Polymorphous Low-Grade Adenocarcinoma

The University of Pittsburgh Experience

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Objective: To reappraise the clinical and histologic variables associated with a more aggressive outcome in polymorphous low-grade adenocarcinoma (PLGA).

Design: Retrospective cohort.

Setting: University hospital.

Patients: Twenty-four patients with PLGA treated from January 1, 1973, through December 31, 2005.

Main Outcome Measure: Analysis of clinical and pathologic variables in 30 biopsy or resection specimens from 24 patients.

Results: Only 4 PLGAs were not initially diagnosed as such. However, 8 non-PLGAs (thus excluded) were incorrectly diagnosed as PLGA. Most carcinomas (14 of 24 [58%]) were palatal. Recurrent carcinomas had a significantly higher mitotic rate (2.7 mitoses per 10 high-power fields) compared with primary tumors (1.2 mitoses per high-power fields, \(P = .046\)), and 3 of 7 (43%) recurrences showed progression to an intermediate-grade histologic type. No patient died of disease. Median disease-free survival was 12.8 years. Four of 24 patients (17%) had regional lymph node metastases, 3 with carcinomas of the base of the tongue. One PLGA metastasized to the subcutaneous tissue of the face, orbit, and lungs at 19.6 years. An extrapalatal site was the only significant determinant of disease-free survival \((P = .03)\).

Conclusions: Diagnosis of PLGA remains a challenge. Extrapalatal carcinomas appear to behave in a more aggressive fashion than those of the palate, and cancer arising from the base of the tongue frequently metastasizes to the cervical lymph nodes, suggesting a role for neck dissection in these patients. Recurrent cancers show evidence of histologic progression, justifying an aggressive approach to achieving initial complete excision.


The term polymorphous low-grade adenocarcinoma (PLGA) was introduced by Evans and Batsakis\(^1\) in 1984 to describe a cytologically bland but architecturally diverse malignant neoplasm of minor salivary gland origin that had been previously recognized as lobular carcinoma,\(^2\) terminal duct carcinoma,\(^3\) and low-grade papillary adenocarcinoma.\(^4\) Despite the fact that this term has existed for nearly 25 years, PLGA remains a diagnostic challenge.\(^5\) Although originally described as cancer of a minor salivary gland origin in the oral cavity, PLGA has also been described at several sites outside the oral cavity, including major salivary glands.\(^6, 8\) Polymorphous low-grade adenocarcinoma should be thought of as distinct from adenoid cystic carcinoma, a common differential diagnostic consideration, because of the more relentless and aggressive behavior of the latter.\(^6\) However, with sufficient long-term follow-up,\(^10\) the recurrence rate for PLGA is high at almost 33%, and distant metastasis or even transformation to a high-grade adenocarcinoma\(^11, 12\) has been noted. The surprisingly aggressive behavior of these adenocarcinomas in some of our patients despite the term low grade prompted the present study.

Perhaps the oldest controversy is whether to consider papillary predominant carcinomas as variants of PLGA or as separate tumors altogether.\(^10, 13, 14\) Regardless of classification, predominantly papillary cancers have been reported to have a more aggressive biological behavior, although this has been validated in only 1 series.\(^10\) Despite the reported frequent occurrence of these tumors,\(^10, 17\) large series in which patients were treated at a single institution are rare.\(^5, 7, 10\) To reappraise and validate prior findings and concepts, we present the clinicopathologic findings of our PLGA cohort.

METHODS

The Head and Neck Oncology Registry of the University of Pittsburgh School of Medicine.
Pittsburgh, Pennsylvania, was assessed retrospectively. This review was approved by the University of Pittsburgh institutional review board. All patients classified as having PLGA were reevaluated by one of us (R.R.S.). Material from patients treated in our institution from January 1, 1973, through December 31, 2005, was available. For patients who presented after the recognition of PLGA at our institution (in 1985), the search terms used included the following: polymorphous low-grade adenocarcinoma; adenocarcinoma, not otherwise specified (NOS); papillary adenocarcinoma; and cribriform adenocarcinoma of tongue. For patients who presented before the use of the term PLGA, search terms included the following: adenocarcinoma, papillary adenocarcinoma, adenoid cystic carcinoma, terminal duct carcinoma, pleomorphic adenoma, and monomorphic adenoma.

The histologic definition of PLGA used for inclusion in this study was a modification of the World Health Organization definition, with additional descriptors derived from the histologic variables gathered from previous series: a monophasic malignant salivary gland adenocarcinoma with polymorphous growth patterns (tubular, cribriform, papillary and/or solid), but bland, monomorphic cytonuclear features including characteristic ovoid nuclei with open vesicular chromatin. Carcinomas arising in the major salivary glands, pharynx, and palate, 14 (hard palate, 9; and soft palate, 5); base of the tongue, 3; nasopharynx, 3; upper lip, 2; tonsil, 1; and parotid, 1.

Gross and histologic variables were recorded. The solid and papillary (because of its reported importance) components were evaluated as separate variables in all patients and estimated to the nearest fifth percentile. Mitotic counts were recorded as number per 10 high-power fields (HPF) (×40 microscopic objective lens). Other oncologically relevant histologic variables, including the status of the margins of resection, perineural invasion (PNI), angiolymphatic invasion (ALI), and bone invasion, were recorded as well. For patients with PNI, the presence of intraneural invasion or large nerve PNI was also recorded. A large nerve was defined arbitrarily as a nerve with a cross-sectional diameter of 0.25 mm or larger (roughly half of 1 HPF, ×40 microscopic objective lens). These histologic variables were linked with clinical and demographic data, including age at diagnosis, sex, treatment, lymph node status, locoregional recurrence, distant metastasis, and survival.

Statistical analyses were performed using SPSS statistical software, version 14.0 (SPSS Inc, Chicago, Illinois). For papillary components, solid percentiles, and mitotic indices, the non-parametric Mann-Whitney test was used for comparison between the 2 groups. For comparison of frequencies of categorical variables between groups, a Fisher exact test was used with a 2-tailed distribution. Overall survival was reported descriptively, and the arithmetic median survival was used. Disease-free survival (DFS) was assessed using the Kaplan-Meier method with groupwise comparisons made via a univariate Cox proportional hazards model. The Kaplan-Meier median (the time at which 0.5 patient remained disease free) was reported. P < .05 was considered statistically significant.

RESULTS

INITIAL DIAGNOSIS

Twenty-eight patients were initially diagnosed as having PLGA. Eight of 28 patients diagnosed as having PLGA (29%) were excluded from this study. Their tumors did not fulfill our definition of PLGA and were compatible with other specific salivary gland malignant neoplasms in 5 patients. Diagnoses for these patients included 3 epithelial-myoepithelial carcinomas (Figure 1); 3 low-grade to intermediate-grade adenocarcinomas, NOS; 1 adenoid cystic carcinoma; and 1 low-grade salivary duct carcinoma (also known as low-grade cribriform cystadenocarcinoma). The low-grade salivary duct carcinoma was seen at our institution before the description of this entity in 1996.18

Four additional patients treated at our institution were not initially diagnosed as having PLGA but, on review, fulfilled the criteria for PLGA. Three of these 4 patients (75%) had their conditions diagnosed before 1984, the year the term PLGA was first used. The original diagnoses for these patients included 1 adenocarcinoma, NOS; 1 pleomorphic adenoma; 1 monomorphic adenoma; and 1 mucoepidermoid carcinoma. Thus, in total, 24 patients were satisfactorily diagnosed as having PLGA.

Fourteen of these 24 patients were initially diagnosed as having PLGA at outside institutions. Of these, 6 (43%) were diagnosed as having PLGA, whereas other diagnoses were 4 adenocarcinomas, NOS; 2 adenoid cystic carcinomas; 1 mucoepidermoid carcinoma; and 1 pleomorphic adenoma.

CLINICAL AND DEMOGRAPHIC FEATURES

The mean age at diagnosis was 59.4 years (range, 26-85 years). There was a female predilection with a female to male ratio of 2.4:1.0. The site distribution was as follows: palate, 14 (hard palate, 9; and soft palate, 5); base of the tongue, 3; nasopharynx, 3; upper lip, 2; tonsil, 1; and parotid, 1.

PATHOLOGIC FEATURES: PRIMARY TUMORS

The slides and reports from the primary cancers, including cancers originally diagnosed at an outside hospital,
were available in 23 of 24 patients; 1 patient had only the recurrences available for review. A gross measurement of tumor size was available in 16 patients. The mean size of the tumor was 2.4 cm (range, 1.1-6.8 cm). The mean size of extrapalatal tumors (3.6 cm; range, 2.2-6.8 cm) was significantly greater than that of palatal tumors (1.4 cm; range, 1.1-1.8 cm) \( (P = .01) \).

Margin status was available in 20 patients. Final margins (even after reexcision of initially positive margins) were positive in 9 patients (45%) (palate, 5; nasopharynx, 2; base of the tongue, 1; and parotid, 1). Gross and/or microscopic bone invasion was present in 6 of 23 primary tumors (26%) overall. All 3 nasopharyngeal PLGAs invaded bone (Figure 2A), whereas 3 of 13 primary palatal tumors (23%) invaded bone.

Overall, PNI was identified in 12 of 23 tumors (52%) (Figure 2B). Relative frequencies based on site are as follows: palate, 8 of 14 (57%); upper lip, 1 of 2 (50%); base of the tongue, 1 of 3 (33%); nasopharynx, 1 of 3 (33%); and parotid, 1 of 1 (100%). Seven of 12 PLGAs with PNI (58%) showed large nerve involvement: palate, 3; base of the tongue, 1; nasopharynx, 1; upper lip, 1; and parotid, 1. Three of 12 tumors with PNI (25%) showed intraneural invasion (palate, 2; and parotid, 1). Angiolymphatic invasion was identified in 7 of 23 patients (30%) overall (Figure 2C). Site distribution was as follows: base of the tongue, 3 of 10 (30%); upper lip, 2 of 2 (100%); nasopharynx, 1 of 3 (33%); and palate, 1 of 13 (8%). The 1 parotid tumor in this study did not show angiolymphatic invasion.

Palatal PLGA had a slightly higher prevalence of PNI (58%) than extrapalatal PLGA (40%). Extrapalatal carcinomas had a significantly higher prevalence of ALI (60%) than those of the palate (8%) \( (P = .02) \). The mean mitotic count for primary PLGA was 1.3 per 10 HPF (range, 0-3.0 per 10 HPF). Mean mitotic counts for palatal PLGA (1.2 per 10 HPF) were similar to those for extrapalatal PLGA (1.3 per 10 HPF).

All carcinomas showed a mixture of tubular, cribriform, and papillary growth patterns (Figure 3A-C). The mean solid component (Figure 3D) overall was 47% (range, 0%-90%). Extrapalatal PLGA had only a slightly higher mean solid component (49%) than palatal PLGA (45%). The mean papillary component overall was 11%, although the range was wide (0%-90%). Extrapalatal PLGA had a slightly higher mean papillary component (18%; range, 0%-90%) than palatal PLGA (6%; range, 0%-40%). These differences were not statistically significant. However, more specific subsite stratification was not attempted because of the small sample size. Nevertheless, descriptively, all PLGAs of the base of the tongue were predominantly solid and papillary and showed by far the highest mean papillary composition (47%; range, 20%-90%) of all sites. All nasopharyngeal PLGAs were predominantly solid to cribriform with only focal papillary areas (mean, 13%; range, 10%-20%). Carcinomas with ALI had a significantly higher percentage of papillary areas (mean, 30%; range, 0%-90%) than those without (mean, 3%; range, 0%-20%) \( (P = .003) \). All carcinomas with more than 20% papillary areas showed ALI. No significant correlations were noted between solid and papillary percentage and PNI of any type or bone invasion.

**PATHOLOGIC FEATURES: RECURRENCES**

Seven of 24 patients (29%) had a local recurrence. Three patients had regional recurrences in cervical lymph nodes (13%), 2 of whom had local recurrences as well, yielding a total locoregional recurrence rate of 33% (8 patients). Slides of these recurrences were available in 7 of 8 patients, from whom 6 paired primary tumors were also available. The mean percentage of solid...
areas in recurrent disease was similar to primary disease (46%; range, 20%-80%). The mean percentage of the papillary component was, however, increased (26%; range, 0%-70%) in recurrence disease, although this difference was not significant. Mean mitotic counts were, however, significantly higher in recurrent disease (2.7 per 10 HPF; range, 1-5 per 10 HPF) \((P = .046)\). In addition, 3 of 7 recurrent cancers showed evidence of histologic progression to an intermediate-grade morphologic type (Figure 4). These 3 patients constituted the higher end of the mitotic range in recurrent cancers (mean, 3.7 per 10 HPF; range, 3-5 per 10 HPF), with 1 patient even showing atypical mitoses. No recurrent disease had high-grade transformation based on criteria reported previously.12

TREATMENT, OUTCOME, AND CLINICOPATHOLOGIC CORRELATIONS

Nineteen patients received primary treatment within our health care system. The other 5 were initially treated elsewhere. Initial treatment included surgery in 19 patients, surgery and adjuvant radion therapy in 4 patients, and radion therapy alone in 1 patient.

One patient was lost to follow-up. Seven of 22 patients (32%) died (median time, 13.7 years; range, 1.2-16.3 years), but no deaths were attributed to PLGA. Median follow-up on surviving patients was 6.6 years (range, 2.7-35.1 years). As noted herein, the locoregional recurrence rate was 33% (8/24), with a median DFS of 12.8 years. Four of 24 patients (17%) had lymph node metastases, 1 on presentation and 3 as regional recurrences as mentioned herein. One patient with the palate as the primary site had a recurrence on the soft palate 7 years later and metastases to the subcutaneous tissues of the face, orbit, and lungs at 19.6 years (Figure 5).

Univariate correlations with DFS are summarized in the Table. Site was the only significant determinant of DFS in this small series \((P = .03)\). Although patients with positive margins, large nerve PNI, bone invasion, and a high percentage of papillary component showed a shorter DFS, differences were not statistically significant.

COMMENT

Polymorphous low-grade adenocarcinoma remains a challenge in diagnosis and management almost a quarter-
century after its initial description. However, our series demonstrates an improved awareness of PLGA as a diagnostic entity. Only 4 PLGAs were initially diagnosed as another entity by us, and 3 of these were diagnosed before the description of this entity in 1984. This increased awareness is also reflected in the original diagnoses from outside institutions in which almost half were correctly identified as PLGAs, which is an improvement compared with the 22% reported by Pogodzinski et al.

In contrast, however, another challenge has emerged: more than one-fourth of the patients originally diagnosed as having PLGA actually had other salivary gland malignant neoplasms. Thus, we report for the first time, to our knowledge, a more frequent overdiagnosis of this entity rather than the underdiagnosis that is traditionally reported. Our analysis of this series demonstrates 2 fundamental patterns of error. The first is the failure to differentiate truly biphasic tumors (namely, adenoid cystic carcinoma and epithelial-myoepithelial carcinomas) from PLGAs. Although the PLGA has a multitude of patterns, it is a monophasic tumor. Although myoepithelial differentiation in PLGA is described, transition to these areas is subtle and gradual, typically only discernible focally on immunohistochemical stains. In contrast, a luminal ductal and abluminal myoepithelial configuration is integral to adenoid cystic carcinoma and epithelial-myoepithelial carcinoma and is typically evident on routine histologic examination. The second pattern of error is the failure to recognize the characteristic nuclear features of PLGA. All cancers reclassified as adenocarcinoma, NOS did not have the monomorphic ovoid and open nuclei with delicate nuclear membranes that essentially define PLGA. To prevent these errors, we suggest that the monophasic nature and classic nuclear features of PLGA be emphasized in the working definition for this entity. The remaining patient misdiagnosed as having a PLGA had a low-grade salivary duct carcinoma, which was not recognized as a distinct entity until the description by Delgado et al in 1996. Of note, three-quarters of these tumors erroneously diagnosed as PLGA were of parotid gland origin, suggesting that true parotid PLGAs are indeed rare.

For the remaining cancers in the PLGA category, findings were generally in keeping with prior series. Despite the innocuous name, PLGA is indeed a malignant neoplasm of salivary gland origin that, in our series,
showed a locoregional recurrence rate of more than 30%. Lymph node metastases were uncommon, and distant metastases were rare. Primary treatment was surgical. Because few patients received initial radiotherapy, the impact of this treatment modality is unclear. However, our limited findings of recurrence despite radiotherapy suggest it is likely of little benefit, as noted in prior series.15 Similar to what has been reported previously, PLGA in our series most commonly occurred in the palate. However, the site distribution was slightly skewed toward unusual locations, such as the base of the tongue and the nasopharynx, probably because ours is a tertiary care center. These extrapalatal PLGAs appeared to display more aggressive features, clinically and pathologically.

Our subset of 3 patients with PLGA of the nasopharynx represents the largest series to date. Skeptics may suggest that our patients have nasopharyngeal papillary adenocarcinomas, which are distinct carcinomas not included in the PLGA family.20 However, all our patients had disease that fulfilled the morphologic criteria we delineated herein and, in addition, did not have papillary-predominant disease. These cancers characteristically invaded bone and invariably recurred locally. Clear margins could not be obtained in any patients in which the original margin status was known, which likely contributed to this high recurrence rate. Two patients received radiotherapy but nevertheless experienced disease recurrence. Although any conclusions about nasopharyngeal PLGAs are limited based on these few patients and those described previously,8 PLGAs arising in the nasopharynx are still intrinsically low grade with low metastatic capacity. Because of the propensity of these tumors for bone involvement and the limited surgical exposure and anatomic limitations, these tumors remain a challenge in surgical management. Radiotherapy is currently of unproven benefit.

The PLGAs that arise in the base of the tongue also represented an interesting subset. Michal et al21 suggested that cribriform adenocarcinoma of the tongue was a more appropriate designation for their series of 8 carcinomas of the base of the tongue that were initially diagnosed as PLGA. The authors’ justification was that the solid and microcystic cribriform pattern was sufficiently unique to recognize even without site designation and that these tumors, unlike PLGAs, invariably metastasized to lymph nodes. In our 3 patients, a solid and papillary architecture was the norm. In addition, we found no histologic novelty in the patterns seen in tumors in the base of the tongue compared with other sites. Similar to cribriform adenocarcinomas of the tongue, however, all patients showed lymph node metastases on presentation or as regional recurrences. Because none of our patients’ conditions fit the description of cribriform adenocarcinoma of the tongue, we cannot confirm or refute the validity of this entity. However, we contend that it is the site of origin of the base of the tongue that im-

<table>
<thead>
<tr>
<th>Variable</th>
<th>Hazard Ratio (95% CI)</th>
<th>P Value</th>
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<tr>
<td>Site (palatal vs extrapalatal)</td>
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<tr>
<td>ALI</td>
<td>5.22 (0.98-27.89)</td>
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<td>Margin status</td>
<td>4.48 (0.46-43.43)</td>
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<tr>
<td>Large nerve PNI</td>
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<td>.40</td>
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<td>Bone invasion</td>
<td>1.71 (0.38-7.67)</td>
<td>.48</td>
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<tr>
<td>Papillary component</td>
<td>1.01 (0.99-1.03)</td>
<td>.41</td>
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Abbreviations: ALI, angiolymphatic invasion; CI, confidence interval; PNI, perineural invasion.

Figure 5. One patient with the palate as the primary site had a recurrence on the soft palate 7 years later and metastases to the subcutaneous tissues of the face, orbit, and lungs at 19.6 years. A, Computed tomogram demonstrating multiple pulmonary nodules (arrows point to right and left lung nodules). B, Fine needle aspiration biopsy specimen demonstrated metastatic polymorphous low-grade adenocarcinoma to the lung (Papanicolaou, original magnification ×400). This cluster of cells shows the characteristic ovoid nuclei with delicate chromatin.
parts the propensity for lymph node metastasis rather than the tumor morphologic type. This is not a unique concept because squamous cell carcinoma of the base of the tongue with its rich lymphatic network has a relatively high propensity for lymph node metastases. Other salivary gland carcinomas involving the base of the tongue may also have an aggressive course. From a practical standpoint, current evidence suggests that a cancer of the base of the tongue in the PLGA family, regardless of its name, will metastasize to cervical lymph nodes. The fact that most of the lymph node metastases in our series were found as recurrence suggests that they were occult. An elective neck dissection should be performed even in a clinically node-negative patient with a PLGA of the base of the tongue.

Evaluations of prognostic markers in PLGA are difficult based on the numbers available in most series, including our own. In addition, many of these variables are likely interdependent. For instance, we found that all PLGAs with papillary components comprising greater than 20% of tumor showed ALI. As noted herein, the distinction between palatal and extrapalatal sites appears to affect outcome the most. Positive margins and bone invasion affected DFS, but the differences were too small to be significant in this series. Similarly, although ALI, papillary-dominant histologic type, and PNI predicted a shorter DFS, none of these factors were statistically significant, perhaps in a larger series similar to that of Evans and Luna, statistical significance; for these variables may be reached.

Similar to primary PLGA, recurrences are typically slow growing and often amenable to reexcision with subsequent favorable outcomes. Only 1 patient in our series had multiple recurrences and a distant metastasis. According to the literature, distant metastases are exceptionally rare, with the lung being the most common site involved. Metastases usually occurred only after poor local control. Although biologically, recurrent tumors appear to retain their indolence, pathologic features of recurrent PLGA have not been well characterized. Cases of transformation to a high-grade adenocarcinoma have been reported, suggesting the capacity for histologic progression, but this appears to be a rare event; no carcinomas in our series fit this description. However, we noticed that almost half of the recurrences in our series progressed to an intermediate-grade morphologic type with more nuclear size variation, nucleolation, and an overall higher mean mitotic rate. Of note, the 1 patient with lung metastases had been preceded by 2 local recurrences during a 19-year period with intermediate-grade morphologic type. Thus, the potential for histologic progression is a legitimate concern in disease recurrences. Because adjuvant therapy is unproven at best, adequate surgical excision even of recurrent disease may be the only useful safeguard against high-grade transformation.

In summary, familiarity with PLGA has increased during the past few decades, although now the current diagnostic challenge may be the prevention of this entity from becoming a default diagnosis for all low-grade carcinomas of salivary gland origin. Although polymorphous in pattern, this carcinoma is actually cytologically monotypic with pathognomonic delicate vesicular nuclei. Polymorphous low-grade adenocarcinoma may follow an indolent course with a favorable outcome, although with adequate follow-up, recurrence may be encountered in almost one-third of patients. This finding suggests the need for lifelong monitoring. Limited experience with radiotherapy fails to support its usefulness.

Extrapalatal PLGAs, particularly those of the base of the tongue and nasopharynx, appear to be more aggressive, and carcinomas of the base of the tongue may present with cervical lymph node metastases. Our patients demonstrate sufficient morphologic overlap to suggest that site-specific differences in PLGA behavior may have an anatomic basis (with regard to resectability and access to lymphatics) rather than a taxonomic one. Carcinomas with positive margins, bone invasion, papillary-dominant growth, and/or ALI may be more aggressive as well, although the size of our series probably prevented these variables from achieving statistical significance. Almost half the recurrent PLGAs showed some degree of histologic progression, supporting the importance of adequate excision of even recurrent disease to prevent the rare but catastrophic outcome of high-grade transformation.

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Author Contributions: All authors had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Seethala, Johnson, Barnes, and Myers.

Acquisition of data: Seethala.

Analysis and interpretation of data: Seethala and Johnson.

Drafting of the manuscript: Seethala.

Critical revision of the manuscript for important intellectual content: Seethala, Johnson, Barnes, and Myers.

Study supervision: Johnson and Barnes.

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