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Prognostic value of PSMA, c-MET and E-cadherin in salivary duct carcinoma

Wim van Boxtel[a], Maike J.M. Uijen[a], Gerald W. Verhaegh[b], Stefan M. Willems[c,d], Marianne A. Jonker[e], PALGA Group, Jack A. Schalken[b], Ilse C.H. van Engen-van Grunsven[f], Carla M.L. van Herpen[a,*]

[a] Department of Medical Oncology, Radboud Institute for Health Sciences, Radboud university medical center, Nijmegen, the Netherlands
[b] Department of Urology, Radboud Institute for Molecular Life Sciences, Radboud university medical center, Nijmegen, the Netherlands
[c] Department of Pathology, University Medical Center Utrecht, Utrecht, the Netherlands
[d] Department of Pathology and Medical Biology, University Medical Center Groningen, Groningen, the Netherlands
[e] Department of Health Evidence, Radboud Institute for Health Sciences, Radboud University Medical Center, Nijmegen, the Netherlands
[f] Department of Pathology, Radboud Institute for Health Sciences, Radboud university medical center, Nijmegen, the Netherlands

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ABSTRACT

Objectives: Salivary duct carcinoma (SDC) is a rare and aggressive subtype of salivary gland cancer. Androgen receptor (AR) (96%) and HER2 (29–46%) expression, and a high propensity for regional lymph node metastases are hallmarks of the disease. We hypothesized that c-MET, E-cadherin, PSMA tumor and PSMA neovascular expression may be prognostic factors in SDC.

Materials and methods: Expression levels of these proteins were established on tissue microarrays containing 165 primary SDC tumor specimens. Association with survival was studied with Kaplan-Meier curves, and univariable and multivariable Cox regression models. Furthermore, association with lymph node status, AR and HER2 expression, and gender was studied.

Results: We found that patients with high PSMA tumor expression showed a significantly longer overall survival (OS) (median 83 vs. 43 months, P = 0.022), a trend towards a longer DFS (median 51 vs. 22 months, P = 0.094), and significantly reduced hazard ratio for death in the univariable Cox regression model (HR 0.46, P = 0.034). In the multivariable model only a high number of tumor-positive lymph nodes and high age (> 80) at diagnosis were prognostic for poor OS. High PSMA tumor expression was also significantly associated with low N-stage (P = 0.001) and expression was higher in women versus men (P = 0.029). High PSMA tumor expression and E-cadherin loss were significantly associated with strong and weak AR-expression, respectively (P = 0.033 and P = 0.007). None of the factors were significantly associated with HER2 expression.

Conclusion: c-MET, E-cadherin, and tumor and neovascular PSMA expression are no independent prognostic factors in SDC.

Introduction

Salivary duct carcinoma (SDC) is an aggressive subtype of salivary gland cancer (SGC) with a median overall survival (OS) of 3–5 years after primary diagnosis [1–4]. Primary treatment of SDC consists of tumor resection, most often in combination with a neck dissection and postoperative radiotherapy. Despite this extensive primary treatment, the recurrence risk is high with a 3-year disease-free survival of only 27.7% in patients presenting with more than 1 regional lymph node metastasis [5]. Better knowledge of prognostic factors is needed to increase our understanding of the pathogenesis of SDC and to guide treatment decisions.

Androgen receptor (AR) and human epidermal growth factor receptor 2 (HER2) expression are key tumor characteristics of SDC, but these are no prognostic factors [1]. Virtually all SDCs are AR-positive (96% in our cohort after expert pathology review) [1], and androgen

Abbreviations: ADT, androgen deprivation therapy; AR, androgen receptor; ASCO, American Society of Clinical Oncology; CAP, College of American Pathologists; CRPC, castration-resistant prostate cancer; DFS, disease-free survival; E-cadherin, epithelial cadherin; FFPE, Formalin fixed paraffin embedded; FISH, fluorescent *in situ* hybridization; H&E, hematoxylin and eosin; HGF, hepatocyte growth factor; OS, overall survival; PALGA, Dutch Nationwide Network and Registry of Histo- and Cytopathology; PFS, progression-free survival; PSMA, prostate-specific membrane antigen; SDC, salivary duct carcinoma; SGC, salivary gland cancer

* Corresponding author at: Department of Medical Oncology, Radboud University Medical Center, Geert Grooteplein Zuid 8, Nijmegen, P.O. box 9101, the Netherlands.
E-mail address: Carla.vanherpen@radboudumc.nl (C.M.L. van Herpen).

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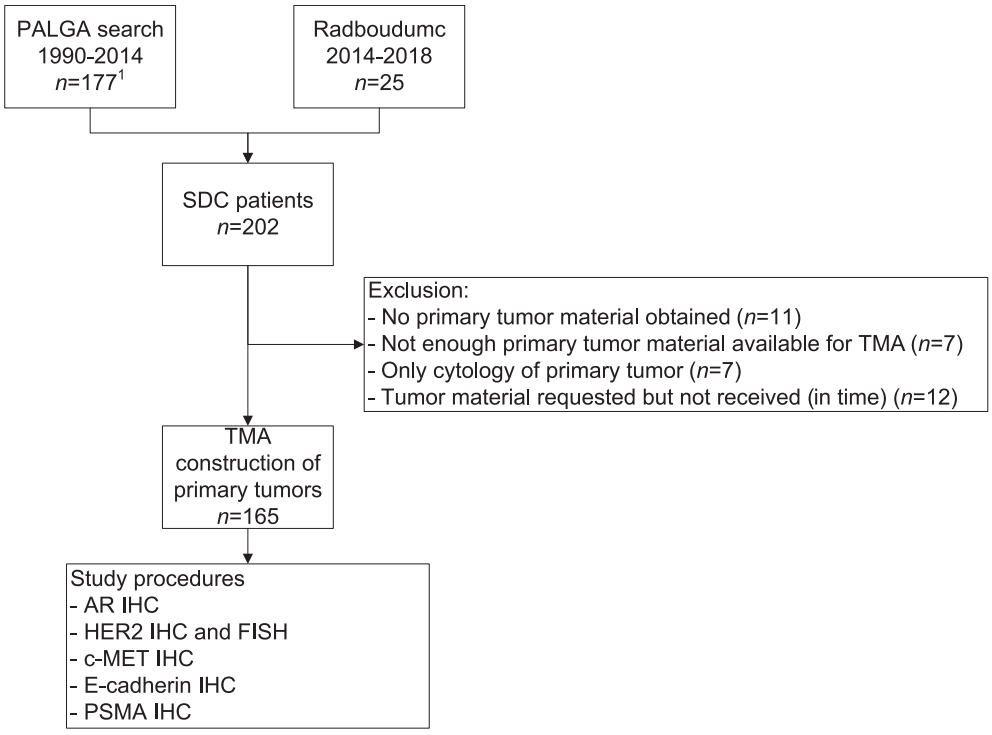

Fig. 1. Flow chart of patient selection and study procedures. Abbreviations: AR: androgen receptor. E-cadherin: epithelial cadherin. FISH: Fluorescence *in situ* hybridization. HER2: Human epidermal growth factor receptor 2. IHC: Immunohistochemistry. PALGA: nationwide network and registry of histo- and cytopathology in the Netherlands. PSMA: prostate-specific membrane antigen. Radboudumc: Radboud university medical center, Nijmegen, the Netherlands. SDC: salivary duct carcinoma. TMA: tissue microarray. [1] Boon E *et al.* Int j cancer 2018;143:758–66.

deprivation therapy (ADT) is often used as first-line palliative treatment with a response rate of 41.7%, median progression-free survival (PFS) of 8.8 months and low toxicity in a prospective phase 2 trial in 36 patients [6]. HER2 overexpression is seen in 29–46% of SDCs [1,7,8] and these patients can be treated with HER2 targeted therapy. Docetaxel plus trastuzumab showed a response rate of 70.2% and median progression-free survival of 9 months in a prospective phase 2 trial in 57 patients with HER2 overexpression [9]. Trastuzumab-emtansine showed a response rate of 90% in 10 SDC patients treated in a basket trial and can also be used as HER2-targeted therapy [10].

A striking clinical feature of SDC is the high propensity for lymph node metastases. At disease presentation, 47–68% of patients are diagnosed with lymph node metastases, and often an abundancy of lymph node metastases (median 4, range 0–97) are observed in the neck dissection specimen [1,11,12]. We previously showed that the absolute number of tumor-positive lymph nodes in the neck dissection is a prognostic factor in a multivariable Cox regression analysis [1]. The cause of the high number of lymph node metastases in SDC remains elusive.

We hypothesized that c-MET expression or E-cadherin loss may be associated with the high propensity for lymph node metastases and may be prognostic factors. c-MET is a receptor tyrosine kinase which can be activated by binding of hepatocyte growth factor (HGF). Activation of the HGF/MET pathway promotes cell proliferation, survival, migration, and invasion [13–16]. c-MET expression was observed in 50% of 28 SDCs in a Korean cohort [17]. The prognostic value of c-MET for survival and its association with lymph node metastases is unclear, although genetic *MET* aberrations were a significant predictor for lymph node metastases in a cohort of 316 SGC cases, including 35 SDCs [18]. Epithelial cadherin (E-cadherin) is a cell-cell adhesion molecule. Loss of E-cadherin is involved in cancer invasion and metastasis [19] and is a predictor of poor prognosis in different tumors [20–24]. Few studies have reported on E-cadherin expression in SGC, but expression in SDC and its prognostic value is unknown [25–27].

Prostate-specific membrane antigen (PSMA) expression in tumor cells or tumor-associated neovasculature may also be prognostic factors in SDC. We recently conducted a phase 2 imaging study using Gallium-68-PSMA-PET/CT in 10 SDC patients, in which we found relevant PSMA-ligand uptake (tumor/liver ratio > 1) in 4 patients. With immunohistochemistry, PSMA expression in tumor cells was positive in 5 patients, and PSMA expression in the tumor-associated neovasculature was positive in 8 patients, but Gallium-68-PSMA uptake could not be predicted with immunohistochemistry. In prostate cancer, high PSMA tumor expression is an independent predictor of recurrence [28]. PSMA expression in the tumor-associated neovasculature is a poor prognostic factor in oral squamous cell carcinoma, renal cell carcinoma, and hepatocellular carcinoma, whereas it has no prognostic value in gastric and colorectal cancer, and is a favorable prognostic factor in medullary thyroid carcinoma [29–33].

The aim of this study was to evaluate the prognostic value of c-MET, E-cadherin, and tumor and neovascular PSMA expression in a cohort of SDC patients. Furthermore, we evaluated whether these factors associated with lymph node status, AR, and HER2 expression.

Material and methods

Patients

Tissue block from patients diagnosed with SDC in the Netherlands between 1990 and 2014 were anonymously collected by use of the Nationwide Network and Registry of Histo- and Cytopathology (PALGA) [34]. In total 177 patients were included [1]. This cohort was expanded by 25 SDC patients visiting the Radboud university medical center, a referral center for SGC patients in the Netherlands, between 2014 and 2018. An expert SGC pathologist reviewed all tumors to confirm the diagnosis. Of these 202 patients, sufficient primary tumor material for construction of TMAs was available for 165 patients. A flow chart of patient selection and analyses is shown in Fig. 1.

Clinical data

Clinical data were collected from the medical records. A no-objection system was used for secondary use of human tissue and medical data in accordance to the code of conduct of the Federation of Dutch Medical Scientific Societies (Human tissue and medical research: Code of conduct for responsible use). For all patients who were alive at the

start of this study, written informed consent was obtained. This study was approved by the local medical ethical committee.

TMA construction

Formalin-fixed paraffin-embedded (FFPE) tumor blocks and hematoxylin and eosin (H&E) stained slides were requested from all patients. From each FFPE tumor block, one to three (depending on tumor size) 2 mm cores of the primary tumor were transferred into a TMA block, using the TMA Grand Master (Sysmex). From these TMA blocks, slides were cut for immunohistochemical analyses.

Immunohistochemistry

Androgen receptor

A rabbit monoclonal antibody against the androgen receptor was used (EP120; Cell Marque) at a dilution of 1:200. Androgen receptor staining was evaluated considering the staining intensity (0 = negative, 1 = weak, 2 = moderate, 3 = strong) as well as the percentage of positive nuclei (staining extent: 0 = < 10%, 1 = ≥10 to < 30%, 2 = ≥30 to < 70%, 3 = ≥70%). The final (semi-quantitative) staining score was recorded as the sum of the staining intensity and the staining extent, in which 0 was regarded as negative, > 0 to < 6 as low expression and 6 as high expression [35].

c-MET

A rabbit monoclonal IgG antibody targeting the C-terminus of human MET (D1C2; Cell Signaling) was used. Staining intensity was evaluated semi-quantitatively (negative, weak, moderate, strong) for cytoplasmic and membranous immunoreactivity [36]. For the statistical analysis, negative and weak staining were regarded as negative, and moderate and strong staining were regarded as positive.

E-cadherin

A mouse monoclonal antibody against E-cadherin (SPM471; Diagnostic Biosystems) was used at a dilution of 1:300 [37]. E-cadherin was scored negative, intermediate or positive. In case of discrepancies between different TMA cores of one tumor, the tumor was scored as intermediate.

PSMA

A mouse antihuman PSMA monoclonal antibody (3E6; DAKO) directed against the internal domain of the PSMA was used at a dilution of 1:80 [38]. For the tumor cells, PSMA staining was classified according to the percentage of positive tumor cells as negative (0–10%), low (positivity of 10–40%), moderate (positivity of 40–70%) and high (positivity of > 70%). The intensity of the staining was scored according to a semi-quantitative 4 grade scale (0 = no staining, 1 = low, 2 = moderate, 3 = high intensity) [39]. PSMA staining in the tumor-associated neovasculature was scored as the number of PSMA-positive vessels in the core [33].

HER2 assessment

HER2 expression was determined by *ERBB2* fluorescent *in situ* hybridization (FISH) according to standard ISH protocol using the *ERBB2* probe of Kreatech (KI-10701, mapping 17q12). Scoring was performed according to breast cancer guidelines of the American Society of Clinical Oncology (ASCO) and the College of American Pathologists (CAP) [40]. In case of an inconclusive ISH results, HER2 IHC was determined using the polyclonal rabbit antihuman c-erbB-2 antibody of DAKO according to protocol [40].

Data analysis

Descriptive statistics were used for patient and tumor characteristics, including the expression levels of AR, HER2 and the potential prognostic factors c-MET, E-cadherin, and PSMA expression in tumor cells and neovasculature. For association with lymph node metastases, AR, and HER2 expression, survival analyses, and Cox regression analyses, the potential prognostic factors were dichotomized: cytoplasmic c-MET, membranous c-MET, combined c-MET, and HER2 were scored negative versus positive, E-cadherin was scored negative/intermediate versus positive, PSMA tumor expression was scored < 4 versus ≥4 (= moderate intensity and extent), and PSMA neovascular expression was scored < 19.25 versus ≥19.25 (= median value).

All potential prognostic factors were tested for differences in N-stage, the absolute number of tumor-positive lymph nodes, the lymph node ratio (number of tumor-positive lymph nodes divided by total number of lymph nodes in the neck dissection), and semi-quantitative scored AR expression using the Mann-Whitney test, and tested for differences in HER2 expression using the chi-square test. Difference in PSMA tumor and neovascular expression in men and women were also tested with the Mann-Whitney test.

Patients with distant metastatic disease at diagnosis (n = 3) were omitted from the prognostic factor analysis. Kaplan-Meier survival curves and log-rank tests were used to test for differences in disease-free survival (DFS) and OS for all potential prognostic factors. Univariable Cox proportional hazard regression models were fitted for relevant clinical and pathological factors (age, gender, ex-pleomorphic adenoma, T-stage, N-stage, absolute number of tumor-positive lymph nodes, lymph node ratio, resection margins, primary tumor site, semi-quantitative AR, HER2) and for the potential prognostic factors (c-MET, E-cadherin, PSMA expression in tumor cells and neovasculature). Second, a multivariable analysis was performed with a forward selection procedure based on the Wald test at significance level of 0.05. Patients with missing values in one or more of the variables were excluded from the multivariable analysis. Analysis were performed using SPSS version 25.0 (IBM).

Data availability

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

Results

Patient characteristics

In this study, 165 patients diagnosed with SDC were included. Median age at diagnosis was 65 years (range 36–92 years) and the male to female ratio was 2.5:1. Of the 163 patients who received primary treatment with curative intent, all but one patient received a primary tumor resection, 129 patients underwent a neck dissection (79%), and 149 patients received postoperative radiotherapy (90%). The number of tumor-positive lymph nodes was 0 in 53 patients (32%), 1–2 in 23 patients (14%), 3–15 in 51 patients (31%), > 15 in 32 patients (19%), and missing in 6 patients (5%). The lymph node ratio could be calculated in 124 neck dissection specimens only.In the rest of the patients the total number of removed lymph nodes was unknown and therefore no ratio could be calculated. It was < 0.20 in 62 patients (50%) and ≥0.20 in 62 patients (50%). AR was negative in 8 patients (5%), expression was low in 87 patients (54%), and strong in 66 patients (41%). HER2 was overexpressed in 47 patients (29%). Patient and tumor characteristics are listed in Table 1.

Protein expression of c-MET, E-cadherin and PSMA

Immunohistochemical staining results are shown in Table 2 and typical staining patterns are shown in supplementary figure 1. Cytoplasmic c-MET expression was present in 67 tumors (42%), membranous c-MET expression in 29 tumors (18%), and cytoplasmic and/or

Table 1
Patient and tumor characteristics.

Characteristics	Number of patients (n = 165)
Age at diagnosis, in years, n (%)	
• ≤50	18 (11%)
• 51–60	41 (25%)
• 61–70	52 (32%)
• 71–80	35 (21%)
• > 80	19 (12%)
Gender, n (%)	
• Male	119 (72%)
• Female	46 (28%)
Carcinoma ex pleomorphic adenoma, n (%)	
• Yes	67 (41%)
• No ("de novo")	98 (59%)
Primary tumor, n (%)	
• Parotid gland	138 (84%)
• Submandibular gland	17 (10%)
• Sublingual gland	1 (1%)
• Other	
○ Minor salivary glands	7 (4%)
○ Lacrimal gland	1 (1%)
○ Unknown	1 (1%)
TNM stadium, n (%)	
• T1/T2/T3/T4/Tx (%)	30 (18%)/49 (30%)/19 (12%)/59 (36%)/8 (5%)
• N0/N1/N2/N3/Nx (%)	53 (32%)/15 (9%)/96 (58%)/0 (0%)/1 (1%)
• M0/M1 (%)	162 (98%)/3 (2%)
Number of tumor-positive lymph nodes, n (%)	
• 0	53 (32%)
• 1–2	23 (14%)
• 3–15	51 (31%)
• > 15	32 (19%)
• Missing	6 (5%)
Lymph node ratio*, n (%)	
• < 0.20	62 (50%)
• ≥0.20	62 (50%)
Overall stage, n (%)	
• I/II/III/IVa-b/IVc/unknown (%)	15 (9%)/18 (11%)/13 (8%)/113 (70%)/3 (2%)/3(2%)
Primary treatment with curative intent (n = 163)	
• Tumor resection + ND	128 (79%)
• Tumor resection without ND	33 (20%)
• Only ND	1 (1%)
• Lacrimal gland resection	1 (1%)
Postoperative radiotherapy, n (%)	
• Yes	149 (90%)
• No	16 (10%)
AR expression[1]	
• Negative	8 (5%)
• Low (> 0 < 6)	87 (54%)
• Strong (=6)	66 (41%)
HER2 expression	
• Negative	113 (71%)
• Positive	47 (29%)

Abbreviations: AR: Androgen receptor. HER2: Human epidermal growth factor receptor 2. ND: neck dissection.

* Number of tumor-positive lymph nodes divided by total number of lymph nodes in the neck dissection.

[1] Locati *et al.*, Head & neck 2016;38:724–31.

membranous expression in 71 tumors (45%). E-cadherin loss was seen in 7 tumors (4%) and intermediate E-cadherin expression in 14 tumors (9%). PSMA tumor cell expression was moderate in 29 tumors (18%) and negative/weak in the other tumors. The mean intensity of PSMA tumor staining was 0.55 ± 0.65 and the mean staining extent was 25.7 ± 31.0%. PSMA expression in the tumor-associated neovasculature was seen in 151 patients (96%).

Table 2
Protein expression patterns.

Proteins	Patients: n (%)
c-MET	
Cytoplasmic c-MET expression	
• Negative	91 (58%)
• Positive	67 (42%)
Membranous c-MET expression	
• Negative	129 (82%)
• Positive	29 (18%)
Combined c-MET expression	
• No cytoplasmic or membranous expression	87 (55%)
• Cytoplasmic and/or membranous expression	71 (45%)
E-cadherin	
• E-cadherin expression	
• Negative	7 (4%)
• Intermediate	14 (9%)
• Positive	137 (87%)
PSMA	
Intensity of PSMA tumor expression	
• Negative (< 1)	105 (66%)
• Weak (≥1 < 2)	42 (26%)
• Moderate (≥2 < 3)	13 (8%)
• Strong (3)	0 (0%)
Extent of PSMA tumor expression	
• Negative (0–10%)	78 (49%)
• Low (10–40%)	30 (19%)
• Moderate (40–70%)	25 (16%)
• Strong (> 70%)	27 (17%)
PSMA tumor expression, sum-score[1]	
• Negative (< 2)	100 (63%)
• Weak (≥2 < 4)	31 (19%)
• Moderate (≥4 < 6)	29 (18%)
• Strong (6)	0 (0%)
PSMA neovascular expression	
• Negative (0 positive vessels)	7 (4%)
• Weak (< 19.25 positive vessels)	72 (46%)
• Strong (> 19.25 positive vessels)	79 (50%)

Abbreviations: E-cadherin: Epithelial cadherin. PSMA: Prostate-specific membrane antigen.

[1] The PSMA tumor sum-score was calculated by adding up staining intensity (0–3) and staining extent (0–3).

Associations

Associations of all potential prognostic factors with lymph node status, AR and HER2 expression, DFS and OS are shown in Table 3. Regarding the lymph node status, we found that high PSMA tumor expression (sum-score ≥ 4) was significantly associated with a lower N-stage (P = 0.001), lower number of lymph node metastases (P = 0.018), and lower lymph node ratio (P = 0.010). Membranous c-MET expression was significantly associated with a lower N-stage (P = 0.040), but not with the number of tumor-positive lymph nodes or lymph node ratio. The other factors were not significantly associated with lymph node status.

Association of the potential prognostic factors with semi-quantitatively scored AR expression, showed that a high PSMA tumor expression (sum-score ≥4) and E-cadherin loss were significantly associated with strong and weak AR expression, respectively (P = 0.033 and P = 0.007). None of the factors were associated with HER2 expression.

Difference in PSMA tumor and neovascular expression in men and women showed a significantly higher PSMA tumor expression in women with a PSMA tumor sum-score of 2.0 ± 1.7 versus 1.4 ± 1.7 in men (P = 0.029). PSMA neovascular expression did not significantly

Table 3
Association of potential prognostics factors with lymph node status, AR expression, HER2 expression, disease-free survival (DFS) and overall survival (OS). Significant results are depicted in bold.

	N-stage Mann-Whitney Mean rank (*P*)	No. of tumor-positive lymph nodes	Lymph node ratio	AR expression[1]	HER2 expression Chi-square (*P*)	DFS Log rank Median DFS (*P*)	OS Log rank Median OS (*P*)
Cytoplasmic C-met expression • Neg vs. pos	82.8 vs 75.1 (p = 0.248)	83.1 vs 74.6 (p = 0.235)	82.9 vs 75.0 (p = 0.271)	78.7 vs 80.6 (p = 0.778)	p = 0.434	24 vs. 25 mo. (p = 0.930)	51 vs. 57 mo. (p = 0.788)
Membranous C-met expression • Neg vs. pos	**82.7 vs. 65.3** **(p = 0.040)**	82.1 vs 67.8 (p = 0.117)	81.8 vs. 69.3 (p = 0.172)	78.5 vs. 84.0 (p = 0.538)	P = 0.831	24 vs. 24 mo. (p = 0.731)	52 vs. 105 mo. (p = 0.713)
Combined c-MET expression • Neg vs. pos	84.0 vs. 74.0 (p = 0.132)	83.8 vs 74.2 (p = 0.176)	83.6 vs 74.4 (p = 0.197)	78.9 vs 80.2 (p = 0.849)	P = 0.721	24 vs. 25 mo. (p = 0.969)	52 vs. 57 mo. (p = 0.799)
E-cadherin expression • Neg/intermediate vs. pos	69.3 vs. 81.1 (p = 0.225)	68.4 vs. 81.2 (p = 0.219)	66.6 vs 81.5 (p = 0.153)	**55.7 vs 83.2** **(p = 0.007)**	P = 0.265	22 vs. 24 mo. (p = 0.435)	44 vs. 52 mo. (p = 0.848)
PSMA tumor sum-score • < 4 vs. ≥ 4	**85.7 vs. 57.1** **(p = 0.001)**	**84.5 vs 62.6** **(p = 0.018)**	**84.8 vs 61.0** **(p = 0.010)**	**76.5 vs 95.8** **(p = 0.033)**	P = 0.389	22 vs. 51 mo. (p = 0.094)	**45 vs. 83 mo.** **(p = 0.022)**
Number of PSMA-positive vessels • < 19.25 vs. ≥ 19.25	76.6 vs. 82.4 (p = 0.383)	78.4 vs. 80.6 (p = 0.754)	77.6 vs. 81.4 (p = 0.597)	81.0 vs 77.0 (p = 0.564)	P = 0.150	23 vs. 25 mo. (p = 0.686)	70 vs. 48 mo. (p = 0.312)
HER2 expression • Neg vs. pos	78.5 vs. 85.3 (p = 0.351)	78.6 vs 85.0 (p = 0.415)	79.7 vs. 82.4 (p = 0.734)	81.0 vs 72.4 (0.258)	n.a.	24 vs. 23 mo. (p = 0.553)	60 vs. 47 mo. (p = 0.678)

[1] Locati *et al.*, Head & neck 2016;38:724–31.

differ between women and men (28.9 ± 30.2 positive vessels vs. 24.3 ± 22.5, $P = 0.646$).

Kaplan Meier survival curves showed a significantly longer OS ($P = 0.022$) and a trend towards a longer DFS ($P = 0.094$) for patients with high PSMA tumor expression versus low PSMA tumor expression (Fig. 2). The other factors were not significantly associated with DFS or OS (supplementary figure 2).

Cox regression analyses

In the univariable Cox regression analyses, high age at diagnosis, high N-stage, high number of tumor-positive lymph nodes, high lymph node ratio, and low PSMA tumor expression were associated with poor OS. In the multivariable analysis, patients with a missing value in any variable were not included, resulting in the inclusion of 135 patients. The multivariable model only contained a high number of tumor-positive lymph nodes and high age at diagnosis. The results of the univariable and multivariable models are shown in Table 4.

Discussion

In this study, we evaluated whether expression of c-MET, E-cadherin, and tumor or neovascular PSMA expression are prognostic factors for SDC using Kaplan-Meier survival curves, univariable and multivariable Cox regression analyses. Patients with high PSMA tumor expression showed a significantly longer OS, trend towards a longer DFS, and significantly reduced hazard ratio for death in the univariable Cox regression analysis. It was not an independent variable for overall survival in the multivariable model, in which only a high number of tumor-positive lymph nodes and high age at diagnosis (> 80 years) were independent variables for poor OS.

High PSMA tumor expression may be associated with survival in the Kaplan-Meier and univariable Cox regression analysis because it is significantly associated with a lower number of tumor-positive lymph nodes, which is an independent poor prognostic factor in the multivariable analysis. In prostate cancer, high PSMA expression is not associated with lymph node status [41]. High PSMA tumor expression was also significantly associated with high AR expression. Therefore, the longer survival might be caused by better responses to ADT, although AR protein expression is not a significant predictive factor of clinical benefit from ADT in SDC [42]. Compared to prostate cancer tumors, PSMA tumor expression is rather low. Mean PSMA tumor intensity was 0.55 ± 0.65 and mean PSMA tumor extent was 25.7 ± 31.0% in SDCs, compared to 2.33 ± 1.11 and 67.8 ± 28.0% in primary prostate cancers [39]. Finally, PSMA expression in tumor cells was significantly higher in women versus men. In prostate cancer patients, ADT results in increased PSMA expression [43]. In line with this, it is possible that the physiological lower levels of androgen in women result in higher expression levels of PSMA in women.

Remarkably, membranous c-MET expression was significantly associated with a lower N-stage, which is opposed to our hypothesis that activation of the HGF/MET signaling pathway may be a causal factor of lymph node metastases. However, membranous c-MET was not associated with the other nodal scores, nor was cytoplasmic c-MET expression. Finally, we found an association between E-cadherin loss and weak AR expression. One may wonder whether SDC tumor cells with a high metastatic potential loose E-cadherin expression and AR expression, but Xu *et al.* showed a high prevalence of AR expression in metastatic tumors (93%), and concordance between in the primary tumor and metastatic tumor in 95% [44].

Although the studied markers do not seem to be independent prognostic factors, they might serve as therapeutic targets. c-MET expressing tumors may be targeted with c-MET inhibitors like the multitarget tyrosine kinase inhibitor crizotinib or cabozantinib. Therefore, we performed a phase 2 clinical trial on the efficacy of cabozantinib in c-MET positive SGC. Unfortunately, this trial was closed prematurely because of severe wound and fistula complications in 32% of patients [45]. Loss of E-cadherin is not an established druggable target, but preclinical data indicate that E-cadherin deficient cancers depend upon ROS1 signaling. Therefore, ROS1 inhibitors such as the tyrosine kinase inhibitor crizotinib or entrectinib may be effective in E-cadherin deficient cancers [46]. PSMA is an important target for imaging and radionuclide therapy in castration-resistant prostate cancer (CRPC) patients, and may be used for these purposes in SDC. Our recently

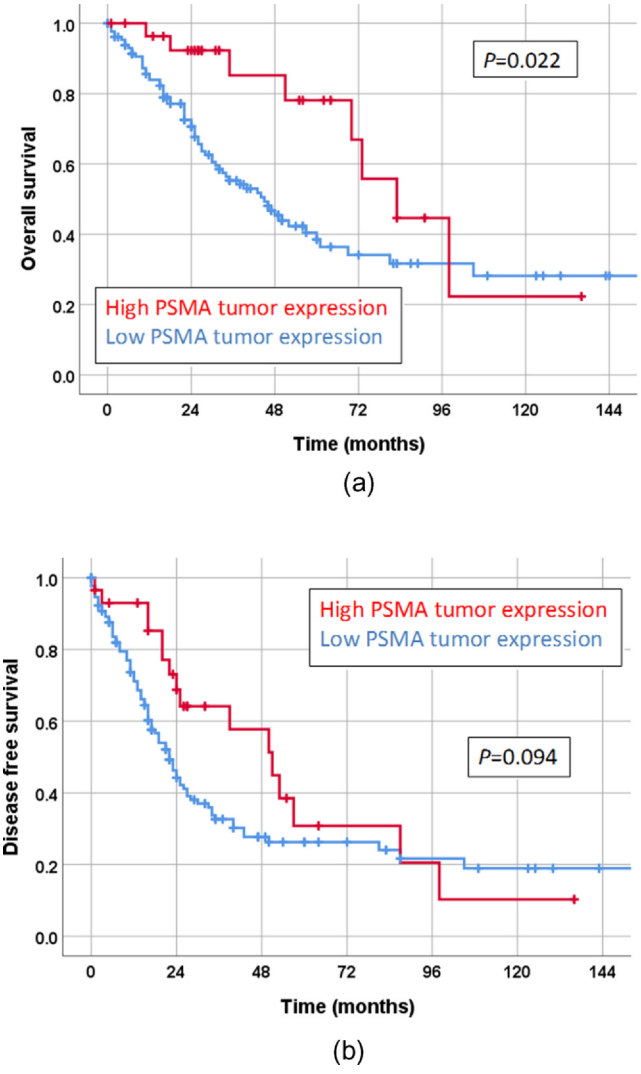

Fig. 2. Kaplan-Meier survival curves of overall survival (**A**) and disease-free survival (**B**) in patients with high (≥4) versus low (< 4) PSMA expression in the tumor cells.

conducted study on PSMA-PET/CT in 10 SDC patients indeed showed relevant PSMA-ligand uptake in 40% of patients [47].

A strength of this study is the use of a large number of tumor samples of this rare cancer, and the availability of relevant clinical and pathological characteristics, which allowed us to analyze the prognostic value in a multivariable analysis. A limitation of this study is that we used TMA's for immunohistochemical staining, which have a risk of sampling error. We tried to avoid this by taking 2–3 cores of every primary tumor whenever possible [48]. Furthermore, no correction for multiple testing was performed, because this was an explorative study.

In conclusion, c-MET, E-cadherin, PSMA tumor expression, and PSMA neovascular expression are no independent prognostic factors in this cohort of SDC patients. Nevertheless, these markers may be therapeutic targets.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Table 4
Univariable and multivariable Cox regression analyses for overall survival.

Univariable Cox regression analyses			
Factor	No. of patients	HR (95% CI)	*P*
Age at diagnosis			0.075
• ≤50	18	1.00	–
• 51–60	40	2.28 (0.92–5.62)	0.075
• 61–70	51	1.55 (0.62–3.87)	0.346
• 71–80	34	1.90 (0.74–4.86)	0.180
• > 80	19	3.83 (1.39–10.59)	**0.010**
Gender			
• Male	116	1.00	–
• Female	46	1.58 (0.91–2.75)	0.105
Carcinoma ex pleomorphic adenoma			
• No ("de novo")	98	1.00	–
• Yes	67	1.00 (0.63–1.57)	0.99
T-stadium			
• T1/T2	79	1.00	–
• T3/T4	76	1.29 (0.80–2.07)	0.292
N-stadium			**0.034**
• N0	53	1.00	–
• N1	15	1.34 (0.56–3.21)	0.511
• N2	93	1.98 (1.15–3.41)	**0.014**
• N3	0	–	–
Number of positive lymph nodes			**0.007**
• 0	53	1.00	–
• 1–2	23	0.79 (0.35–1.80)	0.575
• 3–15	51	1.67 (0.93–3.00)	0.086
• > 15	31	2.67 (1.40–5.10)	**0.003**
Lymph node ratio[1]			
• < 0.20	62	1.00	–
• > 0.20	61	2.06 (1.21–3.52)	**0.008**
Resection margins			0.139
• Free	13	1.00	–
• Close	20	0.48 (0.15–1.52)	0.212
• Tumor-positive margins	126	1.10 (0.50–2.40)	0.819
Primary tumor site			0.765
• Parotid gland	135	1.00	–
• Submandibular gland	17	0.87 (0.41–1.83)	0.711
• Other	9	1.34 (0.53–3.34)	0.536
Semiquantitative AR staining			0.648
• Negative	8	1.00	–
• Low (> 0 < 6)	85	0.67 (0.28–1.60)	0.367
• Strong (=6)	65	0.65 (0.27–1.56)	0.331
HER2			
• Negative	111	1.00	–
• Positive	46	1.11 (0.67–1.84)	0.681
Cytoplasmic C-met expression			
• Negative	89	1.00	–
• Positive	66	0.95 (0.59–1.54)	0.837
Membranous C-met expression			
• Negative	127	1.00	–
• Positive	28	0.85 (0.44–1.62)	0.610
Combined c-MET expression			
• Negative	85	1.00	–
• Positive	70	0.96 (0.59–1.55)	0.855
E-cadherin			0.301
• Negative	7	1.00	–
• Intermediate	13	4.01 (0.50–32.18)	0.191
• Positive	135	3.00 (0.42–21.67)	0.276
PSMA tumor staining			
• Negative (score < 4)	128		–
• Positive (score ≥4)	29	0.45 (0.22–0.94)	**0.034**
PSMA neovascular staining			
• Weak (< 19.25)	78	1.00	–
• Strong (≥19.25)	77	1.25 (0.78–2.00)	0.360

(*continued on next page*)

Table 4 (*continued*)

Univariable Cox regression analyses			
Factor	No. of patients	HR (95% CI)	*P*
Multivariable Cox regression analysis			
Factor	No. of patients	HR (95% CI)	*P*
Age at diagnosis, categories			**0.025**
• ≤50	13	1.00	–
• 51–60	34	2.43 (0.69–8.57)	0.166
• 61–70	44	1.58 (0.45–5.59)	0.477
• 71–80	29	2.29 (0.63–8.26)	0.207
• > 80	17	5.71 (1.53–21.36)	**0.010**
No. of positive lymph nodes			**0.002**
• 0	48	1.00	–
• 1–2	20	1.21 (0.48–3.09)	0.688
• 3–15	46	2.04 (1.03–4.04)	**0.042**
• > 15	23	4.73 (2.09–10.70)	< **0.001**

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.oraloncology.2020.105018.

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