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Polymorphous low-grade adenocarcinoma: A Danish national study

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SUMMARY

Objectives: To present a national series of polymorphous low-grade adenocarcinoma (PLGA) patients, including survival rates and an analysis of prognostic factors.
Materials and methods: By merging three Danish nationwide registries, 73 patients diagnosed with PLGA from 1990 to 2005 were identified. Histological slides were reviewed and data concerning demographics, tumour site, clinical stage, treatment profiles and follow-up were retrieved. Survival estimates and prognostic factors were evaluated by comparing Kaplan–Meier plots using the Mantel–Haenszel log-rank test.
Results: Of the 73 patients, 47 (64%) were female. Median age was 58 years. The most common location was the palate (73%). Median latency was five months. Recurrence was seen in 13% of patients. Overall survival (OS), disease-specific survival (DSS) and recurrence-free survival (RFS) rates after 10 years were 73%, 99% and 83%, respectively. Univariate analyses suggested that free resection margins significantly improve RFS.
Conclusion: PLGA usually has an excellent survival outcome even in cases of advanced stage disease and locoregional recurrence. Primary choice of treatment should be complete surgical excision. Although there is no convincing evidence for the efficacy of adjuvant radiotherapy, it should still be considered, particularly in cases of involved resection margins and advanced stage disease. Late recurrences are common and respond well to salvage therapy.

Introduction

Polymorphous low-grade adenocarcinoma (PLGA) is a slow-growing salivary gland malignancy with a non-aggressive behaviour [1]. PLGA is predominantly found in females in their sixth to seventh decade, and it most commonly arises in the minor salivary glands, with more than half of cases involving the palate [2]. It can also occur in minor salivary glands in the rest of the upper aero-digestive tract, as well as in major salivary glands [1,3]. PLGA accounts for approximately 25% of all intraoral malignant salivary gland tumours [2,4]. It is characterised by an infiltrative growth, always invading surrounding soft tissue, yet distant metastases are rare. Even though the tumour exhibits cytological uniformity, the peculiar morphological diversity in PLGA can be a diagnostic dilemma, as it can resemble both the benign pleomorphic adenoma and the highly malignant adenoid cystic carcinoma [5]. Research has focused on identifying reliable immunohistochemical markers to aid the diagnosis, yet controversy on this subject persists [6,7].

Although PLGA is histologically low-grade, a recent review [1] showed that recurrence rates average close to 20%. Recurrences have been reported to occur more than ten years after diagnosis of primary tumour [1], for which reason a follow-up duration of up to 20 years has been advocated [8]. Since its classification in 1984 [9], approximately 1000 cases have been reported in the English-language literature, of which the largest study [3] contributed 460 patients.

The aim of this study is to present a histologically revised national series of Danish PLGA patients, including a presentation of survival rates and analysis of associated prognostic factors and treatment modalities.

Materials and methods

All patients diagnosed with PLGA in the period from the 1st of January 1990 to the 31st of December 2005 were identified by

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merging three Danish nationwide registries: The Danish Cancer Registry, The Danish Pathology Registry and The Danish National Patient Registry, as described in an earlier publication [10]. These databases include the entire Danish population along with the populations of Greenland and the Faroe Islands. Seventy-three patients were identified and clinical data were available for 71 of these. Sixty-eight of these 71 cases (96%) had been classified and confirmed as true PLGAs, by two experienced salivary gland pathologists, in accordance with the WHO 2005 classification [2]. Eighteen of these 68 had previously been categorised as other subtypes of salivary gland malignancies, of which half (nine slides) were changed from adenoid cystic carcinomas. For comparison with other studies, information on patient demographics, tumour site, clinical stage, treatment profiles and follow-up were retrieved. Primary tumours were staged retrospectively according to the International Union Against Cancer (UICC 2002, 6th edition) classification [11].

Statistical analyses

Survival curves were calculated using the Kaplan–Meier method. Primary end-points were overall survival (OS), disease-specific survival (DSS) and recurrence-free survival (RFS), and survival rates for possible prognostic factors were compared by the Mantel–Haenszel log-rank test. Two-sided p-values < 0.05 were considered significant. Multivariate analysis was not performed, as this was not found meaningful considering the sample size. The database and analysis system MEDLOG was used for data registration and calculations. The follow-up time was calculated from the time of diagnosis until death or the end of data-collection (November 2009).

Results

Clinicopathological findings

The 73 patients identified during the 16-year collection period yield an estimated incidence of 0.08/100.000 inhabitants/year [12–14]. The patient characteristics are presented in Table 1, with data on gender, age and site available for all 73 patients. The remaining, with the exception of data on pathological findings, is for 71 patients.

There were 26 men and 47 women with a median age of 58 years at the time of diagnosis (range 16–86 years). Sixty-six tumours (90%) presented in the oral cavity and the remaining seven (10%) in the parotid gland, pharynx and the nose. A swelling in the oral cavity was the most common initial symptom ($n = 50$, 70%), and 16 tumours (23%) were detected by dentists. In addition, four patients (6%) presented with a palpable nodule in the affected salivary gland, three (4%) with pain, whereas three (4%) cases were incidental findings.

Median time from initial symptom to diagnosis (latency) was 5 months (range 0–241 months). The vast majority of patients (86%) had pathological class T1/T2 tumours and ten (14%) had T3/T4 tumours. Nodal involvement was only seen in three cases (4%), while none of the patients had distant metastasis at diagnosis. Thus, 15% ($n = 11$) presented with advanced disease (overall stage III/IV), and almost all of these were related to high T class. Data on perineural invasion was available for 58 patients with 48% ($n = 28$) positivity. Perineural invasion was defined as all types of nerve involvement; ranging from large nerve involvement to microscopic findings of tumour cells infiltrating small nerves. Free resection margins were obtained in 65% ($n = 45$) of the 69 patients with known margin status. Surgery was performed in 99% ($n = 70$) of the 71 cases. The remaining patient (1%) only had a surgical biopsy performed with no other treatment following. The majority (78%) received no further treatment after surgery, yet fifteen patients (21%) received radiotherapy. Fourteen of the latter had known resection margin status out of which ten (71%) had involved resection margins and four (29%) were free. Adjuvant radiotherapy status was unknown for the remaining one (1%) patient. Finally, three patients (4%) received neck dissection, whereas two (3%) had a single node removed.

Table 1
Patient and tumour characteristics.

Clinicopathological characteristics	No. of patients	Percentage
Gender (male/female)	26/47	36/64
Median age, years (range)	58 (16–86)	
Tumour site		
Parotid	3	4
Oral cavity		
Lip	4	5
Buccal mucosa	7	10
Floor of mouth	2	3
Palate	53	73
Nose	1	1
Pharynx	3	4
Clinical presentation[a]		
Swelling in oral cavity	50	70
Detected by dentist	16	23
Palpable nodule in salivary gland	4	6
Pain	3	4
Incidental finding	3	4
Other	3	4
Median latency, months (range)	5 (0–241)	
TNM		
T1/T2/T3/T4a	49/12/1/9	69/17/1/13
N0/N1/N2a/N2b	68/0/1/2	96/0/1/3
M0/M1	71/0	100/0
Overall stage I/II/III/IV	49/11/1/10	69/15/1/14
Pathological findings		
Perineural invasion (yes/no)	28/30	48/52
Surgical resection margins (pos./close/neg.)	15/9/45	22/13/65
Initial treatment		
Surgery		
Biopsy	1	1
Excision of minor salivary gland	59	83
Parotid gland resection	2	3
Total parotidectomy	1	1
Resection, other	8	11
Single lymph node extirpation	2	3
Neck dissection	3	4
Radiotherapy		
None	55	78
Adjuvant	15	21
Unknown	1	1

[a] The same patient can present with more than one symptom.

Recurrence, survival and prognostic factors

Treatment failure occurred in 9 (13%) of the 71 patients. Eight patients had locoregional recurrences exclusively (11%), out of which the majority ($n = 7$, 10%) were limited to the tumour site. Only one patient (1%) experienced distant recurrences, located to the lungs and bones, and this simultaneously with T- and N-failure. At the end of the last follow-up, 48 patients were alive. The median follow-up duration for all patients ($n = 71$) was 9.0 years (range 1.1–19.5 years) and for patients alive at the end of follow-up it was 10.0 years (range 4.0–19.5 years). Kaplan–Meier plots of OS, DSS and RFS are shown in Fig. 1. The 5- and 10-year OS rates were 89% and 73%, respectively. The DSS rates were markedly higher, as only one event occurred within the period, yielding 5- and 10-year DSS rates of 100% and 99%, respectively. The DSS curve stays flattened from here on until the end