Intraoral adenoid cystic carcinoma: is the presence of perineural invasion associated with the size of the primary tumour, local extension, surgical margins, distant metastases, and outcome?

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Abstract

Adenoid cystic carcinoma (ACC) is the most common malignancy of the minor salivary glands. The biological behavior of ACC is characterized by a slow and indolent growth rate, rare involvement of regional lymphatics, high propensity for perineural invasion (PNI), multiple and/or delayed recurrences, and a high incidence of distant metastases. The aim of this study was to determine the presence of PNI in relation to different prognostic factors. Between January 1st 1984 and May 1st 2008, twenty-six cases of ACC of the intraoral salivary glands, initially treated surgically, were retrospectively reviewed. The most commonly affected site was the palate. PNI was reported in 13 of the 26 resected specimens (50%). There was no significant association between perineural invasion and primary tumour size (OR=1,00; p=1.00), status of the surgical margins (OR=2,08; p=0.399), distant metastases (OR=3,43; p=0.197) and local control (p=0,76), respectively. PNI was present exclusively in patients with local extension. PNI proved to be a statistically significant variable when describing outcome (p=0.04). According to our findings, local extension and disease-specific survival rates were significantly associated with PNI, while primary tumour size, status of surgical margins and distant metastases showed no association regarding PNI. Surgical resection with clear margins is currently considered the standard of care for patients with intraoral ACC. The role of adjuvant irradiation remains controversial. Given the paradoxical and complex biological behaviour of ACC, large studies with long term follow-up

are needed to define clinico-pathologic and immunohistochemical variables associated with outcome as well as the optimal treatment modality.

Keywords: adenoid cystic carcinoma; minor salivary gland; oral cavity tumour; perineural invasion; patterns of recurrence

Introduction

Adenoid cystic carcinoma (ACC) or cylindroma is the most common malignancy of the minor salivary glands.[1] The biological behavior of ACC is characterized by a slow and indolent growth rate, rare involvement of regional lymphatics, high propensity for perineural invasion (PNI), multiple and/or delayed recurrences, and a high incidence of distant metastases.[2] The aim of this study was to examinate the presence of PNI in relation to primary tumour size, local extension, histologic status of surgical margins, distant metastases and outcome in patients with ACC of the intraoral salivary glands.

Materials and Methods

Between January 1st 1984 and May 1st 2008, a total of fourty-four patients with ACC of the intraoral salivary glands were registered at the Department of Maxillofacial Surgery, University Hospital Dubrava, Zagreb. Nine patients had radiotherapy as initial management due to unresectable loco-regional disease. Eight patients were initially treated elsewhere and were referred to our Department because of local recurrence while one patient was lost to follow-up. These patients were excluded from additional examination. The remaining group of 26 patients, who were initially treated surgically, were reviewed retrospectively. Postoperative radiotherapy was used as adjuvant treatment in 15 patients. No strict criteria were used to determine which

patients would be administred postoperative radiotherapy; however patients with PNI were more likely to undergo adjuvant irradiation. Radiotherapy was administered in 84.6% (11 of 13) of those with PNI versus 30.8% (4 of 13) of those without PNI. Other indications for adjuvant radiotherapy were positive/close resection margins, advanced-stage disease, deep infiltration (bone, cartilage or muscle) and regional metastatic disease. One patient was submitted to regional lymphadenectomy confirming lymph node metastasis at the histopathological analysis. The histologic diagnosis of PNI was based on the definition provided by the World Health Organisation (WHO).[3] Endoneural (intraneural) tumour spread was not analysed separately from PNI due the lack of data. A standardised patological specimen analysis was performed. Patients were staged according to the American Joint Committee on Cancer criteria for squamous cell carcinoma of oral cavity.[4] Tumours of the sublingual gland which presented themselves in the floor of the mouth have been classified as being of intraoral salivary gland origin. The diagnosis of local extension was based on microscopic evidence of skin, soft tissue or bone invasion.

Statistical analysis

Odds ratio was calculated with 95% confidence intervals. Follow-up intervals were calculated in months from the date of first treatment at our Department to the date of last follow-up or death. Disease-specific survival and local control rates were calculated using Kaplan-Meier method, while the log-rank test has been used to test differences between the actuarial curves. All analyses were done using MedCalc statistical software (Version 12.3.0 © 1993-2013. MedCalc Software bvba, Acacialaan 22, B-8400 Ostend, Belgium). Only $p<0.05$ was considered statistically significant.

Results

There were 12 male and 14 female patients, giving a female-male ratio of 1.17:1. The mean age was 57.5 years (range 34 to 88 years), the women being older (mean 62.1 years) than the men (mean 52.1 years). The most commonly affected site was the palate, present in 16 of the patients (61.5%), with equal distribution among hard and soft palate. The distribution of patients by primary tumour site is shown in **Table 1**. At the time of diagnosis, 13 patients (50%) were known to have early (T1-2) lesions and 13 patients (50%) presented late stage (T3-4) lesions. PNI was reported in 13 of the 26 resected specimens (50%). There was no significant association between PNI and primary tumour size. The proportion of early (T1-T2) and advanced stages (T3-T4) was equal among patients with and without PNI (**Table 2**, OR=1,00; p=1.00). Eight of 26 resection specimens (30.8%) had positive histological status of surgical margins. In 5 of these 8 resection specimens (62.5%) PNI was present, but there seems to be no significant association between PNI and the status of the surgical margins (**Table 2**, OR=2,08; p=0,399). PNI was present exclusively in patients with local extension; all 8 patients with local exension had PNI, compared with none without local extension (**Table 2**). Distant metastatic spread developed 7 of 26 patients (27%). Time of the distant failure diagnosis ranged from 2 to 136 months, with the mean time of 38.7 months. Distant metastases occured more often in patients with PNI; five of 13 patients (38.5%) with PNI developed metastatic disease, compared with 2 of 13 (15.4%) without perineural spread. However, no statistically significant association was identified (**Table 2**, OR=3,43; p=0,197). Recurrences were documented in 11 of the 26 patients (42.3%). Two patients had local recurrence, while 2 patients experienced loco-regional failure and loco-regional with distant failure respectively; two patients had distant metastases only; four patients had both local recurrence and distant metastatic spread while one patients developed regional recurrence.

The most common pattern of failure was distant metastatic spread with the lungs being the most commonly involved site (66.7% of cases), followed by bones (16.6%) and brain (16.6%). In our series, total, local and distant failure rates were 42.3%, 31% and 27%, respectively. The actuarial local control rates were 78% at 5-year, 58% at 10-year and 15-year. No significant association between PNI and local control was observed (**Figure 1**, p=0.76). Disease-specific survival rates were 62% at 5-year, 53% at 10-year and 27% at 15-year for patients with PNI in comparison to 90% for the patients without PNI for the same follow-up intervals which proved to be statistically significant (**Figure 2**, p=0.04). At study's closing date, 14 of 26 patients (53.8%) had died, 10 of them due to the tumour disease (71.4%). The 30% (3 of 10) of these patients died from distant metastatic spread, 20% (2 of 10) died from local recurrence, 30% (3 of 10) died from both local and distant recurrence, 10% (1 of 10) died from loco-regional recurrence, while 10% (1 of 10) died from loco-regional and distant recurrence. Follow-up information was available for all patients and varied from 7 to 276 months, the average being 117.8 months. All surviving patients had a minimum 5-year follow-up.

Discussion

ACCs or cylindromas are uncommon tumours, comprising less than 1% of all head and neck cancers and 20-25% of all salivary malignancies.[5-7] ACC occurs mainly in the intraoral salivary glands, particularly in the palate, and parotid, followed by submandibular and sublingual salivary glands.[8] Several authors have retrospectively analyzed clinicopathological features of ACC, in order to identify significant prognostic factors, but the findings still remain controversial. Age of the patient, tumour size, type and duration of symptoms, clinical stage, treatment modality,

histological subtype, perineural/vascular invasion, histological status of surgical margins have all been considered.[1,2,8-12]

ACC most commonly occurs during the fifth and sixth decades of life, as in our series. In this study, and also in earlier reports of intraoral ACC, we found a female predilection. However, some authors identified a slight male predilection.[1,2,8] In this study, the palate was the most commonly affected site, which is in accordance with prior reports.[1,2,10,13,14] In our series PNI was present in 50% of the resection specimens of intraoral ACC and is similar with previously reported incidences which vary between 15% and 72%.[1,13,15-17] Similar occurence of PNI was reported in squamous cell carcinoma of the oral cavity, as well.[18] However, in contrast to oral squmous cell carcinoma, ACC has good 5-year survival ranging from 78% to 90%, while 10 and 20-year survival rates are much worse due to negative survival impact of delayed recurrences (range 32-74%).[8,13,14,19,20] We found no statistically significant association between PNI and primary tumour size. On the contrary, van der Wall et al.[1] implicated a significant relation between the size of the tumour and PNI. Vrienlick et al.[15] also identified increased incidence of PNI associated with a higer stage of the primary tumour. Positive histological status of surgical margins was identified in 30.8% of resection specimens which is comparable with the results of other authors.[1,11,13,16] A review of the literature shows a statistically significant association between positive surgical margins and PNI.[1,2] This association is explained by more agressive and infiltrative tumours making it difficult to obtain clear surgical margins.[2] Interestingly, in our series we could not demonstrate such a relation. Local and distant recurrences are common in ACC, leading to low long-term survival rates. Total failure rate varies from 43% to 70%, with local and distant failure rates ranging from 13% to 52% and 8% to 52%, respectively.[8,9,12,21-23]

The incidence of total, local and distant failure in our experience is quite similar to that reported in other studies. In our series, PNI was associated with higher incidence of distant metastases, but this relation was not statistically significant, as observed in other series.[1,13] On the contrary, some authors found that distant metastasis was significantly influenced by perineural invasion.[11,15] In addition, our study demonstrated high incidence of delayed distant metastatic spread with the lungs as the first site of distant failure which is similar to past experiences.[2,8,13] A review of the literature shows significant association between PNI and local control. In most of the series, nerve involvement predicted poor local control rate.[2,16,21] Similarily to Sur et al.[24] in our study, PNI, lost its significance as an independent prognostic factor when describing local control. Disease-specific survival rates decreased significantly at 10- and 15-years of follow-up compared with a 5-year period which strongly supports the idea of late local/distant recurrence leading to poor long term survival. This is completely opposite to the biological behaviour of oral squamous cell carcinoma, in which most of the recurrences occur during the first 5-years of follow up (about 80% during first 2-years). In our series, only one patient with distant recurrence is still alive at the study's closing date. This could be explained by non-standardized care of treatment in the past throughout follow-up periods (without rutine imaging scans) leading to late diagnosis of distant metastases. PNI proved to be a statistically significant variable when describing outcome. Similarly, most of the large studies have shown PNI to be an important predictor of the outcome.[2,11,15,16] On the contrary, in a few series, PNI was not a prognostic factor statistically significant of survival.[13,24]

There is conflicting literature data regarding the role of postoperative adjuvant radiotherapy in patients with adenoid cystic carcinoma of the minor salivary glands. Some authors have shown that postoperative radiotherapy improves local control when adverse prognostic factors are

present (positive resection margins, advanced-stage disease, deep infiltration).[12,25,26] However, several studies could not demonstrate survival benefit or improvement in local control with the addition of postoperative radiation therapy.[8,9,27,28]

This study has all limitations associated with rectrospective study. However, no prospective study regarding prognostic factors in minor salivary gland tumours has ever been conducted. Another clear weakness of this analysis is small sample size as well as wide variability in treatment modalities over a 24-year period. On the other hand, we believe that this data provide insights into the paradoxical biological behaviour of this uncommon disease which may be useful to define optimal treatment of head and neck ACC.

In conclusion, ACC mostly occurs during the fifth and sixth decades of life with a slightly female predilection, although a male or no gender predilection has also been described. Surgical resection with clear margins is currently considered the standard of care for patients with intraoral ACC. The role of adjuvant irradiation remains controversial. Given the paradoxical and complex biological behaviour of ACC, large studies with long term follow-up are needed to define clinico-pathologic and immunohistochemical variables correlating with outcome as well as the optimal treatment modality. In contrast to the vast majority of head and neck malignancies, in which most recurrences occur during the first 5-years of follow-up, ACC is characterized with an increased propensity of delayed recurrences with negative impact on outcome which results in poor long-term survival (10 and 20-years). Local extension and disease-specific survival rates were significantly associated with PNI, while primary tumour size, local recurrence, status of surgical margins and distant metastases showed no association regarding PNI.

Conflict of Interest Statement

All authors disclose any financial and personal relationships with other people or organisations that could inappropriately influence (bias) their work.

Ethics Statement/confirmation of patient permission

This work has been approved by the appropriate ethical committee related to the institution in which it was performed and subjects gave informed consent to the work.

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Figure 1. Kaplan-Meier analysis showing local control for patients with and without PNI.
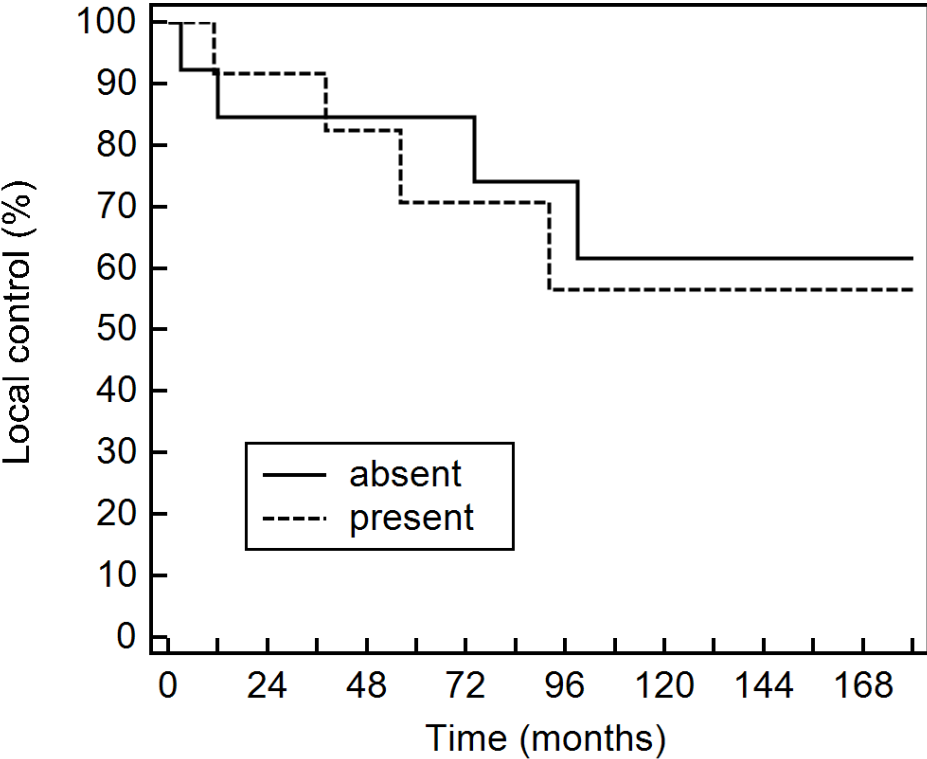
Figure 2. Kaplan-Meier analysis showing disease-specific survival for patients with and without PNI.
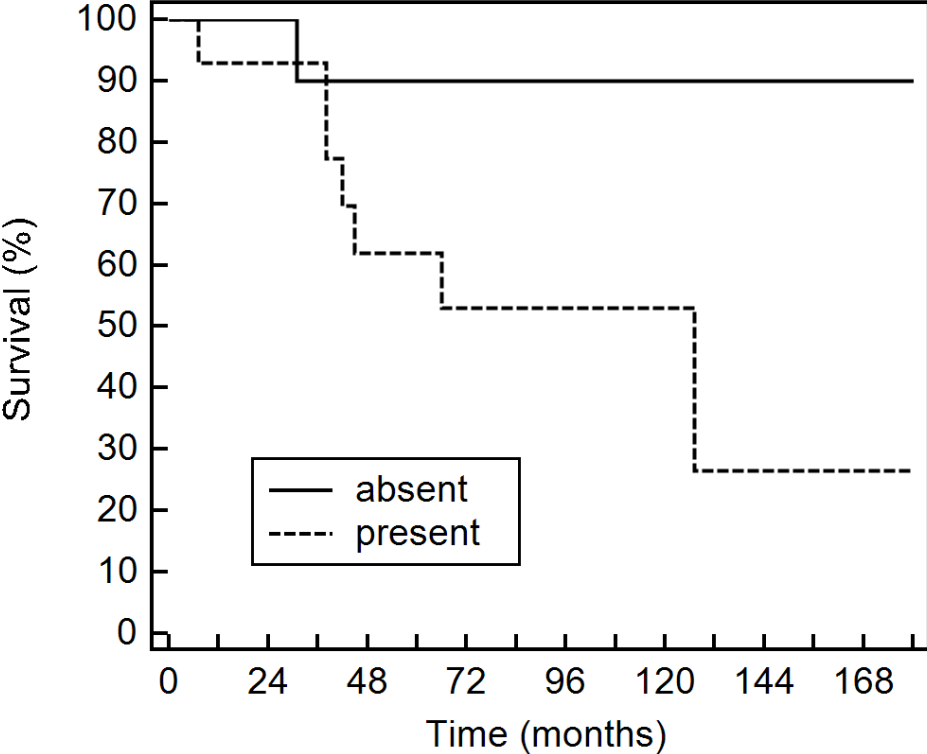
Table 1. Primary tumour subsite.

Site	No of patients (%)
Palate	16 (61.5)
Floor of the mouth	4 (15.4)
Alveolar mucosa	3 (11.5)
Upper lip	2 (7.7)
Cheek	1 (3.9)

Table 2. PNI in relation to different factors.

		PNI	No PNI	Total	OR (95% CI)	p value
Tumour size	T1/T2	8	5	13	1,00 (0,21-4,86)	1,00
	T3/T4	8	5	13		
Surgical margins	Positive	5	3	8	2,08 (0,38-11,48)	0,399
	Negative	8	10	18	*	
Local extension	Yes	8	0	8		
	No	5	13	18		
Distant metastases	Yes	5	2	7	3,43 (0,52-22,43)	0,197
	No	8	11	19		

* Test was not performed because of zero frequency.