

Analysis of functional androgen receptor-pathway activity to predict response to androgen deprivation therapy in salivary duct carcinoma

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Introduction

- Salivary duct carcinoma is an aggressive and often androgen receptor (AR) positive subtype of salivary gland cancer with a median overall survival of 3 to 5 years after primary diagnosis
- Primary treatment consists of tumor resection and neck dissection, frequently followed by adjuvant radiotherapy
- Adding adjuvant androgen deprivation therapy to this regimen increases the disease free survival and overall survival in a recent retrospective case-control study¹
- In case of recurrent and/or metastatic salivary duct carcinoma, patients are often treated with palliative androgen deprivation therapy with a response rate of 18-64.7%²
- Better patient selection for adjuvant and palliative androgen deprivation therapy is needed to improve the response rate and prevent unnecessary treatment
- Tumor-driving signal transduction pathway analysis is a promising new method for selecting targeted therapies based on analysis of the functional signal transduction pathway activity in individual patients³

Aim of this study is to assess the value of AR-pathway analysis to predict response to androgen deprivation therapy in salivary duct carcinoma

Patients and methods

Patients

Androgen receptor pathway analysis was performed in 2 cohorts:

- Palliative cohort: patients with recurrent and/or metastatic SDC who received palliative androgen deprivation therapy (bicalutamide or an LHRH-analog plus bicalutamide)
- Adjuvant cohort: patients with poor-risk (stage 4a) androgen receptor-positive SDC receiving adjuvant androgen deprivation therapy

AR-pathway analysis

- The activity of the AR-pathway was assessed from mRNA levels of the target genes of the pathway-specific transcription factor using a computational Bayesian model as described earlier³
- RNA was extracted from formalin-fixed paraffin embedded sections from tumor tissue prior to treatment
- mRNA expression levels of the AR-target genes were measured using one-step RT-qPCR
- A pathway activity is scored between 0 and 100, 0 being the lowest and 100 the highest score theoretically possible

Response criteria

The clinical benefit rate was used to establish that a patient had a valuable treatment response, including the following:

- Complete remission
- Partial response
- Stable disease for >6 months

Statistical analysis

- The optimal cut-off value for AR-pathway activity was established by constructing a ROC-curve of AR-pathway activity to predict treatment response in the palliative cohort
- Progression free survival and overall survival were assessed in the same cohort for patients with an inactive and active AR-pathway, using the same cut-off value
- This cut-off value was evaluated by assessing disease free survival in the adjuvant cohort, for patients with an inactive and active pathway

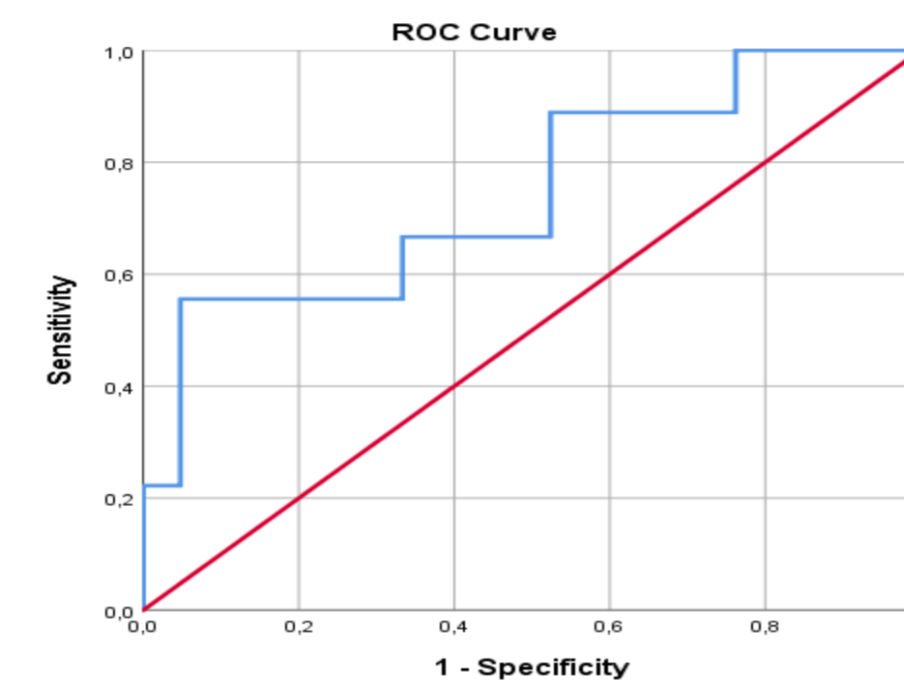
Results

Patient characteristics

	Palliative cohort (n=30)	Adjuvant cohort (n=14)
Disease stage	Recurrent and/or metastatic SDC	Stage 4a SDC
AR-status		
• Positive (%)	30 (100%)	14 (100%)
• Negative (%)	0 (0%)	0 (0%)
Gender		
• Male (%)	22 (73.3%)	12 (85.7%)
• Female (%)	8 (26.7%)	2 (14.3%)
Median age (range)	62 years (36 – 79 years)	61 years (36 – 84 years)
Median FPPE tissue age (range)	49 months (7 – 195 months)	13.5 months (3 – 108 months)
Androgen deprivation therapy		
• Bicalutamide (%)	23 (76.7%)	12 (85.7%)
• LHRH-analog plus bicalutamide (%)	7 (23.3%)	2 (14.3%)

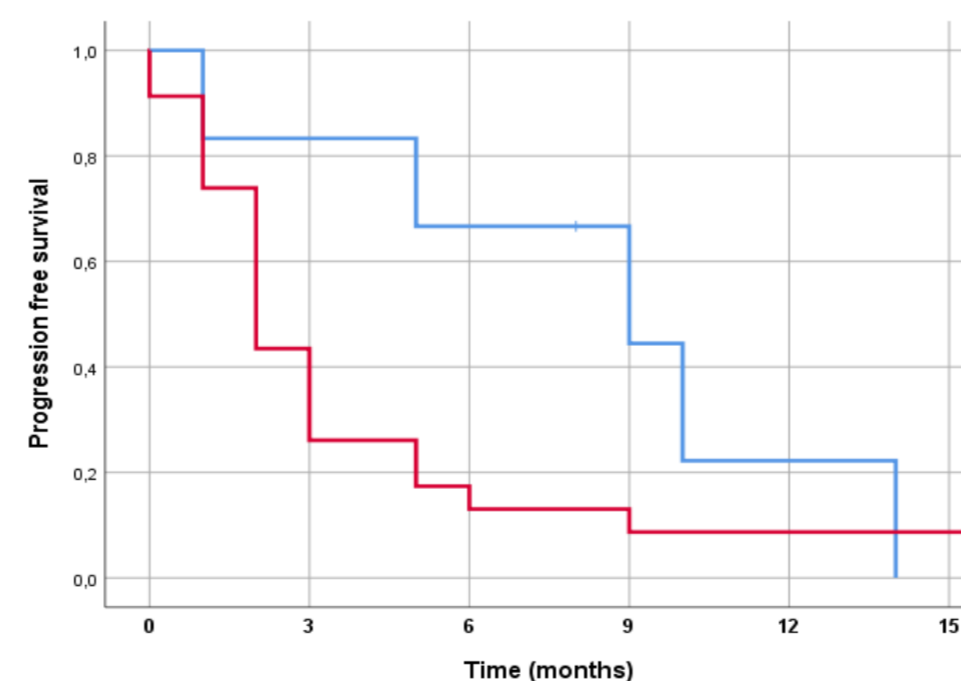
ROC-curve in the palliative cohort

Area under the curve: 0.746 (95% CI 0.543 - 0.949, P=0.035)
Optimal cut-off value: AR-pathway activity of 52.92
Sensitivity: 55.6%, specificity of 95.2%
Positive predictive value: 83.3%, negative predictive value: 83.3%



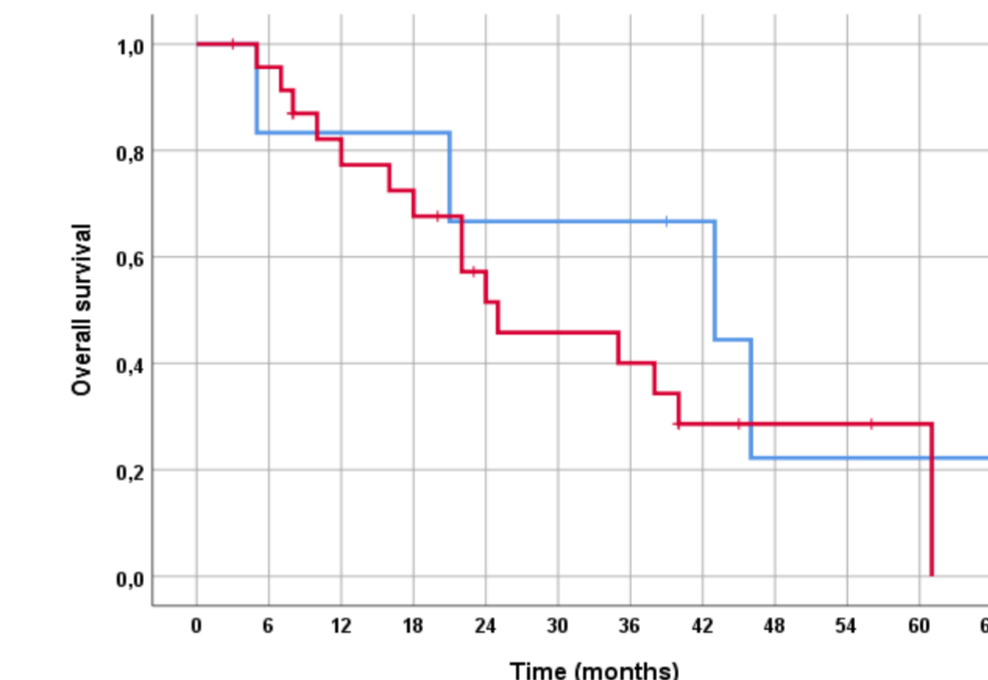
Progression free survival in the palliative cohort

Median progression free survival after treatment with palliative ADT
• Active pathway: 9 months (95% CI 1.2-16.8 months)
• Inactive pathway: 2 months (95% CI 1.3 – 2.7 months)
• Log rank: p=0.131



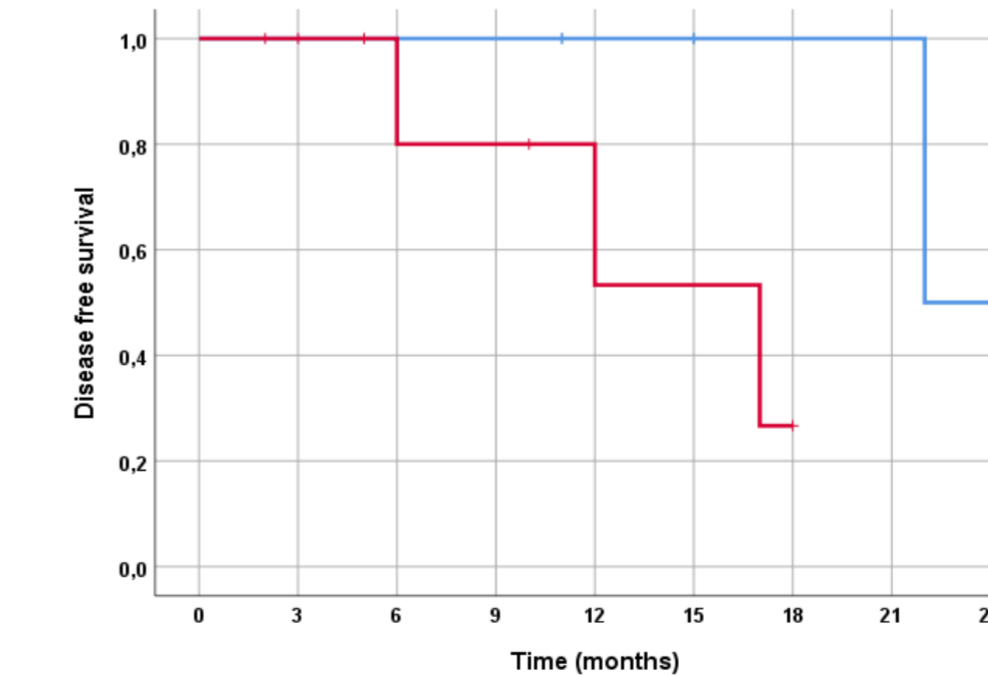
Overall survival in the palliative cohort

Median overall survival after treatment with palliative ADT
• Active pathway: 43 months (95% CI 0.0-86.1 months)
• Inactive pathway: 25 months (95% CI 8.2 -41.8 months)
• Log rank: p=0.408



Disease free survival in the adjuvant cohort

Median disease free survival after treatment with adjuvant ADT
• Active pathway: 22 months (95% CI could not be calculated because only 1 patient had a recurrence)
• Inactive pathway: 17 months (95% CI 7.9 – 26.1 months)
• Log rank: p=0.061



Conclusion

- Both in the palliative and adjuvant cohort high AR-pathway activity is associated with better clinical outcome upon androgen deprivation therapy in salivary duct carcinoma
- Quantitative assessment of AR-pathway activity to predict response to ADT in SDC has proven to be a promising approach for prediction of response to ADT in this small retrospective SDC cohort
- Further validation of these results in an other cohort is warranted

Discussion

Strong points of the study

- This is the first study to evaluate the value of AR-pathway analysis for clinical application in patients with salivary duct carcinoma
- Multi-step approach: Assessment of optimal cut-off value and evaluation of this cut-off value for survival differences in a palliative and adjuvant cohorts

Limitations

- Small cohorts
- Formalin-Fixed Paraffin-Embedded tumor block of up to 16 years old
- Low tumor percentages in some patients

Discrepancies between AR-pathway activity and treatment response (active AR-pathway and no clinical benefit or vice versa) were found in 5 of 30 patients in the palliative cohort (16.74%). Possible explanations included low tumor percentages, activity of other tumor driving pathways, patient decision to stop the androgen deprivation therapy and non-compliance, resulting in treatment failure despite an active pathway.

Raw data: AR-pathway activity

		Mean (SD)
Palliative cohort	Progressive disease (n=18)	43.1 (7.1)
	Stable disease (n=7)	49.0 (6.4)
	Partial response (n=5)	55.2 (8.2)
Adjuvant cohort	n=14	50.3 (6.9)

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