Impact of the chemokine receptors CXCR4 and CXCR7 on metastatic potential and survival in adrenocortical carcinoma

Irina Chifu[1], Carmina Fuß[1], Cristina Ronchi[1], Katja Marienfeld[1], Martin Fassnacht[1], Stefanie Hahner[1], Britta Heinze[1]

[1]Department of Endocrinology and Diabetology, University Hospital Würzburg, Germany

INTRODUCTION Apart from their well-established physiological functions, chemokines appear to play a central role in tumor progression and metastasis in a large number of human cancers. Our study aims to evaluate the prognostic value of CXCR4 and CXCR7 expression in adrenocortical carcinoma (ACC) with regard to developing a new theranostic concept in this tumour entity.

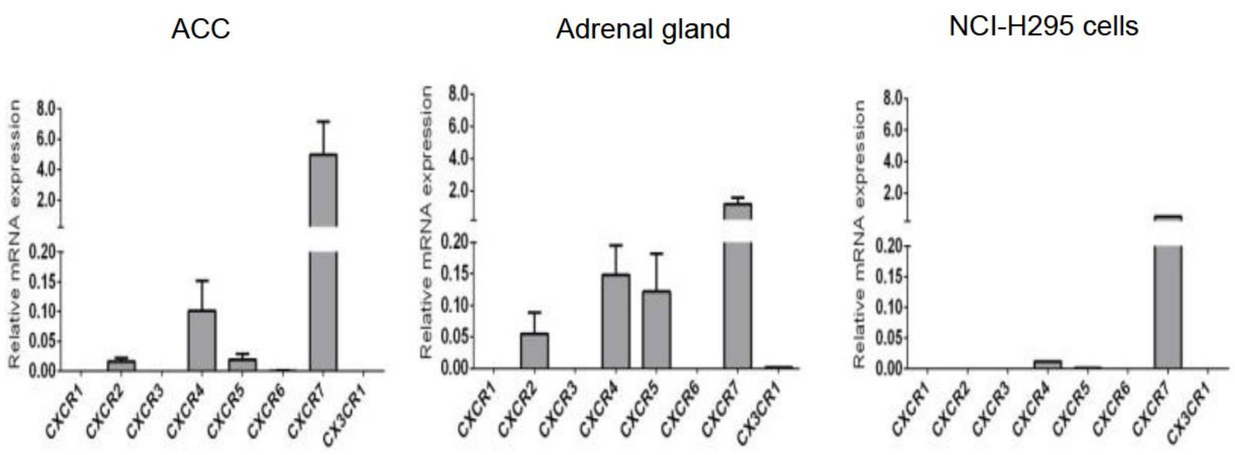

Fig.2 Real Time PCR: Quantitative analysis of chemokine receptor mRNA levels in 4 normal human adrenal glands, 18 adrenocortical carcinomas and in the human adrenocortical carcinoma cell line NCI-h295

METHODS Expression of seven CXC-chemokine receptors was assessed by quantitative real-time PCR in 4 normal adrenals, 18 ACC and NCI-H295 cells. CXCR4 and CXCR7 expression was further investigated by immunohistochemistry in paraffin-embedded sections of 215 ACC tissues (174 primary tumors (PT), 18 local recurrences (LR), 23 metastases (M)). 46.6% (n=104) of patients had an initial R0 resection status. Data were correlated with metastatic status, tumor progress and survival.

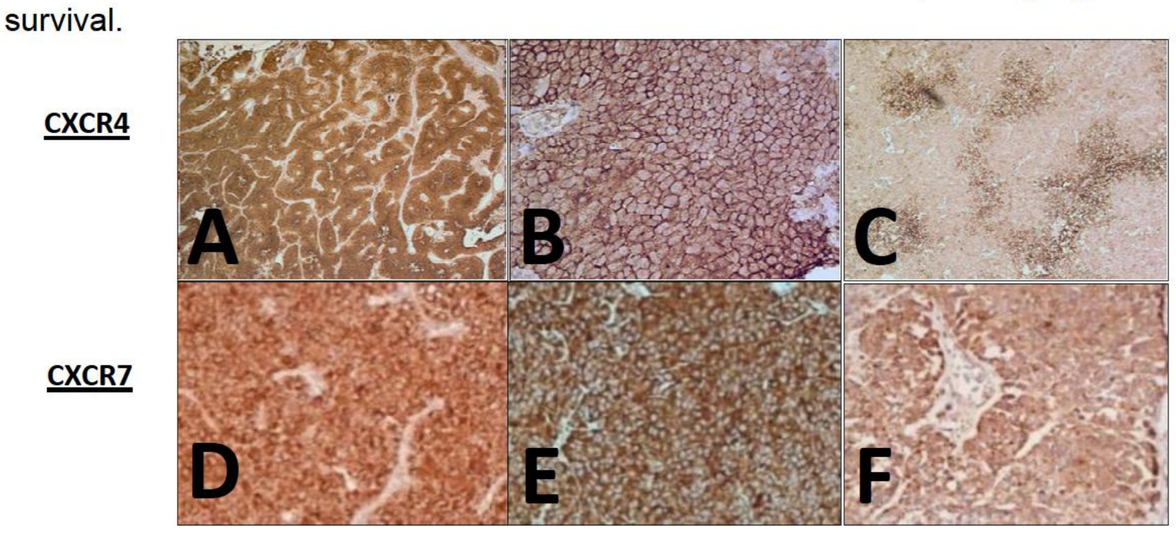

Fig.1 Immunohistochemical staining of CXCR4 (A-C) and CXCR7 (D-F) in adrenocortical carcinoma. A, D-E Example for strong membranous and cytoplasmic staining (magnification 10x, 20x). **B** Example for strong CXCR4 membrane staining (magnification10x). **C** Example for high CXCR4 expression in perivascular tumor cells. (magnification 2.5x). **F** Example for only weak CXCR7 membranous and cytoplasmic staining (magnification 20x)

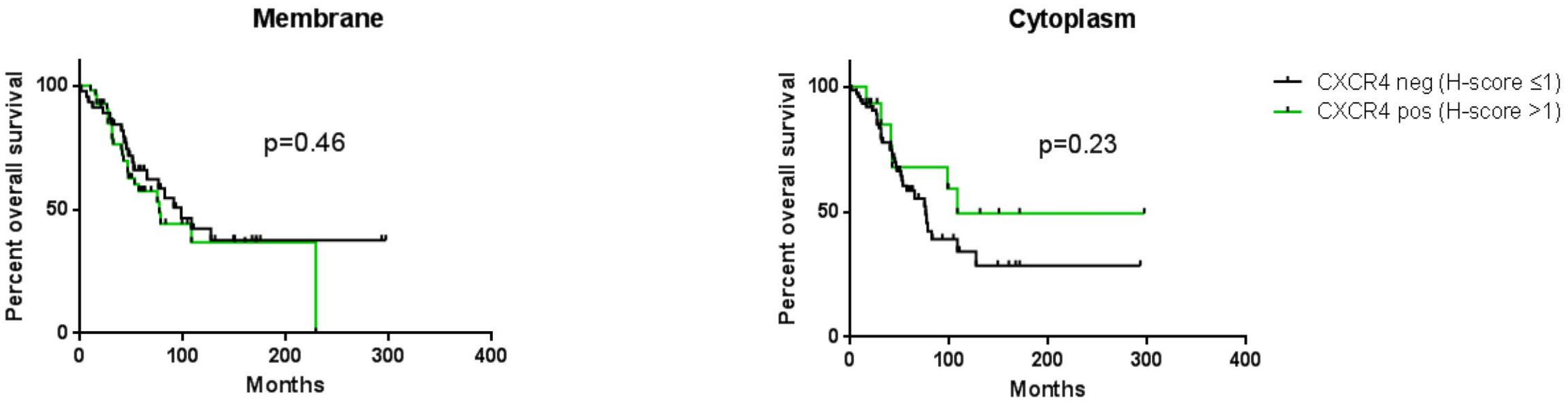

Fig.3 Correlation of overall survival of 102 R0-resected patients with CXCR4 membrane and cytoplasm expression; Kaplan Meier analysis

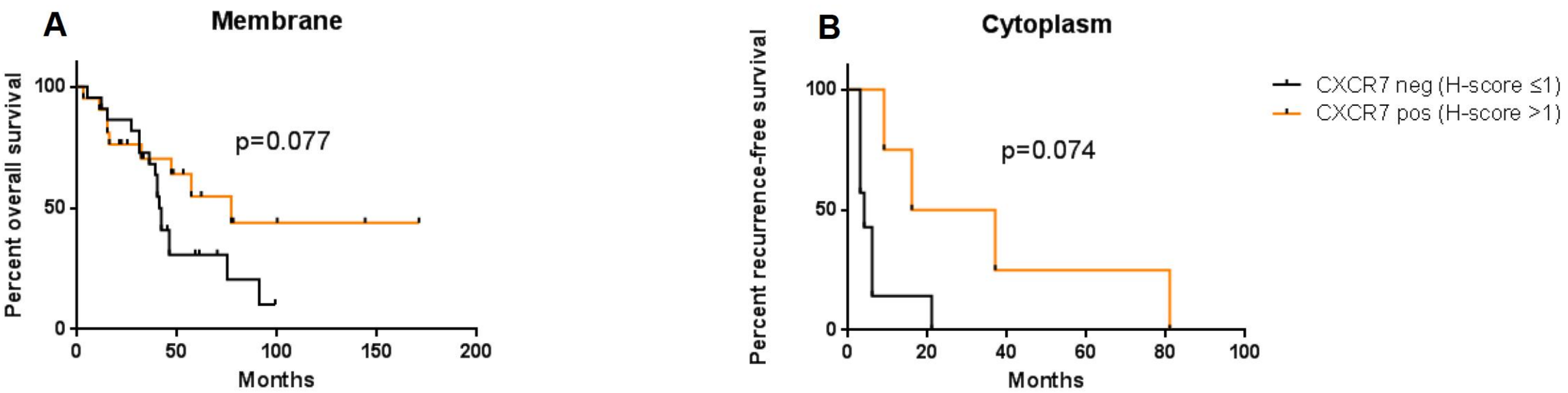

Fig.4 CXCR7 expression: correlation with outcome in patients with low ENSAT stage (I+II): A Impact of CXCR7 membrane expression on overall survival (n=43)
B Impact of CXCR7cytoplasm expression on recurence-free survival (n=11)

RESULTS CXCR4 and CXCR7 showed highest mRNA expression among the investigated chemokine receptors (in normal adrenals, ACC and NCI-H295 cells) and were identified in over 80% of the immunohistochemically analyzed ACC samples demonstrating a predominantly membranous staining. No differences in the protein expression between primary tumor, local recurrence and metastasis were seen, nor did CXCR4 or CXCR7 significantly correlate with clinicopathological or survival data. Along with ENSAT stage, Weiss score and tumor size, CXCR4 membrane overexpression was associated with a trend to higher incidence of metastasis at follow up (p=0.093), whereas its cytoplasmic expression indicated a slightly improved prognosis (108 months vs. 76 months, p=0.124) for the same group. When adjusted for ENSAT stage, CXCR7 membrane overexpression described a trend towards an improved overall survival (77 months vs 41 months; p=0.077) regardless of resection status, whereas cytoplasmic CXCR7 overexpression pointed towards a better recurrence-free survival (16 months vs. 4 months, p=0.074). CXCR7 membrane overexpression was significantly associated with a lower Ki67 index (p=0.007) among the cases with a complete tumour resection. First [68Ga]Pentixafor-Scans of 10 patients with ACC identified more metastatic lesions in 1 patient,while in 4 patients (40%) complementary information was received by [^{68}Ga]Pentixafor and [^{18}F]FDG regarding the number and intensity of lesions.

CONCLUSION CXCR4 and CXCR7 did not significantly influence prognosis in ACC. Their abundant expression both in the normal adrenal and in ACC suggests their functional duality with regard to the normal physiology and tumorigenesis of the adrenal gland. The membranous overexpression of CXCR4 depicts its potential role as diagnostic and therapeutical target in ACC. [^{68}Ga]Pentixafor studies idenified a subgroup of patients suitable for a subsequent radionuclide therapy. CXCR7 on the other hand appears to be a marker of a less aggressive tumor phenotype.

Medizinische Klinik