Spindle Cell Carcinoma of the Oral Cavity and Oropharynx: Factors Affecting Outcome

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Background: Spindle cell carcinoma (SpCC) is considered to be a rare variant of squamous cell carcinoma (SCC). The behavior of such tumors is unclear. The aim of this study was to elucidate the treatment and outcome of oral and oropharyngeal SpCC.

Methods: All the medical records of patients with the diagnosis of SpCC in the oral cavity and oropharynx in our hospital from 1994 to 2005 were reviewed. The clinical features, treatments and survival of the patients were evaluated.

Results: Within the 11-year study period, 18 patients were diagnosed with oral and oropharyngeal SpCC. There were 3 cases of AJCC (American Joint Committee on Cancer) stage I, 3 of stage II, 2 of stage III, 9 of stage IV, and 1 case without definite staging. Twelve patients died of their diseases. The median overall survival time was 8.89 months. The 1-year overall survival rate was 36.7% and the 3-year overall survival rate was 27.5%. In the early stage group, the 1-year and 3-year survival rates were both 100%. In the late stage group, the 1-year survival rate was 9%, and the 3-year survival rate was 0%. The factors influencing overall survival were tumor grade, lymph nodes, metastasis, stage, vascular invasion and distant recurrence. A high local recurrence rate (73.3%) and distant metastasis rate (33.3%) were observed.

Conclusion: The behavior of SpCC seems to be more aggressive than that of SCC at a similar stage. Setting wider safety margins (>2 cm) during surgical intervention is suggested. In the case of locoregional recurrence, salvage operation showed some benefit. Seeking an effective chemotherapy protocol is important for the control of distant recurrence. [*J Chin Med Assoc* 2006;69(10):478–483]

Key Words: mouth neoplasms, oropharyngeal neoplasms, salvage therapy, squamous cell carcinoma, treatment outcome

Introduction

Spindle cell carcinoma (SpCC), also known as sarcomatoid carcinoma, is a rare malignancy of the head and neck regions. It is most frequently encountered in the larynx, and also occurs in the nasal cavity, hypopharynx, oral cavities, esophagus, trachea, skin and breast. In a previous series of laryngeal malignancy, about 1% were diagnosed with SpCC.[1] Male predominance was also noted.

SpCC is an unusual form of poorly differentiated squamous cell carcinoma (SCC) consisting of elongated (spindle) epithelial cells that resemble a sarcoma. Many of these tumors may be easily confused with true sarcomas unless special immunohistologic or ultrastructural analysis is performed. Such analyses show concurrent presence of malignant epithelial and homologous sarcomatoid spindle cell components by co-expression of cytokeratin, epithelial membrane antigen, and vimentin to various degrees.[2,3]

The spindle cell components have been considered to be either a variant growth pattern of SCC, a non-neoplastic mesenchymal reaction, or a malignant admixture of epithelial and mesenchymal neoplasms.[4] However, the majority of the spindle cell components are non-diploid, which indicates that they are neoplastic and not reactive.[5] The vimentin positivity reflects that these bizarre fibroblast-like cells are carcinoma cells with true mesenchymal metaplasia. Electron microscopy often shows the presence of junctional complexes between tumor cells, with or without pericellular basal lamina and cytoplasmic skeins of intermediate filaments.[6]

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When the spindle cell component was compared with its corresponding epithelial component, identical patterns of p53 protein expression were noted in 95% of the biphasic tumors.[7] These comprise evidence that the malignant spindle cells are due to metaplasia from the involved epithelium, not inflammatory reaction or true sarcoma.

To the authors' knowledge, the only published series of more than 10 cases of SpCC in the oral cavity was reported about 25 years ago.[8] In the current study, we report 18 new cases of SpCC, review the factors significant for influencing outcome, and outline the surgical management of these lesions.

Methods

A search of records in Kaohsiung Veterans General Hospital between 1994 and 2005 yielded 18 lesions in 17 patients diagnosed with SpCC in the oral cavity and oropharynx. A retrospective chart review was performed to assess clinical presentation, surgical management, and recurrence. The surgical intervention included wide excision of local tumor with a safety margin of about 1–2 cm, and neck dissection for possible neck disease. Patient-related factors including age, gender, and hazardous habits (cigarette, alcohol or betel nut consumption), and tumor-related factors including the AJCC (American Joint Committee on Cancer) stage, treatment, pathologic findings (surgical margin, tumor invasion, multi-foci, tumor necrosis, poor differentiation), and recurrence pattern were grouped and analyzed (Table 1).

To make a diagnosis of SpCC in a sarcomatoid tumor, the following criteria had to be met: (1) identification of carcinoma, particularly with somewhat squamoid feature, in some part of the tumor (Figures 1 and 2); (2) spindle cells stain positively for cytokeratin and may also have negativity for vimentin (Figures 3 and 4); (3) presence of SCC *in situ*.

The Kaplan–Meier model with log rank test was performed for survival analysis. Fisher's exact test and Student's *t* test were used to determine the relationship between the variables and recurrent pattern. The Mann–Whitney test was used to compare the relationship between time to recurrence and salvage operation. A p value < 0.05 was considered statistically significant.

Results

Eighteen lesions of different portions from the oral cavity and oropharynx were found. There were 17 men (94%) and 1 woman (6%). The median age at onset was 51 years (range, 32–76 years). The mean follow-up time was 14.2 months. The most common disease sites were the tongue (28%) and buccal mucosa (22%). According to the 2002 AJCC cancer staging system, there were 3 cases with stage I disease, 3 cases with stage II, 2 cases with stage III, 9 cases with stage IV, and 1 case without definite staging.

The median overall survival time was 8.9 months. The 1-year overall survival rate was 36.7%, and the 3-year overall survival rate was 27.5%. In the early stage group (stages I and II), the 3-year survival rate was 100%. In the late stage group (stages III and IV), the 1-year survival rate was only 9%, and the 3-year survival rate was 0%. Survival time difference between the early and late stage groups was statistically significant. The factors influencing overall survival were tumor grade, lymph nodes, metastasis, stage, vascular invasion and distant recurrence (Table 2). The following factors did not statistically significantly influence survival: gender, age, tumor site, previous existence of SCC, cigarette smoking, alcohol drinking, betel nut chewing, positive surgical margin, distance of safe margin, nerve invasion, muscular invasion, tumor necrosis, multi-foci, radiotherapy, chemotherapy, combined treatment of surgery and radiotherapy, and local recurrence. A total of 15 patients received surgery, 1 received chemotherapy only, 1 received radiotherapy only, and 1 refused any treatment. In the surgery group, 11 developed local recurrence (recurrence rate, 73.3%). Even the early stage group with negative surgical margin had recurrence. Four patients had local recurrence with regional lymph node metastases; 5 patients had distant metastases (metastasis rate, 33.3%) and subsequently died of metastatic disease.

Seven of the 11 patients with local recurrence received salvage operation and responded well. Salvage operation after local recurrence improved survival (Table 3). The post-recurrence survival was defined as the time interval of survival between the patient's recurrence and the end of the study. The median post-recurrence survival was 22 months for patients who received salvage surgery and only 1 month for patients who did not receive salvage surgery. The relationship between overall survival and salvage operation was also statistically significant. The mean overall survival was 34 months in patients who received salvage surgery and 4 months in those who did not.

The recurrence time was determined as the time interval from treatment to recurrence. The median overall recurrence time was 5.2 months. The median recurrence time in the early stage group was 10.5 months, versus 4.0 months in the late stage group ($p = 0.03$).

Table 1. Patients with spindle cell carcinoma of the oral cavity and oropharynx

Age (yr)	Sex	Site	Cigarettes	Alcohol	Betel nut	Stage	Tx	Surgical margin	Nerve invasion	Vascular invasion	Muscle invasion	Recurrence pattern	Recurrence time (mo)	Salvage operation	Follow-up time (mo)*	Outcome
76	M	Gingival	Y	N	N	T4N2M0	C								2	DOD
75	F	Lingual tonsil	N	N	N	T4N0M0	R					D	1	N	6	DOD
49	M	Mouth floor	Y	Y	?	T4N1M0	S, C	–	N	N	N	L	1	N	2	DOD
59	M	Tongue	Y	Y	Y	T3N3M0	S	–	N	Y	Y				6	DOD
47	M	Palatine tonsil	Y	Y	Y	?	Nil								6	DOD
42	M	Palatine tonsil	Y	Y	Y	T2N0M0	S, R	+	N	N	N				49	NED
44	M	Tongue	Y	Y	Y	T1N0M0	S	–	N	N	N	L	8	Y	23	NED
42	M	Palate	Y	Y	Y	T3N2M0	S, R	–	N	Y	N	L	4	N	9	DOD
75	M	Buccal	Y	Y	N	T1N0M0	S	–	N	N	N	L	26	Y	40	NED
52	M	Buccal	Y	Y	Y	T4N0M0	S, R	–	Y	N	N	D	6	N	6	DOD
32	M	Tongue	Y	Y	N	T4N2M0	S	–	N	Y	Y	L, R	1	N	3	DOD
51	M	Buccal	Y	Y	Y	T1N0M0	S	–	N	N	N	L	32	Y	36	NED
42	M	Lip	Y	Y	Y	T2N1M0	S, C	–	N	N	N	L, R	11	Y	33	DOD
59	M	Gingival	Y	Y	Y	T4N0M0	S	–	Y	N	Y	L, D	4	Y	13	DOD
52	M	Tongue	Y	Y	Y	T2N0M0	S, R, C	–	Y	N	Y	L, R	6	Y	20	NED
51	M	Tongue	Y	Y	N	T4N2M0	S	–	Y	Y	Y	L, R, D	2	N	3	DOD
46	M	Lip	Y	Y	Y	T2N0M0	S, R	–	N	N	N	L	4	Y	8	NED
67	M	Buccal	Y	N	Y	T3N0M0	S, R	–	Y	Y	N	D	5	N	6	DOD

**Follow-up time: time period from first operation until death or last follow-up if still alive. Tx = treatment; Y = yes; N = no; C = chemotherapy; R = radiation; S = surgery; D = distant metastasis; L = local recurrence; R = regional recurrence; DOD = died of disease; NED = no evidence of disease; ? = unknown; + = positive; – = negative.*

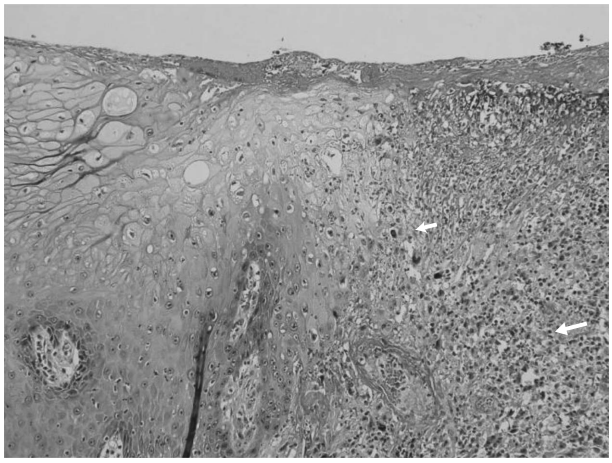

Figure 1. Spindle cell carcinoma of the buccal mucosa: there is presence of both carcinoma *in situ* (short arrow) and sarcomatous components (long arrow) (hematoxylin & eosin; 20×).

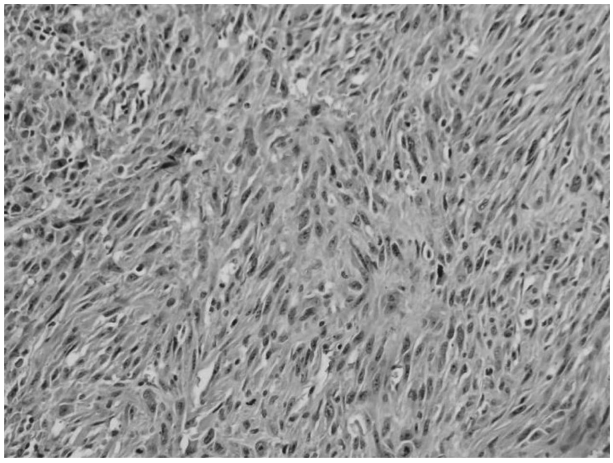

Figure 2. Spindle cell carcinoma of the buccal mucosa with predominance of sarcomatoid components and scattered carcinomatoid elements (left upper corner) (hematoxylin & eosin; 100×).

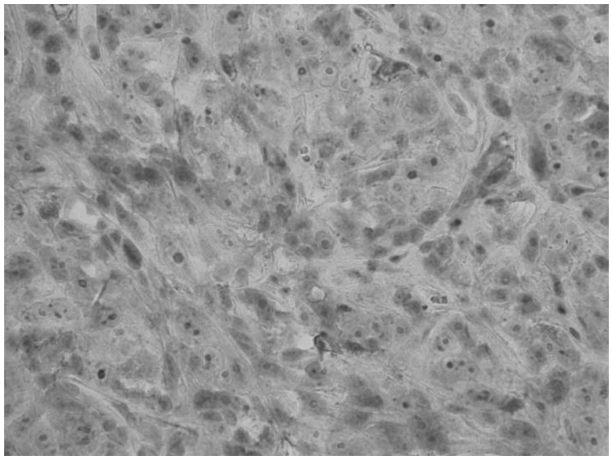

Figure 3. Spindle cell carcinoma of the buccal mucosa shows positive staining in both sarcomatoid and carcinomatoid cells (cytokeratin; 200×).

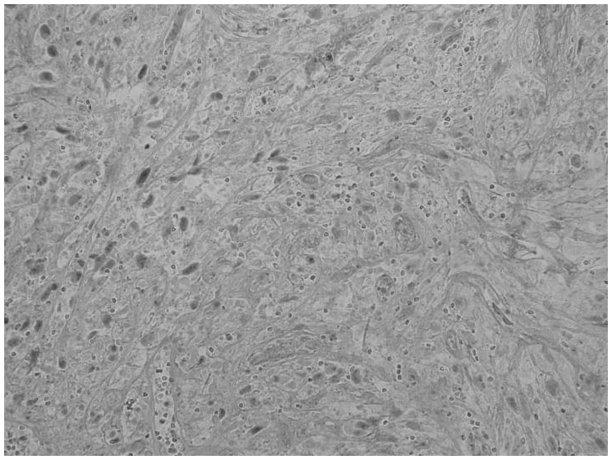

Figure 4. Spindle cell carcinoma of the buccal mucosa shows negative staining in both sarcomatoid and carcinomatoid cells (vimentin; 200×).

Table 2. Significant factors influencing overall survival

	p
T (1, 2; 3, 4)	<0.001
N (0; 1–3)	0.004
Early stage (I, II)/late stage (III, IV)	<0.001
Neck or distant metastasis	<0.001
Vascular invasion	0.005
Distant recurrence	0.042

Table 3. Significant factors influencing post-recurrence survival

	p
T (1, 2; 3, 4)	<0.001
Early stage (I, II)/late stage (III, IV)	0.017
Distant recurrence	0.026
Salvage operation	<0.001

The median recurrence time in patients managed with salvage operation was 8 months, whereas it was 2 months in patients who did not receive salvage operation ($p=0.014$). This suggests that if recurrence time is shorter, the opportunity to perform salvage operation will be lower. The possible cause was that late stage patients experienced recurrence earlier and so usually could not receive surgery. The factors influencing survival after recurrence are listed in Table 3.

After recurrence, having salvage operation or not was influenced by the initial staging factor of T, N and stage ($p<0.01$). This suggests that the higher the initial stage of a patient, the less likely it is that he will receive salvage operation after recurrence.

No patient with recurrence had positive margin during the previous surgery. We used Fisher's exact test to detect the factors influencing the failure pattern. The significant factor for local recurrence was alcohol consumption ($p=0.03$). There were no significant factors for regional recurrence, but muscular invasion ($p=0.05$) was noteworthy. The significant factors for distant metastasis were age < 50 years ($p=0.03$), T stage > T2 ($p=0.03$), and nerve invasion ($p=0.007$).

Discussion

The spindle cells in SpCC are a variant growth pattern of SCC, neither a non-neoplastic mesenchymal reaction nor a malignant admixture of epithelial and mesenchymal neoplasms. The epithelial and spindle components share a common pathway of tumorigenesis despite their conspicuous divergence at the phenotypic level.[7] Here, the question arises, "Is the behavior of SpCC different from that of SCC?"

The survival and reaction to treatment of SpCC are still controversial. Ellis et al[8] reported 59 cases of oral SpCC with a 36% survival rate. Olsen et al[9] reported 34 patients with laryngeal and hypopharyngeal SpCC; recurrence occurred in 10 patients, 8 patients died of their disease, and the 3-year survival rate was 56.8%. Olsen et al considered that SpCC was similar to conventional SCC of the larynx, but there were only 2 cases of stage III and 2 cases of stage IV in their series. In our series, the overall survival rate of oral SpCC was 27.5% at 3 years. This low survival rate might be due to there being many late-stage patients in our series. In our early stage group, the 3-year survival rate was 100%. In contrast, half the patients in our late stage group died within 6 months. Leventon et al[10] found that survival was related to depth of invasion; in patients whose tumors invaded deeply, survival rate was low, whereas in those whose tumors were superficial, survival prospects were excellent.

Alonso et al[11] found that SpCC demonstrated prominent local invasiveness, high angiogenic response, and a 90–100% incidence of lung metastases when inoculated subcutaneously into syngeneic mice. It is known that in the inflammatory state, the epithelioid cell might change its shape into the spindle morphology to aid in migration. Kaposi's sarcoma is another famous example, which is characterized by spindle cell proliferation, inflammatory cell infiltration, angiogenesis, edema, and invasiveness.[12] These facts suggest that the spindle cell pattern might be linked with invasiveness and metastasis.

In our series, the overall survival rate was lower than that of SCC in the oral cavity and oropharynx.[13] The recurrence rate was very high, even in the early-stage patients. The metastatic rate was high in the advanced-stage patients. We would consider that oral and oropharyngeal SpCC has more aggressive behavior. Better treatment of oral SpCC should be aimed at controlling local and distant recurrence.

It appeared strange that none of the patients with local recurrence had positive margin during the initial surgery. The distance of surgical margin was not statistically significant to the recurrence. To improve local control, a much wider safety margin (> 2 cm) for SpCC would be helpful. To identify the recurrence early, close postoperative follow-up is necessary. If recurrence occurs, salvage operation is indicated and is helpful.

In general, results using radiation therapy alone to treat SpCC have not been satisfactory.[14] Olsen et al had 1 case of T1 glottic carcinoma with favorable response to radiotherapy alone without recurrence 49 months after diagnosis. Ampil[15] reported that 2 of 4 cases benefited from the combination of surgery and radiotherapy. The influence of radiotherapy on outcome in our series was not statistically significant. But 1 of our patients with a positive surgical margin did benefit from adjuvant radiotherapy. Therefore, we consider that radiation therapy might be helpful in improving local control in patients with positive surgical margins.

Colozza et al[16] reported an amazing experience of chemotherapy for a patient who had neck and lung metastases by SpCC from an unknown primary site. The patient had a complete response to cisplatin and 5-fluorouracil, and was disease-free 12 months after diagnosis. However, such was not the case for our patient with metastasis. To solve the problem of distant recurrence, chemotherapy will still play a role in the future. Considering the high angiogenic response of SpCC,[11] patients with tumor stage > T2 (included) may require chemotherapy to decrease the risk of distant metastasis or regional failure.

In conclusion, SpCC in the oral cavity and oropharynx is potentially aggressive and seems to recur easily and to metastasize. It should be treated accordingly, and better treatment of oral SpCC should aim at controlling local and distant recurrence. Although it is difficult to predict biologic behavior in every case, patients whose tumors are deeply invasive tend to have a poor prognosis, whereas those with early-stage tumors usually have an excellent prognosis. If local recurrence occurs, salvage operation should be performed and will be beneficial to patients.

Based on the limited number of patients in this study, it would be helpful if more cases were collected for meta-analysis from a multicenter data bank to

answer further questions about the behavior and optimal treatment of SpCC.

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