Laryngeal Dysplasia, Squamous Cell Carcinoma, and Variants

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KEYWORDS

• Carcinoma, squamous cell • Carcinoma, adenosquamous • Carcinoma, verrucous • Larynx • Dysplasia

Key points

- Dysplasia is now separated into 2 categories: low and high grade.
- Verrucous squamous cell carcinoma is usually a clinicopathologic correlation.
- Basaloid squamous cell carcinoma shows abrupt keratinization and comedonecrosis.
- Up to 30% of Spindle cell squamous cell carcinoma lacks epithelial differentiation by immunohistochemistry.
- Exophytic and papillary squamous cell carcinoma usually have a better prognosis than conventional squamous cell carcinoma.

ABSTRACT

Squamous cell carcinoma (SCC) is a malignant epithelial tumor showing evidence of squamous differentiation. It is the most common malignancy of the larynx, with several variants (verrucous, exophytic or papillary, spindle-cell, basaloid, acantholytic, adenosquamous) recognized, with well-established precursor lesions. Dysplasia is now separated into only low-grade and high-grade categories. Each SCC variant has unique cytomorphologic features and histologic differential diagnoses that are important to consider, as management and outcomes are different.

OVERVIEW

Squamous cell carcinoma (SCC) is a malignant epithelial tumor showing evidence of squamous differentiation and is the single most important and most common malignant neoplasm of the larynx. Although not always present, precursor dysplasia is usually seen.[1] In general, men are affected much more frequently than women, usually in the middle to later decades of life, although any age can be affected.[2,3] Symptoms are nonspecific, with hoarseness, dyspnea, stridor, and dysphagia most common.[4] Independently and synergistically, tobacco (cigarette, cigar, pipe) and alcohol use are the most important risk factors,[5–7] whereas transcriptionally active human papillomavirus (HPV) is less common in laryngeal tumors, detected in up to 15% of cases.[8–10] Genetic predisposition (such as with Lynch syndrome, Bloom syndrome, and Li-Fraumeni, among others), susceptibility (immunologic factors and age), and other environmental and occupational factors probably interact in this multifactorial and multistep process.[11,12] Variants of SCC account for up to 4% of tumors,[13–19] and are separated primarily because they show a different clinical presentation and outcome, as well as frequently raising different differential diagnoses. In the United States, most tumors develop in the glottis, followed by the supraglottis and rarely subglottis, although geographic variation is common. Direct

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extension into contiguous structures or lymphovascular invasion is common, the latter resulting in a high incidence of regional lymph node metastases. Surgery, laser therapy, and radiation continue to be the mainstays of therapy, with changes in protocols for the specific histologic variants.[20] Outcomes are heavily influenced by tumor stage, localization (glottic), and age,[20–22] whereas differentiation, invasive pattern, vascular and/or perineural invasion, margin status, and extranodal extension play a significant role.[23–33]

DYSPLASIA (PRECURSOR LESIONS)

Dysplasia is defined by a morphologic spectrum of architectural and cytologic changes in the squamous mucosal epithelium that is associated with an increased likelihood of progression to SCC. Gastroesophageal reflux disease is considered a risk factor in addition to tobacco and alcohol use,[34,35] whereas transcriptionally active HPV seems to be of minor importance.[36–38] There are frequent chromosomal changes and loss of heterozygosity, with *CDKN2A* gene alterations most frequently identified, associated with *TP53* and *cyclin-D1* overexpression and activated telomerase activity, but these are not yet clinically useful.[39–41] The vocal cords are affected most frequently, with rare involvement of the commisures.[42]

Leukoplakia, erythroplakia, or mixed leukoerythroplakia appear in the larynx as localized or diffuse patches or flat to exophytic or papillary lesions that mimic SCC. Therefore, histologic evaluation is mandatory for diagnosis.

Over the years, many different grading schemes have been proposed,[43–45] often subject to significant interobserver variability. With a trend in other organs to a 2-grade system,[46,47] generally lesions that are traditionally considered mild dysplasia would be categorized as "low grade" whereas lesions classified as moderate to severe dysplasia/carcinoma in situ can be categorized as "high grade." **Table 1** highlights the architectural and cytomorphological features used to distinguish between low-grade and high-grade dysplasia (as modified from the World Health Organization Classification of Tumours of the Head and Neck). In general, it is a qualitative and quantitative

Table 1
Dysplasia criteria

Low-grade dysplasia (previously mild dysplasia)	Architecture	• Overall stratification is preserved, whereas basal-parabasal layer is abnormal • Basal-parabasal layer is increased, up to lower half of the epithelium • Spinous layer may be increased, with prickle cells usually seen only in upper half of the epithelium
	Cytology	• Limited pleomorphism • Enlarged nuclei with increased nuclear-to-cytoplasmic ratio, but evenly distributed chromatin; vague cytoplasmic pinking with limited intercellular spinous processes • Isolated dyskeratosis cells • Mitoses (typical forms) limited to lower third of epithelium
High-grade dysplasia (previously moderate and severe dysplasia, and carcinoma in situ)	Architecture	• Keratinizing or nonkeratinizing (basal cell) types • Loss of maturation, with disordered stratification and loss of polarity up to full thickness • Cellular pleomorphism from one-half up to full thickness, frequently severe • Basement membrane remains intact (no stromal changes) around irregular-shaped rete (bulbous, downwardly extending)
	Cytology	• Often conspicuous pleomorphism with marked variation in cell and nuclear size and shape, marked variation in staining intensity (often hyperchromatic), and increased size and number of nucleoli • High nuclear-to-cytoplasmic ratio • Dyskeratotic cells increased throughout the epithelium • Increased mitoses anywhere in the epithelial, to include atypical forms (the latter qualifies as high-grade by itself)

Modified from Gale N, Hille J, Jordan R, et al. Tumours of the hypopharynx, larynx, trachea, and parapharyngeal space: precursor lesions. In: El-Naggar AK, Chan JKC, Grandis JR, et al, editors. Pathology and genetics of head and neck tumours. 4th edition. World Health Organization Classification of Tumours. Lyon, France: IARC Press, 2017, in press.

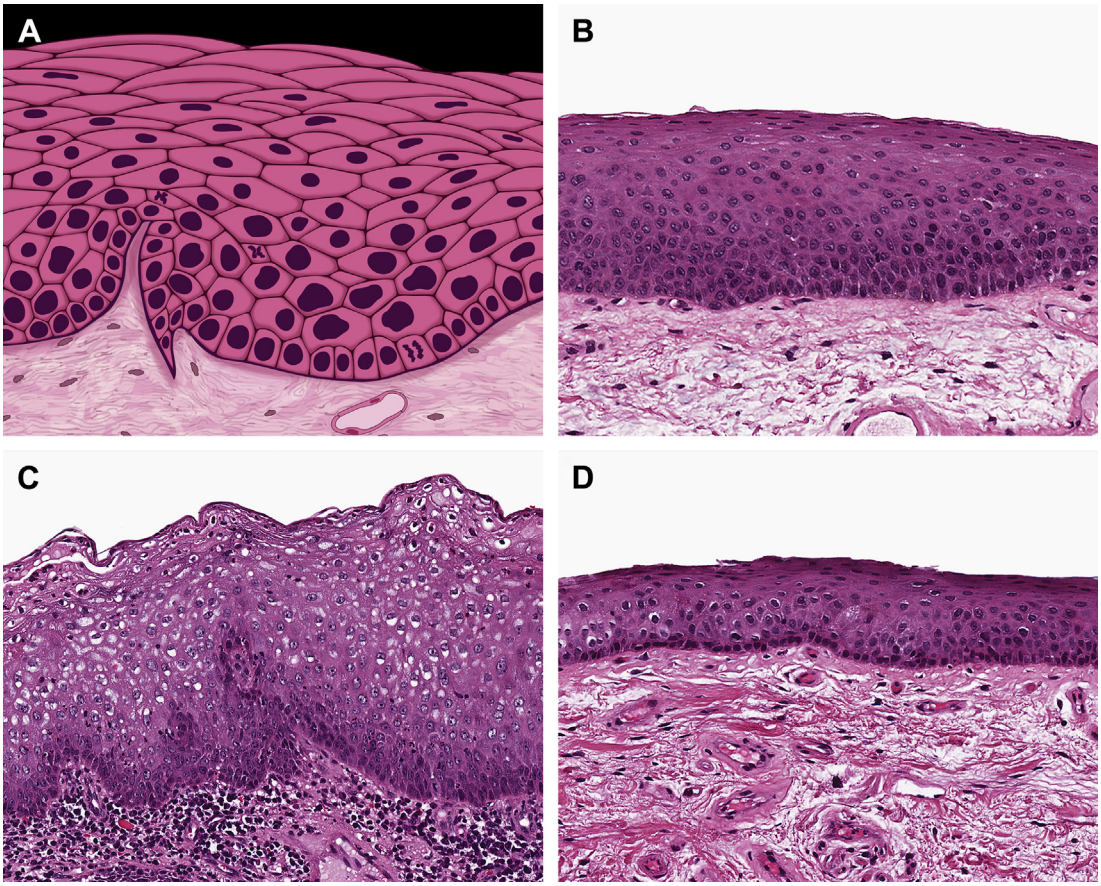

Fig. 1. Low-grade keratinizing dysplasia. (*A*) Schematic showing expanded basal-parabasal zone, nuclear hyperchromasia and irregularities, with increased normal mitoses. (*B*) Disorganized basal zone (lower one-third) with nuclear crowding and increased nuclear-to-cytoplasmic ratio, with maturation. (*C*) Expanded parabasal zone with maturation toward the surface, with nuclear irregularities and cytoplasmic pinking and spinous zone expansion. (*D*) Subtle increased cellularity with nuclear atypia limited to the lower half, showing surface maturation.

accumulation of features that moves a particular lesion into a dysplasia grade. It is important to note, however, that the traditional use of "thirds" in the uterine cervix does not apply to upper aerodigestive tract lesions. Particularly if there is profound pleomorphism and atypical mitoses confined to the lower third, it still represents high-grade dysplasia in the larynx. The vast majority of dysplasia in the larynx is keratinizing, with only a small number non-keratinizing. Loss of maturation, disordered polarity, and expansion of the basal layer (**Fig. 1**) is an architectural feature of dysplasia, whereas increased cell size, increase in nuclear-to-cytoplasmic ratio, nuclear contour irregularities, nuclear chromatin distribution changes, cytoplasmic pinking, prominent intercellular borders, and increased mitoses are some of the cytologic features seen in dysplasia (see **Fig. 1**). Sometimes, the low-power appearance is more innocuous because the dysplasia is often associated with surface maturation and multiple layers of epithelial cells, but careful examination on high power will help reveal the histologic features of dysplasia. Importantly, significant keratosis and parakeratosis only may behave similarly to low-grade dysplasia, showing a similar progression risk. No one feature in isolation is diagnostic, but in general, the presence of atypical mitoses is seen only in high-grade dysplasia (**Fig. 2**). By definition, the process is confined to the surface epithelium or showing gland-duct extension, but without stromal alterations or breach of the basement membrane. There are inconsistent findings with p53 (increased), p21, p27 (decreased), cyclin D1, bcl-2, p16, Ki-67 (increased), β-catenin, and epidermal growth factor receptor (EGFR) when used to separate between dysplasia grading, partly due to immunohistochemistry overexpression not necessarily correlating to molecular alterations or progression of disease.[48–52]

Distinction from epithelial hyperplasia, pseudoepitheliomatous hyperplasia, necrotizing sialometaplasia, verrucous changes, and invasive

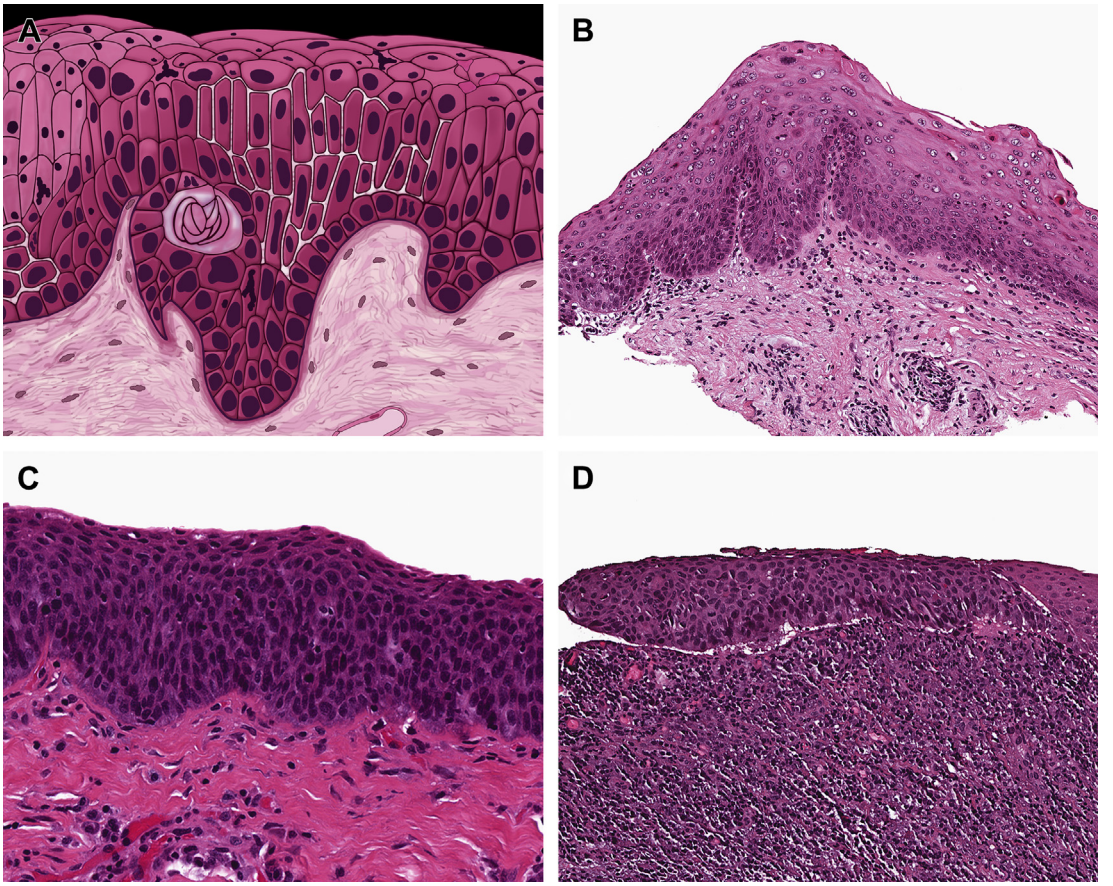

Fig. 2. High-grade keratinizing dysplasia. (*A*) Schematic showing loss of polarity and disorganization of upper half, with dyskeratosis, keratin pearl formation, and atypical mitoses. (*B*) Dyskeratosis at the surface, loss of maturation, and cellular pleomorphism. (*C*) Almost full-thickness atypia, perpendicular nuclear arrangement, increased mitoses, and very high nuclear-to-cytoplasmic ratio. (*D*) Full-thickness disorganization, loss of maturation, increased nuclear-to-cytoplasmic ratio, and pleomorphism. Note right side has uninvolved epithelium.

carcinoma are necessary to assess appropriate risk of progression, modify etiologic contributing risk factors, or to treat adequately, particularly when present intraoperatively at margins (**Table 2**). The sometimes very subtle findings in low-grade dysplasia may make separation of small or tangentially sectioned biopsies very challenging. Keeping in mind what the clinical consequences of each diagnosis will be, may help to apply the criteria more uniformly and reproducibly. High-grade dysplasia is associated with invasive carcinoma development in up to 40% of cases, whereas low-grade dysplasia shows malignant progression in only approximately 2% of cases.[45,53,54]

SQUAMOUS CELL CARCINOMA

SCC may be ulcerated, endophytic, flat, exophytic, polypoid, or verrucous, ranging from minute mucosal thickenings to occlusive masses. The tumors are erythematous to tan-white, frequently firm.

SCC is composed of variable degrees of squamous differentiation associated with invasion (**Fig. 3**). SCC is generally divided into 3 histologic grades (well, or moderately or poorly differentiated), with or without keratinization (see **Fig. 3**). SCC shows a desmoplastic stromal reaction, frequently perineural or lymphovascular invasion, and disruption of the basement membrane by cords, nests, islands, or individual cells (different invading fronts; see **Fig. 3**A). There is a loss of polarity, disorganization, dyskeratosis, and keratin pearl formation. Intercellular bridges are noted between cells that have an increased nuclear-to-cytoplasmic ratio, cytoplasmic opacification, and irregular, polygonal shapes. There are nuclear chromatin irregularities, prominent eosinophilic nucleoli, and increased mitoses, including atypical forms. Well-developed keratinization is not seen in poorly differentiated

tumors (see **Fig. 3**). In poorly differentiated or high-grade tumors, immunohistochemistry studies for CK5/6, p63, p40, and epithelial membrane antigen (EMA) may help confirm the epithelial nature of the proliferation.[55]

Generally, hyperplasia, papilloma, dysplasia, and select SCC variants, mainly verrucous carcinoma (VC) are the major differential diagnostic considerations for a well-differentiated tumor (**Table 2**). Hyperplasia lacks individual cell infiltration and severe pleomorphism, usually showing the infectious agent or perhaps a granular cell tumor in the background. A squamous papilloma lacks significant pleomorphism and is noninvasive. Dysplasia by definition lacks breach of the basement membrane. SCC may develop in the absence of surface dysplasia. VC shows a specific architecture (bulbous rete, no atypia, limited mitoses, parakeratotic crypting, church-spire keratosis) that is not seen in SCC. The differential diagnosis for poorly differentiated SCC may include a variety of different tumor types. Melanoma, lymphoma, and neuroendocrine carcinomas are uncommon in the larynx, but the presence of squamous differentiation and selected, pertinent, and focused immunohistochemistry studies (S100 protein, SOX10, CD45RB, synaptophysin, chromogranin) will help with this distinction.

Prognosis is separated by anatomic site, stage, and other factors, such as age, comorbidities, and the patient's performance status, with overall 5-year survival rate of 80% to 85% for glottic, 65% to 75% for supraglottic, and 40% for subglottic SCCs.[20–22] Stage, including regional and/or distant metastases, depth of invasion, pattern of invasive front (single cells), perineural and lymphovascular invasion, extranodal extension in lymph node metastases, and positive resection margins are all prognostic factors that correlate with increased risk of recurrence, lymph node metastases, and decreased survival.[23–33]

VERRUCOUS CARCINOMA

Table 2
Pitfalls

Tumor Type	Pitfall
Dysplasia	• Pseudoepitheliomatous hyperplasia has bulbous rete, but etiologic agent frequently present • Tangential sections must be carefully reviewed • Gland-duct extension is not invasion • Parakeratosis and keratosis in the larynx are abnormal
SCC	• Basement membrane must be breached • Invasive tumor may develop without surface dysplasia • Poorly differentiated tumors must be evaluated for neuroendocrine carcinoma and mucosa melanoma
Verrucous carcinoma	• Inadequate biopsy precludes definitive diagnosis • Tangential sectioning may overestimate thickness • Do not diagnose verrucous hyperplasia on a biopsy because more extensive sampling may reveal carcinoma
Papillary/Exophytic SCC	• Orientation is critical • Must make sure you have an adequate specimen (ie, stalk or base of lesion)
Spindle cell SCC	• Surface epithelium generally absent • 30% lack epithelial immuno markers • Hypocellular tumors still show atypia
Basaloid SCC	• Must find squamous differentiation • Mucohyaline material mimics adenoid cystic carcinoma • Superficial biopsy fails to show true tumor appearance
Adenosquamous carcinoma	• High-grade mucoepidermoid carcinoma still shows mucocytes • Two distinct populations are seen

Abbreviation: SCC, squamous cell carcinoma.

Comprising approximately 3% of laryngeal SCC,[14,56] VC is not associated with transcriptionally active HPV, with most developing in older men.[57,58] A clinicopathologic correlation with the

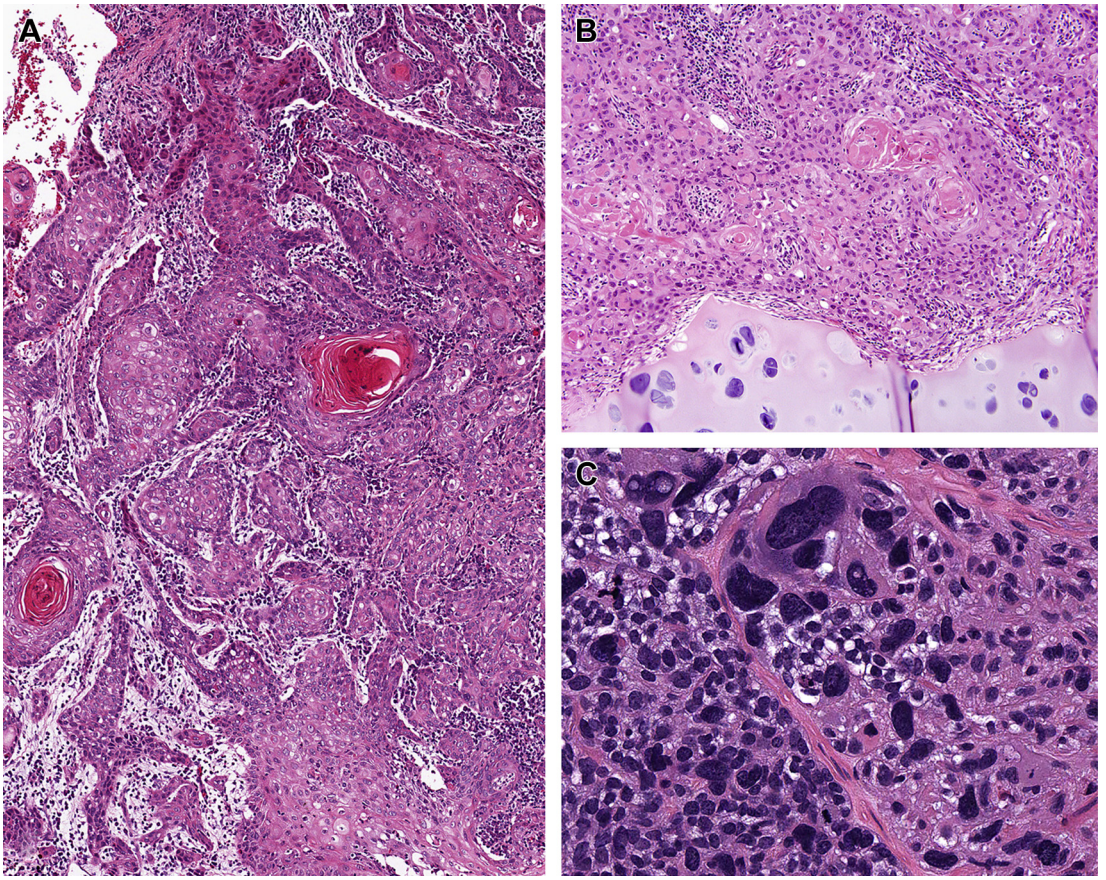

Fig. 3. SCC. (*A*) A deeply invasive, well-differentiated, keratinizing SCC with keratin pearls. (*B*) A moderately differentiated keratinizing SCC shows cartilage invasion. (*C*) Poorly differentiated SCC with marked pleomorphism.

gross or endoscopic appearance of a large, broad-based, warty, exophytic or fungating bulky, firm to hard, tan or white mass, is required in many cases to yield a diagnosis, especially if biopsies are superficial, small, and/or lack a good stromal interface (**Table 3**).[59–62] VCs are important to recognize because they are only locally aggressive without metastatic capacity unless there is a conventional SCC component.

VC is a highly differentiated, slow-growing, locally invasive SCC lacking cytologic features of malignancy, usually affecting the true vocal cord, but any site may be affected. Thickened, club-shaped, broad to bulbous rete pushing into the stroma below the level of the neighboring normal basal cell layer is one of the histologic hallmarks (**Fig. 4**). Desmoplasia is usually absent, but a lymphoplasmacytic infiltrate is common. The extraordinarily well-differentiated epithelium is greatly expanded, showing "church-spire" keratosis, parakeratosis, and parakeratotic cryptings between the exophytic-warty tumor projections. There is absent atypia, orderly maturation toward the surface, and isolated to absent mitoses that are confined to the basal-parabasal zone (**Fig. 5**). In some cases, foci of conventional SCC are seen, diagnosed as a hybrid or mixed tumor, and showing the outcome of conventional SCC.[59,61,62]

The differential diagnosis of VC includes verrucous hyperplasia, squamous papilloma, conventional SCC, papillary and exophytic SCC, and hybrid carcinomas (**Table 2**). The constant challenge is that VC is not cytologically malignant and requires invasion for a definitive diagnosis. If a biopsy is small or superficial, this becomes almost impossible to determine. In fact, it has been argued that the difference between verrucous hyperplasia and VC is only in stage and size, considered to be a developmental spectrum,[63–65] a bias shared by this author. Thus, a definitive diagnosis can be rendered only when the relationship of the lesion to the stroma can be adequately assessed, made more challenging

Table 3
Pathologic key features of SCC variants

	Variant				
Feature	**Verrucous**	**Papillary/Exophytic**	**Spindle Cell (Sarcomatoid)**	**Basaloid**	**Adenosquamous**
Macroscopic	Broad- based, warty and fungating mass	Polypoid, exophytic, bulky, papillary, fungiform	Polypoid mass	Firm to hard with central necrosis	Indurated submucosal mass
Microscopic	Pushing border of infiltration; abrupt transition with normal; large, blunt club-shaped rete; no pleomorphism; nearly absent mitoses; abundant keratin, including parakeratin crypting and "church-spire" keratosis	>70% exophytic or papillary architecture; unequivocal cytomorphologic malignancy; surface keratinization; invasive by definition; koilocytic atypia	Biphasic; SCC present, but ulcerated; transition of epithelial to atypical spindled cells; hypercellular; variable patterns of spindle-cell growth; pleomorphism; opacified cytoplasm; increased mitoses	Deeply invasive; lobular; basaloid component most prominent; peripheral nuclear palisading; high N:C ratio; abrupt squamous differentiation (metaplasia, dysplasia, CIS or invasive); increased mitoses; central comedonecrosis; hyaline stroma material	Biphasic; SCC and adenocarcinoma; undifferentiated clear-cell component; separate or intermixed with areas of transition; infiltrative
Special studies	No transcriptionally active HPV identified	None	30% negative with epithelial immunohistochemistry markers	Keratin, EMA, CK7, and 34ßE12; negative neuroendocrine markers	Mucin-positive glandular/goblet cells
Differential diagnosis	Hyperplasia; squamous papilloma; conventional SCC; hybrid carcinoma	In situ SCC; squamous papilloma; reactive hyperplasia	Inflammatory myofibroblastic tumor; mucosal melanoma; synovial sarcoma; other malignant mesenchymal tumors	Adenoid cystic carcinoma; neuroendocrine carcinoma (small cell carcinoma); adenosquamous carcinoma; mucoepidermoid carcinoma	Basaloid SCC; mucoepidermoid carcinoma; adenocarcinoma with squamous metaplasia; adenoid SCC

Abbreviations: CIS, carcinoma in situ; EMA, epithelial membrane antigen; HPV, human papillomavirus; N:C ratio, nuclear-to-cytoplasmic ratio; SCC, squamous cell carcinoma.

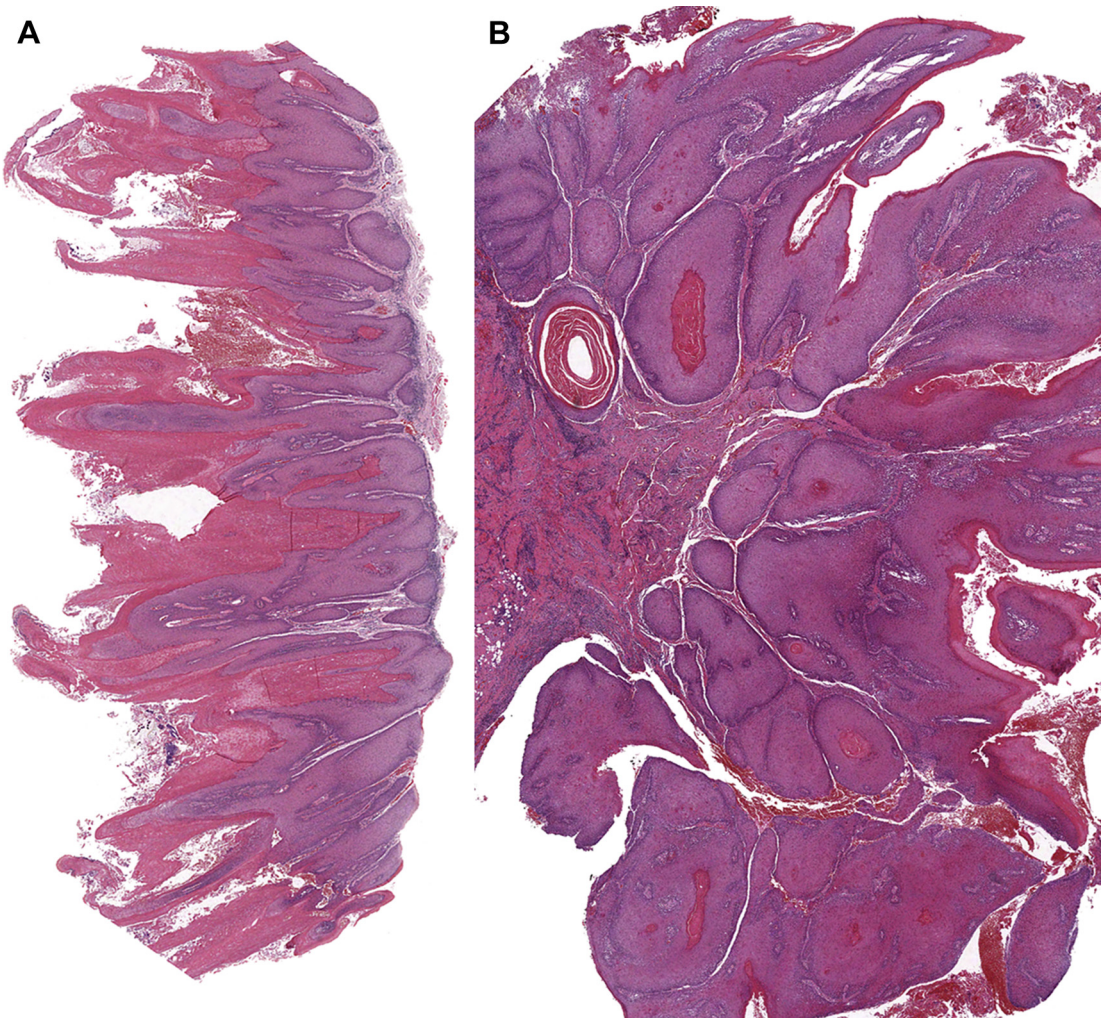

Fig. 4. VC. (*A*) Marked verruciform proliferation with church-spire–type keratosis and club-shaped rete pushing into the stroma. (*B*) Broad pushing border of infiltration by club-shaped rete lacking atypia and associated with keratosis.

with tangential sectioning, sample fragmentation, and frozen section artifacts. Using the term "verruciform squamous proliferation," followed by a comment will provide the necessary guidance to the treating physician and highlight the difficulties experienced. There is often an increased expression of p53 and EGFR in VC versus squamous epithelium alone,[66] but in daily practice almost impossible to apply. Squamous papilloma is usually an exophytic rather than an endophytic growth, often showing koilocytic changes and atypia of the basal-parabasal zones. When conventional SCC is noted within a VC, a hybrid diagnosis is rendered. The amount and extent of the conventional SCC component may determine extent of therapy (ie, managed as conventional SCC).[56]

Radiotherapy or surgery may be used, with an overall 5-year survival of 85% to 95%, with stage the most important prognostic factor.[14,56,62,67–69]

EXOPHYTIC AND PAPILLARY SQUAMOUS CELL CARCINOMA

Rare in the larynx, men are affected more often than women, usually in the seventh decade of life (**Table 3**). Macroscopically, exophytic SCC (ESCC) and papillary SCC (PSCC) are polypoid, exophytic, bulky, papillary, or fungiform tumors, soft to firm, arising from a broad base or from a narrow pedicle/stalk.[16,70–73]

By definition, ESCC and PSCC are de novo malignancies without a preexisting or coexisting

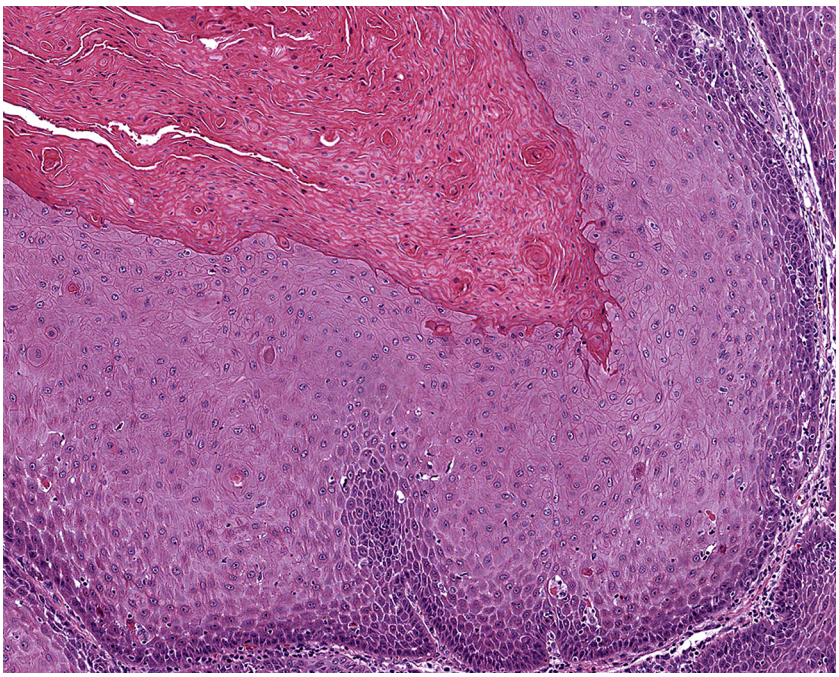

Fig. 5. The proliferation is cytologically bland without mitotic figures but demonstrating a broad, bulbous type infiltration into the stroma. Parakeratotic crypting is noted.

benign lesion, showing severely dysplastic epithelium lining the fronds, frequently lacking well-developed histologic invasion. The neoplasm must demonstrate a dominant (>70%) exophytic or papillary growth with frank cytomorphologic evidence of malignancy.[70] The exophytic pattern consists of broad-based, bulbous growths of rounded atypical epithelium, often with a rounded to lobular surface appearance (**Fig. 6**). The papillary pattern shows multiple, thin, delicate filiform, projections with delicate fibrovascular cores covered by the neoplastic epithelium, creating numerous surface fronds (**Fig. 7**). When both patterns are seen, ESCC is diagnosed. The lining squamous epithelium is frankly malignant, showing similar features to high-grade dysplasia or carcinoma in situ (see **Fig. 6**). Stromal invasion is difficult to document, but present by definition, along with a heavy inflammatory infiltrate.[16,70] "Koilocytic atypia" may be focally noted, correlated with transcriptionally active HPV in some cases.[74]

The cytomorphologic features of malignancy would help distinguish a squamous papilloma and VC from these variants. Reactive hyperplasia may show atypia, but does not have well-developed exophytic or papillary architecture (**Table 2**).

This variant of SCC has a better prognosis than conventional SCC, usually related to low-stage presentation and low metastatic potential because of the exophytic growth, with an approximately 85% 5-year survival.[16,70,71,74]

SPINDLE-CELL SQUAMOUS CELL CARCINOMA

Spindle-cell (sarcomatoid) squamous cell carcinoma (SCSCC) is a morphologically biphasic tumor with a carcinoma that has surface epithelial changes (dysplasia to invasive carcinoma) and an underlying malignant spindle and/or pleomorphic proliferation. This tumor shows a profound male-to-female ratio (11:1), generally presenting in the seventh decade of life, usually involving the glottis, and usually with low tumor stage (**Table 3**).[15,17,75–78]

Nearly all cases are polypoid masses (**Fig. 8**) with a mean size of approximately 2.0 cm. They are frequently ulcerated with a covering of fibrinoid necrosis. They have a firm and fibrous cut surface.[15,17,77]

As a consequence of ulceration, surface origin or transition is difficult to identify. Review of the base of the stalk, invaginated regions or non-eroded areas may help highlight epithelial dysplasia, carcinoma in situ, or infiltrating SCC (see **Fig. 8**; **Fig. 9**). Frequently, limited stromal invasion beyond the stalk is noted, as the tumors are predominantly polypoid. There is an imperceptible blending and continuity of the epithelial to spindled morphology (see **Fig. 8**).[79,80] By definition, the spindled population dominates, arranged

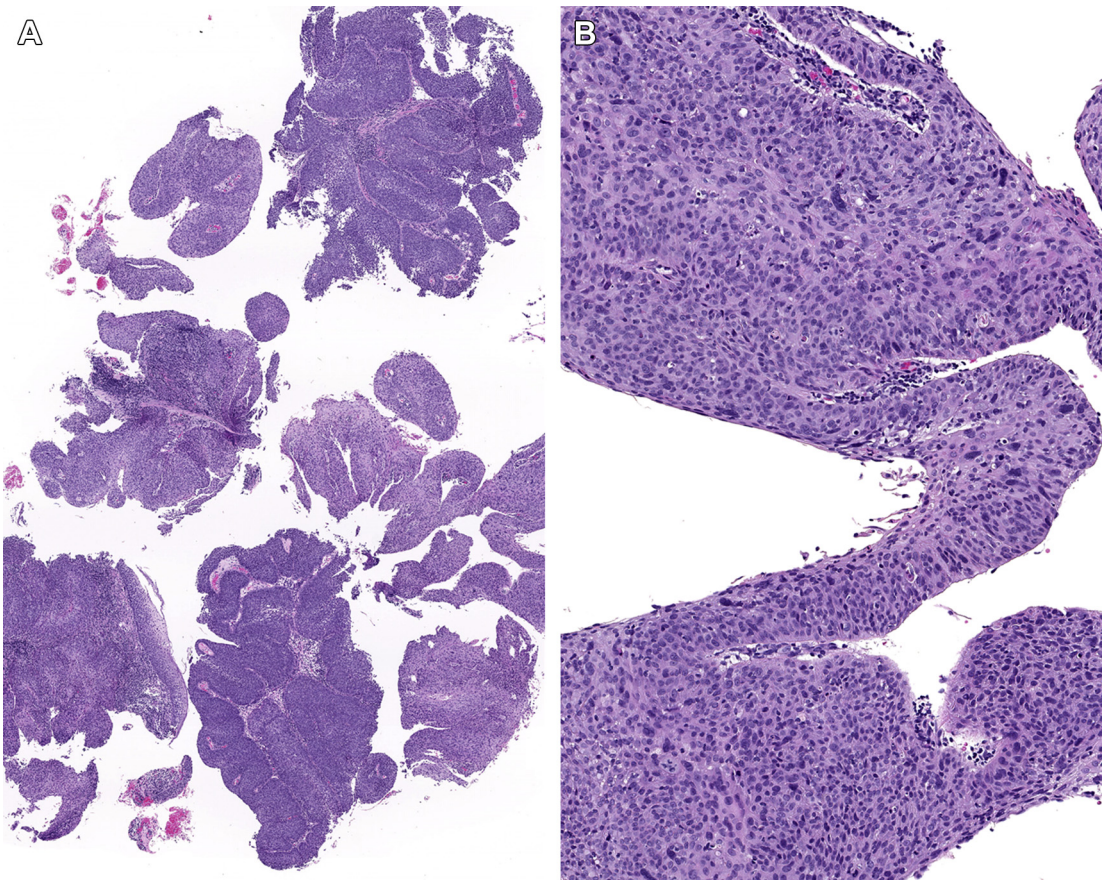

Fig. 6. ESCC. (*A*) An ESCC with fragments of tissue showing broad projections. (*B*) Marked pleomorphism and frank anaplasia.

in a storiform, cartwheel, whorled to intersecting fascicular architecture. Hypocellular areas with collagen deposition contain pleomorphic cells, but can be deceptively bland (see **Fig. 8**). Most tumors are hypercellular, lacking maturation, with easily identified but usually not profound pleomorphism. Tumor cells are fusiform to polygonal (see **Fig. 8**). Opacified, dense cytoplasm suggests squamous differentiation. Easily identified mitoses, including atypical forms, are common, but necrosis is rare.[15,17,77,81] Rarely, metaplastic or frankly neoplastic cartilage or bone or rhabdomyoblastic heterologous elements may be present.[77,82,83]

SCSCC is the most likely SCC variant to benefit from immunohistochemistry evaluation, in which approximately 70% show reactivity for AE1/AE3, EMA, p63, and/or p40.[77,84] p53 is usually overexpressed.[85] Tumors without epithelial reactivity must still be interpreted as SCSCC until proven otherwise. Importantly, focal reactivity for smooth muscle actin, muscle-specific actin, and, rarely, S-100 protein may be seen.[76,77,86,87] This degree of lineage infidelity is expected in tumors that show significant epithelial-mesenchymal–type transition.[79,80]

Given a very limited stroma in the vocal cords, genuine mesenchymal lesions of the larynx are very rare. Thus, a spindled cell proliferation of the larynx must be considered an SCSCC until further evaluation proves otherwise. Inflammatory myofibroblastic tumor, mucosal melanoma, and synovial sarcoma are occasionally seen, whereas fibrosarcoma, pleomorphic sarcoma, leiomyosarcoma, rhabdomyosarcoma, malignant peripheral nerve sheath tumor, and angiosarcoma are vanishingly rare (**Table 2**). The presence of squamous differentiation usually makes distinction possible. The rich inflammatory infiltrate along with a myofibroblastic haphazard spindled cell proliferation with feathery cytoplasm, often with anaplastic lymphoma kinase (ALK) expression and a lack of epithelial features helps to diagnose an inflammatory myofibroblastic tumor.[88,89] A monophasic synovial sarcoma tends to occur in young patients, usually arises in the soft tissues

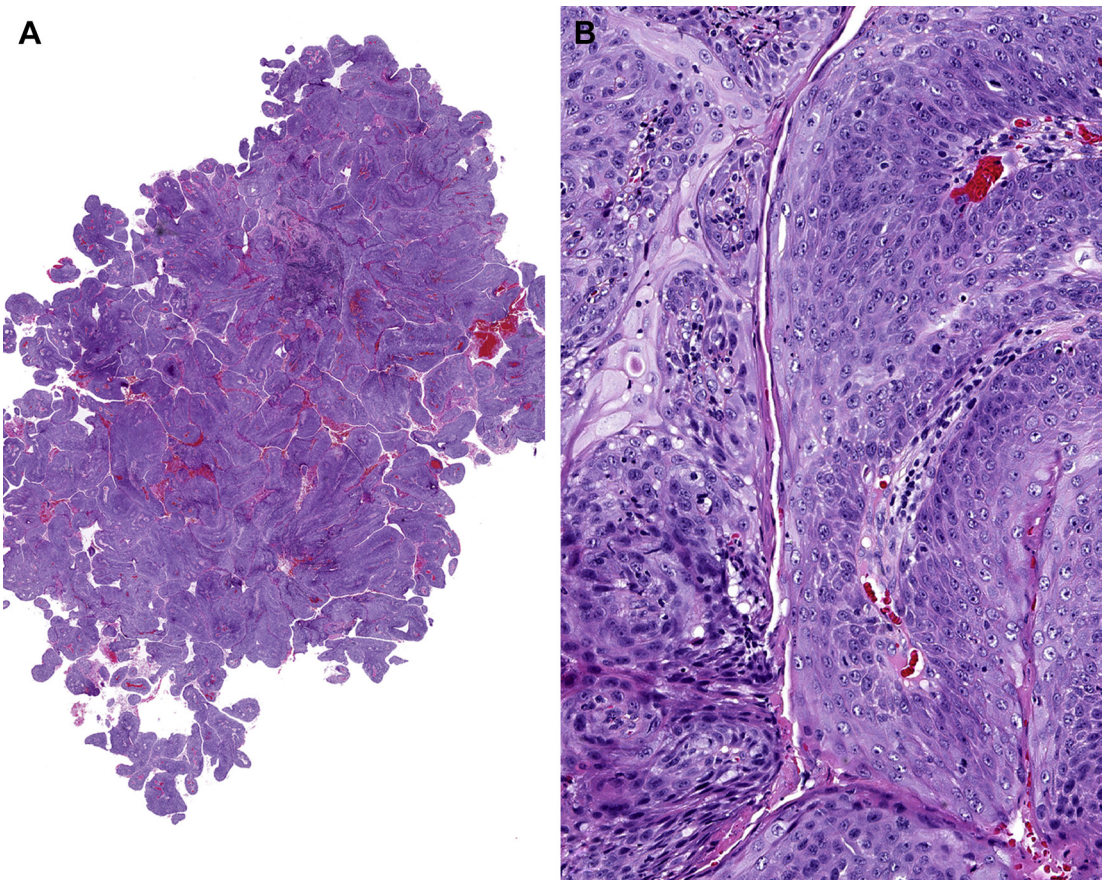

Fig. 7. PSCC. (*A*) A PSCC with numerous individual, delicate fingerlike projections with fibrovascular cores. (*B*) Marked pleomorphism is seen in the lining epithelium of the papillary projections.

of the neck, will show a marbled pattern, expresses TLE1, and will usually show the specific characteristic translocation (*SS18-SSX*).[90,91]

Although the terms "spindle cell" or "sarcomatoid," sound ominous, laryngeal SCSCC, irrespective of T-stage, actually shows a statistically significant better patient outcome when no epithelial marker immunoreactivity can be demonstrated (ie, patients with tumors that are keratin immunoreactive tend to have a worse prognosis), although patients generally show an excellent prognosis in comparison with conventional SCC.[15,17,77]

BASALOID SQUAMOUS CELL CARCINOMA

Basaloid SCC (BSCC) is a high-grade SCC variant showing a prominent basaloid component and evidence of squamous cell differentiation, showing a predilection for the supraglottis, frequently presenting with multifocality, primarily affecting men in the seventh decade of life with frequent advanced stage at presentation (**Table 3**).[18,92–95] There is no significant transcriptionally active HPV association with laryngeal tumors.[94,96,97] Macroscopically, these tumors are usually firm to hard with associated central necrosis.

Histologically, the tumor invades in a submucosal distribution as smooth-bordered lobules, cords, and nests, frequently showing peripheral palisading (**Fig. 10**A). The depth of invasion may not be obvious on a superficial biopsy, and thus generous sampling is necessary for diagnosis. Lymphovascular invasion is common. The basaloid component is the most diagnostic feature, showing closely approximated cells with a high nuclear-to-cytoplasmic ratio and hyperchromatic chromatin. The cells are often separated by a prominent, hyalinized densely eosinophilic stroma that may form small droplets or cylinders within the tumor, creating a jigsaw puzzle appearance (**Fig. 10**B). Glandlike foci often with mucomyxoid material can mimic adenocarcinoma. Squamous differentiation may be in the form of abrupt keratinization, squamous pearls, individual cell

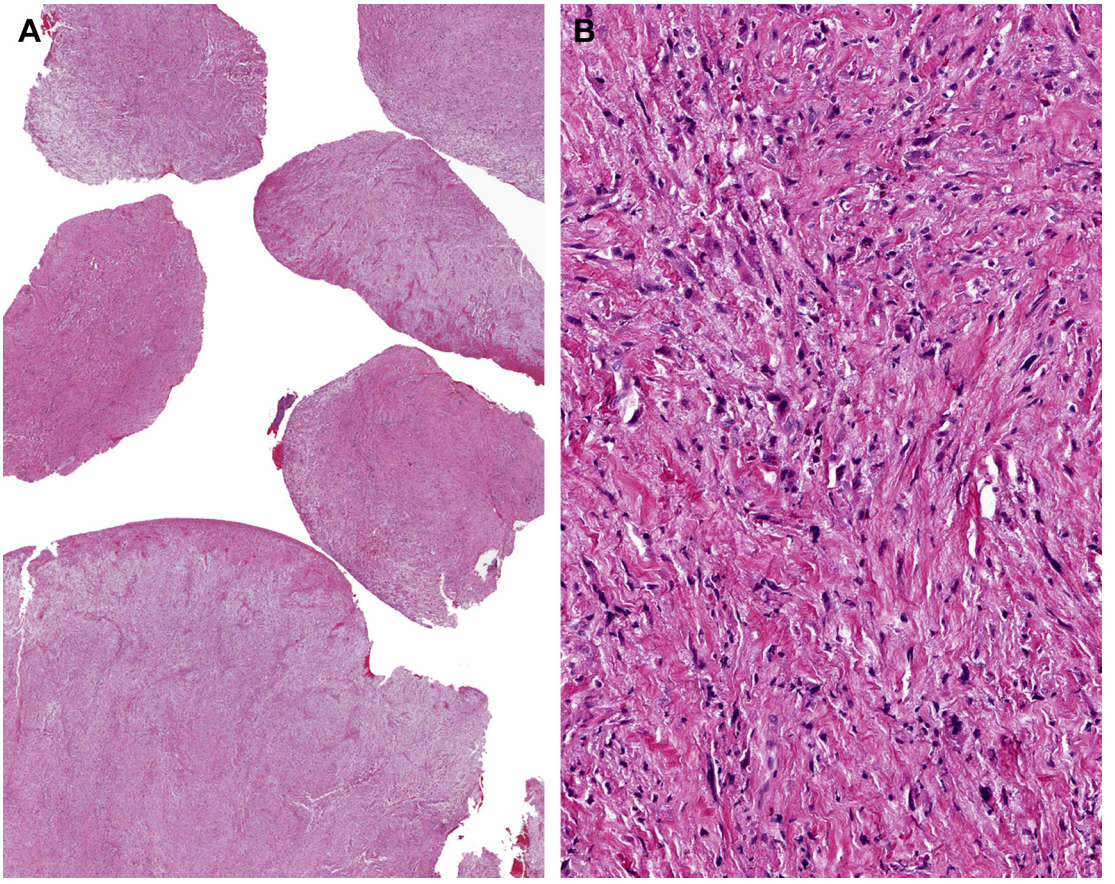

Fig. 8. SCSCC. (*A*) Multiple polypoid fragments of tissue with surface ulceration. (*B*) Hypocellular spindled tumor showing isolated pleomorphic cells with hyperchromatic nuclei.

keratinization, dysplasia, or SCC (in situ or invasive). Although both basaloid and squamous cell components can be seen in metastases, the basaloid features predominate. Epithelial markers (pancytokeratin, CAM5.2, EMA, CK7, 34ßE12) and p63 and p40 are consistently reactive, whereas neuroendocrine markers are negative; p53 is overexpressed.[98–100] A perinuclear "dot" of vimentin immunoreactivity is occasionally seen.[93,101]

The differential diagnosis includes neuroendocrine carcinoma (small cell and large cell types), SCC, adenoid cystic carcinoma (ACC), adenosquamous carcinoma (ASC), and high-grade mucoepidermoid carcinoma (MEC) (**Table 2**). All these diagnoses require sufficient sampling to demonstrate the heterogeneous components of the tumor.[18,99,102] ACC lacks squamous differentiation, usually shows limited mitoses and necrosis, and shows biphasic distribution of p63 and epithelial markers.[93,98,103] *MYB* is seen in ACC and not in BSCC.[104,105] Neuroendocrine carcinoma may show squamous differentiation, but demonstrates nuclear molding, salt-and-pepper nuclear chromatin distribution, and demonstrates neuroendocrine markers.[103] Combined features of true mucinous differentiation with transitional cells would confirm an MEC, whereas two distinct tumors would define an ASC. True glandular elements would define ASC.

BSCC of the larynx has an overall worse prognosis compared with conventional SCC, especially in active smokers, but irrespective of stage, tumor location, or treatment received, and showing high rates of nodal metastases (50%–70%) and distant metastases.[18,94,106]

ADENOSQUAMOUS CARCINOMA

ASC shows an admixture of SCC and adenocarcinoma, often accompanied by an undifferentiated cellular component. The SCC can be in situ or invasive, showing intercellular bridges, keratin pearl formation, and dyskeratosis (**Fig. 11**). The adenocarcinoma shows glandular differentiation (see

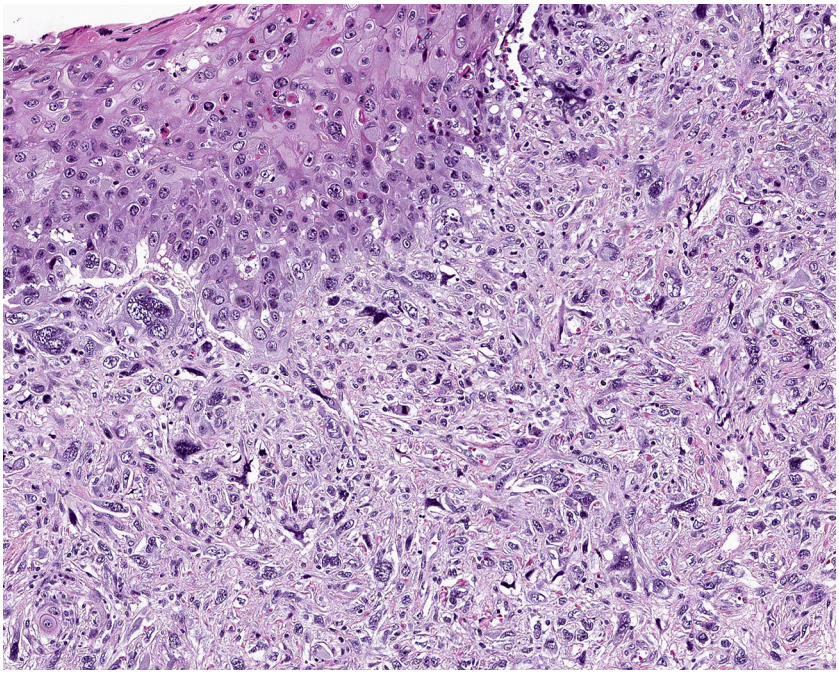

Fig. 9. SCSCC. An SCSCC blending of the surface epithelium with the spindle-cell component. Abrupt transitions with conventional SCC is present (*left*), with focal profoundly pleomorphic cells.

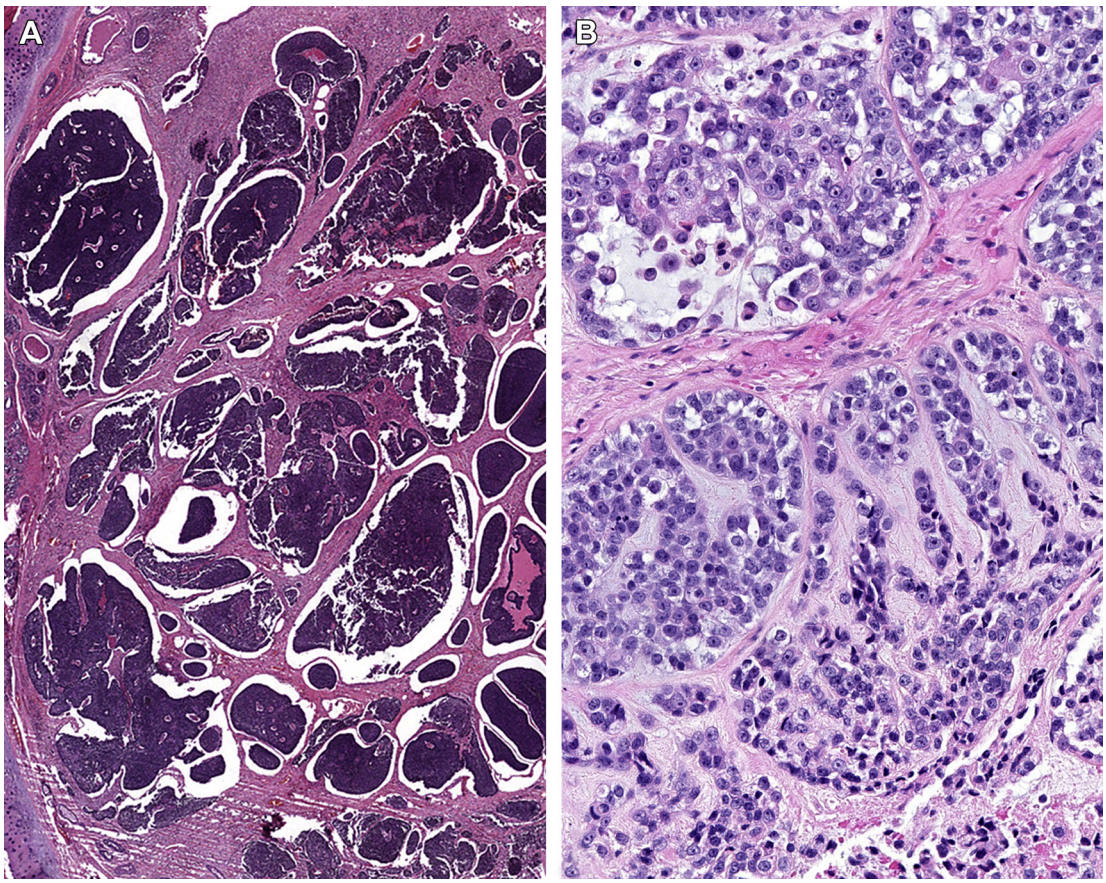

Fig. 10. BSCC. (*A*) There is a lobular architecture, with areas of central comedonecrosis, with cartilage (*far left*). The neoplastic proliferation is highly basaloid. (*B*) A prominent hyalinized material between tumor cells with associated myxoid material. Focal squamous differentiation is noted.

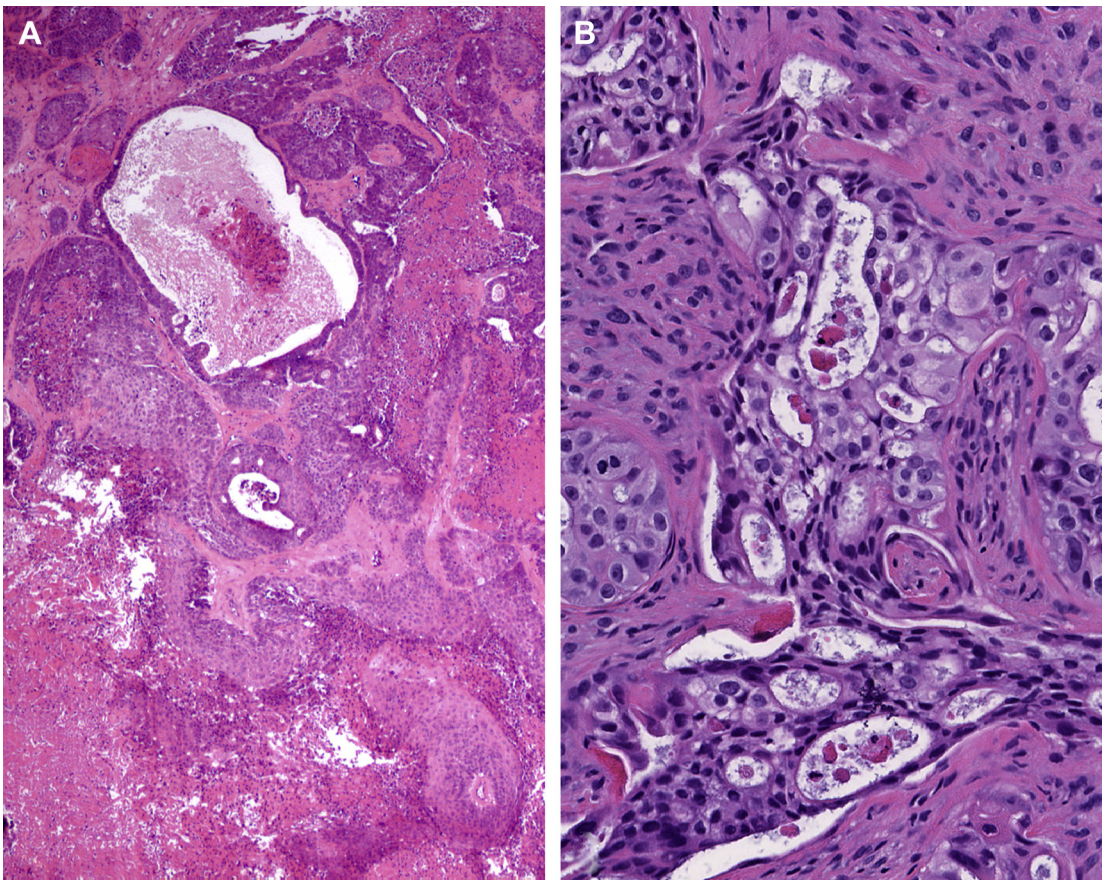

Fig. 11. ASC. (*A*) Low power shows a single tumor mass with an adenocarcinoma (*upper*) blending with a keratinizing SCC (*lower*). (*B*) High power demonstrates blending of an adenocarcinoma and SCC (*far left*) within a single tumor mass associated with desmoplasia.

Fig. 11), including mucocytes or goblet cells (**Table 3**). Basaloid cells in either the SCC or adenocarcinoma may make distinction from BSCC arbitrary. The two tumors may be separate or intermixed, with areas of commingling. The "undifferentiated" transition areas often show cytoplasmic clearing. Increased mitoses and necrosis may be seen.[107–112]

Although impossible to distinguish in some cases, MEC shows intermediate type cells and generally lacks true squamous cell differentiation (**Table 2**). Two distinct tumor populations are not seen in MEC. Further, *CRTC1-MAML2* translocation is not seen in ASC.[108] BSCC shows islands of basaloid cells, peripheral nuclear palisading, and lacks true glandular differentiation. An adenocarcinoma with surface squamous metaplasia lacks the malignant squamous cell component. An adenoid SCC (acantholytic SCC) shows acantholysis of the squamous cells, mimicking glandular differentiation, but lacking a positive mucicarmine reaction.[113] Synchronous collision tumors (SCC and adenocarcinoma) may affect the larynx, with the bulk of the tumors temporally distinct. The overall outcome is historically poor, although recent data suggest no significant differences in outcome as compared with conventional SCC when matched for stage and other variables.[108,112]

RARE VARIANTS

NUT CARCINOMA

NUT carcinoma is exceedingly rare in the larynx and is a poorly differentiated carcinoma often with evidence of abrupt squamous differentiation, at least focally, and defined by the presence of *NUT* (*NUTM1*) gene rearrangement, detected by a strongly expressed NUT protein by immunohistochemistry.[114,115]

SMARCB1-DEFICIENT CARCINOMAS

SMARCB1-deficient carcinomas develop all over the body, although rare, frequently showing poorly

differentiated cells with rhabdoid features and by definition lacking *SMARCB1* (INI-1) protein by immunohistochemistry. They are not yet reported in the larynx.[116]

LYMPHOEPITHELIAL CARCINOMA

Lymphoepithelial carcinoma is an SCC that is identical to nonkeratinizing undifferentiated nasopharyngeal carcinoma, although exceptional in the larynx. There is less of an association with Epstein-Barr virus in the larynx. The histologic features of large cells with high nuclear-to-cytoplasmic ratio, and prominent nucleoli within vesicular nuclei associated with lymphoid cells is characteristic.[117,118]

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