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Salivary duct carcinoma and the concept of early carcinoma ex pleomorphic adenoma

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Aims: The data on the histological type of carcinomatous component and the extent of extracapsular invasion for salivary carcinomas ex pleomorphic adenoma (PA) are conflicting. We aimed to determine the prognostic value of extracapsular invasion in salivary duct carcinomas (SDC) ex PA.

Methods and results: A total of 117 patients with SDC were identified retrospectively; 44 cases involving major salivary glands had pre-existing PA (44 of 117, 37%). The morphological spectrum of SDC ex PA was characterized. The primary endpoint was overall survival (OS). Most SDC ex PA were widely invasive at presentation (27 of 44; 61%). Five patients with intracapsular SDC ex PA experienced no disease progression. The assessment of extracapsular invasion was precluded in eight cases (e.g. positive margins of resection). The rate of lymph node involvement was similar in cases with extracapsular invasion of ≤2 mm (two of three) and >7 mm (22 of 26). Only pT correlated with OS [116 months, 95% confidence interval (CI) 22–210 months for pT1 versus 20 months (95% CI 6–34) for pT4; $P = 0.013$].

Conclusions: Intracapsular SDC ex PA are potentially indolent. SDC ex PA with extracapsular invasion of ≤2 mm are rare, and appear to be clinically aggressive. Several histological parameters preclude assessment of extracapsular invasion.

Keywords: early carcinoma ex pleomorphic adenoma, minimal invasion, pT *in-situ* stage, salivary duct carcinoma

Introduction

Carcinoma ex pleomorphic adenoma (PA) is the most familiar model for tumour progression in the salivary glands. The common assumption is that carcinomas arise initially within a PA and, eventually, invade beyond the PA capsule.[1–5] While many carcinomas ex PA are frankly infiltrative at the time of resection, there are examples of carcinomas captured at a 'minimally invasive' or even 'intracapsular' phase of development. The term 'minimally invasive' was applied historically to carcinomas with 1.5–15 mm of invasion beyond the PA capsule, although the World Health Organization currently utilizes the former value.[6] The cut-off value of 1.5 mm intends to delimit carcinomas ex PA with an essentially benign behaviour. It is uncertain, however, whether 1.5 mm is the optimal cut-off and whether it is applicable to all histological types of carcinoma ex PA.

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It is clear that carcinoma ex PA is not a specific tumour type, but rather a class of tumours unified by its common precursor. In addition to the extent of invasion, selected reports on carcinomas ex PA have shown that histological category or grade of carcinoma ex PA may have prognostic value.[2,4,7]

Salivary duct carcinoma (SDC) is the most common type of carcinoma arising from PA. Given its high frequency and overall aggressive behaviour, SDC appears to be an appropriate model to evaluate the concepts of intracapsular disease and minimal invasion. Because the current understanding of 'early carcinoma ex PA' is essentially derived from studies that have combined all types of carcinoma ex PA, we hypothesized that the focus on a single histological type of carcinoma ex PA (i.e. SDC) would be of practical value. Thus, the goal of this study was to provide an in-depth characterization of the clinicopathological spectrum of SDC ex PA and to determine the prognostic value of the extent of extracapsular invasion.

Materials and methods

PATIENTS

Salivary duct carcinoma ex PA were identified by reviewing SDC from the authors' archives: from 1956 to 2013 from the University of Pittsburgh Medical Center (UPMC),[8] from 2002 to 2012 from the Virginia Mason Medical Center, from 2001 to 2012 from the University of Ottawa, and from 2003 to 2012 from the Southern California Permanente Medical Group (SCPMG). In 10 of 128 retrospectively identified SDC cases, only SDC metastatic to regional lymph nodes ($n = 9$) or distant metastasis ($n = 1$) were available for review, precluding evaluation of the primary SDC focus for pre-existing PA. Of the 118 SDC cases with available primary focus, 45 revealed pre-existing PA. Forty-four cases arose from major salivary glands. One case involving hard palate/maxilla was excluded as a minor salivary gland tumour.[7] Thus, 44 cases of SDC ex PA were included in the analysis (44 of 117; 37%).

HISTOLOGICAL EXAMINATION

All SDC were characterized by a malignant ductal proliferation of pleomorphic cells with eosinophilic cytoplasm, some with apocrine type secretions (apical 'snouts'), with solid, tubular and/or cribriform growth patterns. Pre-existing PA were recognized by benign epithelial ductal elements embedded in chondroid stroma or hypocellular eosinophilic hyalinized stroma/nodule[2,3,9] with myoepithelial cells.[3]

All sampling data were obtained from the gross description section of the original pathology reports. Nine cases were submitted entirely for microscopic examination (including four of five intracapsular SDC ex PA). At least one section per 1 cm of the overall tumour greatest dimension was submitted in all cases. The number of sections varied from three to 17 per case.

In the absence of invasion beyond the PA capsule, the case was categorized as 'intracapsular'. If basal/myoepithelial cells were recognizable on routine haematoxylin and eosin-stained sections and surrounded malignant ductal proliferation, the carcinoma was designated as 'intraductal'. The extent of extracapsular invasion was measured as described previously.[4,5] Briefly, using a $\times 2$ objective, a clear metric ruler was placed directly onto the glass slide. Point 'zero' was the PA capsule or condensed hyalinized stroma at the periphery of the PA. Measurements (in mm) were made perpendicular to the residual PA to the most distant point of the invasive front of the carcinoma. In addition to the above features, the growth pattern of pre-existing PA (i.e. multinodularity, as it complicates assessment of extracapsular invasion) and the primary or recurrent nature of the pre-existing PA were used to reconstruct the histological progression of SDC and to place every case into the morphological spectrum of SDC ex PA (Figure 1).

Tumours were staged according to the 7th edition of the American Joint Committee on Cancer (AJCC).[10] For staging purposes, size was based on the entire tumour including PA and SDC components. For outcome analysis, intracapsular/pT *in-situ* (pTis) cases were staged using the current AJCC recommendation based on tumour size, and intracapsular cases were categorized as pT1 ($n = 3$), pT2 ($n = 1$) and pT3 ($n = 1$). This study was approved by the Institutional Review Boards (UPMC, IRB no. PRO07050360; SCPMG, #5968).

STATISTICAL ANALYSIS

Five patients were followed for <2 months and were excluded from the outcome analysis (these patients were lost to follow-up and did not die in the immediate postoperative period). Follow-up of more than 2 months was available for 39 patients. Overall survival (OS) was assessed from the time of biopsy-confirmed diagnosis to death from any cause. Living

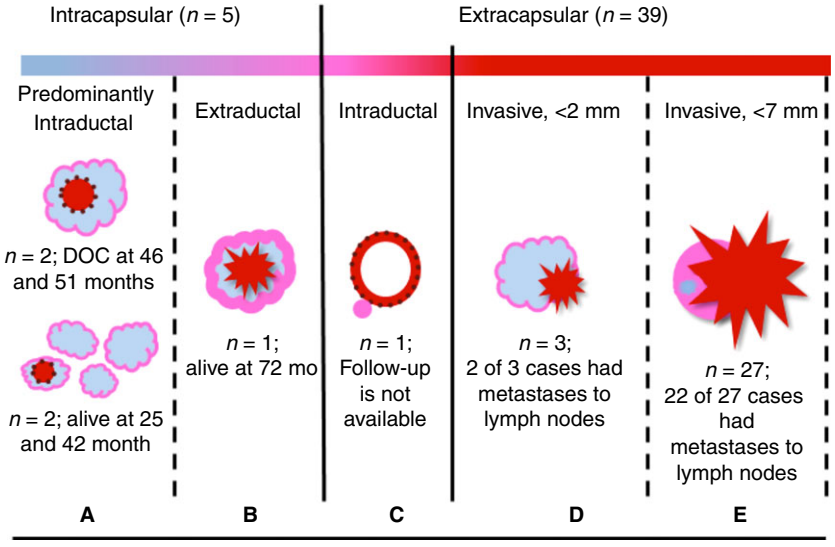

Figure 1. The morphological spectrum of salivary duct carcinomas arising in pleomorphic adenomas (SDC ex PA). SDC ex PA progress from intraductal/encapsulated to invasive (beyond the PA capsule). **A**, Intraductal and intracapsular SDC ex PA are rare and appear to have an indolent clinical course. The prognostic impact of multifocality in recurrent PA or multinodular growth in a subset of primary PAs is unclear. Intracapsular SDC ex PA are staged based on size, as 'pTis' is not in the current AJCC manual. **B**, Extraductal intracapsular SDC ex PA. Rarely, SDC ex PA show invasion beyond the layer of basal/myoepithelial cells of PA ducts but remain confined to the PA capsule. **C**, A single case of extracapsular intraductal cystic SDC ex PA with an adjacent hyalinized PA was identified. **D**, Three SDC ex PA presented with ≤2 mm of extracapsular invasion; however, two of these cases already had lymph node metastases. **E**, Most SDC ex PA are widely invasive at presentation. Lymph nodes were not evaluated in one case. Note: it was difficult to determine the extent of invasion in eight cases. Colour codes: bright red, SDC; light blue, PA; pink, hyalinized nodule; brown dots, basal cells. Abbreviations: DOC, died of other causes; mo, months.

patients were censored at the time of last clinical follow-up. Disease-free survival (DFS) was assessed from the time of biopsy-confirmed diagnosis to disease recurrence (e.g. local recurrence, distant metastasis) or death from disease. A *t*-test was used to characterize the relationship between quantitative variables, and Fisher's exact test to characterize the relationship between categorical variables. Median survival intervals with 95% confidence intervals (CI) were estimated using the Kaplan–Meier method, with statistical significance of differences between groups estimated by log-rank test. A *P*-value of <0.05 was defined as statistically significant. Statistical analysis was performed using SPSS version 21 (Somers, NY, USA).

Results

The study comprised 38 men (86%) and six women (14%). The median patients' age was 65 years (range 45–86 years). Forty-one cases (93%) developed in the parotid gland, and three in the submandibular gland. Only five cases (11%) developed in the recurrent pleomorphic adenoma. Additional parameters are summarized in Table 1.

MORPHOLOGICAL SPECTRUM OF SDC EX PA

The residual PA component was represented by chondroid stroma with benign ductal elements in 17 cases (mean size 25 mm; range 6–80 mm) or by a hyalinized nodule in 27 cases (mean size 7 mm; range 3–25 mm; $P = 0.19$) (Figure 1). The benign PA component comprised >50% of the overall tumour diameter in 10 of 44 cases (23%), including all five intracapsular SDC ex PA. Hyalinized PA stroma was present in the majority of extracapsular cases (31 of 39; 79%).

Four patients had intracapsular and predominantly intraductal SDC ex PA. There was one patient with intracapsular and predominantly extraductal SDC ex PA and one patient with extracapsular but intraductal cystic SDC ex PA. Tumours were submitted entirely for microscopic evaluation in five of the above six cases.

Three cases of SDC ex PA presented at an apparently early histological stage with extracapsular invasion of ≤2 mm: two cases had invasion of 0.5–1 mm (Figure 2) and invasion of 2 mm was identified in the third case. One of the three cases with ≤2 mm of extracapsular invasion was submitted entirely for

Table 1. Additional features of studied patients with salivary duct carcinoma ex pleomorphic adenoma

Clinical parameter	
Tumour size (range), mm	
Overall	27 (5–70)
Intracapsular, *n* = 5	20 (8–50)
Extracapsular, *n* = 39	28 (10–69)
	Number of patients
pT	
1	9/44
2	12/44
3	13/44
4	10/44
pN*	
0	7
1	6
2	22
Adjuvant therapy†	
Radiotherapy	19
Chemoradiotherapy	16

*Nine patients were cN0 and did not undergo neck dissection; none of these patients developed regional recurrence.
†All patients had surgery as primary treatment. Six patients received no adjuvant therapy and details of postoperative therapy were unknown for three patients.

microscopic examination. Angiolymphatic and perineural invasion were identified in two cases, with local invasion of ≤2 mm. Two of the three patients with SDC ex PA with ≤2 mm of extracapsular invasion presented with metastases to regional lymph nodes (level II in one case and levels Ia and II in another). The rate of regional lymph node involvement at presentation was similar in cases with extracapsular invasion of ≤2 mm (two of three) and >7 mm (22 of 26). Of note, there were no cases in which both the extent of extracapsular invasion could be measured precisely (see below), and was between 2 and 7 mm.

The exact extent of extracapsular invasion was difficult to assess in eight cases (of 39; 21%). The most distant point of the invasive front of carcinoma was impossible to assess in cases with positive margins of resection ($n = 4$) or when the invasive component was best appreciated in tissue sections distinct from tissue sections with recognizable PA ($n = 2$). Point 'zero' (the capsule of residual PA) is difficult to define in multinodular primary PA or multifocal recurrent PA ($n = 2$). Additionally, intraductal cancer extension (duct cancerization) without visible direct connection to invasive disease was noted.

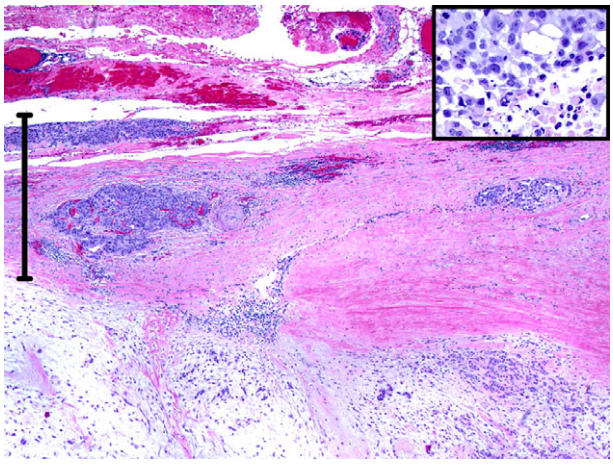

Figure 2. Salivary duct carcinoma arising in a pleomorphic adenoma with extracapsular invasion of approximately 0.5 mm. Right upper corner inset illustrates cytological details. H&E, size bar 0.5 mm.

The majority of SDC ex PA were unequivocally widely invasive (>7 mm, $n = 27$) at presentation.

OUTCOME ANALYSIS

Of 14 deceased patients, two died of causes unrelated to SDC (both patients had intracapsular SDC ex PA). Among 34 patients with extracapsular SDC and follow-up of >2 months, 16 patients developed progression of disease: locoregional recurrence ($n = 10$), distant metastases ($n = 5$) or both locoregional recurrence and distant metastasis ($n = 1$). None of the five patients with intracapsular SDC ex PA had disease progression (Figure 3); of note, two of these five patients received radiotherapy.

Of the three patients who presented with local extracapsular invasion of ≤2 mm, two patients were alive at 25 months and 108 months, respectively, while one patient died of disease at 16 months.

The estimated median overall survival (OS) was 78 months (95% CI 5–150 months). Pathological T stage correlated with OS ($P = 0.013$; Figure 3) with an estimated median OS for patients with pT1 tumours of 116 months (95% CI 22–210 months) and median OS of 20 months for patients with pT4 tumours (95% CI 6–34 months). When intracapsular tumours were combined into pTis, pT staging still

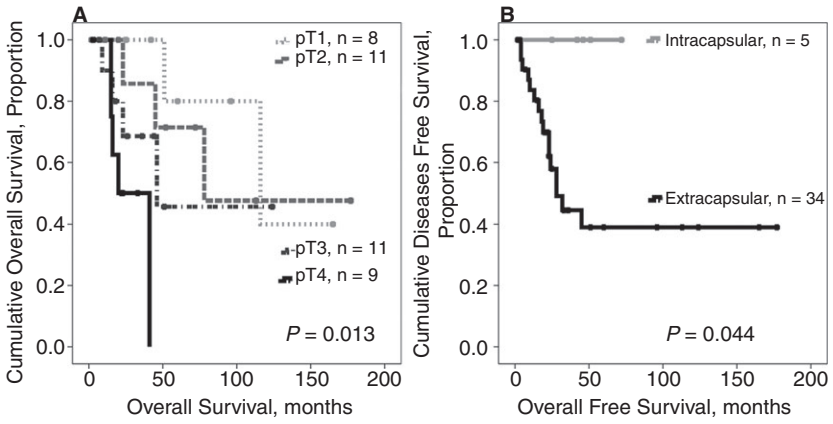

Figure 3. Salivary duct carcinomas arising in pleomorphic adenomas (SDC ex PA), outcome analysis. **A**, pT and overall survival. **B**, Disease-free survival of patients with intracapsular and extracapsular SDC ex PA.

correlated with OS ($P = 0.037$). Patients' gender, tumour size, pN, intracapsular versus extracapsular stage of histological progression, extent of extracapsular invasion (≤2 mm versus >7 mm) or primary versus recurrent nature of the pre-existing PA did not correlate significantly with OS.

The estimated median disease-free survival (DFS) time did not correlate significantly with patients' gender, pN, extent of extracapsular invasion (≤2 mm versus >7 mm) or primary versus recurrent nature of the pre-existing PA. As there were no recurrences among five patients with intracapsular SDC, median DFS time could not be computed.

Discussion

While conceptually attractive, the subcategories of intracapsular and early/minimally invasive carcinoma ex PA have not been studied extensively, given their relative rarity and histological variety.[1,7] The proportion of SDC arising in PA in this series (44 of 117, 37%) is comparable to another recent report.[11] As a subgroup, intracapsular and early invasive SDC ex PA are quite uncommon. Although not designed specifically to characterize the prevalence of early SDC ex PA, other reports lend some credence to the rarity of intracapsular and early invasive SDC ex PA.[12–15]

Decades following the introduction of the carcinoma ex PA concept, unsolved issues include the clinically 'safe' extent of extracapsular invasion, the relevance of the histological type/grade of the carcinomatous component, and the significance of the primary or recurrent nature of the pre-existing PA.[1,4,5,7,16,17]

Previous studies on the extent of invasion included few or no SDC and the definition of 'minimally invasive' carcinoma ex PA has varied from 1.5 to 15 mm of extension beyond the capsule of pre-existing PA (Table 2).[3–5,7,12–15,18,19] Some studies have shown that the specific histological category or grade of the carcinomatous component in carcinomas ex PA may correlate with outcome.[2,4,7] For instance, Tortoledo *et al.*[4] showed that histological grading (high- versus low-grade) correlated with clinical course. More recent studies compared myoepithelial carcinomas ex PA to non-myoepithelial ones and arrived at varying

Table 2. Summary of studies on salivary duct carcinoma ex pleomorphic adenoma (SDC ex PA)

SDC ex PA cases, *n*	Extent of invasion	Reference
25	IC/MI, *n* = 9; WI, *n* = 16	2
24	NR	3
19	NR	15
14	EC, *n* = 13	12
13	NR*	4
4	NR†	19
3	Invasive, NOS	13
1	At least 22 mm‡	5
1	NR	14

IC; Intracapsular; MI: minimally invasive; WI: widely invasive; EC: extracapsular; NR: not reported specifically for salivary duct carcinomas; NOS: not otherwise specified.
*There were no intracapsular cases in this series; SDC arising from minor salivary glands were included.
†All patients presented with regional lymph node metastases and two patients had distant metastases.
‡Arose in recurrent PA; patient died of disease at 56 months.

conclusions.[2,5] It was also shown that the primary or recurrent nature of the pre-existing PA might have prognostic significance. Weiler *et al.*[5] showed that carcinomas ex recurrent PA were associated with lower survival compared to carcinomas ex primary PA. We hypothesized that the above controversies might be best resolved by a study of salivary carcinomas ex PA with single histology and limited to carcinomas arising in major salivary glands. In this series we provide morphological details of the quintessential carcinoma ex PA, namely SDC ex PA. The advantage and limitation of our study is its focus on this single histological subtype. However, this focus removes the confounding heterogeneity of behaviour displayed by other tumour types. Furthermore, it can be argued that SDC is the tumour type for which the clinical stakes are highest in terms of an optimal cut-off for defining potentially indolent behaviour in an otherwise aggressive disease.

Our findings indicate that intracapsular SDC ex PA appear to have an indolent clinical course. The five patients with encapsulated SDC ex PA lacked regional spread and showed no subsequent disease progression. One caveat is that two of five patients in this category were treated with adjuvant radiotherapy, precluding a confident statement on the natural course of intracapsular SDC ex PA with resection alone. None the less, this prognostic information lends support for formal recognition of a 'pTis' category for intracapsular SDC ex PA, as has been advocated by other authors.[5]

In contrast to intracapsular SDC ex PA, 'early' invasive SDC ex PA are even more rare and only two cases fulfilled the WHO criteria for minimal invasion (<1.5 mm). More importantly, the few patients who appeared to have limited local invasion presented with angiolymphatic and/or perineural invasion and metastases to regional lymph nodes, questioning the concept of minimal or early invasion in SDC ex PA. It appears that while confinement to the PA capsule has a protective effect, once the capsule is breached the intrinsic aggression of SDC manifests itself. Thus, for defining minimal or early invasion in carcinomas ex PA, histological subtype might matter. Even if a category of 'minimal' invasion were entertained, the presence of perineural and/or angiolymphatic invasion should probably disqualify such tumours from this category.

We encountered several practical challenges in characterizing the extent of invasion. While trying to place each tumour into the continuum of histological progression (Figure 1), several limitations emerged. For instance, the concept of 'minimally invasive' carcinoma ex PA was previously deemed inapplicable to salivary carcinomas arising from minor salivary glands due to the general lack of encapsulation, and to cases in which extent of invasion could not be assessed accurately (e.g. positive margins).[7] Difficulties in defining the outer border of the PA were also recognized (i.e. multifocality, multinodular growth).[2] Fragmented specimens, malignant transformation extending into pseudopodia, discontinuous or incomplete encapsulation, variation in patterns of capsular invasion (single point of capsular penetration versus broad invasive front) and duct cancerization might further complicate the measurements of extracapsular extension. In our opinion, measurements within 1 mm precision are impractical in most cases of SDC ex PA.

A perpetual limitation in essentially every study, including this one, is that the ideal standard of tumour capsule submission *in toto* is not reached in every case. Practically, if diagnoses of intracapsular or 'minimally invasive' SDC were considered, it would mandate microscopic examination of the entire tumour capsule.[7]

In summary, we would like to strongly encourage the formal recognition of pTis in the staging system to reflect the potentially indolent course of intracapsular SDC ex PA and to facilitate further studies. As several histological parameters preclude accurate assessment of invasion, and SDC ex PA with extracapsular invasion of ≤2 mm are clinically aggressive, it appears that the concept of 'minimal invasion' is not applicable to SDC ex PA. Future studies on extracapsular invasion should be specific to the histological type of carcinoma ex PA.

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Conflict of interest

None declared.

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