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Neutron Therapy, Prognostic Factors and Dedifferentiation of Adenoid Cystic Carcinomas (ACC) of Salivary Glands

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Abstract. *Purpose: Analysis of the efficacy of fast neutron radiotherapy in the treatment of adenoid cystic carcinomas (ACC) of the salivary glands, identification of prognostic variables and dedifferentiation after radiotherapy. Patients and Methods: Histological slides of primary and recurrent lesions of 71 patients were reviewed to confirm the diagnosis and to analyse subtypes. Median follow-up was 52 months. Local control rate and overall survival were analysed in multivariate analysis. Complications are also described. Results: Primary vs. recurrent therapy (p=0.001), margin-status (p=0.01) and subtype (p=0.019) influenced overall survival. Primary vs. recurrent therapy (p=0.001), margin-status (p=0.018) and T-stage (p=0.043) influenced local control rate. Dedifferentiation was seen in only 1/17 cases. Conclusion: The calculated prognostic factors illustrate the importance of a radical primary therapy. Histological subtype is a significant additional factor for overall survival and, in case of dedifferentiation, it is a strong predictor of a detrimental outcome.*

Malignancies of salivary glands are relatively rare. They account for 0.5-3% of all head and neck tumours, of which 35-55% are histological adenoid cystic carcinomas (ACC) arising from the minor and major salivary glands (1). ACC usually grow slowly, but have a high incidence (51%) of local recurrence after surgery (2) and metastases may occur even many years after treatment. Histologically, tumours show infiltrative and invasive growth patterns and frequently perineural spread, often leading to underestimation of the true extent. Compared to other cancers of the head and neck, ACC are more difficult to clear surgically, frequently resulting in positive margins (3). Neck metastases range from 15 to 20% (1, 4). Histologically three different subtypes exist: tubular, cribriform and solid, and prognosis is related to the subtype independent of primary tumour localisation (2, 5, 6). Prognosis is worst in the solid subtype (7, 8), while best in the tubular. Surgery is the treatment of choice for patients with operable tumours. Indications for postoperative radiotherapy include involved surgical margins, perineural invasion, neck node metastases, recurrent tumours and advanced T-stage (9, 10). Battermann *et al.* (11) popularized fast neutron beam therapy as treatment for ACC. Neutron beam therapy improves disease-free and overall survival in patients with unresectable tumours and those with recurrent neoplasm according to some publications (12, 13), but only local control in others (14, 15). In this retrospective study, we reviewed the results of neutron radiotherapy of 71 patients with ACC of the salivary glands who were treated with curative or palliative intent at the Department of Radiation Oncology, University of Hamburg, Germany. Histological slides of the primary tumour and the slides in case of recurrence were reviewed in the Department of Oralpathology (Prof. Donath) and the histological subtypes analysed. We looked for prognostic factors for overall survival and local control rate. In case of recurrence after radiotherapy, we were looking for tumour dedifferentiation as a progression of ACC from high-grade to low-grade histology, indicated by changing of subtype from tubular or cribriform to solid subtype.

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Patients and Methods

Patient characteristics. Between 1985 and 1996, 71 patients with ACC of the salivary glands received neutron radiotherapy at the University of Hamburg, Germany. The median age at therapy was 55 years (range: 26 - 84 years). The tumours of the minor salivary glands were classified according to the topographic localisation

Table I. *Patients characteristic in 71 patients with ACC of salivary glands.*

Site	Parotid gland	Submandibular gland	Minor salivary glands	% of the total collective
Patients	19	20	32	100
Gender: male	4	7	13	34
Gender: female	15	13	19	66
Tumour stage: T1 or T2	7	13	1	29
Tumour stage: T3 or T4	12	7	31	71
N0	17	16	27	85
N+	2	4	5	15
Subtype: solid	6	3	10	27
Subtype: cribriform	7	13	14	48
Subtype: tubular	6	4	8	25
RT: primary	17	13	26	79
RT: recurrent	2	7	6	21
Margin-status: R0 or R1	14	13	12	55
Margin-status: R2/inoperable	5	7	20	45

described by Douglas *et al.* (16). Patients were staged according to the 1992 American Joint Committee on Cancer (AJCC) criteria for squamous cell carcinoma of respective sites. For patients with recurrent disease, the stage at the time of therapy was used for classification. The distribution of the primary tumour sites and of the TNM status is given in Table I. Eight patients were treated with radiotherapy only because of inoperability in cases of locally very progressive disease, general medical contraindications for anaesthesia or because of rejection of surgery. These patients only had biopsies performed. Twelve patients received radical operative therapy with histological clear margins. Twenty-seven patients had microscopic involved surgical margins and 24 gross residual tumours. Fifty-six patients were treated for primary tumours, 51 with neutron therapy alone and 5 patients with a "mixed-beam"-therapy in combination with photons. Fifteen patients (21%) were treated for recurrent disease (13 patients for first recurrence, 2 for second recurrence). Three of these patients had received prior full-dose conventional radiotherapy. Their subsequent fields and doses for neutron radiotherapy were modified to account for doses to critical sites (brainstem, spinal cord, brain). The remaining 12 patients had not previously received radiotherapy. Eleven patients had histological and/or imaging proven lymph node involvement at diagnosis. None of our patients had distant metastases at diagnosis, but 5 had lung metastases when neutron radiotherapy was started. None of them received chemotherapy in the course of disease. In summary, 16 patients (22%) were treated with palliative intention because of age and general condition, manifest pulmonary metastases or locally advanced recurrent disease.

Treatment characteristics. The target volume included the tumour region in consideration of the macroscopic and microscopic tumour extension with a security margin around the gross tumour. We also included the regional lymph nodes in the target volume and the entire ipsilateral neck in case of lymph node involvement. Radiotherapy of the lymph nodes was not carried out in tumours of the paranasal sinus without lymph nodes metastases. For irradiation, low energy neutrons of a 14 MeV DT-generator were used. The number of treatment fields ranged from one to seven (mean 3.6). In macroscopic disease, a total dose of 19.0 Gy D_T was prescribed. The maximum target dose should not exceed 20.0 Gy D_T. In microscopic disease or adjuvant situation, a total dose of 16.0 Gy D_T was dedicated. The median single dose was 0.9 Gy (min: 0.6, max: 1.3 Gy) given four times a week.

Follow-up. Follow-up information was obtained by examination of the patients and by correspondence with patients and their referring physicians. Median follow-up for living patients from the beginning of the neutron therapy was 70 months (range: 25 months – 12.2 years), 52 months for all patients.

Statistical methods and endpoints. Overall survival and local control rate were calculated according to the Kaplan-Meier method (17). Treatment failure with respect to local control rate was defined by the first day of clinical or radiographic suspicion of recurrence or progression. The starting point for the Kaplan-Meier curves was the beginning of neutron radiotherapy. Multivariate Cox regression analysis was used to define predictive factors for overall survival and local control rate with *p*-values below 0.05 considered significant. We tested the influence of the following parameters: histological subtype (solid, cribriform, tubular), early/late tumour-stage (T1 or T2 *versus* T3 or T4), neck node involvement (no neck node involvement at all *versus* positive neck nodes), tumour localisation (minor *versus* major salivary gland), margin-status (clear margins or microscopic residual disease *versus* macroscopic

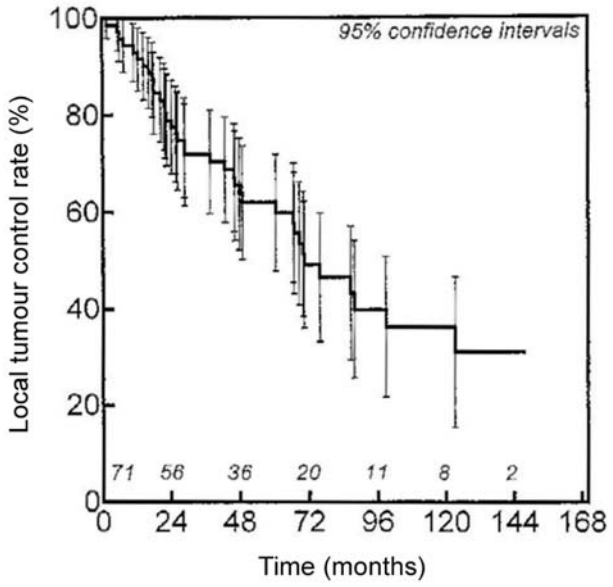

Figure 1. *Overall survival (%) of 71 patients with ACC of salivary glands.*

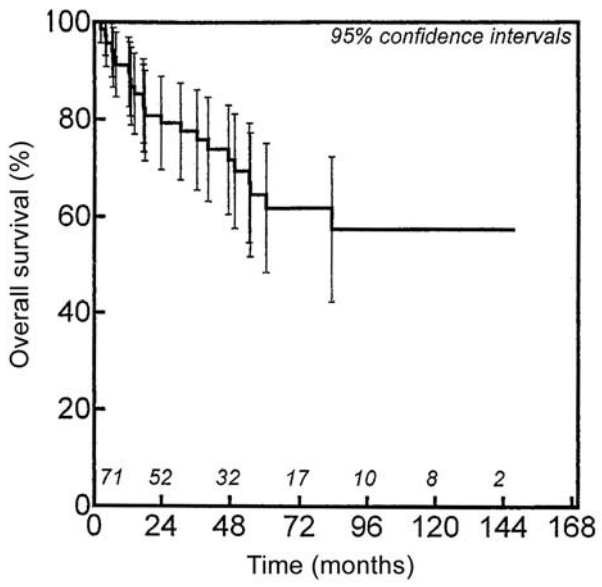

Figure 2. *Local tumour control rate of 71 patients with ACC of salivary glands.*

residual disease or no operation at all) and time of radiation (primary *versus* recurrent therapy). The distribution of all these factors is given in Table I. No factor was tested in univariate analysis.

Results

Histological evaluation. Differentiation of ACC into histological subtypes showed the cribriform subtype of ACC in 34 cases (48%), the solid subtype in 19 cases (27%) and the tubular subtype in 18 cases (25%). In 10 out of 22 cases, we could reanalyse the histology of the first recurrence after radiotherapy. In 9 patients, diagnosis of ACC was confirmed; in 1 patient we saw a poorly-differentiated squamous cell carcinoma as secondary malignancy. No transformation of histological subtype with time was seen. Eight patients developed a second recurrence. In 2 cases the histological slides were not available. Histology of the remaining 6 disclosed ACC in all cases. In 1 case of a 31-year-old woman with ACC of the parotid gland, the histological subtype changed from cribriform to solid. She died 6 years after initial diagnosis with local recurrence and lung metastases. One patient developed a third recurrence. Histology again disclosed ACC without changing subtype.

Survival. Thirty-seven patients (52%) died during the observation period, 22 of them because of their tumour, 5 of other causes and 10 with unclear reason for death. One of the 34 living patients suffered from local progression, 3 patients developed recurrence, 1 of them additional metastases. One patient is living with metastases and local tumour control. Figures 1-2 show overall survival and local tumour control rate.

Local control. Local tumour control was achieved in 49 patients (69%). The median time to local failure was 17 months, with a wide range from 2.3 to 83 months.

Distant metastases. Distant metastases were observed in 20 patients (28%), of which lung metastases were most frequent (50%). Bone metastases were seen in 21%, cerebral metastases in 19% and hepatic metastases in 11%. One patient had retinal metastases. Thirty-five % of patients with distant metastases were disease-free at the primary site. The median time from diagnosis to manifestation of distant metastases was 31 months (range: 8 to 75 months). The frequency of distant metastases was not related to the primary tumour localisation (minor salivary gland tumours 25%, major salivary gland tumours 31%). Distant metastases developed in 42% patients with a solid subtype of ACC, in 28% patients with a cribriform subtype and in 22% patients with a tubular subtype. Forty-five % with primary neck involvement developed distant metastases.

Statistical analysis. Multivariate analysis showed that subtype ($p=0.019$), margin-status ($p=0.01$) and primary *versus* recurrent therapy ($p=0.001$) were significantly related to longer survival. Concerning local control rate, T-stage ($p=0.043$), margin-status ($p=0.018$) and primary *versus* recurrent therapy ($p=0.001$) were significantly related to better local control.

Table II. *Five-year overall survival and local control (%) for ACC of the salivary glands - Review of the literature.*

First Author / Treatment period	Indication for radiotherapy, other therapies	Beam	Number of patients	5-year local control	5-year overall survival	Median follow-up
Cowie (24) 1965-1976	RT primary or postop.	4MeV Photons	82	67	70	Not named
Douglas (19) 1985-1997	RT primary or postop.	Neutrons	159	47	59	32 months
Garden (22) 1962-1991	RT postop. in case of pos., close or neg. margins	60C0, 6-25 Mv Photons, 6-20 MeV Electrons, interstitiell	198	95	82	93 months
Horiuchi (7) 1953-1982	RT primary or postop. or in case of recurrence	Photons, CT, Brachytherapy	68	60.1	61	3-18 years
Miglianico (5) 1951-1980	Only chirurgical, RT primary or postop	Photons, electrons	102	55	70	Min. 5 years
Nascimento (4) 1972-1983	RT primary or postop. with/ without CT, only CT only OP	Not named	61	Not named	37.5	50.5 months
Pötter (2) 1986-1995	RT primary or postop in case of macros-copic residual disease or in case of unrese-ctable recurrence	Neutron	72	73 (3 years)	58	36 months
Szanto (6) 1949-1968	Not clear	Not named	79		60	Min 7 years

CT= Chemotherapy

Complications. Treatment-related morbidity was assessed using the Joint RTOG/EORTC scoring scheme. Side-effects were not evaluated systematically. There were 9 late Grade III/IV treatment-related complications in 8 patients as defined by the RTOG late toxicity criteria. For 47 of the 71 patients (66%) the orbital cavity had to be included in the target volume and the resulting unilateral blindness was a pretherapeutic calculated risk. Therapy-related blindness occurred in 2 of these patients (5%) 12 and 14 months after radiotherapy. Side-effects concerning skin, subcutaneous tissue or mucous membranes revealed later. The latest onset of a side-effect was an osteonecrosis of the petrosal bone with subsequent cerebellitis 11 years after successful neutron irradiation of a parotid tumour. One patient developed tetra paresis 2 years after irradiation of a submandibular lesion. Two patients experienced severe soft tissue fibrosis, 1 necrosis of the skin, another 2 atrophy of either skin or mucous membrane. There were no fatal acute or late toxic effects of radiation.

Discussion

ACC is a rare cancer characterized by a protracted natural history. Efforts to define reliable prognostic factors in this disease have dominated the ACC literature for decades, but there has been no consensus regarding the key prognostic factors. In our sample of 71 patients with ACC, primary *versus* recurrent therapy was identified as a significant independent prognostic factor with regard to overall survival and local control rate. Similarly, Huber *et al.* (14) found the primary therapy to be the most important factor for prolonged survival. The statistical impact of margin-status on overall survival and local control rate underlines the relevance of a primary radical treatment. Primary tumour site had no significant effect on prognosis, which is in agreement with Huber *et al.* (14). Tumour stage as a prognostic factor, as described by Spiro and Huvos (1) and Parsons *et al.* (18), did reach significance in our multivariate analysis concerning local control rate. As described by

Huber *et al.* (14) and Douglas *et al.* (16, 19), neck node involvement at presentation was associated with an increased risk of developing distant metastases in the early course of disease, but in our series this parameter did not reach significance for a diminished survival. A possible explanation could be the small number of neck node-positive patients (15%) in our group. The rate of distant metastases in our series was 28%. Rates in literature range from 27-42% (1, 3, 5, 12, 14). Spiro and Huvos (1) reported the highest rate, which is obviously due to the longest follow-up. The development of distant metastases was not influenced by primary tumour site. Many authors (2, 4, 5, 6, 18) reported the significant influence of the histological subtype on prognosis. In our analysis, solid subtype was a significant predictor for poor overall survival, but subtype did not influence local control rate. Patients with solid subtype developed distant metastases more frequently than patients with other subtypes, which was also shown by Douglas *et al.* (19). Dedifferentiation as histological progression usually occurs in the setting of radiation or chemotherapy or as a spontaneous process over a long period of time. Histological evaluation revealed a transformation from high-grade to low-grade ACC in only 1 out of 17 cases after radiotherapy in our series. Therefore, we conclude that induction of dedifferentiation in ACC by neutron radiation does not seem to be a quantitatively relevant process. This finding is in contrast to the statement of Cheuk *et al.* (20), who suggested, that "radiation is a contributing factor for dedifferentiation" in ACC. They described 3 cases of dedifferentiation, which were associated in 2 cases with a poor clinical outcome. In the third case the follow-up was too short to determine the clinical course. On the other hand, our case of dedifferentiation also led to a very aggressive course of the disease. With this background dedifferentiation might be rare but, on occurrence, it is a strong predictor of a poor outcome. Our overall survival rates were at the lower level of the data reported in the literature (see Table II). This result should be taken into account in a group of 22% palliative-treated patients. The rates of severe late effects for neutrons are in the lower range compared to other reports (14, 21). Rates of local control and overall survival in literature are quite inconsistent – mainly due to the fact that all series include various treatment strategies even within one institution and various tumour stages. Until now nearly all reported results on ACC of salivary glands derive from retrospective, non-randomised reviews and treatment strategies were based on the prognostic factors of individual patients. An overview of different series of ACC is given in Table II. There is only one randomised study, including inoperable primary or recurrent major or minor salivary gland tumours with different histological types like squamous or malignant mixed or others. This study was stopped for ethical reasons after treating a total of 32 patients, because the group receiving fast neutron radiotherapy had a significantly improved local/regional control rate in comparison with the group treated with photons (15). Summarizing the role of neutrons in the treatment of ACC of the salivary glands, they represent the actual therapy of choice especially for unresectable tumours, in recurrent or not completely resected ACC, as described in a detailed analysis of the literature by Krüll *et al.* in 2001 (23). This recommendation has recently been supported by the analysis of Huber *et al.* (14). In their retrospective study, the outcome of patients with advanced ACC treated with either neutron, photon or mixed beam were compared and evaluated. They concluded that neutron therapy provides the highest local control rates without an impact on survival as reported in the RTOG-MRC study (15), because survival was dominated by the high number of distant metastases (39%). In an adjuvant setting, postoperative radiotherapy with photons yielded good results, as reported by Garden *et al.* (22). Neutrons are only available in a few centers worldwide. With this background, the improvement of conventional photon therapy for example with IMRT, dose escalation, hyperfractionation or proton therapy may represent the future therapeutic concept of ACC. Because of the rarity of these tumours, for improvement of therapy all patients should be treated in multicentre studies. At least, their data should be collected in a salivary gland register.

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