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Spindle Cell (Sarcomatoid) Carcinomas of the Larynx

A Clinicopathologic Study of 187 Cases

Lester D. R. Thompson, M.D., Jacqueline A. Wieneke, M.D., Markku Miettinen, M.D., and Dennis K. Heffner, M.D.

Laryngeal spindle cell (sarcomatoid) carcinomas are uncommon tumors, frequently misdiagnosed as reactive lesions or mesenchymal malignancies. The records of 187 patients with tumors diagnosed as laryngeal spindle cell (sarcomatoid) carcinoma were retrieved from the files of the Otorhinolaryngic Tumor Registry of the Armed Forces Institute of Pathology. There were 174 men and 13 women, 35–92 years of age (average, 65.6 years). Nearly all patients experienced hoarseness (n = 165 [88%] patients) for a mean duration of 11.0 months. Patients admitted to smoking (n = 162 [87%] patients) and/or alcohol use (n = 90 [48%] patients). Most tumors were glottic (n = 132 [71%]), T1 (n = 111 [59%]),[1] and polypoid (n = 185 [99%]), with a mean tumor size of 1.8 cm. Histologically, squamous cell carcinoma (n = 157 [84%]) was noted, ulcerated, and blended with the spindle cell component, which was most frequently arranged in a storiform pattern (n = 92 [49%] tumors). Foci of benign or malignant cartilage and/or bone (n = 13 [7%]) were noted in the spindle cell component. All patients were treated with surgery (n = 90 [48%] patients) or surgery with radiation (n = 97 [52%] patients). Recurrences developed in 85 (45%) patients. Overall, T1 glottic tumors managed by complete surgical eradication had the best outcome (mean follow-up, 7.8 years).

Key Words: Larynx—Sarcomatoid carcinoma—Spindle cell carcinoma—Spindle squamous cell carcinoma—Prognosis—Treatment.

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From the Departments of Endocrine and Otorhinolaryngic–Head & Neck Pathology (L.D.R.T., J.A.W., D.K.H.) and Soft Tissue Pathology (M.M.), Armed Forces Institute of Pathology, Washington, DC, U.S.A.

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Address correspondence and reprint requests to Lester D. R. Thompson, MD, Department of Endocrine and Otorhinolaryngic–Head & Neck Pathology, Building 54, Room G066-11, Armed Forces Institute of Pathology, 6825 16th Street, NW, Washington, DC 20306-6000, U.S.A.; e-mail: thompsonl@afip.osd.mil

The histologic classification of malignant tumors is not only of academic interest from a histogenetic viewpoint, but also from that of treatment and prognosis. Laryngeal spindle cell (sarcomatoid) carcinomas (LSCSCs) have been the focus of a great deal of discussion over the years, harkening back to the original descriptions of these tumors.[36,52] Over the years many terms have been applied to the confounding neoplasm under consideration (Table 1). These tumors were considered to be collision tumors, combination tumors, or composition tumors. It was believed that the absence of mingling of the stromal and epithelial elements militated against their being transformed carcinomas; therefore, the spindled process was reactive or reparative.[3,22,36,52] With the passage of time leading to a better understanding of these malignant tumors, the medical community (as reflected in the literature) has come to recognize this peculiar, morphologically biphasic tumor process as a carcinoma that has surface epithelial changes (in situ to invasive carcinoma) and an underlying spindle-shaped neoplastic proliferation. When the malignant surface epithelium is histologically evident, the diagnosis of a spindle cell (sarcomatoid) carcinoma is made with confidence. However, when the surface epithelium is ulcerated or denuded, the correct diagnosis is more difficult to render. Furthermore, the "epithelial" derivation of the spindle cell component has only been suggested in single case reports or small series but not in a large, comprehensive study.[2,4,11,16,17,22,27,29,31,35,37,38,47,49,51,51,52,56,62] Last, but most certainly not least important, the treatment modalities applied in these cases have also not been critically assessed with regard to their efficacy and influence on the patients' long-term prognosis. Therefore, it is the intention of this study to provide a comprehensive analysis of LSCSC encompassing the use of clinical features, histologic findings, immunophenotypic studies, and follow-up information (including staging and adjuvant therapies) applied to a group of 187 patients with this

TABLE 1. *Terms used for spindle cell (sarcomatoid) carcinoma*

Carcinosarcoma
Pseudosarcoma
Pseudocarcinoma
Pseudocarcinosarcoma
Pseudosarcomatous carcinoma
Carcino(pseudo)sarcoma
Spindle cell carcinoma
Spindle cell variant of squamous carcinoma
Squamous cell carcinoma with pseudosarcoma (Lane tumor)
Squamous cell carcinoma with sarcoma-like stroma
Bizarre squamous cell carcinoma
Carcinoma with pseudosarcoma
Pleomorphic carcinoma
Metaplastic carcinoma
Polypoid squamous cell carcinoma

tumor, which is, to the best of our knowledge, the largest single series to date in the English literature (MEDLINE, 1966–2001).

MATERIALS AND METHODS

The records of 533 patients with tumors diagnosed as "spindle cell carcinoma," "sarcomatoid carcinoma," "spindle squamous cell carcinoma," "carcinosarcoma," or "Lane tumor" were identified in the files of the Otorhinolaryngic–Head & Neck Registry at the Armed Forces Institute of Pathology from 1970 to 1997. These 533 patients were identified in a review of 6939 patients (7.7%) with benign and malignant primary laryngeal neoplasms who were seen in consultation during this same time period. However, 346 patients were excluded from further consideration because of at least one of the following reasons: 1) paraffin blocks were unavailable for additional sections; 2) the cases were diagnosed indefinitely, using terms such as "consistent with," "suggestive of," "probably," or "suspicious for"; and 3) the originally submitted case did not have sufficient demographic information supplied from which to obtain adequate and complete follow-up information. Therefore, the remaining 187 patients with LSCSC constitute the subject of this study based on complete follow-up information and sufficient material to at least obtain a definitive or "diagnostic" hematoxylin and eosin-stained slide to confirm a spindle cell (sarcomatoid) carcinoma diagnosis. These 187 patients represented 2.7% of the 6939 benign and malignant primary laryngeal neoplasms, and 4.2% of the 4433 squamous cell carcinomas (SCCs) of the larynx diagnosed during the above referenced period. A total of 146 patients were from civilian sources, including university medical centers, community hospitals, and foreign contributors, 27 patients were from Veterans Administration medical centers, and 14 patients were from military hospitals.

Materials within the Institute's files were supplemented by a review of the patient's demographics (gender, age, and ethnicity), symptoms at presentation (including duration), and past medical history (specifically, a history of previous radiation exposure, tobacco and/or alcohol use). (Heavy alcohol consumption is difficult to define because it varies from patient to patient, but more than 6 alcohol equivalents per day was considered heavy [1 shot of liquor, 1 glass of wine, or 1 beer was considered an alcohol equivalent]). In addition, we reviewed surgical pathology and operative reports and obtained follow-up information from oncology data services by written questionnaires or direct communication with the treating physician or the patient. Follow-up data included exact tumor location, tumor size and stage, treatment modalities, and current patient and disease status. It is important to add that we are a tertiary pathology review center, conducting a retrospective review of these patients and that we did not treat the patients. Whereas tumor stage was obtained as T1a and T1b, T2a and T2b for purposes of statistical analysis, they were compressed into stages T1 and T2, respectively. This clinical investigation was conducted in accordance and compliance with all statutes, directives, and guidelines of the Code of Federal Regulations, Title 45, Part 46, and the Department of Defense Directive 3216.2 relating to human subjects in research.

Hematoxylin and eosin-stained slides from all patients were reviewed for morphologic assessment of LSCSC. A number of observations were recorded for each tumor as follows: polypoid nature of the tumor (Fig. 1), presence of SCC at the surface (with or without ulceration and if blended with the spindle cell component) (Fig. 2), growth pattern (fasciculated, storiform, solid, or a mixture of all three types) (Fig. 3), mitotic index (number of mitotic figures per 10 high power fields using a ×10 objective and ×40 lens), presence or absence of atypical mitotic figures (defined by abnormal chromosome spread, tripolar or quadripolar forms, circular forms, or indescribably bizarre), nuclear pleomorphism (graded as mild, moderate, or severe, as determined by an increased nuclear to cytoplasmic ratio, nuclear contour irregularities, irregular nuclear chromatin distribution, prominent or irregular nucleoli, poikilonucleosis, and anisonucleosis) (Fig. 4), tumor cellularity (subjectively divided into low [few nuclei per high power field, Fig. 5], moderate [average number of nuclei per high power field], or high [nuclear overlapping, crowding, or touching per high power field]), the presence and degree of tumor necrosis (defined as areas of cell death, not simply areas of degeneration) (Fig. 6), presence and type of giant cells (Fig. 4B), presence of acellular bands of fibrosis or collagen deposition, presence of bone or cartilage (either benign or malignant) (Fig. 7), variants of SCC, and the presence of an overwhelming inflammatory component.

Immunophenotypic analysis was performed in 123 cases with suitable material by using the standardized avidin-biotin method of Hsu et al.[28] using 4 μm-thick,

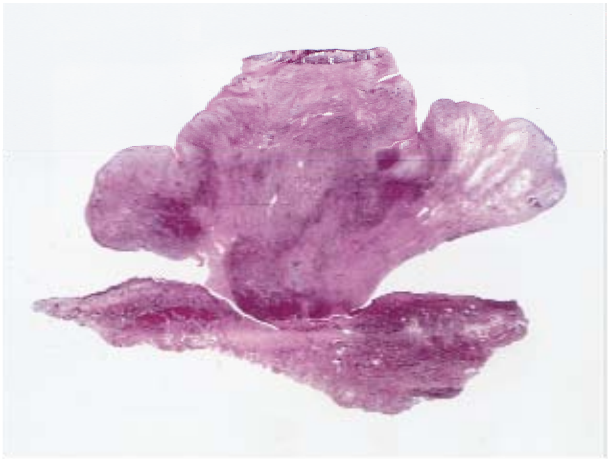
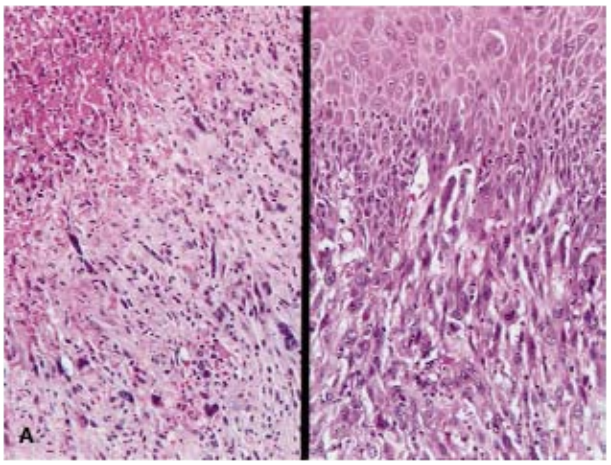
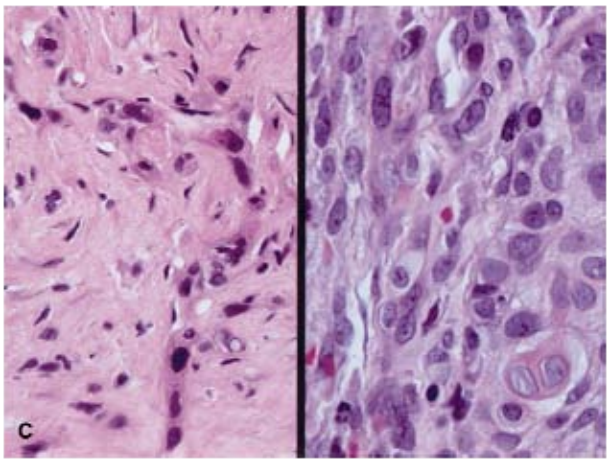


FIG. 1. A macroscopic view demonstrates a polypoid LSCSC attached by a stalk, showing surface ulceration. Surface epithelium is only focally present.





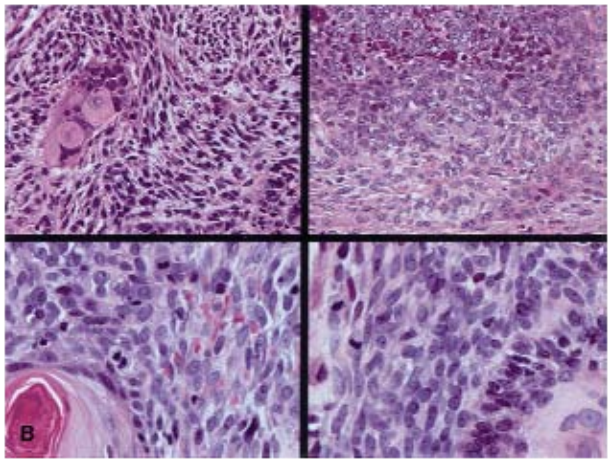
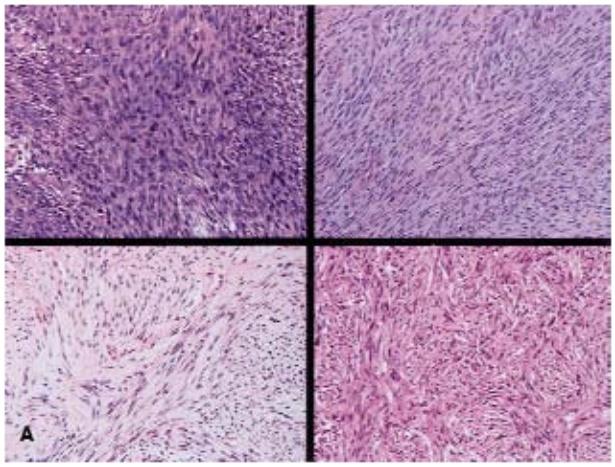


FIG. 2. (A) The surface epithelium was frequently ulcerated, leaving fibrinoid necrosis and inflammation (left). When the surface was present, an imperceptible blending is seen between the surface and the spindle cell component (right). **(B)** Each of these quadrants demonstrates the juxtaposition of the squamous cell carcinoma with the spindle cell part. The upper left shows a small island of squamous epithelium with cytologic atypia, whereas the upper right shows the more subtle epithelial differentiation in the lower corner. The lower left image shows a squamous pearl with the basal cells blending with the spindle cells, as does the lower left image. **(C)** In many cases the spindle cells had a slightly opaque, "hard," or keratinized cytoplasm, which suggests the epithelial or squamous derivation of the tumor (left). In many tumors areas of frank squamous cancer could be seen in the center of a spindle cell area (right), showing how intermingled and related the two components were.



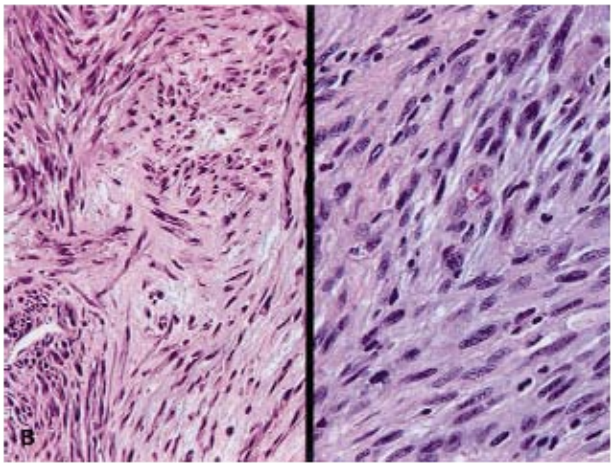


FIG. 3. (A) A number of different patterns of growth were noted, such as solid spindle cell proliferation (left upper), herringbone or chevron-like (upper right), loosely fascicular (lower left), or storiform to cartwheel (lower right). **(B)** Many tumors can take on an interlacing fascicular growth simulating a nodular fasciitis-like pattern (left), whereas the abrupt juxtaposition of the fascicles in a few tumors can simulate a fibrosarcoma-like pattern (right).

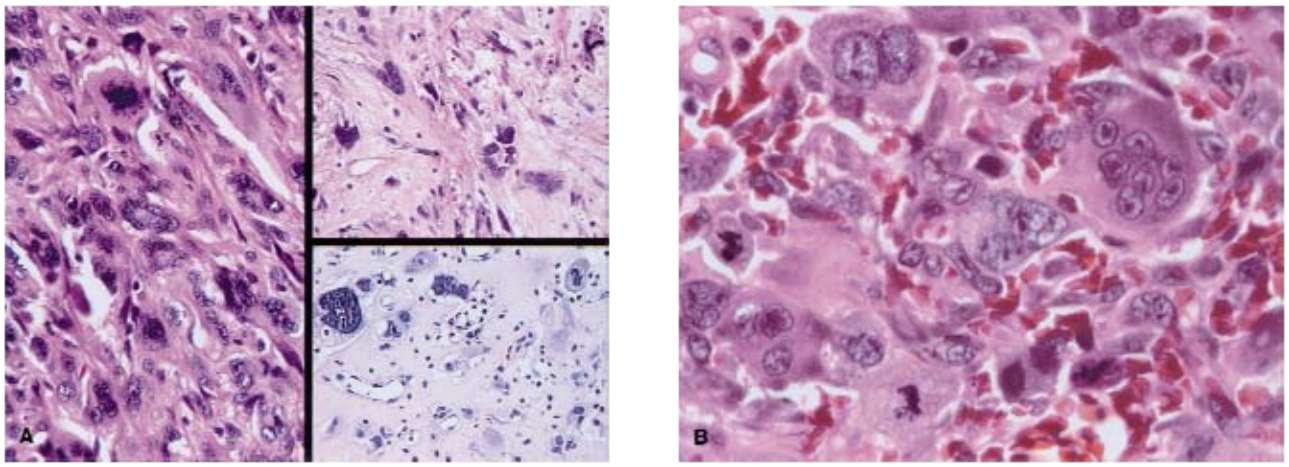


FIG. 4. (A) Bizarre nuclei are present in the spindle and "epithelioid" cells in this LSCSC (left), whereas atypical nuclei can be seen in the spindle cell component (upper right), even when the tumor was hypocellular (lower right). **(B)** Malignant giant cells with prominent nucleoli are seen in this image, which also shows many mitotic figures, including atypical forms.

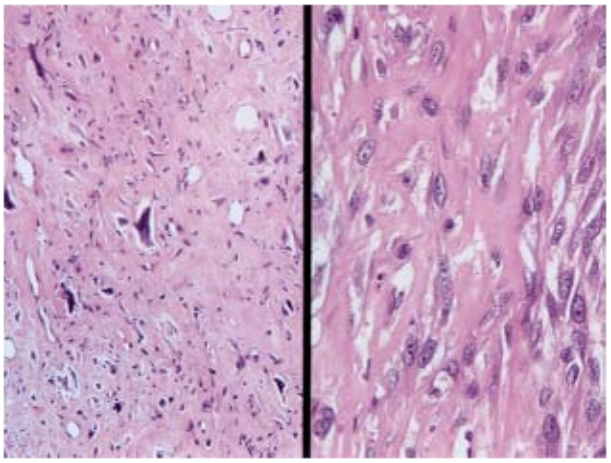


FIG. 5. The remarkable cytologic atypia in the left image is still evident even in this low cellularity tumor, whereas less cytologic atypia is present in the right image of an LSCSC.

formalin-fixed, paraffin-embedded sections. Table 2 documents the pertinent, commercially available immunohistochemical antibody panel used. The analysis was performed on a single representative block in each case, trying to choose a block that showed an area of transition or surface epithelium when present to provide an internal control. When required for cellular conditioning, proteolytic antigen retrieval was performed by predigestion for 3 minutes with 0.05% protease VIII (Sigma Chemical Co., St. Louis, MO, USA) in 0.1-mol/L concentration of phosphate buffer, pH of 7.8, at 37°C. Antigen enhancement (recovery) was performed as required by using formalin-fixed, paraffin-embedded tissue that was treated with a buffered citric acid solution and heated for 20 minutes in a calibrated microwave oven. Afterwards, the sections were allowed to cool at room temperature in a citric acid buffer solution for 45 minutes before con-

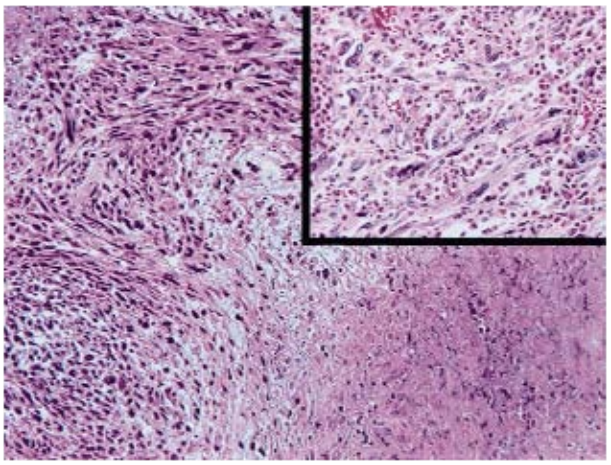


FIG. 6. Tumor necrosis was not a common feature, but when seen demonstrated a coagulative-type necrosis, often in association with degenerative changes. Acute inflammatory cells were not seen frequently but included eosinophils when identified (inset).

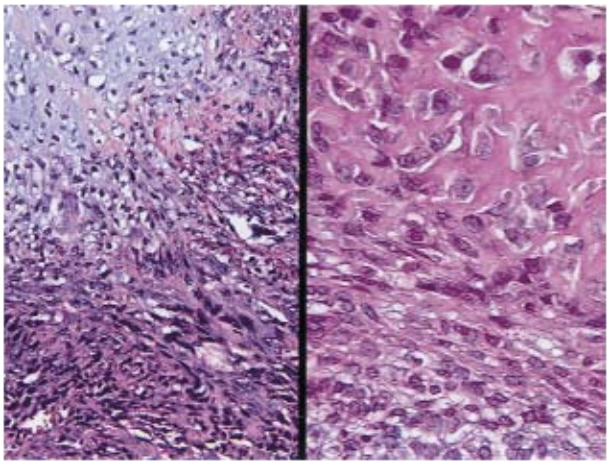


FIG. 7. Chondrosarcoma (left) could be seen in association with the spindle cell component, whereas osteosarcoma (right) was noted in a number of cases. Osteoid is easily identified in association with remarkably atypical cells.

tinuing the procedure. Standard positive controls were used throughout, with serum used as the negative control. The antibody reactions were graded for intensity as weak (1+), moderate (2+), and strong (3+) staining, and the fraction of positive cells was determined by separating the percentage of positive cells into four groups: 1–25% (focal), 26–50%, 51–75%, and 76–100% (diffuse). Immunoreactivity was only sought in the spindle cell component, as the areas of obvious epithelial (squamous) differentiation at the surface or within the tumor would not be of value in the discrimination of the nature of the spindle cell component.

Our review was based on a MEDLINE search from 1966 to 2000 with a few specific earlier articles included for balance and background. However, for purposes of succinctness, we used only research articles that included demographic and treatment information for at least 10 patients and that were written in English (Table 3).

Categorical variables were analyzed using χ^2 tests to compare observed and expected frequency distributions. Comparison of means between groups were made with unpaired *t* tests or one-way analysis of variance, depending on whether there were two groups or more than two groups, respectively. Multiple comparisons were analyzed using the Tukey method. Linear regression was used to investigate two measured variables, and Pearson correlation coefficients were generated to measure the strength of the association. Confidence intervals of 95% were generated for all positive findings. The α level was set at $p < 0.05$. All analyses were conducted using Statistical Package for the Social Sciences (SPSS) software (version 8.0 for PC; Chicago, IL, USA).

RESULTS

Sociodemographic Characteristics

A summary of the clinical information on the patients in this series is provided in Table 4. There was a male-to-female ratio of 13:1. The majority of patients used tobacco (usually cigarettes) (n = 162; 87%) or reported heavy consumption of alcohol (n = 90; 65%). Twelve of the 13 women used tobacco and six reported alcohol use. Because of the nature of this study, an accurate pack-year history was not available in the early cases, and hence none of the results are herein reported.

Hoarseness was the most frequent symptom experienced by the patients (n = 165, 88%), often accompanied by a variety of other symptoms (Table 4). A few patients actually "coughed up" their tumors (n = 3). The patients with previous radiation exposure had a shorter mean duration of symptoms (9.2 months) than the rest of the patients, but this difference was not statistically significant. Similarly, women had a shorter mean duration of symptoms (5.3 months) than the men (11.7 months) ($p = 0.002$). This difference may be accounted for by the smaller luminal diameter of the larynx in women than in men, causing a polypoid tumor to present earlier in women than in men, especially because the mean tumor size in women (mean 2.1 cm) was larger than in men (1.8 cm), although not statistically significant.

Radiation Exposure History

Seventeen patients had a history of radiation exposure. In 14 patients the radiation was therapeutic for a prior SCC of the larynx, pyriform sinus, or base of the tongue, between 1.2 and 16 years before the development of the LSCSC. All were men, all had hoarseness except one, and all had smoked. These patients had 10 stage T1, 3 stage T2, and 4 stage T3 tumors, occurring in the glottis (n = 10 tumors), supraglottis (n = 2 tumors), and subglottis (n = 1 tumor) or were transglottic (n = 4 tumors). The mean size of the tumor was 1.9 cm. Three patients had tumors with osteocartilaginous histology, but this number of patients was not statistically different from the number of patients with osteocartilaginous histology without previous radiation. Three patients' tumors had epithelial immunoreactivity of the seven tested.

Pathology

Macroscopic Features

The overwhelming majority of lesions were received as polypoid tumor masses (n = 185 tumors), with only two tumors described as sessile or ulcerated. When not covered by a fibrinoid necrosis over the ulcerated surface, the tumors were firm and fibrous, usually arising from a stalk of variable breadth (Fig. 1).

Glottic tumors were the most common, especially if one includes the transglottic tumors (Table 5). However, because all transglottic malignant tumors behave in a much more aggressive fashion, they have been separated out in this analysis. The average tumor size in women was 2.1 cm versus 1.8 cm for men, but this was not significant ($p = 0.426$). A total of 154 cases were "biopsy" specimens, with the remaining 33 tumors obtained from wider excision, hemilaryngectomy, or laryngectomy specimens. The clinicians considered the "biopsy" a complete excision, and so the size was based on the "biopsy" specimen, even if the patient had another operation later. Most tumors fell into the T1 group (n = 111 tumors, 59.4%), with 75.8% of the glottic tumors (n = 100 tumors) classified as T1 tumors, in contrast to 23.6% (n = 13 tumors) of the nonglottic tumors (Table 5). All T4 tumors were nonglottic.

Microscopic Features

The demonstration of squamous epithelium at the surface was often difficult because of surface ulceration. Whether present as dysplasia, carcinoma in situ, or in-

TABLE 2. *Monoclonal antibodies, their source and dilution, and the cellular conditioning used in this study*

Polypeptide	Clone	Dilution	Company	Pretreatment
K1	34βB4	1:50	Novacastra, New Castle, UK	Microwave
K4	6B10	1:200	Novacastra	Microwave
K5/6	D51/16B4	1:60	Boehringer Mannheim Biochemicals, Indianapolis, IN	Microwave
K6	LHK6B	1:40	Novocastra	Microwave
	OV-TL			
K7	12/30	1:200	Dako, Carpinteria, CA	Enzyme digestion
K8	C8/144B	1:50	Dako	Microwave
K10	LHP1	1:50	Novocastra	Microwave
K13	KS-1A3	1:100	Novocastra	Microwave
K14	LL002	1:100	Novocastra	Microwave
K15	LHK15	1:50	Novocastra	Microwave
K16	LL025	1:40	Novocastra	Microwave
K17	E3	1:40	Novocastra	Microwave
K18	DC-10	1:40	Novocastra	Microwave
K19	RCK 108	1:50	Dako	Microwave
K20	K_s20.8	1:50	Dako	Enzyme digestion
EMA	E29	1:100	Dako	Enzyme digestion
34βE12	K903	Neat	Enzo, St. Louis, MO	Enzyme digestion
Cytokeratin cocktail	AE1/AE3	1:50	Boehringer Mannheim Biochemicals and	Enzyme digestion
	CK1	1:200	Dako	
CAM 5.2	NCL5D3	1:100	Ventana, Tucson, AZ	Enzyme digestion
Vimentin	V9	1:400	Ventana	N/A
S-100 protein	rp	1:400	Dako	Enzyme digestion
Smooth muscle actin	1A4	1:800	Sigma, St. Louis, MO	Enzyme digestion
Muscle specific actin	HUC1-1	Neat	Ventana	Enzyme digestion
Desmin	D33	1:100	Dako	Enzyme digestion
Desmin	DR11	Neat	Dako	Enzyme digestion
CD34	Qbend/10	1:40	BioGenex, San Ramon, CA	Microwave
HMB-45	HMB45	1:50	Dako	N/A
Chromogranin	rp	1:100	Dako	N/A
Glial Fibrillar Acidic Protein (GFAP)	rp	1:2000	Dako	Enzyme digestion

K, keratin; rp, rabbit polyclonal; N/A, not applicable.

filtrating SCC, the obvious epithelial portion of the tumor was usually minor to inconspicuous with the sarcomatoid part dominating the lesion (Fig. 2A–C). The areas of squamous differentiation were most consistently identified at the base of the polypoid lesion, at the advancing margins, or within invaginations at the surface where the epithelium was not ulcerated or denuded. In a number of cases (n = 28) the SCC was present deep within the stroma, indicative of the invasive nature of the tumor even in the presence of areas of sarcomatoid transformation (Fig. 2B). There was no appreciable difference in the histologic grade of the invasive component of SCC.

The vast majority of cases demonstrated extensive surface ulceration with an eosinophilic, friable, fibrinoid necrosis of variable thickness (n = 144 tumors) (Fig. 2A). Considering the frequency of ulceration, it may be difficult to discern the transition between the surface epithelium and the spindle cell element. In this series because multiple levels or sections were examined and because the "carcinoma" portion was meticulously and diligently sought out, classic SCC or dysplastic squamous epithelium was documented in the majority of cases (n = 149) (Table 6). Albeit the majority of specimens were biopsies, the tumors were usually "superficial," without perineural, vascular, or laryngeal cartilage invasion, frequently confined to the polypoid projection of the main tumor mass.

The carcinomatous and sarcomatoid components abutted directly against one another with areas of barely perceptible blending and continuity between them. At times, the area of elongation and spindling seemed to arise from the basal epithelial cells, making indistinct any demarcation between the surface epithelial origin and the underlying tumor. Blending of the two forms of the tumor were noted in 123 tumors and consisted of "dropping off" of individual carcinoma cells into the underlying stroma giving the impression of "junctional" change. The sarcomatoid or fusiform fraction of the tumors was arranged in a diversity of appearances, each imitating a different mesenchymal process: storiform, cartwheel, or whorled (resembling a fibrous histiocytoma or malignant fibrous histiocytoma) (Fig. 3A), intersecting and interlacing bundles or fascicles (similar to leiomyosarcoma) (Fig. 3A), chevron or herringbone (indistinguishable from fibrosarcoma) (Fig. 3B), hypocellular with dense collagen (comparable with fibromatosis) (Fig. 4A), or loose, random grouping with a degenerated background

TABLE 3. *Laryngeal spindle-cell carcinoma: review of the English literature*[2,4,17,22,27,29,36,40,49,51,54,62]

All patients (n = 194)*	No.
Gender	
Women	16
Men	178
Age at initial presentation (yr)	
Range	33–85
Mean	61.9
Type of presentation	
Hoarseness	153
Other	41
Duration of symptoms	
Range	5 days–33 mo
Mean	5.7 mo
Smoking history	Many
Radiation exposure	15
Primary site	
Glottis	135
Transglottis	15
Supraglottic	33
Subglottic	5
Not reported	6
Tumor stage	
T1	53
T2	23
T3	4
T4	1
Not reported	113
Outcome	
Alive, no evidence of disease (mean yr of follow-up)	96 (7.8)
Alive, with disease (mean yr of follow-up)	4 (1.0)
Dead, no evidence of disease (yr of follow-up)	23 (10.0)
Dead, with disease (mean yr of follow-up)	35 (1.8)
Not reported	36

* The parameter was not always stated in the report, and therefore the numbers do not necessarily equal the total values shown in the columns.

TABLE 4. *Clinical demographic features of spindle-cell carcinoma of the larynx*

	No.
Gender	
Females	13
Males	174
Age at presentation	
All (average)	65.6 yr
All (range)	35–92 yr
All (median)	66 yr
Females: average	64.2 yr
Males: average	65.7 yr
Tobacco use	
Yes	162
No	12
Unknown	13
Alcohol use (more than social)	
Yes	90
No	49
Unknown	48
Radiation exposure (environmental or therapeutic)	
Yes	17
No	170
Type of presentation	
Hoarseness	165
Changes in voice	16
Airway obstruction, difficulty swallowing, dyspnea	13
Sore throat	6
Difficulty breathing, shortness of breath, dysphagia	14
Cough, stridor	6
Duration of symptoms (mo)	
Mean	11.3
Range	0.5–180

(analogous to nodular fasciitis) (Fig. 3B). Whereas one pattern may be dominant, most tumors revealed a remarkable admixture of patterns.

Tumor cellularity varied between and within tumors, with the majority of tumors having a low to intermediate cellularity (n = 148 tumors) (Fig. 5). There was no maturation phenomenon. Although there were usually fewer malignant spindle cells immediately subtending the areas of granulation tissue and ulceration, there was no "cambium layer." Pleomorphism tended to be mild to moderate in degree (n = 167 tumors) (Fig. 4). By this we do not mean to imply that the tumor cells did not appear to be malignant but that the degree of "anaplasia" was frequently not severe. The tumor cells were plump fusiform cells, although they could be rounded and epithelioid. Opacified, dense, eosinophilic cytoplasm, although a "soft" criterion, gave the impression of epithelial, and specifically, squamous differentiation (Fig. 4) rather than the usual appearance associated with fibroblasts or myofibroblasts.

TABLE 5. *Macroscopic features of spindle-cell carcinoma of the larynx*

Feature	No.
Anatomic distribution	
Glottic (true vocal cord, anterior (commissure, posterior commissure)	132 (70.6%)
Transglottic	23 (12.3%)
Supraglottic	28 (15.0%)
Subglottic	4 (2.1%)
Location	
Left	78
Right	67
Bilateral	17
Midline	23
Unknown	2
Size (in cm)	
Range	0.2–8.5
Mean	1.8
Median	1.5
Type of presentation	
Polypoid	185
Sessile, ulcerated	2
Tumor Stage	
T1 (including T1a, T1b, and T1)	111
T2	50
T3	23
T4	3

TABLE 6. *Microscopic features of spindle-cell carcinoma of the larynx*

Feature	No.
Squamous cell carcinoma	
Present	4
Present and ulcerated	18
Present and blended	17
Present, ulcerated and blended	102
"Classic" squamous cell carcinoma present deep in the stroma	28
Absent	14
Absent and ulcerated	16
Absent, ulcerated but blended	4
Completely ulcerated	4
Growth pattern	
Fasiculated	28
Storiform	79
Solid	55
Fasicular, storiform and/or solid	25
Mitotic count (per 10 high power fields)	
Range	0–103
Mean	11.9
Median	5
Atypical mitotic figures (present)	137
Nuclear pleomorphism	
Mild	73
Moderate	94
Severe	20
Overall tumor cellularity	
Low	72
Moderate	76
High	39
Necrosis	
Present, <10% of biopsy area	9
Present, <25% of biopsy area	14
Present, <50% of biopsy area	3
Absent	161
Giant cells	
Multinucleated, gigantiform types	106
Osteoclastic-like	8
Broad bands of fibrosis	93
Remaining tissue	
Benign cartilage and/or bone	7
Malignant cartilage or bone	6
Basaloid squamous cell carcinoma growth	4
Acute inflammatory component prominent	3
Myxoid background	3

Giant cells, whether multinucleated, foreign body-type, osteoclast-type, or peculiar neoplastic cells, were present in the majority of cases (n = 114 tumors), dispersed throughout the neoplasm. Mitotic figures, including atypical forms, were easily identified in the majority of tumors, although there was a complete lack of them in a few tumors (n = 16 tumors). Tumor necrosis (Fig. 6), by definition, did not extend to surface ulceration as the necrosis was most likely related to mechanical trauma of the polypoid tumor rather than legitimate tumor cell necrosis. When present, necrosis was spotty and in aggregate accounted for considerably <25% of the biopsy area (Table 6). Desmoplastic fibrosis frequently separated the tumor cells into fascicles. Occasionally, the collagen deposition was so heavy and abundant that it nearly completely overwhelmed the tumor, yielding a low tumor cellularity (Fig. 5). Most of the tumors contained a certain degree of chronic inflammatory cells.

Metaplastic or malignant osteocartilaginous regions were noted in 13 tumors (7.0%) and was usually only noted focally in the spindle cell population (Fig. 7). The areas of osteosarcoma and/or chondrosarcoma were found within the polypoid tumor masses, indicative of an osseous or cartilaginous metaplasia of the spindle cell component rather than a primary tumor of the laryngeal cartilages.

Immunophenotypic Features

The individual tumor cells of LSCSC reacted variably to the immunohistochemical markers (Table 7). Even in cases when immunoreactivity was noted, none of the markers decorated all of the lesional tumor cells. The most sensitive and reliable epithelial (keratin) markers in LSCSCs appear to be keratin (AE1/AE3), K1, K18, and epithelial membrane antigen (Table 7; Fig. 8). All of the other epithelial markers analyzed seemed to react with only a limited number of cases and often with only a limited number of tumor cells, with the notable exceptions of K4, K10, K20, and CAM5.2, which failed to react at all (Table 7). Overall, 84 tumors (68.3%) demonstrated immunoreactivity at least focally in the spindle cell component with at least one epithelial marker. Where the surface epithelium was present, it was strongly and diffusely immunoreactive for the epithelial markers analyzed. As would be expected, the intermediate filament vimentin was present in all cases tested. Several other mesenchymal markers were focally expressed: smooth muscle actin, 32.5%; muscle specific actin, 15.4%; S-100 protein, 4.9%; and desmin (D33 or DR11), 1.6%. This type of lineage infidelity is to be expected in a tumor that has demonstrated sarcomatoid transformation to the degree seen in LSCSC. Other markers, including HMB-45, chromogranin, glial fibrillar acidic protein, and in nearly all cases CD34, were nonreactive.

Clinical Therapy and Patient Outcome

All patients were managed by surgery (Table 8). The treatment included excisional biopsy alone (n = 24 patients), excisional biopsy followed shortly by definitive operation (n = 66), and operation followed by adjuvant radiation therapy (n = 97 patients). The operations included vocal cord stripping, partial laryngectomy, hemilaryngectomy, supraglottic laryngectomy, or laryngectomy, with or without lymph node dissection (partial, modified, or radical neck dissection). Radiation treatment involved external beam irradiation to the larynx and neck, ranging from 2 to 72 Gy (incomplete treatment

course to full treatment). Because we did not perform the treatments, we relied heavily on the records of the Data Oncology Services (Tumor Registry, Cancer Registry) of the referring facilities.

We performed an actuarial analysis of the entire group but thought it would be of greater value to highlight the findings of six specific groups of patients in a detailed method because the controversies in the literature have centered around these particular findings: 1) patients with postoperative radiation treatment, 2) patients with a history of irradiation exposure (environmental or therapeutic), 3) patients who developed recurrences, 4) patients with benign or malignant osteocartilaginous tissue on histology, 5) women, and 6) patients who demonstrated any evidence of epithelial immunoreactivity.

A slight majority of patients (51.9%) received postoperative radiation (Table 8). It is important to add that radiation therapy was used alone (after the initial "diagnostic biopsy") or in conjunction with a salvage procedure (additional surgery after failure to control the tumor) (Table 8). Overall, patients who were managed by surgery alone had a better outcome than patients managed with surgery and postoperative radiation (mean 7.7 years of follow-up vs mean 6.7 years of follow-up, respectively). We cannot make a specific comment about the possibility that radiation therapy was used only in more clinically advanced cases because we did not determine the specific treatment regimens. Similarly, a lower percentage of patients died of their disease in the surgery only group (18.9%) compared with the surgery and radiation group (42.3%), although there was a longer survival for the patients in the radiation group (3.6 years) than the surgery group (1.9 years). If the percentage of patients who died with their disease is compared between the patients managed by surgery alone and those managed with surgery and radiation separated by T-stage, an overall greater percentage of patients died with disease in the radiation group: 9.5% of patients died treated by surgery alone versus 38.0% treated with radiation in patients with T1 tumors, 27.8% versus 43.3% with T2 tumors, 66.7% versus 50.0% with T3 tumors, and none versus 66.7% with T4 tumors, respectively. However, only 25.0% of patients managed by radiation alone (no salvage) died of their disease, similar to the 18.9% of patients managed by surgery alone (no radiation). Furthermore, it is of interest to note that there is no significant difference in length of survival between the patients managed by radiation alone (no salvage) (mean 3.9 years) versus those patients who had radiation and a salvage procedure (mean 3.9 years), but a much higher percentage of patients died when a salvage procedure was performed (50.9%) than if no salvage procedure was performed (25.0%). Inherent in these statistics, however, is the fact that a salvage procedure would not be performed unless a recurrence developed even though a recurrence also implies a failure to control the tumor by radiation therapy. Therefore, it is best to compare the biopsy followed by radiation alone (no salvage) data to the patients managed by excision alone (without additional surgery) (Table 8). Thus, 16.7% of patients managed by biopsy alone died with disease, whereas 25.0% of patients managed by radiation alone (no salvage) died with disease.

TABLE 7. *Immunohistochemical panel results*

Antigen/antibody	No. (percentage) of positive immunoreactions in spindle cell component (n = 123)*
K1	43/104 (41.0)
K4	0/104 (0)
K5/6	8/117 (6.8)
K6	9/104 (8.7)
K7	5/117 (4.3)
K8	0/104 (0)
K10	0/104 (0)
K13	7/104 (6.7)
K14	16/104 (15.4)
K15	2/104 (1.9)
K16	0/104 (0)
K17	14/104 (13.5)
K18	25/104 (24.0)
K19	5/104 (4.8)
K20	0/117 (0)
Epithelial membrane antigen	21/117 (17.9)
34βE12	10/117 (8.5)
Keratin cocktail (AE1/AE3 and CK1)	32/123 (26.0)
CAM 5.2	0/122 (0)
Vimentin	108/108 (100)
S-100 protein	6/123 (4.9)
Smooth muscle actin	40/123 (32.5)
Muscle specific actin	19/123 (15.4)
Desmin (D33)	2/123 (1.6)
Desmin (DR11)	2/123 (1.6)
CD34	1/123 (0.8)
HMB-45	0/123 (0)
Chromogranin	0/123 (0)
Glial fibrillar acidic protein	0/123 (0)

* The maximum number of tumors tested. Variable for each antibody.

Seventeen patients in this clinical series had a history of radiation exposure (Table 9). Overall, seven patients were either alive (n = 3 patients) or had died of unrelated causes (n = 4 patients) without evidence of disease at last follow-up (average, 9.1 years), whereas 10 patients had died with evidence of disease (average, 4.8 years). Although there was a tendency for a greater percentage of patients to die with disease as the stage increased, with only 17 patients to analyze, statistical significance could not be determined. However, when compared with the patients who did not have radiation exposure, there is a significant difference in these parameters: 60.0% of patients with radiation exposure died with tumor versus 22.0% of patients without radiation exposure with T1 tumors, 33.3% versus 37.5% of patients with T2 tumors, 75.0% versus 54.2% of T3 tumors, respectively ($p < 0.001$).

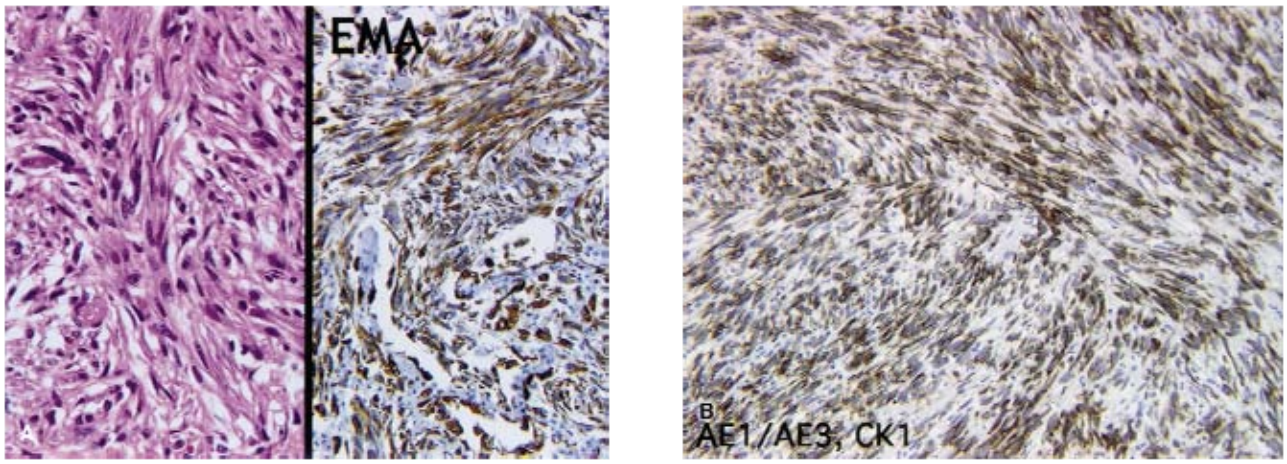


FIG. 8. (A) Epithelial membrane antigen immunoreactivity was strongly identified in the spindle cell component (right), here noted in a metastatic deposit in the lung of a patient whose tumor metastasized to the lung (left). **(B)** Keratin immunoreactivity was frequently strongly and intensely reactive in the spindle cell component of LSCSC.

Eighty-five patients (45%) developed recurrent disease or had residual disease (Table 9). Of these 85 patients, 38 patients were alive (n = 16 patients) or had died (n = 22 patients) without evidence of disease at the last follow-up (mean 9.7 years), whereas 47 had evidence of disease at the last follow-up (mean 3.6 years): 2 patients were alive (mean 5.3 years) and 45 patients had died (mean 3.4 years) (Table 9). These recurrences developed within 2 months (probably more accurately stated to be residual disease) to 9 years later. These results translate to 52.9% of patients who develop a recurrence of their tumor will die *with* or *from* the disease (without taking treatment regimens into consideration). Furthermore, with increasing tumor stage, there was an increased percentage of patients who died with disease: 41.9% of T1 tumors, 55.6% of T2 tumors, 76.9% of T3 tumors, and 100% of T4 tumors. The overall mean survival also decreased as the tumor stage increased (Table 9).

Thirteen patients developed tumors with osteocartilaginous differentiation. These tumors occurred only in men (mean 64.2 years), all of whom smoked, 69% of whom had heavy alcohol use, and three had previous radiation exposure (23%). The average tumor size was 1.9 cm. Nine tumors were glottic, one was transglottic, and three were supraglottic. Eight tumors were T1, four

TABLE 8. *Treatment-based patient outcome (segregated by T-stage)*

Treatment	No. of patients (yr)	A, NED (yr)	A, D (yr)	D, NED (yr)	D, D (yr)
All patients	187 (7.2)	51 (9.6)	2 (5.4)	76 (8.7)	58 (3.1)
Excision biopsy alone	24 (6.2)	8 (6.7)	N/A	12 (7.8)	4 (0.7)
Excision biopsy followed by definitive surgery	66 (8.2)	20 (11.6)	1 (3.1)	32 (8.6)	13 (2.0)
All patients managed by surgery alone	90 (7.7)	28 (10.2)	1 (3.1)	44 (8.4)	17 (1.9)
T1	62 (7.6)	22 (10.2)	1 (3.1)	33 (7.1)	6 (1.5)
T2	19 (8.7)	5 (10.6)	N/A	9 (11.2)	5 (2.8)
T3	9 (6.1)	1 (8.2)	N/A	2 (19.5)	6 (1.2)
All patients with radiation therapy	97 (6.7)	23 (8.9)	1 (7.6)	32 (9.0)	41 (3.6)
T1	49 (6.5)	13 (9.0)	1 (7.6)	16 (7.5)	19 (3.9)
T2	31 (6.9)	7 (8.8)	N/A	11 (10.5)	13 (3.1)
T3	14 (7.2)	3 (9.1)	N/A	4 (10.7)	7 (4.4)
T4	3 (5.9)	N/A	N/A	1 (13.3)	2 (2.2)
Biopsy followed by radiation alone (no salvage)	32 (7.0)	11 (6.8)	N/A	13 (8.7)	8 (3.9)
T1	24 (7.1)	7 (8.0)	N/A	11 (7.4)	6 (5.0)
T2	6 (9.1)	4 (5.8)	N/A	2 (15.6)	N/A
T3	2 (0.5)	N/A	N/A	N/A	2 (0.5)
Biopsy then radiation therapy followed by a salvage procedure	57 (6.5)	10 (9.7)	1 (7.6)	17 (8.9)	29 (3.9)
T1	24 (5.8)	6 (9.8)	1 (7.6)	4 (7.0)	13 (3.2)
T2	21 (6.9)	2 (13.4)	N/A	9 (9.3)	10 (3.7)
T3	11 (7.4)	2 (4.8)	N/A	4 (10.7)	5 (5.9)
T4	1 (3.9)	N/A	N/A	N/A	1 (3.9)

A, NED, alive, no evidence of disease; A, D, alive with disease; D, NED, dead, no evidence of disease; D, D, dead, with disease; N/A, not applicable; years, mean years of follow-up or survival.

TABLE 9. *Outcome in patients with previous irradiation exposure and in patients with recurrences*

Specific feature	No. of patients (yr)	A, NED (yr)	A, D (yr)	D, NED (yr)	D, D (yr)
History of radiation exposure	17 (6.6)	3 (6.5)	N/A	4 (11.0)	10 (4.8)
T1	10 (5.1)	3 (6.5)	N/A	1 (6.7)	6 (3.9)
T2	3 (9.5)	N/A	N/A	2 (9.5)	1 (9.0)
T3	4 (8.4)	N/A	N/A	1 (18.0)	3 (5.1)
Developed a recurrence	85 (6.3)	16 (11.2)	2 (5.3)	22 (8.6)	45 (3.4)
T1	43 (6.5)	12 (11.4)	2 (5.3)	11 (6.3)	18 (3.4)
T2	27 (6.4)	2 (9.2)	N/A	10 (2.5)	15 (3.5)
T3	13 (6.0)	2 (11.1)	N/A	1 (18.0)	10 (3.7)
T4	2 (2.2)	N/A	N/A	N/A	2 (2.2)

A, NED, alive, no evidence of disease; A, D, alive with disease; D, NED, dead, no evidence of disease; D, D, dead, with disease; N/A, not applicable; year, mean years of follow-up or survival.

were T2, and one was T4. Seven patients developed recurrent disease, which was treated by additional surgery (n = 7 patients) and adjuvant therapy (n = 5 patients). Of these 13 patients, eight were either alive (n = 4 patients) or had died (n = 4 patients) without evidence of disease, after an average of 7.3 years of follow-up, while five patients had died with evidence of disease (mean 3.5 years of follow-up).

None of the 13 women had previous radiation exposure. Six women developed recurrent disease and two developed metastases to the lung. Five patients were treated with postoperative radiation therapy. There were seven T1 tumors, two T2 tumors, three T3 tumors, and one T4 tumor. Ten patients were either alive (n = 4) or had died (n = 6) of unrelated causes without evidence of disease with an average follow-up of 11.3 years. Three patients died with disease with a mean survival of 1.5 years: one T1 glottic tumor treated with surgery alone (died 0.1 year) and two supraglottic tumors, one T3 and one T4, both of whom developed lung metastases. The patient with the stage T4 tumor received postoperative radiation therapy and survived 3.9 years.

Of the 123 tumors that had an immunohistochemical profile, 84 tumors demonstrated immunoreactivity with at least one epithelial marker in the spindle cell component (Table 10). Overall, the distribution of T-stage and tumor location is similar between the group with immunoreactivity and the group without, even though there is a difference in absolute number. As a general rule, irrespective of tumor location or T-stage, there is a statistically significant difference in the outcome between patients with epithelial marker immunoreactivity and those who did not have immunoreactivity ($p = 0.003$) (Table 10).

Overall, 127 patients were either alive (n = 51 patients) or had died of unrelated causes (n = 76 patients) without evidence of disease with an average follow-up of 9.1 years. Sixty patients had died with evidence of dis-

TABLE 10. *Patient outcome based on presense (n = 84 patients) or absence (n = 39 patients) of epithelial immunoreactivity in the spindle cells of laryngeal spindle cell (sarcomatoid) carcinoma further separated by T-stage and tumor location*

	All cases (yr)		A, NED (yr)		A, D (yr)		D, NED (yr)		D, D (yr)	
Outcome	E	N	E	N	E	N	E	N	E	N
Glottic	55 (7.2)	26 (10.3)	19 (10.3)	6 (11.4)	1 (7.6)	1 (3.1)	23 (7.1)	14 (11.7)	13 (3.1)	5 (6.3)
T1	42 (7.4)	16 (8.0)	15 (11.7)	4 (6.8)	1 (7.6)	1 (3.1)	17 (6.5)	9 (9.6)	10 (2.4)	2 (5.6)
T2	7 (6.3)	10 (13.9)	2 (3.8)	2 (20.7)	N/A	N/A	4 (8.3)	5 (15.4)	1 (3.4)	3 (6.8)
T3	6 (7.3)	N/A	2 (6.3)	N/A	N/A	N/A	2 (9.4)	N/A	2 (6.3)	N/A
Transglottic	13 (5.1)	4 (5.4)	2 (10.3)	N/A	N/A	N/A	3 (8.1)	2 (3.4)	8 (2.7)	2 (6.8)
T2	8 (3.8)	2 (3.4)	1 (2.7)	N/A	N/A	N/A	2 (5.5)	2 (3.4)	5 (3.3)	N/A
T3	3 (7.3)	2 (6.8)	1 (17.8)	N/A	N/A	N/A	N/A	N/A	2 (2.1)	2 (6.8)
T4	2 (6.9)	N/A	N/A	N/A	N/A	N/A	1 (13.3)	N/A	1 (0.6)	N/A
Supraglottic	14 (4.8)	8 (5.3)	1 (6.2)	1 (11.4)	N/A	N/A	5 (9.9)	2 (6.4)	8 (1.0)	5 (3.7)
T1	5 (4.7)	4 (5.1)	N/A	N/A	N/A	N/A	3 (7.1)	1 (7.5)	2 (1.2)	3 (4.4)
T2	5 (2.1)	4 (5.5)	1 (6.2)	1 (11.4)	N/A	N/A	N/A	1 (5.2)	4 (1.1)	2 (2.7)
T3	3 (7.3)	N/A	N/A	N/A	N/A	N/A	2 (14.2)	N/A	1 (0.4)	N/A
T4	1 (3.9)	N/A	N/A	N/A	N/A	N/A	N/A	N/A	1 (3.9)	N/A
Subglottic	2 (6.8)	1 (0.2)	N/A	N/A	N/A	N/A	N/A	N/A	2 (6.8)	1 (0.2)
T1	1 (10.4)	N/A	N/A	N/A	N/A	N/A	N/A	N/A	1 (10.4)	N/A
T2	1 (3.3)	N/A	N/A	N/A	N/A	N/A	N/A	N/A	1 (3.3)	N/A
T3	N/A	1 (0.2)	N/A	N/A	N/A	N/A	N/A	N/A	N/A	1 (0.2)

E, epithelial immunoreactive; N, absent immunoreactivity; years, mean years of follow-up or survival; A, NED, alive, no evidence of disease; A, D, alive with disease; D, NED, dead, no evidence of disease; D, D, dead, with disease; N/A, not applicable.

ease an average of 3.1 years after initial clinical presentation. This gives a raw survival of 68.0% for LSCSC. These results also yielded an overall raw 5-year survival rate of 58.8%. Survival was also determined based on the T-stage (Table 11) and the anatomic site of origin (Table 12). The higher the stage of disease, the greater the percentage of patients who died with disease: 22.5% of T1 tumors, 36.0% of T2 tumors, 56.5% of T3 tumors, and 66.7% of T4 tumors. Only four patients had metastatic disease in the cervical lymph nodes at the time of initial presentation, which was not specifically related to the T-stage of the tumor.

Overall, glottic tumors had a better prognosis than all other types, with an average follow-up of 7.8 years (Table 12). When further studied, the difference in follow-up or survival between patients who died with disease and those who were alive or had died without evidence of disease was statistically significant in each category: 3.5 years versus 8.9 years for patients with glottic tumors ($p < 0.001$), 3.3 years versus 9.3 years for patients with transglottic tumors ($p < 0.001$), 2.0 years versus 10.3 years for patients with supraglottic tumors ($p < 0.001$), and all patients with subglottic tumors died with disease. In addition, within each tumor location category, as the T-stage increased, the percentage of patients who died with disease increased ($p < 0.001$) (Table 12).

When metastatic disease was present, the lung was the most frequent site of involvement ($n = 18$ patients), followed by the cervical lymph nodes ($n = 14$ patients). However, only five patients had metastatic disease at the time of initial presentation, and all of these were to the local cervical lymph nodes (all of whom died with disease [mean 1.1 years]). Other foci of metastatic involvement included kidney, liver, brain, pleura, and bone (jaw and vertebrae). When the metastatic foci were available for review, epithelial only ($n = 6$), spindle cell only ($n = 6$), and a dual deposit of both components ($n = 11$) could be seen.

DISCUSSION

Taking into consideration the ample number of articles in the English literature that offer a discourse on LSCSC and the collection of patients this clinical report encompasses, we thought it prudent to arrange our discussion in separate sections, analogous to the results to facilitate a logical and orderly exposition on LSCSC.

Sociodemographic Characteristics

Based on a review of all of the consultation cases of the Armed Forces Institute of Pathology of benign or malignant primary laryngeal neoplasms, LSCSC accounted for approximately 2.7%, a finding slightly higher than the results reported in the literature,[4] but given the referral nature of our practice, a true incidence is probably around 1–2%.[11,18,27,51]

Despite the referral nature of the AFIP and its strong military affiliation (only 21.9% of cases were from military or Veterans Administration facilities), there is still a compelling male-to-female ratio in this clinical report of 13:1, similar[11,27,29,35,38,40,49,51] to our review of the literature summarized in Table 3 of 11:1. This strong predominance in men is similar to SCC of the larynx. This tumor usually develops in the 7th decade of life, with the mean age in this clinical series of 65.6 years.[11,22,27,29,35,36,38,40,49,51,52] Nearly all patients complain of hoarseness, in a number cases accompanied by other nonspecific laryngeal symptoms. The symptoms are usually of a relatively short duration (<1 year) before directing the patient to seek medical attention.[11,27,29,35,38,40,47,49,51]

Radiation Exposure History and Tobacco and/or Alcohol Use

It has been suggested in the literature that LSCSC may develop after radiation therapy or because of environmental exposure.[6,11,16,27,35–39,47,49,51,53,56,61] Although

TABLE 11. *Patient outcome based on T-stage (and for complete TNM stage for the cases with metastases at presentation)*

Outcome	All cases	A, NED (yr)	A, D (yr)	D, NED (yr)	D, D (yr)
T1	111 (7.1)	35 (9.8)	2 (5.3)	49 (7.2)	25 (3.2)
T1a	83 (7.5)	31 (9.6)	1 (7.6)	39 (7.1)	12 (3.5)
T1b	27 (5.9)	4 (11.2)	1 (3.1)	10 (7.9)	12 (3.2)
T1N1M0	1 (1.0)	N/A	N/A	N/A	1 (1.0)
T2	48 (7.6)	12 (9.5)	N/A	20 (10.8)	16 (3.2)
T2N1M0	2 (1.9)	N/A	N/A	N/A	2 (1.9)
T3	22 (6.8)	4 (8.9)	N/A	6 (13.6)	12 (3.2)
T3N1M0	1 (0.1)	N/A	N/A	N/A	1 (0.1)
T4	3 (5.9)	N/A	N/A	1 (13.3)	2 (2.2)

A, NED, alive, no evidence of disease; A, D, alive with disease; D, NED, dead, no evidence of disease; D, D, dead, with disease; years, mean years of follow-up or survival; N/A, not applicable.

TABLE 12. *Patient outcome based on T-stage and tumor location*

Outcome	All cases (yr)	A, NED (yr)	A, D (yr)	D, NED (yr)	D, D (yr)
Glottic	132 (7.8)	45 (9.5)	2 (5.3)	59 (8.4)	26 (3.5)
T1	100 (7.2)	34 (9.6)	2 (5.3)	45 (7.4)	19 (2.9)
T2	24 (10.1)	8 (10.4)	N/A	11 (12.2)	5 (4.8)
T3	8 (8.4)	3 (5.9)	N/A	3 (11.9)	2 (6.3)
T4	N/A	N/A	N/A	N/A	N/A
Transglottic	23 (6.2)	3 (10.4)	N/A	8 (8.9)	12 (3.3)
T2	13 (5.2)	2 (6.6)	N/A	6 (6.6)	5 (3.3)
T3	8 (7.3)	1 (17.8)	N/A	1 (18.0)	6 (3.8)
T4	2 (6.9)	N/A	N/A	1 (13.3)	1 (0.6)
Supraglottic	28 (5.6)	3 (11.2)	N/A	9 (9.9)	16 (2.0)
T1	10 (6.0)	1 (16.0)	N/A	4 (7.2)	5 (3.1)
T2	12 (5.1)	2 (8.8)	N/A	3 (10.9)	7 (1.5)
T3	5 (6.1)	N/A	N/A	2 (14.0)	3 (0.8)
T4	1 (3.9)	N/A	N/A	N/A	1 (3.9)
Subglottic	4 (3.5)	N/A	N/A	N/A	4 (3.5)
T1	1 (10.4)	N/A	N/A	N/A	1 (10.4)
T2	1 (3.3)	N/A	N/A	N/A	1 (3.3)
T3	2 (0.1)	N/A	N/A	N/A	2 (0.1)
T4	N/A	N/A	N/A	N/A	N/A

A, NED, alive, no evidence of disease; A, D, alive with disease; D, NED, dead, no evidence of disease; D, D, dead, with disease; years, mean years of follow-up or survival; N/A, not applicable.

radiation-induced LSCSC may occur in a few patients (9.1% of this clinical series and 7.7% in our review of the literature), the presence of a sarcomatoid pattern of growth in so many patients who have not been exposed to radiation suggests that radiotherapy is not a major etiologic factor. The determination of radiation risk is further complicated by the exposed patients receiving varying doses and having variable latent periods (in this clinical series between 1.2 years and 16 years from the radiation exposure to development of the LSCSC).[6,11,16,22,38,40,49,61]

In contrast to radiation exposure, however, tobacco use and excess alcohol consumption seem to be strong candidates as causative agents.[11,22,31,35,37,38,47,49,51] In this clinical series 87% of patients, both male and female, had a documented use of tobacco products, usually smoking cigarettes. Early reports in the literature did not systematically investigate the tobacco usage of the patients they studied but suggested a high incidence of use.[47] Although a history of alcohol use was elicited in only 48% of patients, the association of alcohol use and the development of LSCSC seem to be quite likely.

Pathology

Most of the tumors recorded in the literature were polypoid, pedunculated, or exophytic, with nearly all of our cases either endoscopically or macroscopically characterized as being polypoid or pedunculated (98.9%).[11,22,27,29,35,37,38,47,49,51,53,61] Given that these lesions tended to obstruct the larynx and cause symptoms early in the disease, the vast majority of the tumors were found at an early stage (86.1% stage T1 or T2), which generally correlates with a better prognosis.[6,7,11,35,36,47]

Comparable with the literature, LSCSC in this clinical series tends to involve the glottis more frequently than other locations.[11,22,27,29,35,38,49,51] This tumor distribution pattern is similar to laryngeal SCC, where the majority of tumors are glottic.[26] Moreover, the majority of the tumors in our clinical series (60%) and those in the literature were T1 tumors.[11,27,29,35,38,49] It is noteworthy that the frequency of T1 and T2 tumors is similar to laryngeal SCC without spindle cell change.[26]

The data from this collected group of LSCSC substantiate the more favorable prognosis associated with glottic lesions (mean 7.8 years) versus supraglottic (mean 5.6 years) or subglottic (mean 3.5 years) tumors. This clinical series yielded a raw 5-year survival for glottic tumors (of all stages) of 64.4%. However, if one excludes the patients who died of other causes before 5 years, the figure improves to 78.7% for all glottic tumors. This improved prognosis with glottic LSCSC parallels that expected for SCC involving the glottis. The 79% 5-year survival may be related to an earlier detection of the tumor and to the very sparse lymphatic drainage from the vocal cord region.[26,32] Furthermore, it is known that tumors confined to the vocal cords alone rarely metastasize. As noted by other authors,[22,29,35–38,49,50] we also believe that tumor location and stage are important prognostically, especially based on this large clinical cohort of patients.

Although overall there was a 19.3% metastatic rate for all of the tumors at any time during the course of their

disease, the metastatic rate from all of the glottic tumors was 12.1%, and metastatic deposits were observed in 26.1% of the transglottic tumors, 35.7% of the supraglottic tumors, and 100% of the subglottic tumors. These metastatic rates are similar to those presented in the literature, where nonglottic tumors exceed those of the glottis by a ratio of >2:1.[6,29,35,36,38,49] The finding of increased metastatic potential for nonglottic tumors is statistically significant ($p < 0.001$), and indeed, a nonglottic tumor location was predictive of an increased metastatic potential ($p = 0.004$).

It is self-evident that whereas size of the tumor may be significant ($p < 0.001$), the TNM classification scheme of the American Joint Committee on Cancer Staging has partially built in the size of the tumor into the T-staging scheme. Tumor size, location, and stage have all been implicated as prognostic indicators of biologic behavior for LSCSC, and a difference in patient outcome can be independently attributed to size ($p < 0.001$), location ($p < 0.001$), and T-stage ($p < 0.001$).

The most controversial aspect of LSCSC described in this clinical series is the pathogenesis, the determination of which influences the prognosis and treatment. Given the number of cases in this study, it is perhaps difficult for us to completely bring to a conclusion the controversy of their origin or derivation, but we think that the epithelial nature of the tumor is strongly supported by the clinical, histologic, and immunophenotypic expression. This conclusion therefore impacts the choice of therapy.

A number of different histogenetic theories have been developed over the years, with a few principal theories, including: 1) a separate epithelial and mesenchymal cell, each becoming malignant—carcinosarcoma or collision tumor, 2) an epithelial cell that differentiates into both squamous and spindle cell components—spindle cell carcinoma, 3) a carcinoma that stimulates a benign reactive stromal response—carcinoma with pseudosarcoma, and 4) a malignant epithelial cell that "dediffer entiates" into a sarcoma—carcinosarcoma.[5,6,11,22,38,52,53,62] Although it may be difficult to prove any of these theories, we think there is overwhelming compelling evidence in favor of an epithelial cell that differentiates into both a carcinoma and a spindle cell component, the latter still maintaining epithelial differentiation no matter how meager.[43] This evidence especially includes the following: their occurrence in the exact sites that normally have squamous epithelium and a preponderance of carcinomas rather than sarcomas; a superficial location; a polypoid appearance; the direct continuity and smooth transition of the spindled cells with areas of squamous epithelium, be it benign, dysplastic, or frankly carcinomatous (even if the transition zone is frequently indistinct due to surface ulceration or necrosis); immunoreactivity with epithelial antigens; a dual expression of epithelial and mesenchymal differentiation with double labeling techniques in some neoplastic spindle cells; and the presence of epithelial only, sarcomatous only, or a duality of expression in metastatic deposits from LSCSC.[2,6,7,11,20,22,27,29,35,38,39,47,49,51–53,60,61] There are many well-documented cases of metastatic disease of both squamous and spindled elements in the same lymph node or organ, or independent metastasis of each element to different locations, confirming that the sarcomatoid component is part of the tumor, fully capable of metastasis and not just a reactive change.[6,7,29,35,38,45,50,52,55,62] Therefore, we think that LSCSC is an epithelial neoplasm in which the spindle cell component is a metaplastic or transformed epithelial cell, qualifying the entire tumor for the designation of a spindle cell (sarcomatoid) carcinoma, abandoning all of the other terms cited earlier.

The presence of divergent differentiation, including bone and cartilage, was noted in 7.0% of tumors in this clinical series and typically made up a minor fraction of the overall tumor volume.[2,6,11,35,38,45,47,48,53,55,61,62] The presence of malignant transformation of the bone or cartilage did not yield a worse patient outcome (mean 8.8 years) when compared with the presence of benign bone or cartilage (mean 5.0 years), but with only 13 cases statistical analysis could not be performed. Furthermore, the presence of osteocartilaginous differentiation did not adversely affect the patient outcome when compared with patients who did not have this histologic feature ($p = 0.377$). We must add that the presence of osteocartilaginous histologic features was statistically significantly correlated to previous radiation exposure ($p < 0.001$) (23% vs 8% radiation exposure for the remaining patients), a finding similar to the literature.[2,6,11,35,38,47,48,53]

Special Studies (Immunohistochemical, Ploidy, Ultrastructural)

The results of a variety of immunohistochemical studies have been reported in the literature, but usually only on a limited number of cases with a limited epithelial and mesenchymal panel.[27,38,47,56,57,62] Keratins can be seen in myofibroblasts, transformed fibroblasts, smooth muscle cells, myoepithelial cells, and endothelial cells.[47] However, these cell types are not atypical or generally arranged in a pattern similar to the tumor cells of an LSCSC.[20,34,38,42–44,56,60] In 68% of cases in this clinical series, similar to the literature, at least one epithelial antibody of the 18 keratin and epithelial antibodies analyzed was immunoreactive in each tumor tested.[7,17,27,38,40,49,56,62] However, if only keratin, epithelial membrane antigen, K1, and K18 are included, then 64% of cases tested were immunoreactive for at least one of these four antibodies. Therefore, it would seem that the use of the full panel of 18 epithelial antibodies is not cost-effective. If epithelial markers are tested, we would suggest performing a panel of keratin (AE1/AE3, "CK1"), epithelial membrane antigen, K1, and K18. As a point of clarification, the

"CK1" in the keratin cocktail is not at all related to K1 and is instead a simple epithelial keratin antibody that has been poorly named.

Keratin expression is usually decreased as the degree of epithelial differentiation decreases, to the point that keratin expression may be lost entirely.[33,43,59] Whereas a positive epithelial marker can help to declare the diagnosis of an LSCSC, a nonreactive or negative result should not dissuade the pathologist from the diagnosis. In this clinical study evidence of transformation zones, blending, and transition areas was clearly evident in cases that were negative with epithelial antibodies (n = 27) and, contrariwise, there was positive epithelial immunoreactivity in cases without areas of obvious squamous differentiation or transition (n = 13 tumors). Therefore, as a group LSCSCs may or may not express epithelial markers despite proclaiming their epithelial differentiation with other features. Thus, a single case may be negative for immunoepithelial antibodies and still be an LSCSC. Furthermore, a number of technical or histologic factors may confound the pathologist's ability to demonstrate epithelial differentiation. These conditions include subjectivity of the reviewer, sampling error or nonhomogeneous tumors, poor preservation or fixation, inappropriate antibody or technique, or epithelial features less than the threshold of detection immunohistochemically or ultrastructurally. The immunohistochemical results can be improved by performing the antibody panel of four antibodies suggested above and using a steam or microwave cellular conditioning method.

A divergent mesenchymal differentiation of the tumor cells seems to be supported by the carcinoma cells acquiring the potential to express a mesenchymal phenotype at the light microscopic, immunohistochemical, and ultrastructural levels.[7,8,20,22,27,31,33,36,38,46,47,49,53,56,58,62] All of the cases tested in this series (100%) expressed vimentin, with 33% demonstrating reactivity with smooth muscle actin, 15% with muscle specific actin, 5% with S-100 protein, and 2% each with desmin–D33 and desmin–DR11. At first it may seem that mesenchymal marker expression may gainsay an epithelial derivation. However, it is well known that neoplastic epithelial cells express vimentin and other mesenchymal markers, usually demonstrating an increasing expression of mesenchymal markers both qualitatively and quantitatively as the neoplastic cells become spindle shaped and have reduced cell-to-cell contact,[7,9,13,17,20,33,34] occasionally taking on a myofibroblastic differentiation or even true rhabdomyomatous differentiation, suggesting true mesenchymal divergent differentiation.[7,46] Therefore, whereas epithelial expression decreases from 100% in the surface epithelium to nonexistent in the spindle cell component in a fair percentage of cases, vimentin has the exactly inverse relationship (100% of the spindle cells to nonreactive in the surface epithelium). Consequently, the presence of mesenchymal marker immunoreactivity, even in the absence of epithelial immunoreactivity, does not preclude the diagnosis of an LSCSC but may indeed lend support to the true nature of the neoplasm that has become so transformed. It appears that the epithelial cells go through a spectrum of progressive phenotypic changes: metamorphosing to a spindle shape, undergoing a loss of cellular polarity, producing mesenchymal matrix components, gaining vimentin while losing keratin expression, and acquiring a mesenchymal pathway of differentiation. It has been demonstrated that during embryogenesis there is an interconversion from epithelium to mesenchyme, a process that is continued after fetal life. This phenotypic plasticity is expressed by a loss of intercellular cohesion, elongation of the cells, loss of basement membrane, production of connective tissue (collagen), and invasion into the stroma.[8,20,23–25,33,53,60] Furthermore, these same researchers suggest that the acquisition of mesenchymal-like phenotype seems to be associated with factors known to participate in the development of malignancy. The degree of change and the number of cells involved in the phenotypic conversion will give differing morphologies and immunohistochemical results. Ultrastructurally, the tumor cells have been demonstrated to contain tonofibrils and tonofilament-associated desmosomes, all features usually associated with epithelial differentiation, especially squamous cell origin.[8,22,27,38,39,62] Based on these findings, we believe there is *no* support for the notion that the spindle cell component is a non-neoplastic, reactive, or reparative phenomenon, as suggested earlier,[3,22,36] but instead is a metaplastic epithelial cell. We did not perform ploidy analysis in this series of cases, but according to the literature, the majority of cases demonstrate a nondiploid pattern in both the epithelial and spindle cell fractions.[14,38,49] Furthermore, both the epithelial and spindle cell components when tested separately yielded concordant results, furnishing additional support for a common cell of origin.[38]

Clinical Therapy and Patient Outcome

It is axiomatic that the goals of treatment encompass cure of the cancer, laryngeal preservation to the greatest degree possible, good voice quality post-therapeutically, and a low risk of complications. With these objectives in mind, there are a number of various management options available. As previously noted, the remarkable histologic composition and varied natural history of these tumors have prohibited reaching a consensus with respect to appropriate management. Having said this, all authors seem to agree that tumor location (glottic, supraglottic, subglottic, and transglottic) and tumor stage (T1, T2, T3, and T4) are the two most important factors influencing the management and outcome of patients with LSCSC.[41]

Considering our thought that LSCSC is a carcinoma, it is important to use the usual management for SCC as a point of comparison. In general, after the initial biopsy, glottic SCC of stage T2 or less can be managed conservatively with the use of limited field irradiation to give the best local control and voice preservation, with the least likelihood of long-term complications.[4,26,32,41] Using the compilation data reported by these authors, there is between 70% and 96% local control of disease at 5 years using radiation alone for glottic tumors of stage T1 or T2, and between 79% and 98% ultimate control of local disease at 5 years when combined with salvage procedures for recurrent disease.[4,6,26,32,41] With surgery alone, the local control at 5 years ranged between 100% for T1b tumors to 63% for T2b tumors.[4,6,10,35,41]

It is imperative to reiterate that all patients had a diagnostic biopsy before the definitive therapy, both in this clinical series as well as for cancers (LSCSC or SCC) reported in the literature. We cannot overemphasize enough the concept that the tumors are polypoid and exophytic with "nearly all" of the tumor cells contained within the polypoid projection without invading into the underlying stroma, especially in glottic tumors. Therefore, the polypoid nature of most LSCSCs allows for almost complete elimination with the diagnostic "biopsy." To say that radiation therapy alone may control the disease is misleading because the diagnostic biopsy (surgery) may have already conferred tumor control. LSCSCs have been treated with local resection, partial laryngectomy, total laryngectomy, and radiation therapy or a combination of these modalities. The efficacy of these various treatment modalities is difficult to elucidate, however, because of the omission of important clinical staging in most of the studies. It is for this reason that we think it is difficult to accurately compare the results of this clinical study with those of the literature for either LSCSC or SCC. If the tumor has been completely eradicated by the "biopsy," the use of further treatment at the time of initial clinical presentation seems unnecessary and surfeit.

As a referral facility there was no detailed information about the radiation timing (before or after a salvage surgery), dose, field, and specific fraction given to the patients, or specific documentation about the extent of recurrent disease when present. Even with these limitations, there was no statistically significant difference in patient outcome between those treated with surgery alone versus those who were treated with surgery and radiation therapy ($p = 0.454$). A much greater percentage of patients died with disease in the group managed with radiation (42.3%) than those managed by surgery alone (18.9%). However, on average, stage for stage, the patients who died with disease who were managed with surgery and radiation lived for a greater number of years (3.6 years) than those treated by surgery alone (1.9 years). It would seem, therefore, based on these findings and those reported in the literature, that the initial excisional biopsy should be the primary mode of treatment. If recurrent disease develops, after a salvage surgery, radiation therapy can be used, where it may be of value in extending the patient's life, although not necessarily changing the final outcome of the disease.[2,4,10,11,22,22,27,29,35,36,38,40,49,51,61,62]

It has been reported in the literature that patients with a history of radiation exposure tend to have a poor prognosis.[2,6,27] In this clinical series, 17 patients had a history of radiation exposure (Table 9). Of these 17 patients, most were T1 tumors (58.8%) and most were glottic (58.8%), not significantly dissimilar from the rest of the patients ($p = 0.489$). However, a far greater percentage of patients who had been exposed to radiation died with disease than patients who had not been exposed to radiation ($p = 0.013$).

Our overall raw 5-year survival was 58.8%, similar to that reported in the literature (63% to 94%), but these values are frequently given as a 3-year survival.[4,22,27,29,35,38,49,49,51,61] In addition, survivals are given for specific stages, specific locations, and for specific treatment regimens, without giving a general overall prognosis. When overall prognosis is given, the overall lethality of the tumor is 30–32%.[2,6,21,22,27,29,35,37,50,61,62]

As expected, pathologic tumor stage (T-stage) ($p < 0.007$), tumor location (glottic vs other locations; $p < 0.001$), vocal cord mobility ($p = 0.013$), previous irradiation ($p = 0.013$), and necrosis ($p = 0.017$) were all significant factors. However, none of the following factors had a statistically significant impact on patient outcome: male gender ($p = 0.473$), age (using four different cutoff points of >50, 55, 60, or 65 years; $p = 0.259$), size ($p = 0.074$), polypoid growth ($p = 0.624$), presence of SCC ($p = 0.653$), pattern of tumor growth ($p = 0.199$), increased cellularity ($p = 0.044$; but not significant between the three group means using Bonferroni comparisons), cellular anaplasia ($p = 0.373$), presence of giant cells of any type ($p = 0.751$), number of mitotic figures (using three different cutoffs of 1, ≤ 5, and ≤ 10) per 10 high power fields ($p < 0.120$), atypical mitotic forms ($p = 0.284$), presence of desmoplastic fibrosis ($p = 0.277$), or presence of bone or cartilage ($p = 0.377$).

Unexpectedly, the survival rate among patients with a negative immunohistochemical profile for epithelial markers was significantly greater than that of patients with positive immunoreactivity for epithelial markers ($p = 0.003$) (Table 10). This finding has been suggested in the literature but without explanation.[49]

Differential Diagnoses

The differential diagnosis for any spindle cell tumor, and specifically for LSCSC, is one of the most challeng-

ing. It includes a number of benign and malignant processes, such as fibrosarcoma, malignant fibrous histiocytoma, leiomyosarcoma, rhabdomyosarcoma, malignant peripheral nerve sheath tumor, osteosarcoma, mesenchymal chondrosarcoma, Kaposi's sarcoma, angiosarcoma, synovial sarcoma, malignant melanoma, fibromatosis, leiomyoma, nodular fasciitis, and reactive epithelial proliferations, to name just a few. It is easy to see how the magnitude of diagnostic differentials can be a source of frustration for the pathologist. An exhaustive review of each of these lesions in this article is precluded by spatial constraints, but suffice it to say that authentic primary laryngeal sarcomas (with the obvious exclusion of chondrosarcoma) or benign mesenchymal tumors are exceedingly rare.[6,11,19,29,30,47,61] Many of the case reports of sarcomas of the larynx, when examined in detail, seem to represent LSCSC based on clinical and histologic parameters because many were reported before immunohistochemical, ultrastructural, or molecular studies.[12,15,19] Given the polypoid nature of the tumor (in nearly all of our cases), the glottic proclivity (82.9% of this series), and the presence of squamous differentiation (either in the overlying surface or immunophenotypically), an accurate discrimination between these tumors is usually possible. Synovial sarcoma (especially monophasic) may cause the most diagnostic difficulty, but the age at presentation (children), tumor location (usually posterior laryngeal soft tissues), and the presence of a specific chromosomal translocation t(X, 18) can aid in this distinction.[47] It is probably wise to view all atypical spindle cell neoplasms of the larynx as LSCSCs to assure appropriate therapy, rather than diagnose these lesions by another term that would deliver inappropriate therapy.

Many of the cases in this clinical series that were referred to our institution for review were diagnosed inaccurately, with the most frequent specific diagnoses including reactive epithelial changes (n = 21 cases); granulation tissue or contact ulcer (n = 12 cases); malignant fibrous histiocytoma (n = 10 cases); dysplasia, polyps with granulation tissue, and fibrosarcoma (n = 5 cases each); fibromatosis, leiomyosarcoma, and rhabdomyosarcoma (n = 4 cases each); and fibrohistiocytoma, leiomyoma, and neurofibroma (n = 3 cases each). In addition, many cases were diagnosed as squamous cell carcinoma (n = 26 cases) or by more descriptive diagnoses such as spindle cell tumor, sarcoma, or carcinoma. Therefore, even given the greatest benefit of the doubt, 42% of cases were incorrectly diagnosed at the time of referral. This fact emphasizes that although the tumors remain enigmatic histologically, it is important to be aware of the existence of this type of laryngeal neoplasm to be able to document the epithelial derivation of the neoplasm and thereby ensure the appropriate clinical management based on the location and stage of the tumor. Patients of young age (<65 years), without prior radiation, with tumors of low stage, glottic location, and with no epithelial immunoreactivity have the most favorable long-term prognosis when managed by surgery, using radiation therapy after a salvage procedure to yield the longest possible survival. □

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