# Psoriasin expression is associated with survival in patients with human papillomavirus-positive base of tongue squamous cell carcinoma

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**Abstract.** Patients with human papillomavirus-positive (HPV+) base of tongue squamous cell carcinomas (BOTSCC) have an improved survival compared with patients with HPV-negative BOTSCC and it has been suggested that treatment should be tailored. Before individualized treatment can be introduced, additional prognostic markers are required. A prognostic role of psoriasin has previously been demonstrated outside BOTSCC. Therefore, the present study aimed to examine psoriasin in BOTSCC, with focus on HPV+ BOTSCC, in relation to prognosis. A total of 72 BOTSCC samples were stained for psoriasin by immunohistochemistry, and the association between expression and clinical outcomes was analyzed. Patients with low psoriasin expression exhibited significantly improved overall survival (OS; P=0.001) and disease-free survival (DFS; P=0.007), which also was observed in patients with HPV+ BOTSCC (OS, P<0.001; DFS, P=0.02). Furthermore, psoriasin was a significant prognostic factor in univariable and multivariable analyses. In conclusion, psoriasin could be used as a prognostic marker in HPV+ BOTSCC.

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*Abbreviations:* BOTSCC, base of tongue squamous cell carcinoma; DFS, disease-free survival; FFPE, formalin-fixed paraffin-embedded; HNSCC, head and neck squamous cell carcinoma; HPV, human papillomavirus; HPV-, human papillomavirus-negative; HPV+, human papillomavirus-positive; IHC, immunohistochemistry; OPSCC, oropharyngeal squamous cell carcinoma; OS, overall survival

*Key words:* oropharyngeal cancer, prognosis, psoriasin, s100A7, human papillomavirus

## Introduction

Human papillomavirus positive (HPV+) oropharyngeal squamous cell carcinomas (OPSCC) are increasing in incidence and patients with HPV+ OPSCC have a much better clinical outcome, as compared to patients with HPV negative (HPV-) OPSCC. Therefore, today, HPV+ and HPV- OPSCC are considered as two separate entities and are staged separately according the new AJCC/IUCC staging manual (TNM-8). Over the last years, it has also been debated if oncological treatment of patients with HPV+ OPSCC can be tapered, but previous attempts have not been successful (1). Notably, however, accumulated recent data advocate that HPV+ OPSCC should be divided into its sub-sites, when categorizing by HPV status and prognosis, more specifically tonsillar squamous cell carcinoma (TSCC), base of tongue squamous cell carcinoma (BOTSCC) and squamous cell carcinoma of the soft palate and the pharyngeal walls (other OPSCC) (2). Data from others and us clearly indicate that patients with HPV+ TSCC/BOTSCC have a better survival than patients with HPV- TSCC/BOTSCC, but this survival benefit of having HPV was not observed in patients with other OPSCC (3-7). Nevertheless, although the survival in general is favorable in patients with HPV+ TSCC/BOTSCC, prognostic markers are still needed to identify those few patients with a poor clinical outcome, before treatment can be tapered (8).

Psoriasin, or s100A7, is a protein part of the S100 family containing calcium-binding motifs and is an important cell mediator for e.g. cell survival and maturation. Increased expression of the protein has been reported in malignant and premalignant lesions and overexpression has also been correlated with clinical outcome (9-14). In a previous study by Tripathi *et al* (15), the expression of psoriasin was correlated to a worse prognosis in patients with head and neck carcinomas (HNSCC), but neither HPV status nor sub-site was considered in that study.

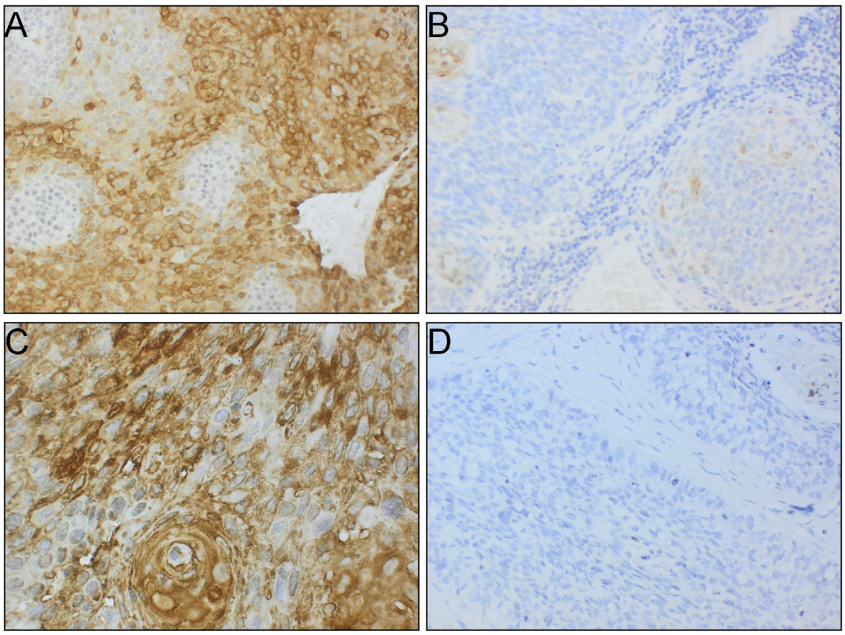


Figure 1. Representative images of psoriasin immunohistochemistry staining. Magnification, x400. (A) High expression in HPV+ BOTSCC. (B) Low expression in HPV+ BOTSCC. (C) High expression in HPV- BOTSCC. (D) Low expression in HPV- BOTSCC. BOTSCC, base of tongue squamous cell carcinoma; HPV, human papillomavirus; HPV+, HPV DNA-positive; HPV-, HPV DNA-negative.

Hence, in this study, we wanted to examine the previously reported prognostic significance of psoriasin staining obtained in a heterogenous HNSCC patient cohort, in a homogenous pilot cohort of only BOTSCC. This specific cohort had also previously been tested for the presence or absence of HPV DNA and p16 overexpression (16,17) and was therefore useful for examining psoriasin expression in correlation to HPV status, as well as to clinical outcome.

## Materials and methods

*Patients and tumors*. Patients diagnosed with BOTSCC 2000-2007 in the County of Stockholm, previously tested for HPV DNA by Luminex Multiplex PCR and $p16^{INK4a}$ (p16) overexpression (>70% cytoplasmatic and nuclear tumor expression) by immunohistochemistry, were identified (16,17). Available formalin-fixed paraffin-embedded (FFPE) pre-treatment biopsies (obtained through an ENT forceps biopsy) were collected from the Department of Clinical Pathology, Karolinska University Hospital. Patient data were collected from patients records. The study was conducted according to ethical permissions 2009/1278-31/4 and 2017/1035-31/2, Karolinska Institutet.

*Immunohistochemistry and staining evaluation*. Tumor sections (4 $\mu$m) were cut and deparaffinized in Xylene and rehydrated in graded ethanol. Heat-induced antigen retrieval was performed with citric acid buffer (pH6) using a microwave oven for 10 min, which was followed by $H_2O_2$ treatment in order to block endogenous peroxidase. The slides were then incubated with horse serum, followed by incubation with primary antibody (mouse mAb S100A7 dilution 1:100, clone 47C1068; Santa Cruz Biotechnology) overnight. Secondary anti-mouse antibody (1:200; Vector Laboratories, Inc.) was then added followed by the ABC kit (Vectastain; Vector Laboratories, Inc.). The staining was developed in DAB followed by hematoxylin counterstaining. The staining was evaluated by three researchers blinded for clinical outcome (LH, DL and AN). The percentage of positive tumor cells per total tumor cells was evaluated for each section and a cut-off value of 30% (more specifically, the proportion of immunostained cells, irrespective of whether the staining was cytoplasmic or nuclear) was applied as previously described, and since we here wanted to compare out data to such studies by others (15).

*Statistical analysis*. Differences in continuous and categorical variables were assessed with double-sided t-test and Chi-square test, respectively. Three-year overall survival (3-year OS) was defined as days from diagnosis until death. All patients were censored after three years. Three-year disease-free survival (3-year DFS) was defined as time from diagnosis until a relapse in disease. Patients that never became tumor free were censored at day 0. All patients were censored after 3 years. Differences in survival were estimated with the log-rank test and visualized with the Kaplan-Meier method. The Cox proportional hazards regression analysis was used for the calculation of hazard ratios (HR) with 95% confidence intervals (95% CI) in the univariable and multivariable analysis. Besides S100A7 expression, established prognostic markers in OPSCC (age, TNM-status, smoking status and treatment) were included. P-values <0.05 were considered significant. All calculations and analyses were performed using IBM SPSS Statistics, (version 25.0; IBM. Corp.)

## Results

*Patients, tumors and psoriasin expression*. In total, 76 patients diagnosed with BOTSCC between 2000-2007

Table I. Patient and tumor characteristics.

| Characteristics | Low psoriasin expression | High psoriasin expression | All patients | P-value |
|---|---|---|---|---|
| Age at diagnosis, years (mean) | 62 | 60 | 61 | 0.5 |
| Sex, n (%) | | | | |
| Female | 19 (35) | 4 (22) | 23 (32) | 0.4 |
| Male | 35 (65) | 14 (78) | 49 (68) | |
| Stage (TNM-8), n (%) | | | | |
| I | 21 (39) | 6 (33) | 27 (38) | 0.4 |
| II | 11 (20) | 2 (11) | 13 (18) | |
| III | 14 (26) | 4 (22) | 18 (25) | |
| IV | 8 (15) | 6 (33) | 14 (19) | |
| Treatment[a], n (%) | | | | |
| RT | 25 (46) | 14 (78) | 39 (54) | 0.03 |
| CRT | 29 (54) | 4 (22) | 33 (46) | |
| Radiotherapy[b], n (%) | | | | |
| Conventional | 39 (72) | 12 (67) | 51 (71) | 0.8 |
| Accelerated | 15 (18) | 6 (33) | 21 (29) | |
| Cetuximab treatment[c], n (%) | | | | |
| No | 52 (96) | 18 (100) | 70 (97) | >0.9 |
| Yes | 2 (4) | 0 (0) | 2 (3) | |
| Current smoker[d], n (%) | | | | |
| No | 42 (78) | 8 (44) | 50 (69) | 0.02 |
| Yes | 12 (22) | 10 (56) | 22 (31) | |
| HPV DNA status[e], n (%) | | | | |
| Negative | 6 (11) | 10 (56) | 16 (22) | <0.001 |
| Positive | 48 (89) | 8 (44) | 56 (78) | |
| p16 upregulation[e], n (%) | | | | |
| Negative | 9 (17) | 11 (61) | 20 (28) | <0.001 |
| Positive | 45 (83) | 7 (39) | 52 (72) | |
| HPV DNA and p16 upregulation[e], n (%) | | | | |
| Negative | 10 (19) | 10 (56) | 20 (28) | 0.005 |
| Positive | 44 (81) | 8 (44) | 52 (72) | |

[a]RT given externally to 68 Gy. CRT given as induction chemotherapy with Cicplatin + 5Fu with/without Capecitabine followed by RT. [b]Conventional RT given as 2.0 Gy/day in 6.5-7 weeks; total dose 68 Gy. Accelerated RT given as 1.1+2.0 Gy per day in 4.5 weeks; total dose 68 Gy. [c]Cetuximab given concomitant. [d]Smoking status was defined as smoker/non-smoker upon diagnosis. [e]Data obtained from previous study (7). RT, radiotherapy; CRT, chemo-radiotherapy; HPV, human papillomavirus; p16, p16INK4a; ns, not significant.

in Stockholm, treated with curative intent and with tumors tested for possible presence of HPV DNA (HPV DNA positive by PCR) and overexpression of p16 were identified from previous publications (16,17). Tumor slides, available from 72 of these 76 patients, were subsequently stained for S100A7 (psoriasin) expression. Patients and tumor characteristics of these 72 patients are depicted in Table I.

Psoriasin expression varied greatly in the invasive tumor areas, ranging from no staining to 100% stained tumor cells. The majority of tumors (n=36) had no (absent) psoriasin staining (0%) in invasive BOTSCC. When a cut-off of 30% positivity was applied [as previously suggested by others (15)], 18 tumors were positive in their invasive tumor component and were defined as having high psoriasin expression (Fig. 1A and C). Remaining patients (n=18) had low psoriasin expression in their invasive BOTSCC (Fig. 1B and D), and were grouped with the patients with tumors not expressing psoriasin (low psoriasin expression group).

Patients with BOTSCC and low psoriasin expression were significantly more often treated with chemo-radiotherapy, were significantly more often not a current smoker, and their tumors were significantly more often HPV+ (Table I). Psoriasin expression was not correlated to histological grade (data not shown).

*Psoriasin expression and correlation to prognosis in patients with HPV+ and HPV- BOTSCC*. Patients with HPV+ BOTSCC (presence of HPV DNA) and having high psoriasin

Table II. Univariable and multivariable analysis of OS and DFS in patients with human papillomavirus DNA-positive base of tongue squamous cell carcinoma.

| | OS | | | | | | DFS | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Univariable | | | Multivariable | | | Univariable | | | Multivariable | | |
| Variables | HR | 95% CI | P-value | HR | 95% CI | P-value | HR | 95% CI | P-value | HR | 95% CI | P-value |
| TNM-8 stage | | | | | | | | | | | | |
| I and II | 1 | | | 1 | | | 1 | | | 1 | | |
| III and IV | 4.7 | 0.94-23 | 0.06 | 3.4 | 0.60-19 | 0.2 | 0.82 | 0.15-4.5 | 0.8 | 0.15 | 0.010-2.3 | 0.2 |
| Age[a] | 1.0 | 0.96-1.1 | 0.5 | 1.1 | 0.97-1.2 | 0.2 | 1.1 | 0.97-1.2 | 0.2 | 1.3 | 1.0-1.6 | 0.03 |
| Treatment | | | | | | | | | | | | |
| CRT | 1 | | | 1 | | | 1 | | | 1 | | |
| RT | 0.59 | 0.14-2.5 | 0.5 | 1.1 | 0.23-5.0 | 0.9 | 0.46 | 0.084-2.5 | 0.4 | 0.28 | 0.022-3.6 | 0.3 |
| Current smoker | | | | | | | | | | | | |
| Yes | 1 | | | 1 | | | 1 | | | 1 | | |
| No | 0.32 | 0.075-1.4 | 0.1 | 0.45 | 0.093-2.2 | 0.3 | 0.17 | 0.034-0.84 | 0.03 | 0.0060 | 0-0.21 | 0.005 |
| Psoriasin | | | | | | | | | | | | |
| Low | 1 | | | 1 | | | 1 | | | 1 | | |
| High | 8.3 | 2.1-33 | 0.003 | 13 | 2.0-88 | 0.007 | 6.0 | 1.1-33 | 0.04 | 230 | 3.8-14000 | 0.01 |

[a]Age, continuous variable. CRT, chemo-radiotherapy; RT, radiotherapy; OS, overall survival; DFS, disease-free survival; HR, hazard ratio; 95% CI, 95% confidence interval.

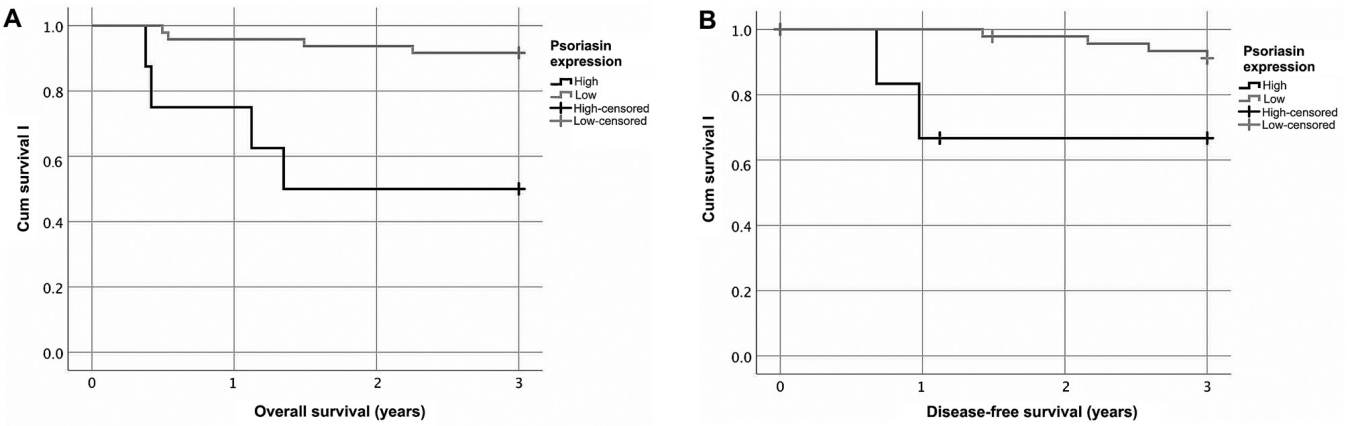


Figure 2. Kaplan-Meier curves of (A) OS and (B) DFS in patients with HPV+ BOTSCC. Tumors were stratified into a high (≥30%; 'high') and a low (<30%; 'low') fraction of psoriasin-positive tumor cell expression in immunohistochemistry. High tumor cell expression of psoriasin was significantly associated with (A) a worse OS (P<0.001) and (B) a worse DFS (P=0.02) in patients with HPV+ BOTSCC. The OS in patients with HPV+ BOTSCC was 85.7% (91.7% in patients with low psoriasin expression vs. 50% in patients with high psoriasin expression). Similarly, the DFS in patients with HPV+ BOTSCC was 89.3% (91.7% in patients with low psoriasin expression vs. 66.7% in patients with high psoriasin expression). BOTSCC, base of tongue squamous cell carcinoma; cum, cumulative; DFS, disease-free survival; HPV, human papillomavirus; HPV+, HPV DNA-positive; OS, overall survival.

expression (≥30%) had a significantly worse overall survival (OS) and disease-free survival (DFS), as compared to patients with HPV+ BOTSCC and having a low psoriasin expression (log rank test: OS P<0.001; DFS P=0.02; Fig. 2). Similar results were obtained when HPV status was defined as p16 overexpression (>70% p16 positive tumor cells) alone (log rank test: OS P<0.001; DFS P=0.02; data not shown) or when HPV DNA positive combined with over expression of p16 (log rank test: OS P<0.001; DFS P=0.03; data not shown) was tested. Moreover, high psoriasin expression was independently correlated to a worse OS and DFS both in uni- and multivariable analysis, including previously known prognostic factors (Table II).

In contrast, however, no differences in survival were observed in patients with HPV DNA negative BOTSCC between low and high psoriasin expression (log rank test: OS P=0.8; DFS P=0.9; data not shown). Similarly, no differences were identified when HPV negative status was defined as no

p16 overexpression or as absence of HPV DNA in combination with no p16 overexpression (data not shown).

Finally, low psoriasin expression as compared to having a high psoriasin expression in BOTSCC, irrespective of HPV DNA or p16 status, correlated significantly to a better 3-year OS and DFS in these patients (P=0.001 and P=0.007, respectively; data not shown).

## Discussion

In this short study, we demonstrate a prognostic role of psoriasin in a pathological homogenous cohort of only BOTSCC, and more specifically in HPV associated BOTSCC, suggesting that psoriasin could potentially be used as a prognostic marker also in HPV associated OPSCC.

Numerous previous studies have established the prognostic role of HPV in OPSCC and there is a discussion if and how treatment can be tapered in patients with HPV+ OPSCC (1,18). Nevertheless, before such de-escalation may be introduced, additional prognostic markers are needed to stratify these patients, in order to avoid undertreatment. Many such markers have been proposed in HPV+ OPSCC, but few have been validated in separate cohorts/studies (8). In this study, we confirm the previously reported prognostic role of psoriasin expression in head and neck cancer (15) in a homogenous cohort of BOTSCC, supporting that psoriasin expression correlates to an unfavorable clinical outcome, especially in patients with HPV+ BOTSCC.

Furthermore, recent data indicate, several prognostic markers could be assessed together in different prognostic algorithms in order to better separate patients with HPV+ OPSCC and a favorable clinical outcome from those with HPV+ OPSCC and a poor clinical outcome (19). It is possible that psoriasin also should be included in such algorithm.

There are some limitations in this study. No prognostic effect of psoriasin expression could be observed in patients with HPV DNA negative BOTSCC, however only 16 such patients were included, and data on the HPV DNA negative BOTSCC group should therefore be interpreted with great caution. In addition, in this pilot study, patients with TSCC and otherOPSCC were not included. In future studies, to assess the role of psoriasin expression in OPSCC and its subgroups, it would be beneficial to include larger patient groups, including more patients with HPV associated and non-associated BOTSCC, TSCC and otherOPSCC. Larger, studies would also allow for studies of a potential correlation of the presence of high psoriasin expression and smoking as well as other characteristics of the patients and their tumors.

Finally, one could argue, that it could be possible to use other cut-off values for psoriasin positivity, rather than a cut-off of 30%, used here and by others (15). In this specific patient material, an optimal cut-off value according to Youden's index would be 15% for OS and 7.5% for DFS (data not shown). However, new cut-off levels for evaluating psoriasin positivity and survival, would also be needed to be validated in separate and larger cohorts. Therefore, the present cut-off should be regarded as a validation of a similar previously published cut-off (15).

Nevertheless, increased expression of S100A7 protein has been described in various cancer types (e.g. breast, bladder and head and neck carcinomas) and often with a correlation to poor clinical outcome (9-14,20). In addition, S100A7 has been shown to be functionally linked to oncogenic properties in oral SCCs, as depletion of this gene inhibited cell growth, invasion and migration (21). A handful of these prognostic studies have utilized IHC to quantify psoriasin expression. However, different quantification approaches and different cut-off levels for psoriasin expression have been used (10,14,15). For this reason, we here applied a cut-off value previously used in HNSCC. Moreover, to our knowledge, the vast majorities of studies examining psoriasin expression in correlation to prognosis have shown a poor prognostic value of high psoriasin expression. However, in a study by Tiveron *et al* (22), where psoriasin expression was analyzed in correlation to prognosis in laryngeal carcinoma, an increased expression did not correlate to prognosis. Therefore, still, more studies are needed to verify the prognostic role of psoriasin. Moreover, it may be possible, that examining possible amplifications of mutations or methylation of the S100A7 gene in cases where psoriasin expression is correlated to poor prognosis could give more information. Nevertheless, interestingly is that it seems that psoriasin more often is expressed in in situ tumor component as compared to invasive tumor (14,23), which also applies for HPV+ OPSCC (24). In line with that assumption, only a fraction of our invasive tumors showed high psoriasin expression.

Taken together, this short report confirms a prognostic role of psoriasin and the results imply that psoriasin may have a prognostic effect in HPV+ BOTSCC. In order to identify patients with HPV+ BOTSCC and a favorable clinical outcome with high sensitivity and specificity, it is possible that psoriasin should be included in such prognostic algorithm.

In conclusion, high psoriasin expression was here shown as an independent poor prognostic factor in a homogenous cohort of patients with HPV+ BOTSCC.

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## Availability of data and material

All data generated or analyzed during this study are included in this published article.

**Authors' contributions**

MZ, LH, TD and AN formulated the research question and came up with the study design. Sample selection and collection was performed by MZ, LH, LM and DL. LH and MZ performed immunohistochemistry (IHC). LH, DL and AN evaluated the IHC staining. LM and DL collected information from the patient case reports regarding response to treatment, clinical performance and survival. All raw data has been assessed by MZ, LM, TD and AN to ensure its legitimacy. MZ, LM, TD and AN analyzed, summarized and interpreted the data and wrote the manuscript, which was revised and approved by all co-authors. All authors read and approved the final manuscript.

**Ethics approval and consent to participate**

The present study, including patient information and consent, was conducted according to ethical permissions 2009/1278-31/4 and 2017/1035-31/2 from the Ethics Committee at Karolinska Institute, Stockholm, Sweden.

**Patient consent for publication**

Not applicable.

**Competing interests**

The authors declare that they have no competing interests.

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