Exophytic and papillary squamous cell carcinomas of the larynx: A clinicopathologic series of 104 cases

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Exophytic and papillary squamous cell carcinomas (SCCs) are uncommon variants of SCC of the upper aerodigestive tract mucosa. The histomorphologic distinction between these variants has not been previously attempted or correlated with prognostic outcome. One hundred four cases of exophytic and papillary SCCs of the larynx were identified in the files of the Armed Forces Institute of Pathology from 1971 to 1991. The patients included 25 women and 79 men, aged 27 to 89 years (average 60.7 years). Patients had hoarseness at presentation, and many patients were using tobacco (n = 87) and/or alcohol (n = 49). Tumors measured up to 6 cm in greatest dimension. The larger tumors were associated with vocal cord impairment (n = 39). Histologically, the SCCs were divided into 2 growth patterns: papillary-frond (n = 12) or broad-based, exophytic (n = 92). Patients were treated with excisional biopsy, vocal cord stripping, and/or laryngectomy, in conjunction with radiation therapy (n = 70). Eighty-seven patients had no evidence of disease at last follow-up (average follow-up 8.6 years). Seventeen patients with an exophytic pattern died with disease (10 disseminated disease; 7 local disease). No patients with papillary patterns died of disease, although there had been 4 recurrences. In conclusion, patients with papillary and exophytic SCCs have a better prognosis than those with conventional SCCs, and the prognosis for those with papillary SCCs is even better. (Otolaryngol Head Neck Surg 1999;120:718-24.)

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Squamous cell carcinoma (SCC) is generally divided into 3 histologic categories: in situ, superficially invasive, or deeply invasive with additional modifiers based on histologic grade, including well, moderately, or poorly differentiated. With the exception of the unique histomorphologic and clinical parameters associated with a verrucous carcinoma,[1-3] limited distinction has been made between the various patterns of exophytic and papillary growth identified in SCC, especially when correlated to treatment, clinical outcome, or prognosis.[4]

With this study we will try to define exophytic and papillary growth patterns in SCC and combine this histologic architectural pattern with an analysis of the clinical presentation, treatment, and clinical outcome. We believe a set of histologic criteria can be used to identify exophytic and papillary patterns in SCC, which have a better clinical outcome when compared with other SCCs, not otherwise specified, of a similar stage.

METHODS AND MATERIAL

One hundred four SCCs of the larynx with a predominantly exophytic or papillary growth pattern were identified in the files of the Otorhinolaryngic Tumor Registry at the Armed Forces Institute of Pathology. Exophytic or papillary growth patterns accounted for 104 of 1450 (7.2%) of our laryngeal SCC consultation cases and 3.9% of all primary laryngeal tumors (104 of 2683). Ninety-four cases were obtained from civilian sources, 7 from military hospitals, and 3 from Veterans Administration hospitals.

Inclusion in this study required the neoplastic proliferation of the larynx to demonstrate a dominant (greater than 70%) exophytic or papillary architectural growth pattern with unequivocal cytomorphologic evidence of malignancy. By definition, SCC can be ulcerative, flat, polypoid, verrucous, or exophytic. All of the cases were de novo malignancies; none of the cases was associated with a preexisting or coexisting benign tumor (ie, papilloma). All tumors were classified according to the American Joint Committee on Cancer staging and end results reporting TNM classification.[5] Reactive inflammatory hyperplasia, squamous papilloma, verruca vulgaris, verrucous hyperplasia, and verrucous carcinoma were excluded. Also, adequate demographic and clinical follow-up data had to be available: materials in the files of the Armed Forces Institute of Pathology were supplemented by review of the clinical records, admitting history and physical examina-

Table 1. Clinical characteristics

Characteristic	Exophytic pattern (n = 92)	Papillary pattern (n = 12)
Females/males	22/70	3/9
Age (yr)*	27-89 (60.9)	30-74 (50.5)
Caucasians/Aftrican-Americans	78/9	11/1
Nonsmokers	16	2
Smokers	77	10
Alcohol users	44	5
Duration of symptoms (mo)*	1-240 (10.3)	1-240 (41.8)
Size (cm)*	0.3-6.0 (1.43)	0.5-2.5 (1.1)

*Data expressed as range (average).

tion, laryngoscopy findings, and by specific questionnaires. Hematoxylin and eosin–stained slides were available in all cases and were reviewed. Follow-up information, for periods ranging from 3 to 23 years, was obtained in all cases. Tumors were defined as metachronous if they recurred at the original site of the reference tumor, with metastatic disease defined as SCC identified in lymph nodes or distant organs.

In 41 cases a sufficient number of unstained slides were available to perform in situ hybridization for human papillomavirus (HPV). The slides were deparaffinized, dehydrated, and digested with proteinase K solution followed by application of the specific probe before the slides were denatured at 90°C to allow hybridization. After posthybridization wash, immunohistochemistry was performed with the standard ABC method of Hsu et al[6] (mouse monoclonal, 1:2000 dilution; Dako, Carpinteria, CA) followed by the biotinylated anti-mouse IgG vector. The hybridization products were visualized with diamino-benzidine. Slides were counterstained with Mayer's hematoxylin. Probes were to HPV 6, 11, 16, 18, 31, 33, and 51 (mouse monoclonal; Enzo Diagnostics, Farmingdale, NY). Appropriate positive controls were performed in all cases.

RESULTS

Clinical

The patients included 25 women (24%) and 79 men (76%) (Table 1). Their ages ranged from 27 to 89 years, with a mean age at presentation of 60.7 years. Eighty-nine patients (86%) were Caucasians, and 10 (9.6%) were African-American; in 5 the race was unknown. Eighty-seven patients (83.7%) had a history of tobacco use (almost exclusively cigarettes), and 49 patients (47%) acknowledged alcohol use, with 40 patients (38.5%) admitting to moderate or heavy use. The alcohol use was unknown in 14 patients.

The most common presenting symptoms were phonation problems, including hoarseness and husky voice. Other symptoms included dysphagia, sore throat, cough, and/or hemoptysis. The duration of symptoms ranged from 1 to 240 months for all cases (average 13.9 months). Patients with the exophytic pattern had a shorter duration of symptoms (average 10.3 months), whereas those with the papillary pattern had a much greater duration of symptoms (average 41.8 months). Thirty-three tumors were multifocal or bilateral, involving the anterior commissure or the posterior larynx; 34 tumors arose on the right; 25 tumors arose on the left; and no side was stated in 12 cases. The most common site for the papillary-type of SCC was supraglottic (7 patients [58%]), with 5 patients (42%) presenting with glottic tumors (Table 2). The exophytic-type SCCs were supraglottic (24 patients [26%]), glottic only (43 patients [47%]), subglottic (3 patients [3%]), or transglottic (22 patients [24%]). Of the nonglottic tumors (n = 56), 31 were supraglottic (papillary, n = 7; exophytic, n = 24), 22 were transglottic (all exophytic), and

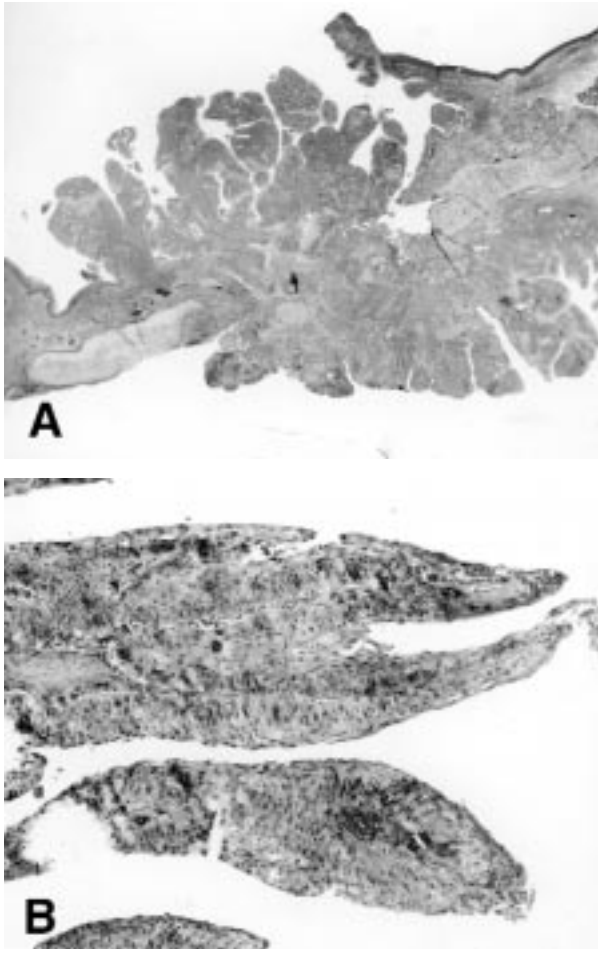

Fig 1. A, Exophytic variant with exophytic bulbous, rounded projections, demonstrating cartilaginous infiltration. **B,** Papillary variant with individual, delicate, finger-like projections containing delicate fibrovascular cores.

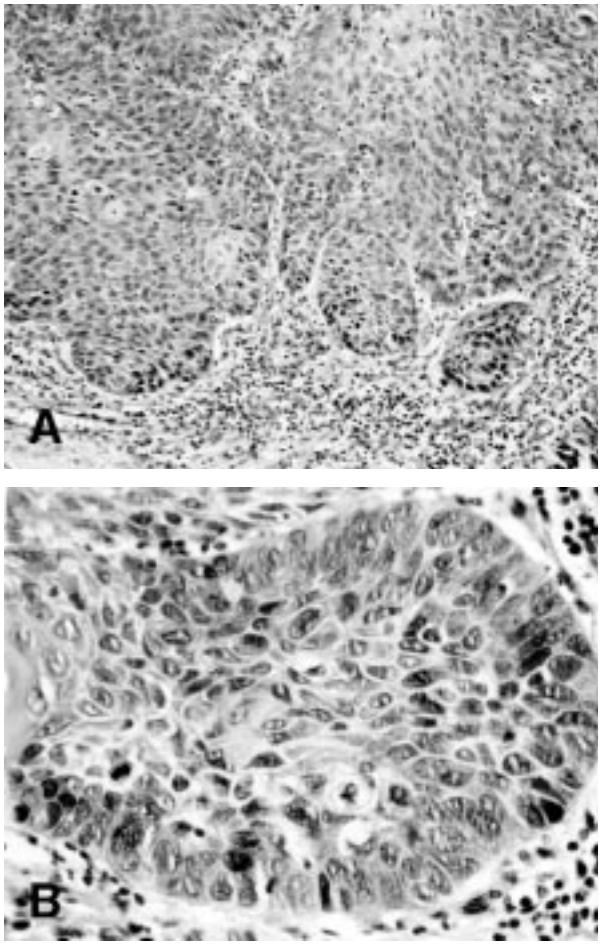

Fig 2. A, Exophytic variant with disorganization, loss of polarity, nuclear variability, mitotic figures, and stromal invasion. **B,** Papillary variant with surface keratinization, loss of polarity, nuclear pleomorphism, and mitotic figures.

Table 2. Pathology and clinical outcome

	Exophytic pattern (n = 92)		Papillary pattern (n = 12)	
Pathology & outcome	**NED**	**DOD**	**NED**	**DOD**
Location				
Supraglottic	17	7	7	0
Glottic	34	9	5	0
Transglottic	17	5	0	0
Subglottic	3	0	0	0
Recurrences	18	17	4	0
Alive, NED: Average follow-up (yr)	10.1		11	
Alive, NED: Range of years (yr)	3-23		7-19	
Dead, NED: Average follow-up (yr)	7.0		3.0	
Dead, local disease:				
Average survival (yr)		3.9		NA
Dead, disseminated disease:				
Average survival (yr)		5.2		NA

NED, No evidence of disease; *DOD,* died of disease; *NA,* not applicable.

3 were subglottic (all exophytic) in location. The average sizes of the exophytic and papillary tumors were 1.43 cm and 1.1 cm in greatest dimension, respectively (range 0.3 to 6 cm). Sixty-eight cases were biopsy specimens, with the remaining 36 obtained from excision, hemilaryngectomy, or laryngectomy specimens. The clinicians considered the biopsy as complete excision; therefore the size was based on the biopsy specimen.

Most lesions fell into the T1 group (n = 65 [62.5%]), with 37 of the glottic tumors (77%) and 28 of the nonglottic tumors (50%) presenting as T1 lesions. There were 10 glottic (21%) and 16 nonglottic (29%) T2 tumors, 8 nonglottic (14%) T3 tumors, and 1 glottic (2%) and 4 nonglottic (7%) T4 tumors.

Pathologic Features

Most lesions were received as multiple, irregular fragments, clinically described as polypoid, exophytic, bulky, papillary, or fungiform. The tumors were soft or firm and were exophytic or papillary in growth architecture, frequently arising from a stalk, although broad-based lesions were also seen (Fig 1).

Two specific histologic patterns could be separated from conventional SCC. The exophytic pattern consisted of a broad-based, bulbous to exophytic growth of the squamous epithelium. The projections were rounded and cauliflower-like in growth pattern (Fig 1*A*). Tangential sectioning would yield a number of central fibrovascular cores, but the superficial aspect was lobular, not papillary (Fig 1*A*). The papillary pattern consisted of multiple, thin, delicate filiform, finger-like papillary projections (Fig 1*B*). The papillae contained a delicate fibrovascular core surrounded by the neoplastic epithelium (Fig 1*B*). Tangential sectioning would yield commonly 1 or occasionally a number of central fibrovascular cores but would appear more like a bunch of celery cut across the stalk. Cases in which there was extensive overlap were placed in the exophytic pattern, which was usually the predominant growth pattern.

All lesions (irrespective of type) demonstrated features of SCC, with surface keratinization (focal to abundant), dyskeratosis, architectural disruption and distortion with loss of cellular polarity, nuclear enlargement, an increased nuclear-to-cytoplasmic ratio, prominent nucleoli, and numerous mitotic figures (Figs 1*B* and 2). Focal areas were more atypical than others. Surface keratinization was absent in 4 cases. Stromal invasion was present and included cohesive tumor nests (Fig 2*A*), as

Table 3. Treatment

Treatment		Exophytic pattern (n = 92)		Papillary pattern (n = 12)	
		NED	DOD	NED	DOD
Biopsy only	17	11	3	3	0
Biopsy and radiation	51	38	8	5	0
Biopsy, radical surgery	13	9	1	3	0
Biopsy, radical surgery and radiation	23	15	7	1	0

NED, No evidence of disease; *DOD*, died of disease.

Table 4. Survival based on T stage and growth pattern

	T1		T2		T3		T4	
	DOD	NED	DOD	NED	DOD	NED	DOD	NED
Papillary								
Glottic	0	5	0	0	0	0	0	0
Nonglottic and transglottic	0	3	0	2	0	1	0	1
Exophytic								
Glottic	5	27	4	6	0	0	0	1
Nonglottic and transglottic	2	23	5	9	1	6	2	1

DOD, Died of disease; *NED*, no evidence of disease.

well as single cells, although it often required multiple sections and reorientation of the biopsy specimen to demonstrate definitive invasion. An associated rich chronic inflammatory response was present (Fig 2*A*). There was no appreciable difference in the histologic grade of the invasive component, nor was there a difference in the growth pattern of the invasive component between the papillary and exophytic patterns. Even though most were biopsy specimens, the invasion was usually superficial, without perineural, vascular, or osseous invasion (Fig 2*A*). This was also true on the laryngectomy specimens, although there was a single case that demonstrated cartilage invasion (Fig 1*A*). Many (n = 58) of the lesions demonstrated so-called "koilocytic atypia" as seen by the presence of hyperchromatic, crenated nuclei surrounded by a clear halo of cytoplasm and an accentuated cell border. There was no evidence of a preexisting papilloma in any of the cases.

In Situ Hybridization

Only 1 of 41 cases tested demonstrated reactivity with the in situ hybridization technique used to identify HPV types 6/11. The reactivity was in a dot or chromosomal pattern, in which most of the cells demonstrated 1 or 2 distinct dots within the nucleus. This patient was a 64-year-old man with an exophytic-type tumor, without previous disease. None of the other cases demonstrated any reactivity.

Treatment and Follow-up

Follow-up ranged from 3 to 23 years (Table 2). As a group, patients with the exophytic growth pattern survived an average of 10.1 years without evidence of disease; patients with the papillary type survived an average of 11 years. Of the patients who died of their disease (all of whom had the exophytic growth pattern), the average survival until local recurrence (n = 7) was 3.9 years, with an average survival for disseminated disease (n = 10) of 5.2 years. Disseminated tumors included both visceral and nodal metastases (although we did not have the lymph nodes to examine).

Fifty patients (48%) were treated with biopsy and supplemental radiation therapy. Twenty-three patients (22%) were treated with multiple biopsies before undergoing a hemilaryngectomy or total laryngectomy with radiation therapy. Thirteen patients (12.5%) were treated with biopsy followed by hemilaryngectomy or total laryngectomy. Eighteen patients (17.3%) were treated with biopsy only (no radiation therapy or additional surgery) (Table 3).

One third of patients with papillary type and 35% with the exophytic type had local recurrences. No patients with the papillary type died of their disease, irrespective of the type of treatment, tumor stage, or number of recurrences.

Glottic tumors with exophytic growth pattern (Table 4). Of the patients with glottic exophytic tumors

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treated with biopsy alone, all 7 had T1 lesions, and local recurrences developed in 3 of them; all were alive without evidence of disease an average of 15.3 years after initial presentation. Likewise, all 5 patients who received additional surgery for their glottic tumors (laryngectomy), were alive without evidence of disease (irrespective of T stage) an average of 9.8 years after initial presentation. After the initial biopsy, radiation was used to treat 24 patients, 2 of whom died of disease 2 and 7 years, respectively, after initial presentation with T1 tumors. Three other patients died of disease 4, 9, and 11 years, respectively, after initial presentation with T2 tumors. Nineteen patients were alive without evidence of disease an average of 9.8 years after initial presentation, although recurrences developed in 3 and necessitated vocal cord stripping. The final set of patients (n = 7) are those who had an initial biopsy followed by surgery (laryngectomy and/or lymph node dissection) and radiation therapy. Four of these patients died of disease (3 T1 tumors and 1 T2) 2, 6, 9, and 10 years, respectively, after initial presentation. The remaining 3 patients are alive and free of disease 5, 8, and 20 years after initial presentation, after having 2, 6, and 4 recurrences, respectively.

Supraglottic, subglottic, and transglottic tumors with exophytic growth pattern (Table 4). Of the patients with supraglottic, subglottic, or transglottic exophytic tumors treated with biopsy alone, 4 had T1 lesions, 2 of whom had recurrences. One patient died within 1 year of widely disseminated disease, whereas 3 patients are alive and free of disease 8, 15, and 23 years, respectively, after initial presentation. Three T2 tumors were treated with biopsy only, and 2 of the patients died of disease 1 and 8 years, respectively, after initial presentation. Of patients who received additional surgery for their tumors (laryngectomy), 4 of 5 were alive without evidence of disease (irrespective of T stage) an average of 6 years after initial presentation. One patient (T1 stage) died of disseminated disease 8 years after initial presentation. After initial biopsy, radiation was used to treat 22 patients, 2 of whom died of disease 1 and 4 years, respectively, after initial presentation with T2 tumors, and 1 of whom died of disease 4 years after initial presentation with a T3 tumor. Nineteen patients were alive without evidence of disease an average of 7.4 years after initial presentation, although 1 had 3 recurrences, which required vocal cord stripping. The final set of patients (n = 15) are those who had an initial biopsy followed by radical surgery (laryngectomy and/or lymph node dissection) and radiation therapy. Three patients died of disease (1 T2 tumor and 2 T4) 1, 1, and 9 years, respectively, after initial presentation. The remaining 12 patients are alive and free of disease an average of 6.7 years after initial presentation, after 5 patients had recurrences resulting in laryngectomy.

Glottic and supraglottic tumors with papillary growth pattern (Table 4). One T1 glottic papillary tumor was treated by biopsy and radiation therapy, whereas 3 T1 glottic tumors were treated by biopsy alone. One T1 glottic tumor was treated by laryngectomy alone. Two T1, 1 T2, and 1 T4 supraglottic tumors were treated with combination biopsy and radiation therapy. One T1 supraglottic tumor was treated with laryngectomy and radiation therapy. One T2 supraglottic tumor and 1 T3 supraglottic tumor were treated with laryngectomy without radiation therapy. All patients with papillary growth patterns were alive without evidence of disease at last follow-up. There were no transglottic or subglottic papillary tumors.

DISCUSSION

SCCs are the most common malignant tumors encountered in the larynx, accounting for more than 90% of all malignant tumors.[7] The category of SCC includes conventional SCC, as well as a number of histologic variants of conventional SCC, including verrucous carcinoma,[1-3] spindle cell SCC,[8-12] basaloid SCC,[13-15] adenosquamous carcinoma,[16-19] and adenoid SCC.[20]

Conventional SCC includes in situ, superficially invasive, and deeply invasive cancers. The histologic differentiation of these tumors may include well, moderately, or poorly differentiated SCC. We believe that a select group of conventional SCCs can be further subdivided into exophytic or papillary on the basis of growth pattern. The exophytic pattern is composed of broad projections with bulbous ends and a cauliflower-type growth, whereas the papillary pattern is composed of delicate, finger-like papillary fronds. We stress that the papillary or exophytic growth pattern must be the predominant pattern (>70%) of the tumor's architectural growth, not merely representing a minor component in a conventional SCC. Tumors that have a mixture of exophytic and papillary patterns behaved in a fashion similar to that for the exophytic tumors. Therefore, if both patterns are present (irrespective of the percentage of either growth pattern), these tumors should be classified as exophytic for prognostic purposes.

All of the tumors in our study qualify as carcinomas on the basis of cytomorphologic features. These carcinomas would be classified as well-to-moderately differentiated. Further, despite their exophytic or papillary growth characteristics, we view all of these tumors as infiltrative carcinomas. In a few biopsy specimens it may be very difficult to definitively discern invasion, and the carcinomatous epithelium mostly suggests an

in situ carcinoma. However, the significant proliferation of this carcinomatous epithelium, often forming a very appreciable clinical lesion, is rather beyond the general concept of carcinoma in situ. When it is difficult to be completely confident of frank histologic invasion, the significantly proliferated appearance of the lesion should be weighed when trying to determine whether the appellation of SCC is appropriate. In none of our cases was there evidence of a preexisting or concomitant papilloma. The cytomorphologic features of malignancy would exclude the diagnosis of a papilloma, as well as the consideration of a verrucous carcinoma. The latter is a very well-differentiated carcinoma, lacking any evidence of dysplasia.[1-3] However, in some instances the cytologic features of malignancy were not blatant, and careful evaluation may be necessary to distinguish a papillary carcinoma from an atypical papilloma.

Both exophytic and papillary patterns of growth demonstrated features of so-called "koilocytic" change, with hyperchromatic, crenated nuclei surrounded by a clear halo of cytoplasm ending in an accentuated, thick cell border. The presence of koilocytic cells is suspicious for HPV infection. However, even though koilocytosis has been associated with human HPV, we were able to demonstrate only HPV type 6/11 in a single case. It was of interest that the reactivity was in a dot or chromosomal pattern, with 1 or 2 small dots within the nucleus of the cells. The chromosomal pattern of expression suggests that there is incorporation of the HPV DNA into the host cell genome. Because we tested only HPV types 6, 11, 16, 18, 31, 33, and 51, we cannot comment on the possibility of infection by other HPV subtypes.

Approximately one third of patients with the exophytic and papillary patterns had recurrences, often in less than 1 year but occasionally up to 10 years after the initial diagnosis. The recurrences looked remarkably similar in histomorphologic appearance to the primary tumors, with only 2 of the 36 patients with recurrences demonstrating a nonexophytic growth pattern in the recurrence, both of which occurred at a slightly different site than the original tumor. Of the 35 patients with recurrent tumors, 21 had multiple recurrences, and 14 had a single recurrence. Most of the recurrences were treated with conservative measures, although laryngectomy was used for recalcitrant cases (n = 14).

Nineteen patients (20.7%) with the exophytic pattern had recurrences and died of disease caused by locally aggressive disease or widely metastatic tumor. Metastatic sites of involvement included regional lymph nodes, lung, liver, and bone. An additional 13 patients with the exophytic pattern had recurrences but did not die of their diseases. Four patients with papillary growth patterns had recurrences, but no patients died of their diseases. There were, on average, 2.8 recurrences per patient with the exophytic pattern and only 1.5 recurrences with the papillary pattern (of the patients who had recurrences; n = 36 for all cases). There does not appear to be a correlation with recurrences and T stage, in either the papillary or exophytic tumor types.

The distinction between an exophytic and papillary pattern seems to have prognostic significance irrespective of the size, location, and histologic grade of the tumor. Although 75% of the papillary growth pattern tumors were T1 lesions, there was still a 100% survival rate, compared with the T1 exophytic growth pattern (86%). The percentage of patients who died of their disease with glottic tumors (18.8%) is almost identical to that of patients who died of their disease with transglottic, subglottic, or supraglottic tumors (17.9%). This finding is in contrast to conventional SCC in which glottic tumors tend to have a better prognosis and outcome when compared with transglottic or nonglottic tumors.[21-27] Although the exophytic pattern is more clinically aggressive than the papillary pattern, it has a better overall prognosis than conventional SCC.[21,25] The absolute 5-year survival for the exophytic type (irrespective of T stage) is 88%, with 100% for the papillary type (excluding the patients who died before 5 years of unrelated causes). We do not have an explanation, based on the clinical or histomorphologic findings, for the apparent better clinical outcome of the papillary versus the exophytic growth pattern. As the stage of the exophytic pattern increases, so does the number of deaths related to disease as a percentage of the overall cases. However, the outcome of exophytic or papillary SCC compared with that of conventional SCC is still better when comparing stage for stage.[21-26] Previously, there has been no specific study of patient outcome (prognosis) compared with tumor growth patterns in conventional SCC. Therefore the cases in the literature may include the growth patterns described herein. However, in general, SCC is usually described as ulcerative, flat, or polypoid (with the obvious exception of verrucous carcinoma, which was not considered in this study). Therapeutic intervention may be modified on the basis of the overall excellent prognosis of patients with exophytic or papillary growth pattern SCC.

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