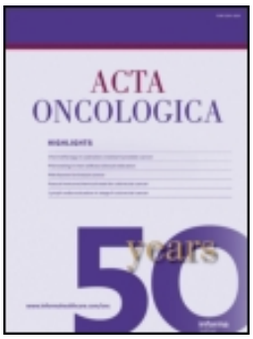

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ORIGINAL ARTICLE

Carcinoma ex pleomorphic adenoma of the parotid gland. Study and implications for diagnostics and therapy

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Abstract

Background. Carcinoma ex pleomorphic adenoma (CXPA) is a rare parotid malignancy and until today no standardized concept exists for its therapy apart from recommendations for parotid carcinoma in general. Prognosis is thought to be poorer than for other parotid malignancies. We sought to describe a general diagnostic and therapy strategy and assess factors predicting the outcome. *Methods*. We retrospectively analysed the courses of 22 patients with a CXPA of the parotid gland treated at a tertiary medical care centre for otorhinolaryngology. We examined parameters of medical history, diagnostics, surgical and adjunctive therapy and analysed overall and disease-specific survival. *Results*. About half of the patients had evidence of a parotid mass of up to 1 year only while maximum of the others was 48 years. Nine patients were primarily operated without suspicion for malignancy. Both 5-year disease-specific and overall survival were 60%. Recurrence-free survival rate after 5 years was 85%. Any patients with a stage I or II disease had an uneventful follow-up. To date, no patient with a stage IV disease has survived longer than 5 years. *Conclusion*. Surgical therapy (total or radical parotidectomy) is the method of choice for CXPA of the parotid gland. Stage I tumors have a very good and stage IV tumors a bad prognosis.

Tumors of the salivary glands are rarely seen neoplasms with a yearly incidence of only 0.4–2.5 tumors per 100 000 residents [1]. However, the salivary glands are beset by a greater variety of neoplasms than any other organ in the body. Approximately 80% of all salivary gland tumors occur in the parotid gland and again roughly 80% of these are said to be benign tumors. In respect to all neoplastic processes in the major salivary glands, the pleomorphic adenoma (PA) is the most frequent one with an incidence of 67.5% [2]. As numerously mentioned in the literature, the benign PA can transform into a carcinoma ex pleomorphic adenoma (CXPA), however reported prevalences in the literature differ greatly (3–15%) [3–5]. Many authors claim that the risk of malignant transformation increases with the duration of history as well as with tumor size [1,4,6]. Due to the entity's low incidence, so far no standard concept exists for its treatment. Most literature sees CXPA in general having a very bad prognosis. As we were able to detect a rather young population with early diseases, we sought to investigate whether early diagnosis and treatment could lead to an improved clinical course and outcome.

Materials & methods

We retrospectively analysed 22 patients treated at the Department of Otorhinolaryngology, Head and Neck Surgery at the University Hospital of Cologne for a histopathologically verified carcinoma ex pleomorphic adenoma (CXPA) of the parotid gland from 1987 to 2006.

We recorded personal variables and preoperative clinical and diagnostic results. Follow-up included routine physical examination and if necessary imaging of the primary site. When required, the referring physician was contacted to obtain relevant data.

Statistical analyses were performed using SPSS software for medical statistics (release 12.0). When

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comparing two groups, unpaired t-tests or Mann-Whitney-u-tests were calculated. Tests of association of categorical variables were performed using a χ^2 statistic or Fisher's exact test. The confidence interval (CI) was 95% and significance levels were $p = 0.05$. Percentage numbers are rounded in the text.

Results

Patients' characteristics

The sex ratio among the affected persons was balanced (12 women, 10 men). The overall incidence peak was the fifth decade of life and continuously thereafter. Mean age was 57 years (range: 29–82 years). The mean lead time (clinical evidence of a parotid mass) was 9 years (range 0.1–48 years).

Preoperative findings are listed in Table I.

Therapy and findings

At the end of all preoperative diagnostics (including at least the history, physical examination, ultrasound and FNA; where required added by CT and/or MRI) nine patients were thought to have a pleomorphic adenoma of the parotid gland before operation. Eight patients were under suspicion of having a parotid malignoma. In only three cases the suspected diagnosis was CXPA. Depending on the suspected diagnosis patients received either a superficial, total or radical parotidectomy. When histological analyses revealed the CXPA, six patients were re-operated. In sum, 15 patients received a total, four patients a radical parotidectomy. In three patients having received a superficial parotidectomy only, we abstained from further intervention due to the small size of the carcinomatous part. These patients were in disease stage I or II and to date remain with an uneventful follow-up.

In 20 patients the primary parotid tumor could be removed totally (R0). The two remainders with carcinoma unclear surgical margins (R1) were both found to have distant metastasis. Twelve patients received an additional ipsilateral neck dissection revealing a pathologic N-positive disease in half of them with one case of extracapsular extension.

All the T1 ($n = 8$) and T2 tumors ($n = 7$) were without any locoregional or distant metastasis and thus classified for their correlating TNM/AJCC [7] disease stage I, respectively stage II. All others were classified stage IV ($n = 7$).

The carcinoma histology was adenocarcinoma in 14 cases. Second were adenoid ($n = 3$) and myoepithelial carcinomas ($n = 2$) with remaining malignancies being an anaplastic, an undifferentiated and a polymorph microinvasive carcinoma.

Table I. Preoperative findings

	Total	Percent
Gender		
Female	12	(55)
Male	10	(45)
Age		
<50	9	(41)
50–70	5	(23)
>70	8	(36)
Side		
Left	15	(68)
Right	7	(32)
Fixation		
Yes	11	(50)
No	3	(14)
Unknown	8	(36)
Pain		
Yes	2	(9)
No	14	(63)
Unknown	6	(27)
Facial palsy	5	(23)
B symptoms	0	(0)
Nicotine		
Yes	5	(23)
No	8	(36)
Unknown	9	(41)
Alcohol		
Yes	4	(18)
No	10	(45)
Unknown	8	(36)
Lead time		
up to 1 year	11	(50)
1–5 years	6	(27)
5–30 years	0	(0)
>30 years	5	(23)
Fine needle aspiration	20	(91)
Adenocarcinoma	8	(49)
Pleomorphic adenoma	7	(35)
No diagnosis	5	(25)
Sonography	22	(100)
Malignancy suspicion	3	(14)
No malignancy suspicion	17	(77)
Unknown	2	(9)
CT scan	6	(27)
Malignancy suspicion	2	(9)
No malignancy suspicion	4	(18)
Unknown	16	(73)
MRI scan	12	(55)
Malignancy suspicion	5	(23)
No malignancy suspicion	7	(32)
Unknown	10	(46)

In total, twelve patients were postoperatively radiated and their mean age was 63.8 years compared to 50.2 years for the not radiated patients. The radiation dose ranged from 48 Gy to 72 Gy (mean dose 61 Gy). Four patients had a combined radiochemotherapy with carboplatinum.

Table II shows operative and postoperative characteristics.

Follow-up and survival

Mean observation time for all patients was 51 months (range 11–155 months). The overall survival after 5 years was 57% (mean 97 months; CI: 65–128 months).

The 5-year disease-specific survival was 60% with four patients having died of their disease. According to the Kaplan-Meier calculation, the mean postoperative disease-free time was 124 months (i.e. 10 years; CI: 97–152 months). In those subjects with a total resection of a CXPA (R0), the recorded recurrence-free survival rate after 5 years was 85%.

Of all patients with a stage I or II disease (n = 15), none had a tumor recurrence and no case of disease-specific death was recorded (mean follow-up 57 months; mean age 53 years). The group of stage IV tumors (n = 7) included all four cases of disease-specific death and both cases of tumor recurrence (mean follow-up 40 months; mean age 67 years). So far none of these patients has survived more than 5 years, though many lived for at least 4 years (Figure 1).

Table II. Operative and postoperative findings

	Total	Percent
Surgery under suspicion of malignancy		
Yes	9	(41)
No	9	(41)
Unknown	4	(18)
Surgery		
Parotidectomy superficial	3	(14)
Parotidectomy total	15	(68)
Parotidectomy radical	4	(18)
Neck dissection	12	(55)
Carcinoma Histology		
Adenocarcinoma NOS	14	(63)
Adenoidcystic	3	(14)
Myoepithelial	2	(9)
Others	3	(14)
T stage		
T1	8	(36)
T2	7	(32)
T3	1	(5)
T4	6	(27)
N+	6	(27)
M+	3	(14)
Stage		
I	8	(36)
II	7	(32)
IV	7	(32)
Postoperative radiation	12	(55)
Postoperative chemotherapy	4	(18)
Recurrence	2	(9)
Residual disease	2	(9)
Disease-specific death	4	(18)

Overall recurrence-free survival rate of radiated patients was 50% after 5 years compared to 100% of unradiated patients (p = 0.029).

Patients receiving chemotherapy had a lower overall survival rate (50%) after 5 years than those receiving no chemotherapy (63%). This result however shows no significance due to the low number of patients receiving adjuvant chemotherapy at all.

The following variables were significantly associated with disease-specific death: disease stage (p = 0.007), age (p < 0.001), T stage (p = 0.11), M stage (p = 0.003), N stage (p = 0.002), tumor recurrence or residuum (p = 0.001).

No parameter was statistically associated with overall survival.

Discussion

The CXPA is the malignant derivative of the benign mixed tumor or pleomorphic adenoma. Literature says that CXPA usually emerges in the 6th or 7th decades of life span [8–11]. In our sample about half of the patients were older than 50 years, but four of our 22 patients were less than 40 years old and with this our sample is younger than any other population previously described. Higher disease stage tended to be associated with older age (p = 0.058) with a mean age of 53 years for patients with stage I or stage II disease, compared to 67 years for patients with a stage IV disease (range: 45–82 years). This item has not been discussed before in the literature, and deserves further investigation.

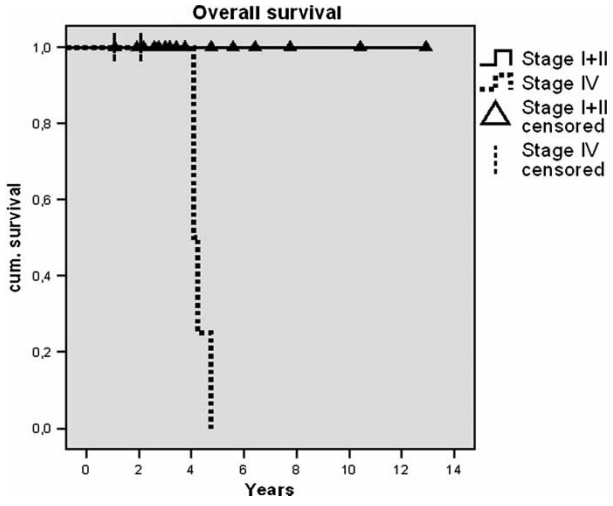

Figure 1. Kaplan-Meier calculation shows none of the stage IV patients surviving more than 5 years after diagnosis, though many live for at least 4 years. Overall survival for stage I and stage II patients is excellent.

Lead time in our sample was on average 9 years. The literature shows an inconsistently but meaningful picture with either rather short (9 months) or long durations of symptoms (23 years) [10,11].

Compared to the literature we do not only seem to have acquired a rather young, but also a rather early CXPA group with 68% stage I or II patients. Statistical analysis suggests that there is a causal correlation between these two items. Taken together, the frequency of stage I and stage II of CXPA and the short history suggest that a synchronous development of carcinomas and pleomorphic adenomas is at least possible.

A quarter of our patients had undergone parotidectomy on the ipsilateral side before. Accordingly the repeated excisions of recurrent PA do not seem to engender malignancy [12]. Apart from a very long history no other apparent risk factors are known for the development of a CXPA.

For the preoperative facial nerve palsy our number (23%) is comparable to others in the literature and numbers for the suspected microscopic or confirmed histologic infiltration of the facial nerve are likewise [9–11,13].

The therapy of choice for a CXPA in the parotid gland is surgery. In our sample the follow-up has indicated that superficial parotidectomy can be a sufficient surgical approach for very small carcinomas inside PA, but otherwise a total if not radical parotidectomy is recommended. A neck dissection has a diagnostical and a therapeutical meaning, but still for very small carcinomas at a clinically inconspicuous neck the procedure might be dispensable.

In line with the literature we used the following indication criteria for postoperative irradiation in our sample: high grade disease, question of resection adequacy with possible histologic margin involvement, lymph nodes beset, perineural invasion or lymphangiosis carcinomatosa. Statistically, in our study the use of postoperative radiation therapy was associated with a significant reduction in recurrence-free survival rate, but this result largely depends on the fact that any recurrence occurred only in stage IV patients and all these had been radiated. We support the notion that, in general, surgery followed by postoperative radiation should be considered the standard of care for patients with CXPA [9]. However, as unradiated patients with a stage I or II disease had an uneventful follow-up in our study, surgery alone can be a therapy option for small carcinomas.

The role of additional postoperative chemotherapy for CXPA remains unclear [5]. Our decisions on whether treating patients with adjuvant chemotherapy or not were based on a combination of patients' general condition, age, tumor stage and pathologic details. This field clearly needs more research exploration.

The prognosis of parotid tumors in general is said to decline with the extent of the tumor and the existence of locoregional metastases [5]. Recurrence and R1 resection of a malignant parotid gland tumor indicates an unfavorable long-term prognosis [10]. CXPA in general is said to have the worst prognosis of all parotid malignancies with a disease-specific 5-year survival rate of only 44% and a locoregional control of 66%. Our specific sample with low stage disease may explain the slight improvement in overall (57%) and disease-specific survival (60%) after 5 years compared to data published so far [9,10].

Conclusions

The CXPA of the parotid gland is a rare tumor which has its peak incidence in the 6th and 7th decade of life. Depending on the lead time, patients either present with a low or high stage disease. Currently preoperative diagnostics cannot reliably predict the correct diagnosis. Adenocarcinoma is the malignant component in the majority of cases. Surgical therapy (total or radical parotidectomy) is the method of choice for CXPA of the parotid gland. For small carcinomas a pure surgical concept alone without any adjunctive therapy has shown no disadvantage in our sample, while for greater CXPA postoperative radiotherapy is recommended. The role of postoperative chemotherapy is still unclear. In general stage I tumors have a very good and stage IV tumors a comparatively bad prognosis.

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