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ORIGINAL ARTICLE

MMP-7 expression may influence the rate of distant recurrences and disease-specific survival in HPV-positive oropharyngeal squamous cell carcinoma

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Abstract

The objective of this study was to determine if matrix metalloproteinase-7 (MMP-7) expression is related to human papilloma virus (HPV) status, clinical parameters, and outcome in oropharyngeal squamous cell carcinoma (OPSCC). Tumor tissue specimens from 201 OPSCC patients treated with curative intent were available for immunohistochemistry, and the samples were stained with monoclonal MMP-7 antibody. All the patients were followed up at least 3 years or until death. MMP-7 expression did not differ between HPV-positive and HPV-negative patients. MMP-7 was not prognostic among patients with HPV-negative OPSCC. In the HPV-positive subgroup, patients with moderate, high, or very high MMP-7 expression had significantly worse 5-year disease-specific survival (DSS) (56.6%) than patients with absent, or low MMP-7 expression (77.2%), and MMP-7 expression appeared as a prognostic factor in the multivariate analysis. In addition, among HPV-positive OPSCC with moderate, high, or very high MMP-7 expression, the 5-year distant recurrence-free survival was significantly lower (69.6%) than in those who had low or absent MMP-7 expression (97.5%). Our results suggest that among HPV-positive OPSCC patients, high MMP-7 expression is related to worse 5-year DSS and increased rate of distant recurrences.

Keywords Oropharyngeal cancer · Matrix metalloproteinase-7 · MMP-7 · HPV · Survival analysis

Introduction

The incidence of oropharyngeal squamous cell carcinoma (OPSCC) has been rising in the USA and Europe [1–3]. This trend is mainly attributed to human papilloma virus (HPV), which is often responsible for tumors originating from the tonsils and the base of tongue [4–8]. Patients with HPV-positive OPSCC have typically less cigarette and alcohol exposure than those with a virus-negative tumor, and their survival is also more favorable [7–10].

Matrix metalloproteinases (MMPs) are zinc-dependent endopeptidases, proteolytic enzymes that are able to degrade almost all extracellular matrix components [11]. They can also process chemokines, cytokines, and cell-signaling factors modifying immune responses [12]. MMPs are thought to be critical factors for tumor invasion, metastasis, and angiogenesis [13].

MMP-7 is shown to be present in cell populations susceptible to HPV infection both in the cervix [14] and in the tonsillar cryptal reticulated epithelium [15]. Although MMP-7 is expressed in normal ductal and glandular epithelium, it has also been linked to many malignant tumors [16, 17]. MMP-7 expression is usually restricted to tumor cells, whereas other MMPs are typically expressed also in the stroma tissue surrounding the tumor [16, 18, 19].

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In the study by Chuang et al., MMP-7 immunostaining was found in tumor and non-neoplastic buccal epithelium, but MMP-7 was active only in tumor nests [20]. de Vicente et al. studied MMP-7 in oral squamous cell carcinoma (SCC) and found its expression in cancer cells, but not in normal oral epithelial cells [21]. In many cancer types, MMP-7 is related to the occurrence of regional lymph node or distant metastasis [22, 23]. For example, upregulation of MMP-7 and its immunoexpression have been linked to worse survival and the presence of nodal metastasis in head and neck squamous cell carcinoma (HNSCC) [21, 24, 25].

However, the role of MMP-7 in OPSCC remains open. The objective of this study was to determine if MMP-7 expression is related to HPV status, clinical parameters, and outcome in OPSCC.

Patients and clinicopathological data

The present patient cohort with known HPV status has been presented in detail previously [26]. Altogether, 331 patients were diagnosed with oropharyngeal malignancies at the Departments of Otorhinolaryngology - Head and Neck Surgery and Oncology, Helsinki University Hospital (HUS), Helsinki, Finland, between 2000 and 2009. The following ICD-10 codes were used for patient inclusion: C01, C02.4, C05.1, C05.2, C05.8, C05.9, C09.0, C09.1, C09.8, C09.9, C10.0, C10.2, C10.3, C10.8, and C10.9. We excluded from the analyses the patients with palliative treatment ($n = 44$), concurrent HNSCC ($n = 5$), earlier treated HNSCC ($n = 11$), histology other than SCC or subtype of SCC ($n = 18$), or tumor tissue unavailability ($n = 52$). Altogether, tumor tissue samples from 201 patients were available for immunohistochemistry.

Clinicopathological data were available in the hospital registries. The medical records were manually reviewed and details were collected on patients' age, sex, tumor histology, grade, TNM class, stage, primary treatment (i.e., surgery [Sx], radiotherapy [RT], and chemoradiotherapy [CRT]), tumor recurrence, and status at the last follow-up. Dates and causes of death were provided by Statistics Finland. All patients were followed up for at least 3 years or until death.

Of the 201 patients, 129 underwent primary Sx, and 115 received adjuvant oncological treatment (RT or CRT). Postoperative oncological therapy was not delivered for 14 patients because of Stage I–II disease (five cases), or patient-related factors (nine cases). Definitive CRT or RT was delivered for 72 patients, of whom salvage Sx was delivered for 11 patients in the primary treatment phase (primary site only $n = 1$, neck only $n = 7$, primary site and neck $n = 3$). In two cases, only post-radiation tumor tissue was available for immunohistochemistry. The HPV status of the study patients had been determined for our previous study using in situ hybridization. The primary tumor was HPV-positive in 104 (51.7%) of the patients, and negative in 97 (48.3%) of the patients.

Immunohistochemistry

Tissue microarray (TMA) blocks were prepared and immunohistochemical staining was performed as previously described [26]. The primary antibody used in this study was monoclonal MMP-7 antibody (1:1000 dilution, clone 141-7B2; Millipore, Temecula, CA). Pancreas tissue was used as a positive control, and for a negative control, the specimens were processed without a primary antibody.

Immunoscoring

Two researchers (S.V. and J.H.) independently scored the TMA slides that were temporarily decoded to avoid their being identified. The percentage of MMP-7-positive tumor cells was evaluated. No positivity was graded as 0 (absent), positive cells up to 20% as 1 (low), 21–50% as 2 (moderate), 51–80% as 3 (high), and over 80% as 4 (very high) (Fig. 1).

Statistical analysis

SPSS Version 22.0 (SPSS, Inc., Chicago, IL, USA) was used in the statistical analysis. Statistical differences between categorical variables were calculated using the chi-square test with asymptotic and exact P values when best suited. Independent samples t test was used with continuous variables, and normality distribution was determined from histograms. The 5-year disease-specific survival (DSS) rates and recurrence-free survival (RFS) rates were calculated with the Kaplan-Meier (KM) estimate using the log-rank test as the statistical test of survival. The follow-up time was taken as the time period between the last treatment day and end of follow-up or death from disease for DSS or detection of recurrence for RFS. Follow-up biases were minimized limiting the follow-up time to 5 years. In RFS analysis, only cancer recurrence was considered as an event. We used Cox proportional analysis for DSS multivariate analysis to select clinically relevant variables. The proportional hazards assumptions were tested with KM curves. A two-sided P value < 0.05 was considered statistically significant.

Results

MMP-7 expression and its association with clinicopathological parameters in OPSCC

Of the total 201 tumors, MMP-7 was expressed in 134 (66.7%) and was absent in 67 (33.3%). When present, MMP-7 expression was low in 105 (52%), moderate in 22 (10.9%), high in six (3%), and very high in one patient (0.5%).

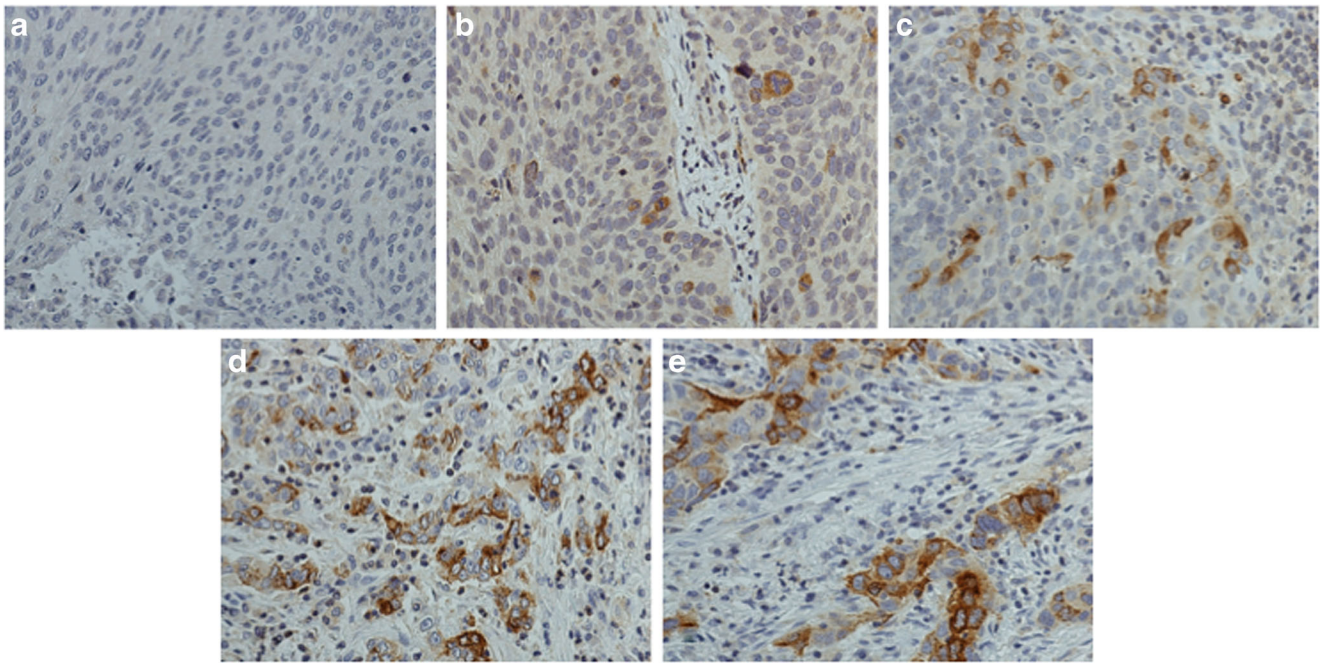

Fig. 1 The percentage of MMP-7 -positive OPSCC tumor cells was graded for level groups from 0 to 4. **a** No positivity = 0 (absent). **b** Positive cells up to 20% = 1 (low). **c** Positive cells 21–50% = 2 (moderate). **d** Positive cells 51–80% = 3 (high). **e** Positive cells over 80% = 4 (very high)

In statistical analysis, we combined expression level groups 0–1 (weak) and 2–4 (strong). The statistical association of MMP-7 with clinicopathological parameters is presented in Table 1. MMP-7 expression did not differ between HPV-positive and HPV-negative patients. MMP-7 expression was lower among males. There were no other statistical associations with MMP-7 and clinicopathological variables.

MMP-7 expression and its association with survival

Patients who had a primary tumor with at least moderate expression of MMP-7 had worse 5-year DSS (56.6%) than those who had a primary tumor with low or with no MMP-7 expression (77.2%; Fig. 2) ($p = 0.013$). The expression of MMP-7 seemed to correlate with worse survival figures exclusively among patients who had a HPV-positive OPSCC; among them, the 5-year DSS figures were 56.3% (moderate, high, or very high expression) and 86.8% (absent or low expression) ($p = 0.001$). Among patients with HPV-negative OPSCC, no statistically significant difference in DSS figures over MMP-7 expression categories was seen and the corresponding 5-year DSS rates were 57.5% for moderate, high, or very high MMP-7 expression and 66.5% for absent or low MMP-7 expression.

In multivariate analysis (Table 2), strong MMP-7 expression (level 2–4) was an independent factor for poor DSS ($p = 0.013$). In addition, patients with HPV negative tumors had worse survival. Therefore, we performed the multivariate analysis separately for patients with HPV-negative and HPV-positive OPSCC. Among those patients who had HPV-positive OPSCC, MMP-7 expression was an independent prognostic factor ($p = 0.010$), but it had no statistically significant impact on DSS among patients with HPV-negative OPSCC.

MMP-7 expression and its association with recurrences

A locoregional recurrence appeared in 24 patients. The median locoregional RFS from treatment completion was 9.5 months (range 3.2–57.2). The expression of MMP-7 had no impact on 5-year locoregional RFS neither in the whole series nor in the subgroups with HPV-positive or HPV-negative OPSCC. A distant recurrence appeared in 12 (6%) patients. The median distant RFS from treatment completion was 5.6 months (range 0.4–38.5).

The 5-year distant RFS figures were significantly worse among patients with MMP-7 expression levels 2–4 (81.3%) than among those with expression levels 0–1 (94.8%; Fig. 3) ($p = 0.027$). Among HPV-negative OPSCC patients, there was no statistically significant difference in 5-year distant RFS between MMP-7 expression level categories. Among those HPV-positive OPSCC patients who had MMP-7 expression levels 2–4, the 5-year distant RFS was significantly lower (69.6%) than in those who had MMP-7 expression levels of 0–1 (97.5%) ($p < 0.001$).

Discussion

Our results suggest that strong MMP-7 expression in OPSCC may be an independent factor for poor DSS in HPV-positive

Table 1 Matrix metalloproteinase 7 (MMP-7) expression and its association with clinicopathological factors

		MMP-7		*P*
		Absent – Low (Weak)	Moderate – High–Very high (Strong)	
Sex	Male	132	17	
	Female	40	12	*0.039**
Age (mean)		58.3	59.4	0.573**
Smoking	Never	21	5	
	Ex	43	6	
	Currently	82	14	0.719*
Heavy drinking	Never	50	11	
	Earlier	22	2	
	Currently	31	7	0.942*
T class	T1-T2	99	14	
	T3-T4	73	15	0.353*
N class	N0-N1	59	7	
	N2-N3	113	22	0.282*
Stage	I-II	27	3	
	III-IV	145	26	0.455*
HPV status	Positive	88	16	
	Negative	84	13	0.689*
Grade	I	15	3	
	II	65	13	
	III	92	13	0.433*
Site	Lateral wall	50	11	
	Anterior wall	102	14	
	Posterior wall	3	0	
	Superior wall	17	4	0.590***

Statistically significant *P* values are given in italics

*Chi-square test with an asymptotic *P* value

**Independent samples *t* test

***Chi-square test with an exact *P* value

OPSCC. Among patients with HPV-negative tumors, MMP-7 had no impact on DSS. Similarly, differences for this issue between HPV-positive and HPV-negative OPSCC were seen in the distant RFS rates, i.e., patients with HPV-positive OPSCC more frequently developed a distant recurrence if MMP-7 expression was strong, which is a phenomenon not seen among the HPV-negative patients. It is well established that HPV positivity is associated with a better response to treatment and to modality-independent survival benefit [10]. Nevertheless, heterogeneity in both clinical and biological behaviors among HPV DNA-positive patients has been observed in many studies [27, 28]. It has been speculated that this may be due to differences in viral load, viral gene expression, or both [29].

More than 30 types of MMPs have been identified. In a study by Lee et al., the expression of MMP-9 and -13 and tissue inhibitors of metalloproteinases were found to be significantly different in tonsillar SCC and in control tissues [30]. Furthermore, patients with MMP-9 expression in tumor cells had significantly worse survival.

Treatment can cause long-term morbidity to the patients. As patients with HPV-positive OPSCC compared with their virus-negative counterparts are typically younger, have less comorbidities [31, 32], and have typically favorable survival [10] with smaller risk of developing second primary tumors [33], overtreatment should be avoided especially among these patients. Therefore, several treatment de-escalation studies for HPV-positive OPSCC are currently ongoing [27]. Although patients with HPV-positive OPSCC have significantly lower risk of developing locoregional recurrence than their virus-negative counterparts, distant metastases still appear nearly at the same rate [10, 34]. In order to minimize the pitfall of deintensification-related failures, patient selection in de-escalation studies must be done with caution. In 2010, Ang et al. hypothesized that the low-risk OPSCC patient group, i.e., patients who have HPV-positive tumors and either smoked less than 10 pack years or neck status N0-N2a, could be suitable for treatment de-escalation [10]. Moreover, O'Sullivan et al. showed that the patients who have a HPV-positive OPSCC and bilateral or contralateral neck metastasis (N2c) have an increased risk of developing distant metastasis if they are treated without chemotherapy [34]. Interestingly, among our study patients with HPV-positive tumors, moderate or high MMP-7 expression was significantly prognostic for the development of distant recurrence, suggesting a possible novel immunohistochemical method of identifying patients with increased risk of distant metastasis. Noteworthy, the association of disease mortality and MMP-7 expression was also seen in multivariate analysis.

Several studies have explored the association between MMPs and cancer. Dunne et al. showed that high MMP-9 expression correlated with advanced T class, advanced N class, and advanced stage of OPSCC [35]. In addition, Burduk et al. found that enhanced MMP-2 expression of stroma surrounding cancer cells and high MMP-9 expression both in cancer cells as well as surrounding stroma predict lymph node metastasis in OPSCC [36]. Significant correlations between MMP-7 and distant metastasis have also been found in other carcinomas, e.g., in renal cell carcinoma and in early invasive colorectal carcinomas [22, 23]. Thus, MMPs may play a role in the metastatic behavior of OPSCC, which is supported by our results. In our previous study, MMP-7 immunoexpression was investigated in 70 patients with early-stage oral tongue SCC. The study showed that MMP-7 expression was associated with the occurrence of metastatic

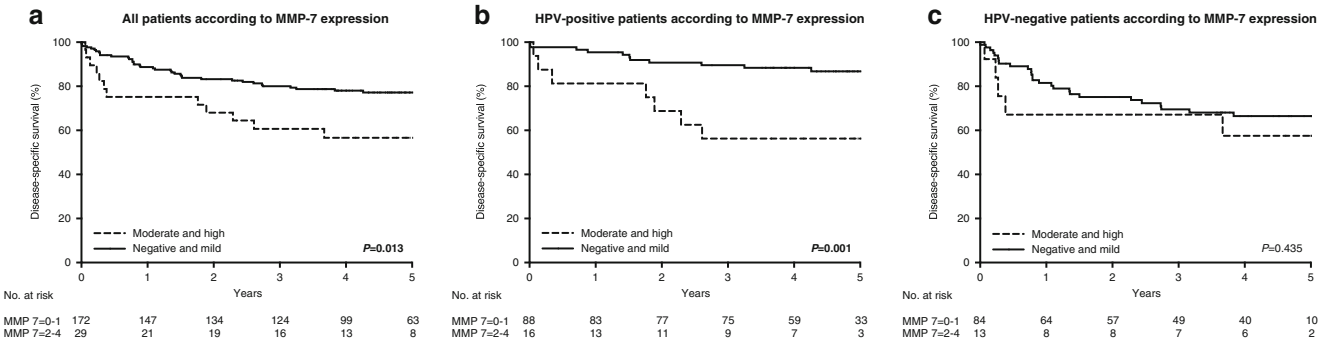

Fig. 2 Disease-specific survival curves according to MMP-7 expression in OPSCC, also separately in HPV-positive and HPV-negative OPSCC. **a** MMP-7 expression in OPSCC. Moderate, high, or very high expression is associated with increased disease mortality. **b** MMP-7 expression in HPV-positive OPSCC. Moderate, high, or very high expression is associated with increased disease mortality. **c** MMP-7 expression in HPV-negative OPSCC. No impact on disease-specific survival was found

disease, deeper tumor invasion, and it was predictive for poor overall survival but not for worse disease-specific survival [25]. None of the six control samples from normal tongue tissue revealed MMP-7 immunopositive cells. Yet, a recent review on MMPs in head and neck cancers emphasized that although there is little doubt that MMP-7 has an important role in the progression of HNSCC, its molecular mechanisms have not yet been identified [37].

The present study on OPSCC showed MMP-7 expression in two-thirds of the tumors. It was low or moderate in most cases and rarely high or very high. Morbini et al. evaluated MMP-7 expression in normal tonsils and in OPSCCs fully characterized for HPV [15]. They found that MMP-7 was expressed in the reticulated epithelial cells of tonsillar crypts, but in OPSCC, MMP-7 positivity was observed in 51.2% of the cases, which is slightly less than in our material. In their study, as well as in our study, MMP-7 expression was not associated with the HPV status of the tumors.

It has to be taken into account that our results are based on a retrospective series, which lacks randomization, and further, data on parameters such as smoking status were not available in some cases. Therefore, we excluded smoking status from

Table 2 Univariate and multivariate Cox regression analysis of disease-specific survival (DSS) for all oropharyngeal squamous cell carcinoma patients and separately for patients with HPV-positive tumors and HPV-negative tumors

	Univariate analysis All patients			Multivariate analysis All patients			Multivariate analysis HPV-positive patients			Multivariate analysis HPV-negative patients		
	HR	95% CI	*P*	HR	95% CI	*P*	HR	95% CI	*P*	HR	95% CI	*P*
Sex												
Male vs. female	2.2	1.0–4.9	0.054	2.2	1.0–5.0	0.065	1.3	0.3–4.7	0.737	*3.7*	*1.2–11.1*	*0.021*
Smoking			*0.038*			0.349						
Earlier vs. never	1.7	0.5–6.0	0.439	1.6	0.4–5.8	0.489						
Currently vs. never	*3.3*	*1.0–10.7*	*0.048*	2.3	0.7–8.2	0.194						
T class												
T3–T4 vs. T1–T2	1.5	0.9–2.8	0.114	1.4	0.8–2.5	0.267	1.7	0.6–4.4	0.307	1.0	0.5–2.2	0.901
N class												
N2–3 vs. N0–1	*2.1*	*1.0–4.2*	*0.037*	2.1	1.0–4.3	0.054	2.6	0.5–12.2	0.239	*2.4*	*1.0–5.5*	*0.039*
MMP-7												
2–4 vs. 0–1	*2.2*	*1.2–4.3*	*0.015*	*2.4*	*1.2–4.9*	*0.013*	*3.6*	*1.4–9.7*	*0.010*	2.1	0.8–5.9	0.145
HPV												
HPV− vs. HPV+	*2.2*	*1.2–4.0*	*0.007*	*2.2*	*1.1–4.5*	*0.027*						
Treatment												
(C)RT ± Sx vs. Sx ± (C)RT	1.0	0.6–1.8	0.975									

Statistically significant *P* values are given in italics, *HR* hazard ratio, *95% CI* 95% confidence interval, *(C)RT ± Sx* (chemo)radiotherapy ± surgery, *Sx ± (C)RT* surgery ± (chemo)radiotherapy

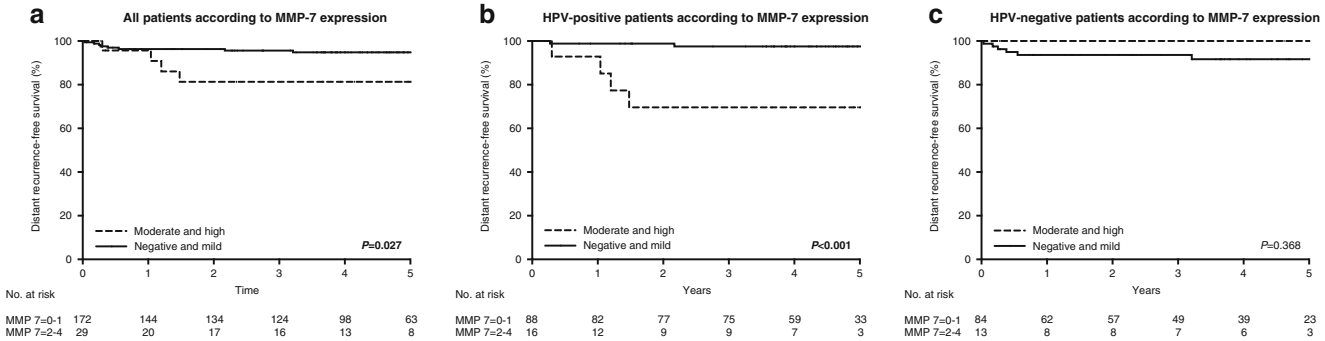

Fig. 3 Distant recurrence-free survival curves according to MMP-7 expression in OPSCC, also separately in HPV-positive and HPV-negative OPSCC. **a** MMP-7 expression in OPSCC. Moderate, high, or very high expression is associated with the increased occurrence of distant recurrence. **b** MMP-7 expression in HPV-positive OPSCC. Moderate, high, or very high expression is associated with the increased occurrence of distant recurrence. **c** MMP-7 expression in HPV-negative OPSCC. No impact on occurrence of distant recurrence was found

the multivariate analysis in order to maintain a larger sample size. Multivariate analysis was also tested with the available details on smoking status, but the significant results still remained evident. Our results concerning the relation of MMP-7 expression in relation to outcome are based on a relatively small series of patients. This is partly due to the low occurrence of disease-specific mortality among HPV-positive patients. Therefore, robust conclusions on MMP-7 expression and outcome in OPSCC must be avoided. In addition, two patients had only post-radiation tumor samples available for immunohistochemistry, but the results of survival analysis did not change even when these patients were excluded from the analysis.

Conclusion

MMP-7 expression did not differ between HPV-positive and HPV-negative tumors, but our results suggest that strong MMP-7 expression is related to poor DSS among patients with HPV-positive tumors. This finding seems to be due to higher occurrence of distant recurrence among patients with strong MMP-7 expression. Therefore, we suggest that the HPV-positive OPSCC patient population may be stratified into various subgroups regarding the risk of distant failure based on their MMP-7 expression status. This finding calls for further validation in other cohorts.

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Compliance with ethical standards

An institutional research permission was granted, and the study design was approved by the Research Ethics Board of the Helsinki and Uusimaa Hospital District.

Conflict of interest None declared.

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