 2014 were included. Biopsy material underwent immunohistochemical staining for the aforementioned markers, and staining extent and intensity in the tumour and corresponding stroma were assessed, and their association with clinical outcome was investigated. Patients with analogous staining intensity of HLA class I in the tumour tissue to that in the stromal tissue had significantly fewer recurrences, as compared with those with lower HLA class I intensity staining in the tumour than in the stroma. By contrast, $CD8^+$, $CD4^+$ and $FOXP3^+$ staining was not significantly associated with recurrence. Furthermore, none of the markers were associated with overall survival. Moreover, patients with clinical stage I and II had fewer recurrences than those with stage III and IV AdCC. In conclusion, among the investigated biomarkers, only an analogous HLA class I expression in tumour tissue relative to that in the stromal tissue was associated with a reduced risk of recurrence in AdCC. These findings suggest a potential role of HLA class I as a prognostic marker in this rare malignancy.

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Key words: adenoid cystic carcinoma, HLA class I, $CD8^+$, $CD4^+$, FOXP3, prognostic markers

Introduction

Adenoid cystic carcinoma (AdCC) is a rare type of cancer, evolving from salivary glands, with a so far unknown aetiology (1-5). It accounts for around 10% of all cancers in the major salivary glands and 30% of all cancers in the minor salivary glands in the head and neck region, and is therefore regarded as one of the most common malignant salivary tumours (2). AdCC can, however, also arise in other locations within the head and neck region and in salivary glands outside of this region, as well as throughout the body (2). It is more common in females as compared to males, and prevalent between 50-70 years of age, although it can occur at all ages (3,5). Its symptoms are unspecific, and its diagnosis is challenging, due to its slow and indolent growth. Moreover, there is a lack of reliable specific diagnostic and prognostic markers (3,5). However, genetic alterations, such as MYB-NFIB and MYBL1-NFIB fusions, and mutations in the Notch-1 signalling and DNA damage repair pathways, have recently been disclosed (6,7). Currently, patients are initially treated with surgery, often followed by adjuvant radiotherapy. However, despite the intensive treatment, late relapses are frequent (3). Clearly, AdCC therefore presents both a diagnostic and clinical challenge. In other cancers, e.g., head and neck squamous cell carcinomas, it has been shown that a high presence of $CD8^+$ infiltrating lymphocytes or a high $CD8^+$/FOXP3 coefficient, or HLA class I staining could be of prognostic benefit, as a normal/high expression of HLA class I staining (8-12).

In this exploratory study, we therefore attempted to evaluate whether staining by immunohistochemistry (IHC) of HLA class I, CD4, CD8, and FOXP3, markers of immunologically prognostic interest for other cancers, could be of prognostic value.

Patients and methods

Patients. Of patients diagnosed with AdCC between 2000-2014 in the Stockholm region of Sweden, and included in prior

studies (13,14), all were regarded as eligible to be included in the present investigation. Of these, 72 had paraffin-embedded diagnostic material available for further analysis in this study. The characteristics of these patients and their tumours are presented in Table I.

IHC. IHC was done by manual processing, with a standard avidin-streptavidin method on three tissue microarrays (TMAs) (9,10,15). Each TMA comprised two 1-mm cores per case, including one tumour core and one matched adjacent normal tissue core. TMA sections were deparaffinized and rehydrated, followed by antigen retrieval (citrate buffer pH 6.0), and the endogenous peroxidase was blocked. The slides were then incubated in horse serum, followed by incubation at 4˚C overnight with the primary antibodies. Three primary antibodies were from Abcam, Cambridge, UK and diluted 1:200 and these were the anti-CD4 antibody (clone EPR6855), an IgG, rabbit, monoclonal; the anti-FOXP3 antibody (clone 236A/E7) an IgG, mouse monoclonal; and the anti-HLA Class I ABC antibody (clone EMR8-5), recognizing human HLA class I A, B, and C, an IgG, mouse monoclonal. The anti-CD8 antibody was obtained from Leica Biosystems, Mölndal, Sweden (Novocastra Laboratories clone 4B11), diluted 1:40, and was an IgG2b mouse monoclonal.

The sections were incubated with a biotinylated secondary anti-mouse IgG or anti-rabbit IgG followed by incubation with an avidin-streptavidin complex (VECTASTAIN Elite ABC-kit, Vector Laboratories, Burlingame, CA, USA) for detection and DAB for visualization. The slides were counterstained with haematoxylin.

Staining evaluation. Tumour sections and normal adjacent tissue were examined independently by two researchers (MZ and MB) blinded for clinical outcome. CD4, CD8 and FOXP3 were quantified as number of positive cells in epithelial tumour and tumour stroma. HLA-I staining was quantified as percentage of stained tumour tissue, as well as intensity of staining in the tumour tissue compared to that in the stroma (equal intensity or lower). Any disagreements were resolved by consensus through consultation with AN (specialist in clinical pathology).

Statistical analysis. The χ^2 or Fisher's exact test was used for categorical data, while comparison of mean values was done with paired or unpaired Student's *t*-tests, when appropriate. Clinical outcome data were obtained from medical records. Overall survival (OS) was calculated in years from the date of diagnosis until the date of death or the date of OS assessment (11-12 May 2022). Disease-free survival (DFS) was calculated in years from the date of diagnosis until the first documented recurrence or until the date of DFS assessment (11-12 May 2022). Patients without a disease-free period were censored at day 0, and patients who died without a documented recurrence were censored at their date of death. For HLA class I data, the Kaplan-Meier estimator was used to visualize OS and DFS, and the log-rank test was applied to assess differences in survival. $P<0.05$ was considered to indicated a statistically significant difference. All analyses were performed using IBM SPSS Statistics for Mac, version 31 (IBM Corp.).

Results

Patients, their clinical characteristics and treatment, as well as tumour staging in association with presence or absence of recurrence. Patient and tumour characteristics of the 72 AdCC patients are depicted in Table I. More specifically, there were 45 female and 27 male patients, with a mean age of 55 years (Table I). Most patients had surgery, which was not radical for most, and this was followed by radiotherapy in all patients, irrespective of whether surgery was radical or not.

According to the Union of International Cancer Control (UICC) staging, 23 patients had stage I tumours and of these 5/23 (21.7%) had a recurrence; 20 patients had stage II tumours and of these 5/20 (25%) had a recurrence; 11 patients had stage III tumours and 9/11 (81.1%) had recurrences; and 18 patients had stage IV tumours and 15/18 (83.3%) had a recurrence (Table I). Altogether, 34/72 (47.2%) of the patients encountered a recurrence, however, of note, patients with stage I and II tumours 10/43 (23.3%) had significantly fewer recurrences than those with stage III and IV tumours 24/29 (82.8%), $P<0.0001$ (χ^2).

We also examined whether sex, smoking or age had any prognostic impact regarding presenting a recurrence, but as shown previously (8), this was not the case. Regarding sex, 21/45 (46.7%) of women and 13/27 (48.1%) of the men had a recurrence ($P=0.903$, χ^2). Additionally, there was no difference regarding smoking status among the patients who had a recurrence, with 16/34 (47.1%) never smokers and 18/38 (47.4%) ever smokers presenting with recurrence ($P=0.973$, χ^2). Lastly, there was no difference in mean age between the 38 patients with and the 34 patients without recurrence (55.3 vs. 54.6 years, $P=0.848$, unpaired t-test).

HLA class I staining by IHC in the tumour and the stroma in patients with and without recurrence. Most patients 64/72 (88.9%), had HLA class I staining in their tumours, but the difference in intensity of the staining between tumour and stroma varied. 44/72 (59.7%) samples had equal intensity staining in the tumour compared to that in the stroma. Fig. 1 demonstrates normal/equal intensity HLA class I staining in the tumour compared to that in the stroma and weaker/lower intensity HLA class I staining in the tumour compared to the stroma.

A weaker HLA class I staining, as compared to the surrounding stroma, was observed significantly more often in patients with recurrence compared to those without [18/34 (52.9%) vs. 10/38 (26.3%), $P=0.021$, χ^2]. There was no significant difference in fraction of positive cells between patients with and without recurrence [28/34 (82.4%) vs. 36/38 (94.7%), $P=0.138$, Fisher's exact test].

Kaplan Meier curves for DFS and OS and HLA class I staining are presented in Fig. 2. For DFS, the 5-year survival was 63% in patients with normal/equal to stroma staining vs. 54% in those with weaker tumour staining. The corresponding 10-year figures were 60% vs. 29% (log rank test: $P=0.048$). For OS, the 5-year survival was 88% vs. 75%, and the 10-year survival was 50% vs. 30%; differences that did not reach significance (log rank test: $P=0.10$).

CD8, CD4 and FOXP3 staining by IHC in the tumour and stroma in patients with and without recurrence. CD8, CD4

Table I. Characteristics of patients with adenoid cystic cancer and their tumours.

Characteristic	Value
All patients, n (%)	72 (100.0)
Age at diagnosis, years	
Mean (SD)	55 (14.5)
Sex, n (%)	
Male	27 (37.5)
Female	45 (62.5)
Subsite, n (%)	
Parotid gland	19 (26.4)
Oral cavity	16 (22.2)
Submandibular gland	23 (31.9)
Nasal cavity & paranasal sinuses	7 (9.7)
Lip	1 (1.4)
Oropharynx	5 (6.9)
Nasopharynx	1 (1.4)
Stage, n (%)	
I	23 (31.9)
II	20 (27.8)
III	11 (15.3)
IV	18 (25.0)
Smoking, n (%)	
Ever	38 (52.8)
Never	34 (47.2)
Treatment, n (%)	
Surgery	66 (91.7)
Radical surgery	9 (12.5)
RT	51 (70.8)
CRT	21 (29.2)
Induction ChT	3 (4.2)
Recurrence, n (%)	
Locoregional	16 (22.2)
Distant metastasis	31 (43.1)
None	38 (52.8)

RT, radiotherapy; CRT, chemo-radiotherapy; ChT, chemotherapy.

and FOXP3 staining in the tumour and/or stroma varied from 0 to >300 positive cells per mm^2. Examples of CD8, CD4 and FOXP3 staining are illustrated in Fig. 3.

For CD8$^+$ staining, the overall mean cell infiltration was higher in stroma than in tumour tissue (59.8 vs. 40.5 CD8$^+$ cells), but this difference was not statistically significant (paired t-test: P=0.15). Patients without recurrence showed higher CD8$^+$ levels compared to those with recurrence, both in tumour (52.7 vs. 27.1) and stroma (78.1 vs. 39.9). However, these differences were not significant (independent t-test: P=0.3 and 0.2, respectively).

For CD4$^+$ staining, the overall mean infiltration was similar between tumour and stroma (144.7 vs. 162.8 CD4$^+$ cells, paired t-test: P=0.40). There was no notable difference between patients without and with recurrence in tumour (140.7 vs. 148.9, independent t-test: P=0.96) or stroma (166.5 vs. 158.8, independent t-test: P=0.82).

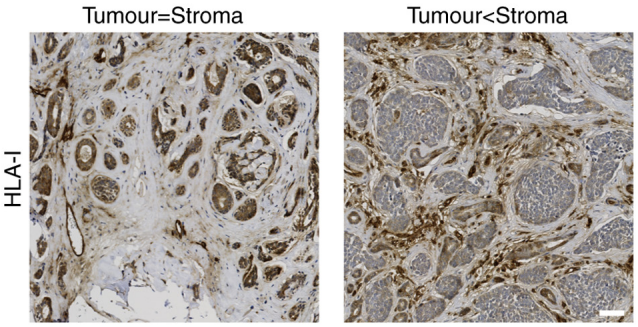

Figure 1. **Different presentations of HLA class I using immunohistochemistry.** HLA-I staining revealing differential expression patterns with an analogous intensity staining in tumour compared to the stroma (left) or a lower intensity HLA class I staining in the tumour compared to the stroma (right). Magnification: x20, scale bar (white): 50 μM.

For FOXP3, the overall mean infiltration was low in both compartments (13.3 in stroma and 6.8 in tumour, paired t-test: P=0.22). There were no significant differences in FOXP3 infiltration between patients with or without recurrence (independent t-test: stroma: P=1.0 and tumour: P=0.4).

Discussion

In this exploratory study, we evaluated the prognostic relevance of the immune markers HLA class I, CD8, CD4, and FOXP3, markers known to be of prognostic value in several carcinomas. In addition, clinical parameters, including stage, age, and sex were assessed. Here, of the assessed markers, only low intensity HLA class I tumour staining was significantly associated with an increased risk of recurrence. Among the clinical factors, low stage (I-II) disease was, as expected, also significantly associated with fewer recurrences compared to high stage (III-IV) disease.

That normal expression of HLA class I staining in the tumour was associated with having less recurrences, was immunologically not unexpected, but of interest since data on HLA class I expression in AdCC are limited. Moreover, HLA class I molecules are well-known to be critical to adapt immune responses to tumours and viral infections by conveying proteosome-generated tumour and viral antigen peptides to CD8$^+$ T-cells (16-22).

Here, almost 40% of the patients had lower HLA class I staining in the tumour compared to that in the stroma, which concords with a report that roughly half of the samples from 15 AdCC patients had downregulated HLA-antigens in their tumours upon transcriptomic analysis (23). Moreover, in another report, studying the immune landscape of AdCC, a near-complete absence of beta-2-microglobulin (B2M) expression and decreased HLA class I expression was disclosed in 20/24 examined AdCC patient samples (24). However, it was also shown that B2M and HLA class I could experimentally be partially restored using interferon-γ, or a stimulator of the interferon genes (STING) agonist *in vitro* (24). The authors concluded that this could potentially be of benefit for patient treatment and they also described that treatment of a patient

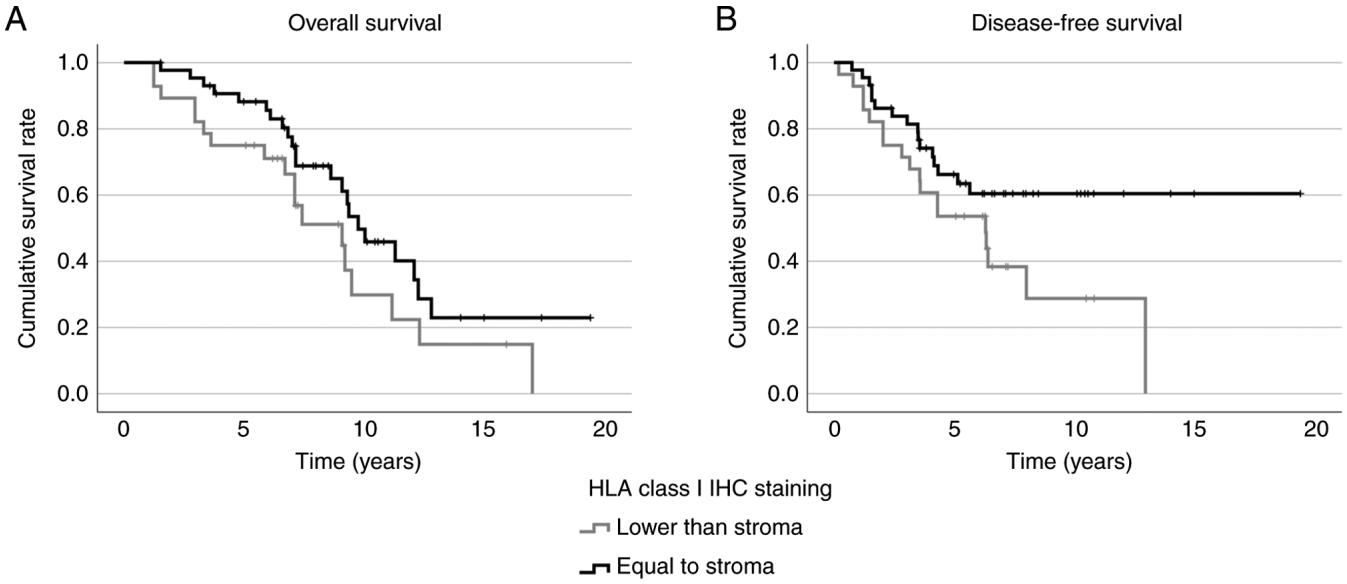

Figure 2. Kaplan Meier curves illustrating (A) DFS and (B) OS in patients with tumours showing HLA class I equal to the surrounding stroma (black line) or lower than that observed in stroma (grey line). For DFS, 5-year survival was 63% vs. 54%, and 10-year survival was 60% vs. 29% (log-rank test: P=0.048). For OS, 5-year survival was 88% vs. 75%, and 10-year survival was 50% vs. 30% (log-rank test: P=0.10). DFS, disease-free survival; IHC, immunohistochemistry; OS, overall survival.

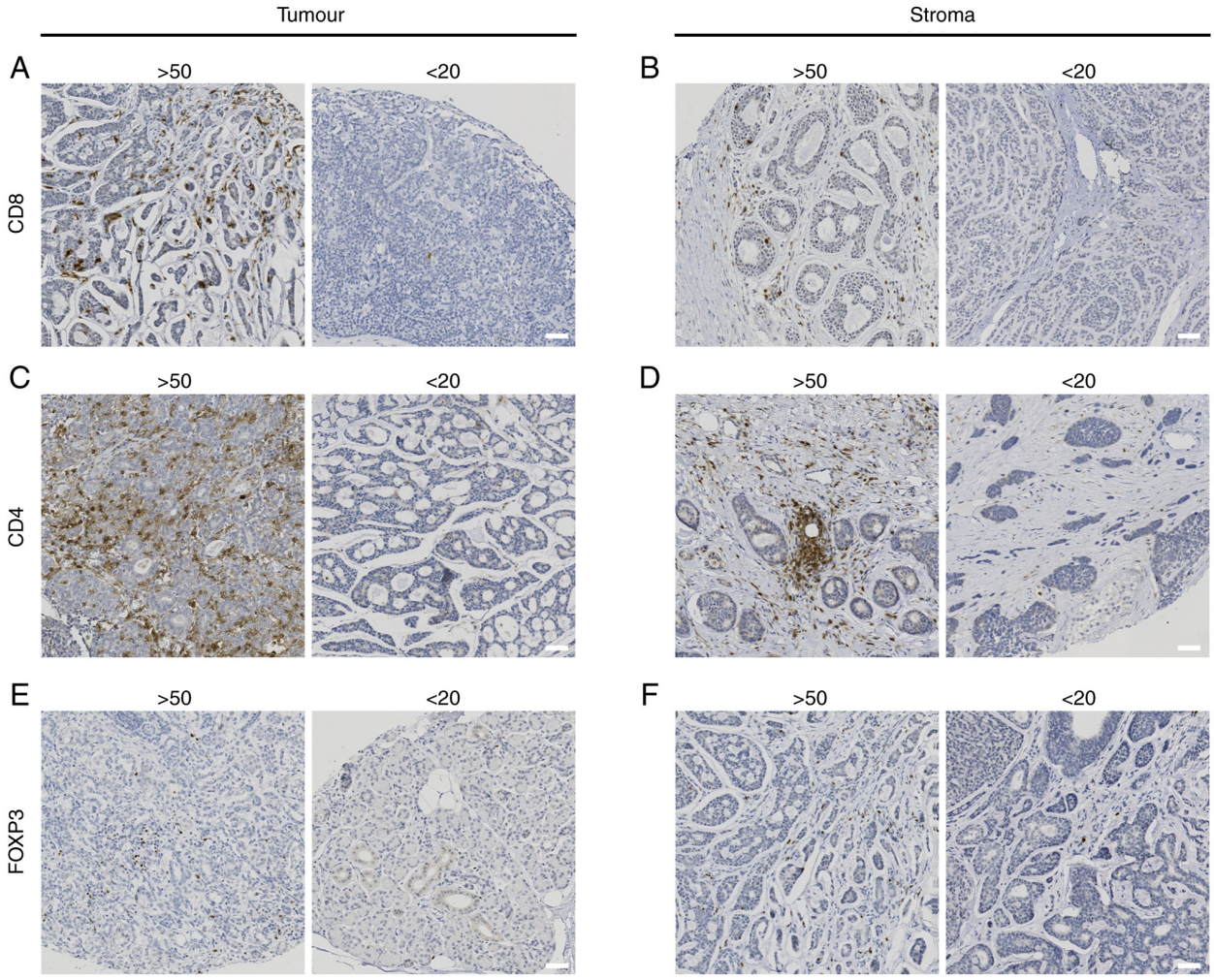

Figure 3. Expression of T-cell markers in adenoid cystic carcinoma. Immunohistochemistry staining of CD8 in the (A) tumour and (B) stroma. Immunohistochemistry staining of CD4 in the (C) tumour and (D) stroma. Immunohistochemistry staining of FOXP3 in the (E) tumour and (F) stroma. Numbers indicate cell number per 1 mm^3, thereby illustrating examples of tissues with higher or lower concentrations of the corresponding stained cells. Magnification: x20, scale bar (white): 50 μM.

with a metastatic breast AdCC with a STING agonist and pembrolizumab led to a partial response (24). The latter could be of potential future therapeutic interest and pinpoints the importance of HLA class I expression for an adequate immune response in AdCC.

That high numbers of $CD8^+$ and $CD4^+$ cells, or a low number of $FOXP3^+$ cells in tumour and stroma, did not correlate with a reduced risk of recurrence was disappointing, as these markers have shown prognostic relevance in other cancers (8,9,18,22,24). Moreover, our findings partly contradict previous reports indicating a high complexity of the microenvironment (25). However, our findings may be explained by the fact that, although high HLA class I expression is important for an effective immune response, the generally low HLA class I expression in AdCC could abrogate potential effects of immune cells, as also suggested by others (20-24). This phenomenon is not unusual in relation to viral infections, where many viruses downregulate HLA expression, e.g. where the E5 protein of Human papillomavirus and the adenovirus type 12 E1A that target and downregulate HLA class I expression (26,27).

Unfortunately, as noted there are limited studies on the immune microenvironment in AdCC for comparison. However, in one report, the combination of having a high PD1 expression score (>5%) together with high $CD8^+$ TIL abundance in the peritumoral microenvironment was associated with worse prognosis (28). In another study, in 50 AdCC patients, sections were stained for CD3, CD4, CD8 and CD20 and evaluated regarding their distribution of TILs (29). Patterns were determined as infiltrated-excluded, infiltrated-inflamed and presence of tertiary lymphoid structures. In the inflamed phenotype $CD3^+$ cells were the most abundant lymphocyte subtype, and within this compartment, $CD8^+$ T cells dominated. However, there was no influence on survival by any of the TIL patterns. The authors indicated that this was due to the very low immunogenicity of AdCC and that even abundance of lymphocytes did not seem to improve prognosis for this disease (29). The latter is in concordance with our findings.

Likewise, there are limited numbers of investigations on the potential association of FOXP3 staining and recurrence rates of AdCC, and in this report none were indicated. This could correlate very well with AdCC being an indolently growing tumour with low immunogenicity. In the report of Li *et al* (24), above like ours, FOXP3 expression was low, suggesting a limited number of Tregs in AdCC.

Of note, in this study stage I and II AdCC presented fewer recurrences than stage III and IV disease, which was in concurrence with our previous studies and that of others (14,30,31). Likewise, in this smaller cohort, like the previously examined whole group, we did not disclose age, sex or smoking as prognostic factors (14). Nevertheless, others have reported that older age is correlated with more advanced disease stages and worse prognosis (31,32). Therefore, the association of age to increased recurrence rate should likely still be pursued further.

This study has some limitations. First, the cohort was small, however, it was quite comparable to other studies (32). Furthermore, subsite, histomorphology markers, and perineural growth were not included in the analysis, and despite perineural growth not being considered a prognostic factor by us previously per se, it can be shown as such when combining several studies e.g. in a systematic review (14,33). Finally, assaying markers in TMAs has its limitations, since core samples do not represent the tumour's entire immune landscape or HLA class I representation, and this in turn could lead to an underestimation or the opposite of the markers true prognostic value.

To conclude, we were able to show that analogous HLA class I staining in the tumour as compared to the stroma was associated with a significant decrease in recurrence as compared to that in patients with low HLA class I staining in the tumour. Our finding is in concordance with others, and with the suggestion by others that ways to increase HLA class I expression in AdCC may be beneficial for AdCC patients; however, the latter needs to be further investigated.

Acknowledgements

Not applicable.

Funding

The Swedish Cancer Foundation (grant no. 23700PJ), the Stockholm Cancer Society (grant nos. 221082 and 241131), the Stockholm City Council, the Swedish Cancer and Allergy Foundation (grant no. 10662), Swedish Society of Medicine (grant no. SLS-999914), the Karolinska Institutet, the Sigurd and Elsa Golges Memory Foundation (grant no. LA2023-0042), the Magnus Bergvalls Stiftelse (grant no. 2024-1334), the Tornspiran Foundation 2024 and the Serafimerlasarettet Foundation 2024 are greatly acknowledged for supporting this research.

Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

AN, MZ, MB and TD designed the study. MZ, MB, TD and AN contributed to data acquisition, formal analysis, and validation. SF contributed to data acquisition and formal analysis. MB and MZ confirm the authenticity of all the raw data. MZ, MB, TD and AN contributed to funding of the project. TD initiated the writing of the original draft together with MB. All authors read and approved the final manuscript.

Ethics approval and consent to participate

The present study was conducted according to ethical permissions 99-237, from the Ethics Committee at Karolinska Institutet (Stockholm, Sweden); 2005/431-31/4, 2009/1278-31/4, 2012/83-31/2, 2017/1035-31/2, 2019-05211 from the Stockholm Regional Ethical Review Board (Karolinska Institutet, Stockholm, Sweden) and 2022-05287-02 from the Swedish Ethical Review Authority (Uppsala, Sweden). Written informed consent was obtained from all patients to participate in this study.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

References

1. Young A and Okuyemi OT: Malignant salivary gland tumors. In: StatPearls. StatPearls Publishing, Treasure Island, FL, 2025.
2. Ouyang DQ, Liang LZ, Zheng GS, Ke ZF, Weng DS, Yang WF, Su YX and Liao GQ: Risk factors and prognosis for salivary gland adenoid cystic carcinoma in southern china: A 25-year retrospective study. Medicine (Baltimore) 96: e5964, 2017.
3. Dillon PM, Chakraborty S, Moskaluk CA, Joshi PJ and Thomas CY: Adenoid cystic carcinoma: A review of recent advances, molecular targets, and clinical trials. Head Neck 38: 620-627, 2016.
4. Liu Y, Han T, Guo D, Chen D and Li Y: Exploring potential treatment opportunities in a head and neck tumor patient with AdCC: A novel germline ERCC2 mutation case report. Medicine (Baltimore) 104: e41233, 2025.
5. Zupancic M, Näsman A, Friesland S and Dalianis T: Adenoid cystic carcinoma, clinical presentation, current treatment and approaches towards novel therapies. Anticancer Res 44: 1325-1334, 2024.
6. Ferrarotto R, Mitani Y, Diao L, Guijarro I, Wang J, Zweidler-McKay P, Bell D, William WN Jr, Glisson BS, Wick MJ, *et al*: Activating NOTCH1 mutations define a distinct subgroup of patients with adenoid cystic carcinoma who have poor prognosis, propensity to bone and liver metastasis, and potential responsiveness to notch1 inhibitors. J Clin Oncol 35: 352-360, 2017.
7. Wagner VP, Bingle CD and Bingle L: Myb-nfib fusion transcript in adenoid cystic carcinoma: Current state of knowledge and future directions. Crit Rev Oncol Hematol 176: 103745, 2022.
8. Nordfors C, Grün N, Tertipis N, Ährlund-Richter A, Haeggblom L, Sivars L, Du J, Nyberg T, Marklund L, Munck-Wikland E, *et al*: CD8+ and CD4+ tumour infiltrating lymphocytes in relation to human papillomavirus status and clinical outcome in tonsillar and base of tongue squamous cell carcinoma. Eur J Cancer 49: 2522-2530, 2013.
9. Näsman A, Romanitan M, Nordfors C, Grün N, Johansson H, Hammarstedt L, Marklund L, Marklund L, Munck-Wikland E, Dalianis T and Ramqvist T: Tumor infiltrating CD8+ and Foxp3+ lymphocytes correlate to clinical outcome and human papillomavirus (HPV) status in tonsillar cancer. PLoS One 7: e38711, 2012.
10. Näsman A, Andersson E, Nordfors C, Grün N, Johansson H, Munck-Wikland E, Massucci G, Dalianis T and Ramqvist T: MHC class I expression in HPV positive and negative tonsillar squamous cell carcinoma in correlation to clinical outcome. Int J Cancer 132: 72-81, 2013.
11. Koike K, Dehari H, Shimizu S, Nishiyama K, Sonoda T, Ogi K, Kobayashi J, Sasaki T, Sasaya T, Tsuchihashi K, *et al*: Prognostic value of HLA class I expression in patients with oral squamous cell carcinoma. Cancer Sci 111: 1491-1499, 2020.
12. Caballero-Borrego M, Grau JJ, Basté N, Castillo PC, Teixido C, Valduvieco I and Vilaseca I: Cancer stem cell biomarkers in locally advanced head and neck squamous cell carcinoma. Braz J Otorhinolaryngol 91: 101689, 2025.
13. Zupancic M, Holzhauser S, Cheng L, Ramqvist T, Du J, Friesland S, Näsman A and Dalianis T: Analysis of human papillomavirus (HPV) and polyomaviruses (HPYVS) in adenoid cystic carcinoma (ADCC) of the head and neck region reveals three HPV-positive cases with adenoid cystic-like features. Viruses 14: 1040, 2022.
14. Zupancic M, Nasman A, Berglund A, Dalianis T and Friesland S: Adenoid cystic carcinoma (ADCC): A clinical survey of a large patient cohort. Cancers (Basel) 15: 1499, 2023.
15. de Flon CH, Haeggblom L, Holzhauser S, Kostopoulou ON, Zupancic M, Dalianis T, Munck-Wikland E, Marklund L and Näsman A: High levels of FGF11 correlate with poor survival in patients with human papillomavirus (HPV)-positive oropharyngeal squamous cell carcinoma. Cancers (Basel) 15: 1954, 2023.
16. Rötzschke O, Falk K, Deres K, Schild H, Norda M, Metzger J, Jung G and Rammensee HG: Isolation and analysis of naturally processed viral peptides as recognized by cytotoxic T cells. Nature 348: 252-254, 1990.
17. Schulz M, Aichele P, Schneider R, Hansen TH, Zinkernagel RM and Hengartner H: Major histocompatibility complex binding and T cell recognition of a viral nonapeptide containing a minimal tetrapeptide. Eur J Immunol 21: 1181-1185, 1991.
18. Dersh D, Hollý J and Yewdell JW: A few good peptides: MHC class I-based cancer immunosurveillance and immunoevasion. Nat Rev Immunol 21: 116-128, 2021.
19. Yang K, Halima A and Chan TA: Antigen presentation in cancer-mechanisms and clinical implications for immunotherapy. Nat Rev Clin Oncol 20: 604-623, 2023.
20. Kong S, Zhang J, Wang L, Li W, Guo H, Weng Q, He Q, Lou H, Ding L and Yang B: Mechanisms of low MHC I expression and strategies for targeting MHC I with small molecules in cancer immunotherapy. Cancer Lett 611: 217432, 2024.
21. Darabi A, Thuring C and Paulsson KM: HLA-I antigen presentation and tapasin influence immune responses against malignant brain tumors-considerations for successful immunotherapy. Anticancer Agents Med Chem 14: 1094-1100, 2014.
22. Emtiazi N, Zolfi E, Mehr FK and Moradi Y: The role of the major histocompatibility complex (MHC) class I in prostate cancer therapy: A review. Crit Rev Oncol Hematol 215: 104897, 2025.
23. Tang YF, An PG, Gu BX, Yi S, Hu X, Wu WJ and Zhang J: Transcriptomic insights into adenoid cystic carcinoma via RNA sequencing. Front Genet 14: 1144945, 2023.
24. Li A, Gonda BL, Codd EM, von Paternos A, Mitchell DR, Herrmann MD, Kalyan P, Flynn SE, Dzu TQ, Gao C, *et al*: Reversible downregulation of HLA class I in adenoid cystic carcinoma. J Immunother Cancer 13: e011380, 2025.
25. Mosconi C, de Arruda JAA, de Farias ACR, Oliveira GAQ, de Paula HM, Fonseca FP, Mesquita RA, Silva TA, Mendonça EF and Batista AC: Immune microenvironment and evasion mechanisms in adenoid cystic carcinomas of salivary glands. Oral Oncol 88: 95-101, 2019.
26. Campo MS, Graham SV, Cortese MS, Ashrafi GH, Araibi EH, Dornan ES, Miners K, Nunes C and Man S: HPV-16 E5 down-regulates expression of surface HLA class I and reduces recognition by CD8 T cells. Virology 407: 137-142, 2010.
27. Georgopoulos NT, Proffitt JL and Blair GE: Transcriptional regulation of the major histocompatibility complex (MHC) class I heavy chain, TAP1 and LMP2 genes by the human papillomavirus (HPV) type 6b, 16 and 18 E7 oncoproteins. Oncogene 19: 4930-4935, 2000.
28. Kesar N, Winkelmann R, Oppermann J, Ghanaati S, Martin D, Neumayer T, Balster S, Rödel C, Rödel F, von der Grün J and Balermpas P: Prognostic impact of CD8-positive tumour-infiltrating lymphocytes and PD-L1 expression in salivary gland cancer. Oral Oncol 111: 104931, 2020.
29. Doescher J, Meyer M, Arolt C, Quaas A, Klußmann JP, Wolber P, Bankfalvi A, Schildhaus HU, Bastian T, Lang S, *et al*: Patterns of tumor infiltrating lymphocytes in adenoid cystic carcinoma of the head and neck. Cancers (Basel) 14: 1383, 2022.
30. de Morais EF, da Silva LP, Moreira DGL, Mafra RP, Rolim LSA, de Moura Santos E, de Souza LB and de Almeida Freitas R: Prognostic factors and survival in adenoid cystic carcinoma of the head and neck: A retrospective clinical and histopathological analysis of patients seen at a cancer center. Head Neck Pathol 15: 416-424, 2021.
31. Spiro RH and Huvos AG: Stage means more than grade in adenoid cystic carcinoma. Am J Surg 164: 623-628, 1992.
32. Ko JJ, Siever JE, Hao D, Simpson R and Lau HY: Adenoid cystic carcinoma of head and neck: Clinical predictors of outcome from a canadian centre. Curr Oncol 23: 26-33, 2016.
33. Ju J, Li Y, Chai J, Ma C, Ni Q, Shen Z, Wei J and Sun M: The role of perineural invasion on head and neck adenoid cystic carcinoma prognosis: A systematic review and meta-analysis. Oral Surg Oral Med Oral 122: 691-701, 2016.