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Westergaard-Nielsen, Marie; Möller, Sören; Godballe, Christian; Grau Eriksen, Jesper; Larsen, Stine Rosenkilde; Kiss, Katalin; Agander, Tina; Parm Ulhøi, Benedicte; Charabi, Birgitte; Ehlers Klug, Tejs; Jacobsen, Henrik; Johansen, Jørgen; Kristensen, Claus Andrup; Andersen, Elo; Andersen, Maria; Bjørndal, Kristine

Published in:
Head and Neck

DOI (link to publication from Publisher):
10.1002/hed.26672

Publication date:
2021

Document Version
Accepted author manuscript, peer reviewed version

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Running title: Prognostic scoring models in parotid gland carcinoma

Key words: Parotid gland carcinoma, prognosis, prognostic scoring model, recurrence risk, follow-up

Grant support: The study was conducted as part of PhD funded by grants from University of Southern Denmark, Region of Southern Denmark, Danish Cancer Research Fund, and Danish Cancer Society.

Abstract

Background: The aim was to identify prognostic factors and test three prognostic scoring models that predicted the risk of recurrence in patients with parotid gland carcinoma.

Methods: All Danish patients with parotid gland carcinoma, treated with curative intent, from 1990 to 2015 (*n* = 726) were included. Potential prognostic factors were evaluated using Cox regression and competing risk analyses. The concordance of each prognostic model was estimated using Harrel's C index.

Results: The study population consisted of 344 men and 382 women, with a median age of 63 years. Age above 60 years, high grade histology, T3/T4 tumour, regional lymph node metastases, and involved surgical margins were all associated with a significant reduction in recurrence-free survival. The prognostic model that agreed best with actual outcomes had a C-index of 0.76.

Conclusion: Prognostic scoring models may improve individualised follow-up strategies after curatively intended treatment for patients with parotid gland carcinoma.

Introduction

Parotid gland carcinoma constitutes only 1–3 % of all head and neck cancers [1-4], and clinical studies are difficult to perform because the disease is rare and heterogeneous. Parotid gland carcinomas are histologically categorised into 22 subtypes with different biological behaviours and malignancy grades [5] that affect disease outcomes and prognoses [1, 5-7].

Prognostic factors reportedly include both patient and tumour characteristics, as well as treatment modalities. Age [6, 8-14], sex [8], comorbidities [15], histological subtype or grade [1, 6-8, 10, 11, 14, 16, 17], tumour size or T-classification [1, 6-10, 12-14, 17-19], metastatic spread [6, 8, 11, 13, 18, 20], invasion of adjacent tissue and nerves [7-10, 12, 16, 18], surgical strategies, resection margins [9, 13, 14], treatment of cervical lymph nodes, and radiotherapy [12, 13] have all been associated with disease prognosis.

Because it is difficult to evaluate various prognostic factors and assess the risk of disease recurrence, prognostic scoring models and nomograms have been developed. These models are designed to provide the clinician with useful tools for planning follow-up strategies after primary treatment, but they may be based on different patient and tumour characteristics, diagnostic work-ups, and treatment modalities, or they may have been generated from selected patient groups. Therefore, to ensure they are generalisable, the models must be validated using an external group of patients.

In this study, we describe outcomes and prognostic factors in a cohort of Danish patients with parotid gland carcinoma over a period of 26 years. The results are used to validate and compare prognostic models developed by Vander Poorten [8, 9, 17, 21, 22], Carrillo [10, 17] and Ali [11, 23]. The aim was to identify a reliable and simple prognostic scoring model for predicting recurrence after curatively intended treatment for primary parotid gland carcinoma.

Material and Methods

Patients were identified from the Danish Head and Neck Cancer Group (DAHANCA) database, which contains extensive data on Danish patients with salivary gland carcinoma [6]. Inclusion criteria were patients with primary parotid gland carcinoma who were treated with curatively intended surgery between 1 January 1990 and 31 December 2015. A total of 870 patients were diagnosed with primary parotid gland carcinoma during the inclusion period, and clinical data were available for 830 patients.

When available, histological specimens were re-evaluated by experienced salivary gland pathologists (SRL, KK, TA, and BPU). Re-evaluation was performed according to the World Health Organization (WHO) 2005 classification system for patients diagnosed with salivary gland carcinoma before 1 January 2006, and according to the WHO 2017 classification system for patients diagnosed with salivary gland carcinoma after this date. Mucoepidermoid carcinomas, adenocarcinomas, and squamous cell carcinomas were graded as high, intermediate, or low-grade. Adenoid cystic carcinomas were graded according to their growth patterns (i.e., solid or tubulo-cribriform). Histological subtypes were categorised as high- or low-grade subtypes according to the Danish National Guidelines [24], as shown in Supplementary Table A. Tumours were classified according to the Union for International Cancer Control (UJCC) TNM classification of malignant tumours. Surgical margins of 5 mm or more were defined as clear. If the facial nerve was involved in the tumour, it was sacrificed to obtain free surgical margins. If the tumour was close to, or directly on, a facial nerve but without involvement and it was possible to preserve the nerve during surgery, the margins were considered close.

Patient and tumour characteristics, treatment details, and follow-up data were extracted from the DAHANCA database, medical records, and pathology reports. To ensure any recurrence after the end of clinical follow-up was recorded for patients included in the study, we searched The Danish Pathology Data Bank, which contains all the histological and cytological pathology records in Denmark. If data on status at follow-up were not available, date of death and cause of death were extracted from the national Danish

Central Person Register and the Cause of Death Register. Follow-up time was calculated from the date of first surgical treatment to the date of death or end of data collection.

Statistics

Overall survival (OS), recurrence-free survival (RFS), and disease-specific survival (DSS) were estimated using the Kaplan–Meier method. Univariate analyses of prognostic factors were performed using the Mantel–Haenszel log-rank test. Cox regression analysis was used for multivariate analyses of factors that were significant in the univariate tests. Competing risk analyses using the Fine–Gray method and subhazard ratio (SHR) were used in univariate and multivariate analyses of factors potentially associated with recurrence. Diagnosis of local, regional, or distant disease after curatively intended treatment and then a disease-free interval was defined as recurrence. Death from causes unrelated to parotid gland carcinoma was considered a competing risk. Tests were two-sided and a p-value < 0.05 was considered statistically significant.

The Vander Poorten [9] and Carrillo [10] prognostic scores were calculated according to the algorithms published in the respective papers. The Vander Poorten score consisted of the pre-treatment score (PS1) based on pain, age, T-classification, N-classification, skin invasion, and facial nerve impairment and the PS2, with pathological factors, based on age, T-classification, N-classification, skin invasion, facial nerve impairment, histological perineural invasion, and involved surgical margins. The Carrillo score was based on age, histological differentiation, T-classification, facial nerve impairment, and surgical margins. To use the Ali nomogram [11], we converted the nomogram into numerical values by measuring distances marked on the nomogram. These numerical values were then used to calculate a final score. The variables in the Ali nomogram were age, histological grade, vascular invasion, perineural invasion, and positive lymph nodes. All scores were split into the groups suggested by the original publications. We performed survival analyses with time from inclusion to recurrence or death, censoring at the end of follow-up. For each score, we used the Kaplan–Meier method to construct survival curves for each group and compared these using log-rank

tests and competing risk analyses. Moreover, we used Cox regression for the numerical scores (C-numerical) and their groupings (C-categorical) reporting hazard ratios (HRs) with 95% confidence intervals (CIs) as well as Harrel's C-index as a measure of concordance.

Data were stored in a RedCap database provided by the Open Patient data Explorative Network (OPEN). Statistical analyses were performed using Stata software ver. 16 (StataCorp LLC, College Station, Texas, USA).

Results

Of 830 patients reviewed, 726 met the inclusion criteria. Patients with distant metastases at primary diagnosis (*n* = 40), patients with macroscopic residual tumour after primary treatment (*n* = 51) and patients with inoperable disease (*n* = 13) were excluded. This resulted in a study group consisting of 344 males (47.4%) and 382 females (52.6%). The median age was 63 years (range, 6–93 years). Most patients presented with T1 (*n* = 262, 36.1%) or T2 (*n* = 213, 29.3%) tumours. Eighty-six patients (11.9%) had T3 tumours, 136 (18.7%) had T4a tumours, and 21 (2.9%) had T4b tumours. For eight patients (1.1%), T-classification could not be assessed. Facial nerve function at diagnosis was normal in 615 patients (84.7%). A total of 111 patients (15.3%) had facial nerve impairment. Preoperative pain was reported by 78 patients (10.7%).

Histological specimens were re-evaluated in 708 of the patients (94.1%). Acinic cell carcinoma was the most frequent histological subtype (*n* = 136, 18.7%), followed by mucoepidermoid carcinoma (*n* = 98, 13.5%), carcinoma ex pleomorphic adenoma (*n* = 93, 12.8%) and adenoid cystic carcinoma (*n* = 88, 12.1%).

Overall, 440 patients (60.6%) had partial and 286 patients (39.4%) had total parotidectomies. The facial nerve was preserved in 556 patients (76.6%). In 163 patients (22.4%), the facial nerve was partly or totally sacrificed. For seven patients (1%), the surgical reports had no information regarding facial nerve involvement. Sacrifice of the facial nerve was significantly more likely in patients with involved surgical

margins (OR, 2.7; 95% CI, 1.8–3.8; $p < 0.001$) and in patients with perineural invasion (OR, 6.4; 95% CI, 4.1–10.0; $p < 0.001$).

Overall, neck dissection was performed in 318 patients (43.8%). Therapeutic neck dissection was performed in patients with clinically or radiographically suspected regional metastases ($n = 70$, 9.6%), and elective neck dissection was performed in 248 patients (34.2%) with clinically negative cervical lymph nodes. Additionally, 147 patients (20.2%) had excisional lymph node biopsies of one or two lymph nodes. Cervical lymph node metastases were diagnosed in 142 patients (19.6%), 41 (5.7%) of whom had N1, eight (1.1%) had N2a, 90 (12.4%) had N2b, 2 (0.3%) had N2c, and one had (0.1%) N3a disease.

In the pathology reports, surgical margins were reportedly clear in 259 patients (35.7%), close in 184 patients (25.3%), and involved in 257 patients (35.4%). Margin status was not described for 26 patients (3.6%). Perineural invasion was reported in 219 patients (30.2%) and vascular invasion was reported in 111 patients (15.3%). Information on perineural and vascular invasion was missing for 294 (30.6%) and 313 (43.1%) patients, respectively.

Indications for adjuvant radiotherapy were close or involved surgical margins, T3/T4 tumours, high-grade histology, regional metastases, and perineural invasion. Adjuvant radiotherapy was administered to 467 patients (64.3%), 34 (4.7%) of whom received less than 60 Gy, for various reasons. Curatively intended doses of 60 to 70 Gy (with 2 Gy per fraction) were administered to 424 patients (58.4%). For nine patients (1.2%), the dose of radiotherapy was not specified. Only eight patients (1.1%) received chemotherapy and the majority of these patients had lymphoepithelial carcinoma (6/8, 75%).

Patient and tumour characteristics and treatment information are summarised in Table 1.

Median follow-up time was 6.4 years (range, 0.1–28.2 years). For patients alive at the end of follow-up ($n = 359$, 49.4%), the median follow-up time was 10.2 years (range, 2.2–28.2 years). Median follow-up time for patients alive with no disease was 7.8 years (range, 0.1–28.2 years). For patients with no evidence of

disease after salvage, the median follow-up time was 13.2 years (range, 2.4–27.4 years) and for patients alive with recurrence, the median follow-up time was 2.4 years (range, 0.3–22.8 years).

During the follow-up period, 215 patients (29.6%) experienced recurrence. Isolated recurrence at the primary site was observed in 74 patients (10.2%), whereas 16 patients (2.2%) had locoregional recurrence. Distant metastases were observed in 101 patients (13.9 %), with the most frequent sites being the lungs (63/101, 62.4%), followed by the bones (29/101, 28.7%), liver (19/101, 18.8%), and heart (19/101, 18.8%). Recurrence at a distant site was diagnosed in patients with salivary duct carcinomas (*n* = 21, 21%), adenocarcinomas (*n* = 17, 17%), carcinoma ex pleomorphic adenomas (*n* = 16, 16%), adenoid cystic carcinomas (*n* = 15, 15%), and other subtypes (*n* = 32, 32%). The recurrence pattern is illustrated in Figure 1. The mean and median times to recurrence after completion of curative intended treatment were 2.7 years and 1.3 years, respectively (range, 0.1–17.8 years). In multivariate analyses, T3/T4 tumours (HR 1.5; *p* = 0.019) and regional lymph nodes metastases (HR, 1.7; *p* = 0.004) were associated with significantly shorter times to recurrence.

Parotid gland carcinoma was the cause of death in 164 patients (22.6%), and 6 patients (0.8%) died during treatment. Death was caused by other cancers in 75 patients (10.3%) and by other diseases in 100 patients (13.8%). Two patients died by suicide (0.3%). The cause of death was unknown in 20 patients (2.8%). Of the 359 patients alive at the end of follow-up, 321 (89.4%) showed no recurrence after primary treatment, 27 (7.5%) were treated for recurrence and had no evidence of disease, and 11 (3.0%) were alive with recurrence.

Kaplan-Meier curves showing OS, RFS, and DSS with 95% CIs are illustrated in Figure 2. Survival rates with 5-, 10- and 15-year probabilities are summarised in Table 2. The 20-year OS was 34% (95% CI, 29–39) and the 25-year OS was 28% (95% CI, 22–34).

Univariate analyses identified age above 60 years, high-grade histology tumours, T3/T4 tumours, regional metastases, facial nerve impairment, perineural and vascular invasion, and involved surgical margins as

significant factors having a negative impact on OS, RFS and DSS. In addition, male sex and preoperative pain had significantly negative impact on both RFS and DSS and on DSS alone, respectively. In the univariate competing risk analyses age above 60 years (SHR, 1.7), male sex (SHR, 1.5), high-grade histology tumours (SHR, 2.8), T3/T4 tumours (SHR, 5.7), regional metastases (SHR, 4.6), facial nerve impairment (SHR, 4.2), perineural invasion (SHR, 3.2), vascular invasion (SHR, 3.8), and involved surgical margins (SHR, 3.1) were significantly associated with recurrence.

In multivariate analyses, significant negative prognostic factors for OS and RFS were age above 60 years, high-grade histology tumours, T3/T4 tumours, regional metastases and involved surgical margins. High-grade histology was not significantly associated with DSS. Results of the multivariate Cox regression analyses are shown in Table 3. In multivariate competing risk analyses, only T3/T4 tumours, regional metastases, and involved surgical margins were significantly associated with recurrence. The SHR for experiencing recurrence was 2.7 for patients with T3/T4 tumours compared to T1/T2 tumours, provided that the patients had not died from causes unrelated to parotid gland carcinoma. Results of the multivariate competing risk analyses of recurrence risk are shown in Table 3.

Patients were categorised into different prognostic groups using the Vander Poorten PS1 and PS2 [9], the Carrillo score [10], and the Ali nomogram [11]. Based on the Vander Poorten PS1, 63% of the patients were assigned to level I, 18% to level II, 11% to level III, and 7% to level IV. Only 481 patients were included in the Vander Poorten PS2 calculation due to missing data on perineural invasion. Based on the PS2, 29% of the patients were assigned to level I, 27% to level II, 25% to level III, and 29% to level IV. All 726 patients were included in the Carrillo score calculation, with 62% being assigned to the low-risk group, 29% to the intermediate-risk group, and 9% to the high-risk group. Only 397 patients were included in the Ali nomogram calculations due to missing data on perineural and vascular invasion. These patients were assigned to three groups, with 54% being assigned to group 1, 27% to group 2, and 19% to group 3.

RFS outcomes for each prognostic group within the different prognostic scoring systems are illustrated using Kaplan–Meier curves in Figure 3. The HRs and SHRs that may be used to compare the prognostic levels and groups are summarised in Table 4. The concordance between the predicted RFS from the Vander Poorten PS1 and PS2 and the observed RFS was 0.70 and 0.74, respectively. The numerical C-statistic, which represents the concordance between predicted and observed RFS based on individual numerical scores, was 0.76 for both PS1 and PS2. The C-statistic for the Carrillo score was 0.61 for both groups and individual scores. For the Ali nomogram, the C-statistic was 0.62 for group and 0.61 for individual scores. These C-statistics are reported in Table 4.

Discussion

In this study, we reported results from a complete national cohort of patients with parotid gland carcinoma treated with curative intent. We estimated RFS using three different prognostic scoring models and we found that the Vander Poorten scores, PS1 and PS2, agreed well with the observed outcomes. The high levels of concordance were confirmed by C-statistics above 0.7 for both PS1 and PS2. We found that age above 60 years, high-grade histological tumours, T3/T4 tumours, regional lymph node metastases, and involved surgical margins all had a significantly negative impact on RFS.

The C-statistics suggest that the Vander Poorten score is a reliable tool for predicting RFS in Danish patients. The numerical C-statistic, based on individual scores, was 0.76 for both PS1 and PS2, indicating a high concordance with actual outcomes. As illustrated in Figure 3, the PS2 model shows good separation of the different groups. However, although the Vander Poorten PS2 model worked well for our patient population, it consists of eight variables and some of these are not consistently reported in medical records. The concordance results from our study are consistent with previous international validations of the Vander Poorten score by Paderno *et al*. [8] and Lu *et al*. [17]. In a study by Takahama *et al*. [40], the

Vander Poorten and Carrillo prognostic models were less reliable, presumably because of epidemiological differences among the relevant the cohorts.

The C-statistics for the Ali nomogram and the Carrillo score were below 0.7, indicating that these models are less suitable for predicting recurrence in our patient cohort. A possible explanation for the lower concordance of the Ali nomogram in this study is that the nomogram was developed for carcinomas in all major salivary glands, whereas we included only patients with parotid gland carcinoma. In addition, to calculate prognostic scores, the nomogram was adapted and converted into numerical values and this may have decreased the level of concordance.

Lower levels of concordance may also be explained by epidemiological differences among patient cohorts. The patient population described by Carrillo *et al*. [10] was younger (mean age: 53 years) than that used in this study or that used by Vander Poorten *et al*.[9] or Ali *et al*. [11] (mean ages: 63, 63 and 62 years, respectively). Importantly, the male to female ratio in our cohort was similar to those in the other three studies. The proportion of patients with T3/T4 tumours in this study (34%) and in the studies described by Vander Poorten *et al*. (36%) [9] and Ali *et al*. (34%) [11] were similar. Carrillo *et al*. [10] reported a higher proportion of patients with T3/T4 tumours (74%). In addition, the proportion of patients with regional metastases was high (39%) in the study described by Carrillo *et al*. [10]. In our study, 20% of the patients presented with regional metastases, which is similar to the proportions of patients with regional metastases reported by Vander Poorten *et al*. (21%) [9] and Ali *et al*. (25%) [11].

The treatment modalities differed among the studies. In our study, 64% of the patients received adjuvant radiotherapy, whereas 82% of the patients studied by Carrillo *et al*. and only 53% of the patients studied by Ali *et al*. had adjuvant radiotherapy. Vander Poorten *et al*. reported a 5-year RFS of 64% [9], whereas Carrillo *et al*. reported a 5-year RFS for each prognostic group of 18.7% (high risk), 53.9% (intermediate risk), and 99.9% (low risk) [10]. Ali *et al*. reported a 5-year recurrence rate of 33% [11]. A comparison of the

results from this study and those described by Vander Poorten *et al*. [9], Carrillo *et al*. [10], and Ali *et al*. [11] is shown in Supplementary Table B.

Carrillo *et al*. [10] reported histological differentiation data (well differentiated, moderately differentiated, poorly differentiated, or undifferentiated), and Ali *et al*. [11] reported histological grade data (low, intermediate, or high grade). In our study and that described by Vander Poorten *et al*. [9], histological assessments were based on the WHO classification procedure (i.e., high, intermediate, or low-grade histology). This illustrates the diverse methods for grading salivary gland carcinomas. Some studies assess histological grade based on pathological characteristics [25, 30-35], whereas other studies classify the biological behaviours of histological subtypes [20, 36-38]. Although it complicates comparisons among study cohorts, this diversity may not be problematic when comparing prognostic scoring models. Van der Schroeff *et al*. [39] studied salivary gland carcinomas in the minor and major glands using OS as the endpoint, and they compared three versions of a prognostic model. These researchers concluded that incorporating cytology or histology data into the prognostic models had limited value. Interestingly, histology data are not included in the Vander Poorten scores [9]. We found that high-grade histology as well as age above 60 years, T3/T4 tumours, regional metastases, and involved surgical margins were independent negative prognostic factors in predicting RFS. In contrast, histological grade was not significantly associated with DSS. In the multivariate competing risk analyses only T3/T4 tumours, regional metastases, and involved surgical margins were significantly associated with recurrence. Tumour sizes, regional metastases, skin invasion, and perineural and vascular invasion are all associated with histological grade which may influence the multivariate analyses. This complies well with the Vander Poorten PS2 score [9].

In our study, the 5-year RFS was 80%, and the 10-year RFS was 71%. In similar studies, 5-year RFS has varied from 50% to 78% [8, 9, 16-18, 21, 22, 27] and 10-year RFS from 58% to 67% [8, 10, 22]. The relatively high RFS observed in this study may be because we included only patients treated with curative intent, as well

as being partly due to the high proportion of low-grade histological subtypes (e.g., acinic cell carcinoma and low-grade mucoepidermoid carcinoma). The inclusion criteria were chosen to match the clinical material on which the prognostic scoring models were based.

The strengths of this study were the inclusion of a complete national cohort of patients. This cohort consisted of many patients compared to previous validation studies [8-11, 17, 40]. Histological specimens were re-evaluated, and the median follow-up time was 10.2 years for patients alive at the end of follow-up. Using data from this cohort in the prognostic models meant that the long follow-up period could be utilised. Consequently, the models could be validated over a period in excess of 5 years, which has been the maximum time period evaluated in previous studies [8, 17].

The main limitations of this study were its retrospective design and incomplete data, particularly regarding perineural and vascular invasion. Data on these variables were not reported consistently in the pathology reports and this influenced the number of patients who could be included in calculations for the Vander Poorten PS2 [9] and the Ali nomogram [11]. Perineural and vascular invasion may also have been reported more frequently when present than when absent, resulting in a risk of bias. Patients were included over a period of 26 years. During this time, diagnostic imaging and histological evaluation techniques have improved and more immunohistochemical and molecular markers have become available. Furthermore, the WHO classification system was updated in 2017 [5] and secretory carcinoma is now classified as a separate subtype. Treatment strategies have also improved over the study period, especially with regard to radiotherapy, although time was not associated with increased survival rates in the analysis of all Danish patients with salivary gland carcinoma [6].

Conclusions

Current follow-up strategies for patients treated for parotid gland carcinoma are standardised with regard to the timing and frequency of subsequent consultations. However, by calculating the expected risk of

recurrence or RFS, follow-up strategies may be tailored to individual patients. A suitable prognostic scoring system must be based on a simple model and variables that are easy to access from the medical records. After comparing the RFS estimates predicted by three different prognostic scoring models, we found that the Vander Poorten scores were highly concordant with actual outcomes [9]. Implementing this prognostic scoring system may facilitate individualised follow-up strategies after curatively intended treatment for patients with parotid gland carcinoma.

Acknowledgements and declarations

This study was supported by the Danish Head and Neck Cancer Group (DAHANCA) and by Open Patient data Explorative Network (OPEN), Odense University Hospital, Denmark.

Grants were provided from the University of Southern Denmark, the Region of Southern Denmark, the Danish Cancer Research Fund, and the Danish Cancer Society.

None of the authors have conflicts of interest to declare. This work was approved by all affiliated institutions.

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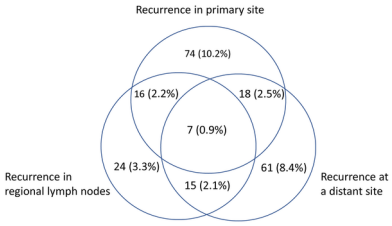

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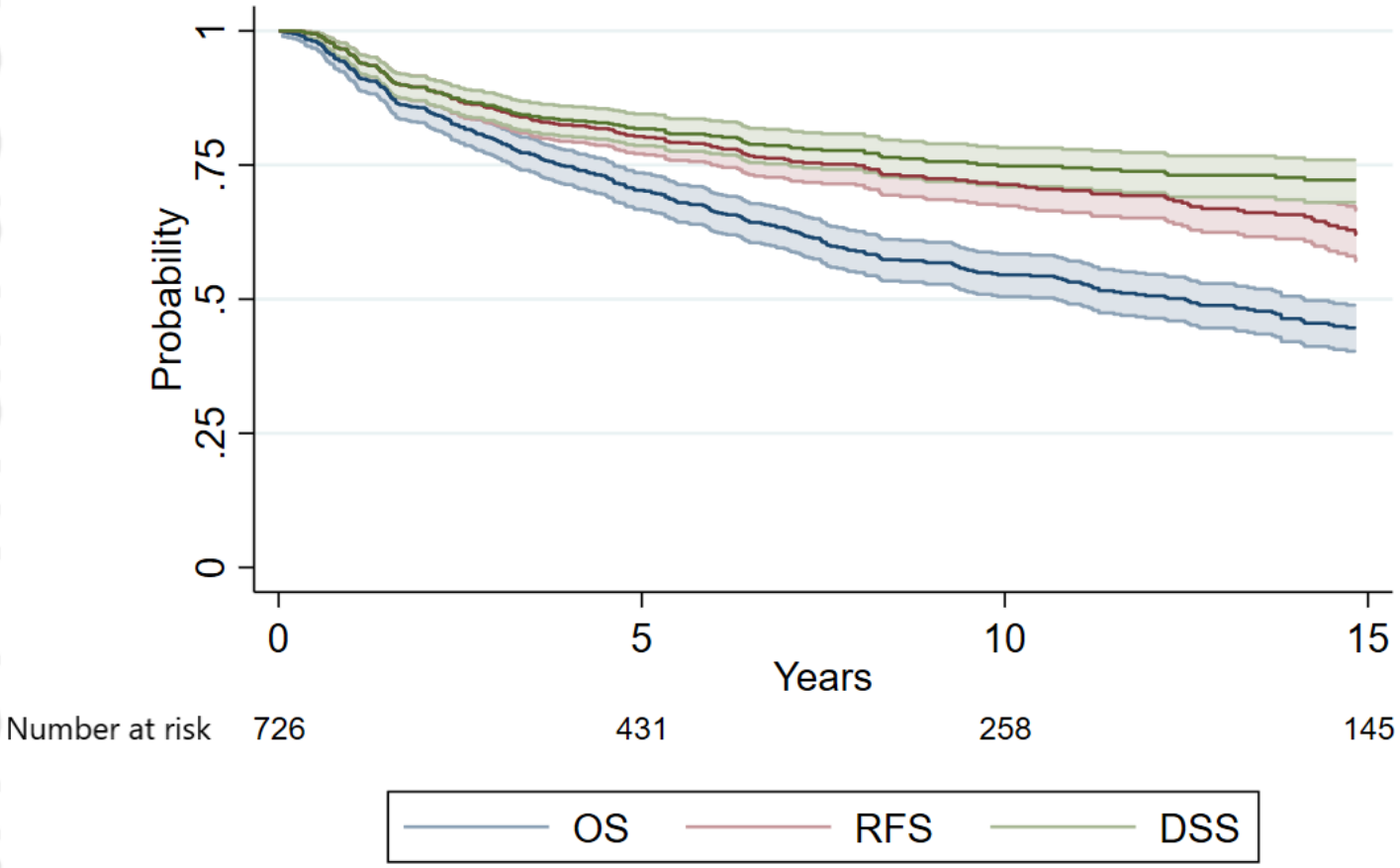

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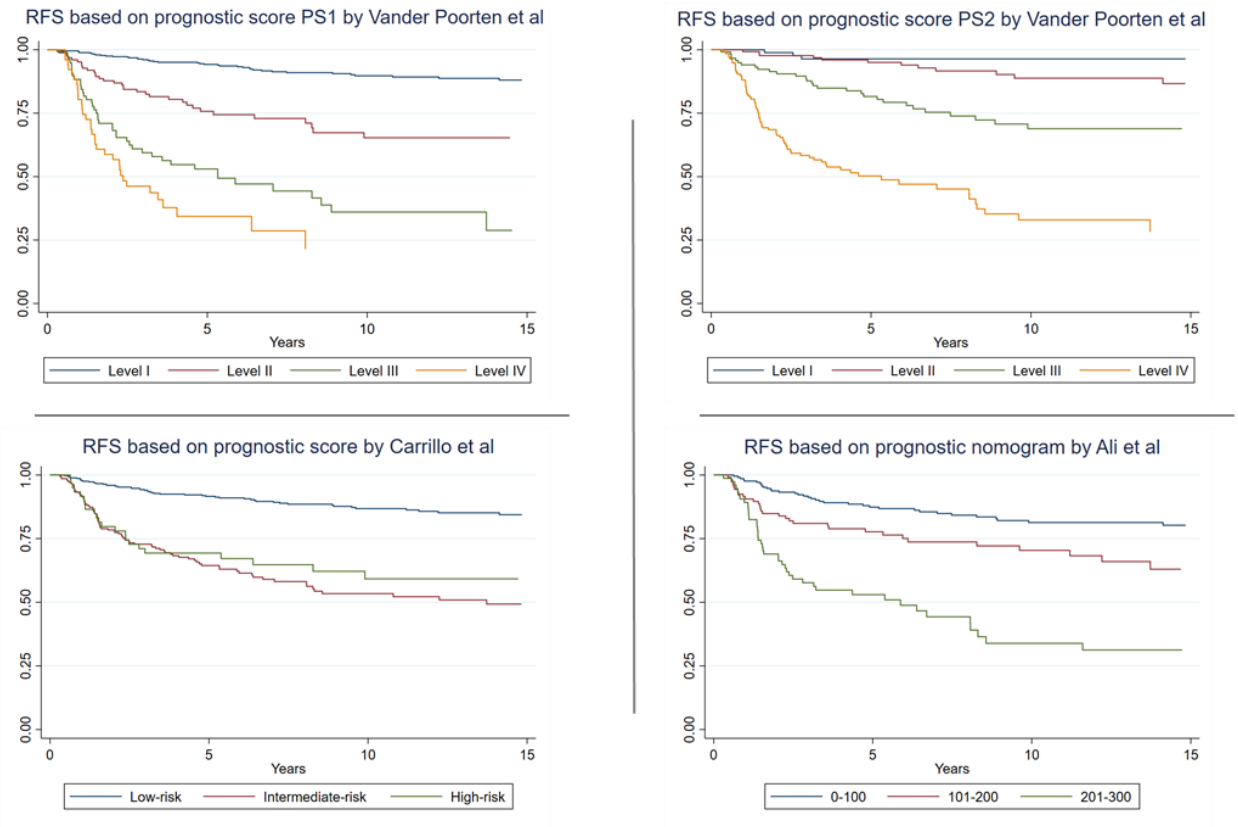

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Table 1. Patient and tumour related characteristics of Danish patients with parotid gland carcinoma, treated with curative intent, from 1990 to 2015.

Variables	Number of patients (%)
Gender	
Male	344 (47.4%)
Female	382 (52.6%)
Age	Median 63 Range 6 - 93
Histological subtype	
Salivary duct carcinoma	63 (8.7%)
Adenoid cystic carcinoma	88 (12.1%)
Solid	*11 (12.5%)*
Tubulo-cribriform	*74 (84.1%)*
Unknown	*3 (3.4%)*
Squamous cell carcinoma	43 (5.9%)
Adenocarcinoma	58 (8.0%)
Low-grade	*6 (10.3%)*
High/intermediate-grade	*45 (77.6%)*
Unknown grade	*7 (12.1%)*
Mucoepidermoid carcinoma	98 (13.5%)
Low-grade	*72 (73.5%)*
High/intermediate-grade	*24 (24.5%)*
Unknown grade	*2 (2.0%)*
Acinic cell carcinoma	136 (18.7%)
Oncocytic carcinoma	14 (1.9%)
Undifferentiated carcinoma	19 (2.6%)
Carcinoma ex pleomorphic adenoma	93 (12.8%)
Clear cell carcinoma	3 (0.4%)
Basal cell carcinoma	24 (3.3%)
Lymphoepithelial carcinoma	10 (1.4%)
Polymorph adenocarcinoma	4 (0.6%)
Poorly differentiated carcinoma	5 (0.7%)
Epithelial-myoepithelial carcinoma	43 (5.9%)
Myoepithelial carcinoma	7 (1.0%)
Carcinosarcoma	4 (0.6%)
Secretory carcinoma	8 (1.1%)
Other	6 (0.8%)
Histological grade	
High-grade	249 (34.3%)
Low-grade	477 (65.7%)
Tumour size	
Median 2.5 cm	
Range 0-20 cm	
≤4 cm	591 (81.4%)
>4 cm	119 (16.4%)
Unknown	16 (2.2%)
T-classification	
T1/T2	475 (65.4%)
T3/T4	243 (33.5%)
TX	8 (1.1%)
N-classification	
N0	584 (80.4%)
N+	142 (19.6%)

Pain	
Yes	78 (10.7%)
No	648 (89.3%)
Facial nerve impairment	
Yes	111 (15.3%)
No	615 (84.7%)
Surgical treatment	
Partial parotidectomy	440 (60.6%)
Total parotidectomy	286 (39.4%)
Neck dissection	
No	261 (36.0%)
Yes	318 (43.8%)
Lymph node excision	147 (20.2%)
Treatment modality	
Surgery alone	259 (35.7%)
Surgery and postoperative RT	467 (64.3%)
Surgical margin	
Clear	259 (35.7%)
Close	184 (25.3%)
Involved	257 (35.4%)
Unknown	26 (3.6%)
Perineural invasion	
Yes	219 (30.2%)
No	285 (39.2%)
Unknown	294 (30.6%)
Vascular invasion	
Yes	111 (15.3%)
No	302 (41.6%)
Unknown	313 (43.1%)

Tabel 2. Survival rates for patients with parotid gland carcinoma, treated with curative intent, in Denmark from 1990 to 2015.

Abbreviations: CI = confidence interval

	5-year (95% CI)	**10-year (95% CI)**	**15-year (95% CI)**
Overall survival	70 (67, 74)	55 (50, 58)	45 (40, 49)
Recurrence-free survival	80 (77, 83)	71 (67, 75)	62 (57, 66)
Disease-specific survival	82 (79, 84)	75 (71, 78)	72 (68, 76)

Table 3. Multivariate analyses on factors associated with survival rates. Significant values are noted with bold text.

Abbreviations: CI = confidence interval

	Overall survival		**Disease-specific survival**		**Recurrence-free survival**		**Recurrence risk**	
	Hazard Ratio (95% CI)	*p*-value	Hazard Ratio (95% CI)	*p*-value	Hazard Ratio (95% CI)	*p-value*	Subhazard Ratio (95% CI)	*p-value*
Age >60 years	**4.2 (3.2,5.4)**	***<0.001***	**1.6 (1.1,2.2)**	***0.013***	**1.9 (1.4,2.5)**	***<0.001***	1.1 (0.8,1.6)	*0.624*
Male	not included		1.0 (0.7,1.4)	*0.973*	1.0 (0.8,1.4)	*0.761*	1.0 (0.7,1.3)	*0.805*
High-grade histology	**1.5 (1.2,1.8)**	***0.002***	1.4 (1.0,2.0)	*0.074*	**1.5 (1.1,2.0)**	***0.019***	1.3 (0.9,1.9)	*0.209*
T3/T4	**1.9 (1.5,2.4)**	***<0.001***	**2.9 (2.0,4.3)**	***<0.001***	**2.1 (1.5,2.9)**	***<0.001***	**2.7 (1.8,4.2)**	***<0.001***
N+	**1.6 (1.2,2.0)**	***0.001***	**2.5 (1.8,3.5)**	***<0.001***	**2.2 (1.6,3.1)**	***<0.001***	**2.3 (1.5,3.4)**	***<0.001***
Pain	not included		1.3 (0.8,2.0)	*0.258*	not included		1.4 (0.9,2.1)	*0.142*
Facial nerve impairment	1.3 (1.0,1.7)	*0.076*	1.4 (1.0,2.1)	*0.074*	1.3 (0.9,1.8)	*0.170*	1.4 (0.9,2.0)	*0.138*
Involved surgical margins	**1.5 (1.2,1.9)**	***<0.001***	**1.9 (1.4,2.7)**	***<0.001***	**1.9 (1.4,2.5)**	***<0.001***	**1.8 (1.2,2.6)**	***0.002***
Perineural invasion	1.1 (0.8,1.4)	*0.731*	1.2 (0.8,1.9)	*0.328*	1.4 (0.9,2.0)	*0.100*	1.2 (0.8,2.0)	*0.364*
Vascular invasion	**1.6 (1.1,2.1)**	***0.007***	**1.6 (1.0,2.5)**	***0.039***	1.3 (0.9,2.0)	*0.149*	1.5 (0.9,2.3)	*0.107*

Table 4. Calculation of prognostic scores based on Vander Poorten *et al*. (9), Carrillo *et al*. (10), and Ali *et al*. (11). C-statistical values were calculated for the groups in each model (categorical) and for the individual scores in the model (numerical). Abbreviations: CI = confidence interval.

Score	**Group**	**Number of patients (%)**	**Subhazard Ratio (95% CI)**	***p*-value**	**Hazard Ratio (95% CI)**	***p*-value**	**C-statistic (categorical)**	**C-statistic (numerical)**
Carrillo	Low	452 (62%)	1 (Reference)		1 (Reference)		0.6094	0.6098
	Intermediate	211 (29%)	4.2 (3.0, 5.9)	<0.001	2.13 (1.72, 2.63)	<0.001		
	High	63 (9%)	4.1 (2.6, 6.6)	<0.001	1.75 (1.27, 2.41)	0.001		
Vander Poorten PS1	Level I	448 (63%)	1 (Reference)		1 (Reference)		0.7027	0.7646
	Level II	128 (18%)	3.2 (2.0, 5.0)	<0.001	3.11 (2.42, 3.99)	<0.001		
	Level III	81 (11%)	7.9 (5.2, 12.0)	<0.001	5.06 (3.79, 6.75)	<0.001		
	Level IV	53 (7%)	11.1 (6.9, 17.8)	<0.001	7.83 (5.66, 10.82)	<0.001		
Vander Poorten PS2	Level I	90 (29%)	1 (Reference)		1 (Reference)		0.7357	0.7584
	Level II	132 (27%)	2.8 (0.8, 9.8)	0.115	2.58 (1.53, 4.35)	<0.001		
	Level III	120 (25%)	8.6 (2.6, 28.3)	<0.001	4.79 (2.88, 7.96)	<0.001		
	Level IV	139 (29%)	23.3 (7.4, 74.4)	<0.001	13.54 (8.23, 22.27)	<0.001		
Ali	Group 1	213 (54%)	1 (Reference)		1 (Reference)		0.6188	0.6077
	Group 2	108 (27%)	2.1 (1.3, 3.3)	0.003	1.59 (1.18, 2.15)	0.002		
	Group 3	76 (19%)	4.9 (3.2, 7.6)	<0.001	3.12 (2.30, 4.25)	<0.001		