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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 is the most common malignancy of the minor salivary glands, and its biological behaviour is characterised by slow and indolent growth; rare involvement of regional lymph nodes; a high propensity for perineural invasion; multiple or delayed recurrences, or both; and a high incidence of distant metastases. Our aim was to find out the relation between the presence of perineural invasion and these factors. Between 1 January1984 and 1 May 2008, 26 cases of adenoid cystic carcinoma of the intraoral salivary glands, which had initially been treated surgically, were reviewed retrospectively. The most common site was the palate, and perineural invasion was reported in 13 of the 26 resected specimens. There was no significant association between it and the size of the primary tumour (OR = 1.0; $p = 1.00$), invasion of the surgical margins (OR = 2.08; $p = 0.4$), the presence of distant metastases (OR = 3.43; $p = 0.197$), or local control ($p = 0.76$). It was exclusively present in patients with local extension, and was significantly associated with outcome ($p = 0.04$). Resection with clear margins is the gold standard of care for patients with intraoral adenoid cystic carcinoma, and the role of adjuvant irradiation remains controversial. Given its paradoxical and complex biological behaviour, large studies with long term follow-up are needed to define the clinicopathological and immunohistochemical variables associated with outcome, as well as the optimal treatment.

Keywords: Adenoid cystic carcinoma; Minor salivary gland; Oral cavity tumour; Perineural invasion; Patterns of recurrence

Introduction

Adenoid cystic carcinoma (or cylindroma) is the most common malignancy of the minor salivary glands.[1] Its biological behaviour is slow and indolent growth; rare involvement of regional lymph nodes; likelihood of perineural invasion; multiple or delayed recurrences, or both; and a high incidence of distant metastases.[2] The aim of this study was to find out if perineural invasion had any relation to size of primary tumour, local extension, histological state of surgical margins, presence of distant metastases, and outcome in these patients.

Patients and methods

Between 1 January 1984 and 1 May 2008, a total of 44 patients with adenoid cystic carcinoma of the intraoral

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salivary glands were recorded at the Department of Maxillofacial Surgery, University Hospital Dubrava, Zagreb. Nine patients were initially treated with radiotherapy because of unresectable locoregional disease. Eight patients were initially treated elsewhere and were referred to our department with local recurrence, and one patient was lost to follow-up. These patients were excluded from the study.

The remaining 26 patients, who were initially treated surgically, were reviewed retrospectively. Postoperative radiotherapy was used as adjuvant treatment in 15. No strict criteria were used to assess which patients would be given postoperative radiotherapy; but patients with perineural invasion were more likely to have it. Radiotherapy was given to 11/13 of those with perineural invasion compared with 4/13 without. Other indications for adjuvant radiotherapy were invaded or close resection margins, advanced disease, deep infiltration (bone, cartilage, or muscle) and regional metastases. One patient had a regional lymphadenectomy to confirm lymph node metastases on histopathological analysis.

The histological diagnosis of perineural invasion was based on the definition provided by the World Health Organization.[3] Endoneural (intraneural) spread of tumour was not analysed separately from perineural invasion because of lack of data. Patients were staged histopathologically according to the American Joint Committee on Cancer criteria for squamous cell carcinoma of the oral cavity.[4] Tumours of the sublingual gland that presented in the floor of the mouth have been classified as originating in the intraoral salivary gland. The diagnosis of local extension was based on microscopic evidence of invasion of skin, soft tissue, or bone.

Statistical analysis

Odds ratios were calculated with 95% CI. 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 the Kaplan–Meier method, while the log-rank test has been used to test differences between the actuarial curves. All analyses were made with the aid of MedCalc statistical software (Version 12.3.0© 1993–2013. MedCalc Software bvba, Acacialaan 22, B-8400 Ostend, Belgium). Probabilities of less than 0.05 were accepted as significant.

Results

There were 12 men and 14 women, giving a female:male ratio of 1.2:1. The mean age was 58 (range 34–88) years, the women being older (mean 62) than the men (mean 52). The most commonly affected site was the palate ($n = 16$, 62%), with equal distribution among hard and soft palate (Table 1). At the time of diagnosis, half the patients were known to have early (T1–2) lesions and half late stage (T3–4) lesions.

Table 1
Sites of primary tumours ($n = 26$).

Site	No. (%) of patients
Palate	16 (62)
Floor of mouth	4 (15)
Alveolar mucosa	3 (12)
Upper lip	2 (8)
Cheek	1 (4)

Perineural invasion was reported in half the resected specimens. There was no significant association between perineural invasion and size of the primary tumour.

Eight of the 26 resection specimens (31%) had invaded surgical margins on histological examination. Five of these 8 also included signs of perineural invasion, but there was no significant association between the 2 (Table 2, OR = 2.08; $p = 0.4$). Perineural invasion was present exclusively in patients with local extension, in that all 8 patients with local extension had signs of it, compared with none without local extension (Table 2). The time of the diagnosis of distant failure ranged from 2 to 136 months (mean 39), respectively. Two patients had distant metastases only, and 4 had both local recurrence and distant metastatic spread while one patient developed regional recurrence.

The most common pattern of failure was distant metastatic spread to the lungs in a third, followed by bones and brain. Rates of total, local, and distant failure were 42%, 31%, and 27%, respectively. The actuarial local control rates were 78% at 5 years, and 58% at 10 and 15 years. There was no significant association between perineural invasion and local control (Fig. 1, $p = 0.76$). Disease-specific survival rates were 62% at 5 years, 53% at 10 years, and 27% at 15 years for patients with perineural invasion compared with 90% for those patients who did not have invasion at the same follow-up intervals, which was significant (Fig. 2, $p = 0.04$).

At the end of the study, 14 of the 26 patients had died (54%), 10 of them of their tumours. Three of the 10 died from

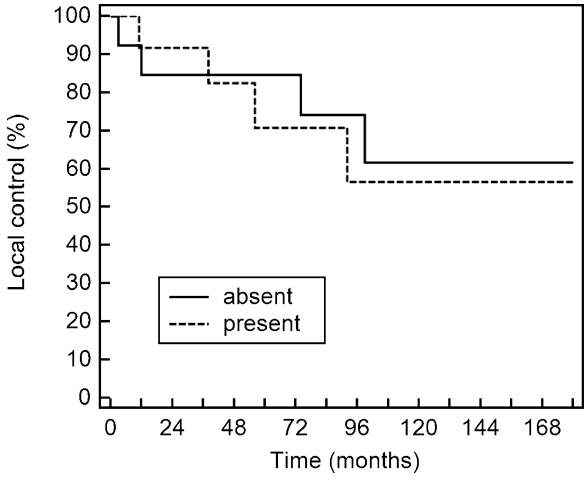

Fig. 1. Kaplan–Meier curves showing local control for patients with and without perineural invasion.