Prognostic Factors of Squamous Cell Carcinoma of the Buccal Mucosa: A Retrospective Study of 168 Cases in North China

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Purpose: Buccal mucosa squamous cell carcinoma (BSCC) is considered a rare and aggressive malignancy that has a high rate of locoregional recurrence. The aim of this study was to analyze the outcome of surgical therapy as a treatment for BSCC in a North Chinese population over a period of 14 years.

Materials and Methods: A retrospective study was performed by reviewing the records and pathologies of 168 patients with BSCC who were treated at the Department of Oral and Maxillofacial Surgery, Stomatological Hospital, Peking University, from June 1999 to September 2013.

Results: The rates of local, regional, and locoregional recurrence were 47.3%, 13.5%, and 6.8%, respectively. The neck metastasis rate in patients classified as having cN0 was 28.4%, and the occult metastasis rate in patients with BSCC stages T2 to T4 was higher than 15%. Neck metastases were most common at levels I and II. The 3-year disease-free survival, overall survival, and disease-specific survival rates were 60.6%, 74.6%, and 78.0%, respectively. Gender, T stage, pathologic node status, and pathologic grade were significant factors in determining disease-specific survival. However, only pathologic node status (P = .002) was an independent predictive factor of 3-year disease-specific survival.

Conclusions: Buccal carcinoma is an aggressive disease with high rates of local and regional recurrence. In seeking to offer better prognoses and quality of life, extensive resection of the primary tumor, supraomohyoid neck dissection, and preferred free flap reconstruction are the therapies that have been recommended and used in the authors' hospital during the past 10 years.

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Squamous cell carcinoma of the buccal mucosa (BSCC) is relatively uncommon in North China. Because betel quid chewing is rare in North China, the pathogenesis, clinicopathologic features, and prognosis of BSCC may be significantly different from those of patients in southern Asia.[1] To optimize treatment, accurate predictors of prognosis should be sought when treating BSCC. Currently, many investigators agree that BSCC behaves aggressively and has a high rate of recurrence.[2,3] However, others have

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argued that there are no significant differences between BSCC and other cancers when evaluating pathologic staging and prognosis.[4]

Treatment studies of BSCC tend to focus on resection of primary sites. However, data from North China are still rare and lack horizontal comparisons between other populations and regions. Furthermore, the potential treatments for BSCC of the neck vary and are not always well defined. There is no consensus on whether neck dissection (ND) is necessary when treating early BSCC, and an optimal treatment modality of ND has not been established.

Currently, there is sparse high-level information on the recommended treatment for patients with BSCC in North China, which has a population of more than 600 million people and accounts for approximately half the Chinese population. The aims of this retrospective study were *1)* to investigate the clinicopathologic features, patterns of neck nodal metastasis, and prognostic factors of BSCC in the North Chinese population; *2)* to compare the oncologic behavior of BSCC in a homogeneous population with that in areas where betel nut use is endemic, such as India and Taiwan, and areas where the betel nut is not commonly chewed, such as North America and Europe; and *3)* to describe the authors' 14-year experience with this disease.

Materials and Methods

PATIENT CHARACTERISTICS

The institutional review board of the Stomatological Hospital of Peking University (Beijing, China) approved this study. Because of the retrospective nature of the study, it was granted an exemption in writing by the institutional review board. From June 1999 to September 2013, 168 consecutive patients diagnosed with primary BSCC were enrolled in this study. All patients underwent presurgical computed tomography or magnetic resonance imaging to determine tumor extent, in addition to chest radiography, baseline complete blood cell counts, and biochemistry tests. Clinical staging was based on the clinical and imaging findings, and pathologic staging was based on each patient's pathology report.

In recording the site of oral SCC, the authors adhered strictly to the Unión International Contra la Canrum and American Joint Committee on Cancer TNM classifications, which recognize the buccal mucosa as the upper and lower lips, cheek, retromolar areas, and upper and lower bucco-alveolar sulci.

To optimize the accuracy of these data, the authors compared the patients' medical records and excluded any with inaccurate site codes. Oral cavity tumors with secondary extension to the buccal mucosa or those that had been previously treated with surgery were excluded. Patients with prior nonsurgical treatment also were excluded. Data on the deceased patients and their causes of death were obtained from return visits or telephone interviews.

SURGERY AND POSTOPERATIVE RADIOTHERAPY REGIMEN

Primary tumors were excised with 1- to 2-cm safety margins (peripheral and deep margins) in cases of posterior buccal cancer. When treating anterior buccal cancer, preservation of the facial skin depended on whether subcutaneous tissue was involved; the commissure was excised if the safe distance was shorter than 1 cm. Tumor margin tissue was sent for cryosectioning; if a margin was positive, additional tissue was excised and sent for cryosectioning until the margin was free of tumor. Depending on the tumor extent, marginal mandibulectomy, segmental mandibulectomy, or infra-maxillectomy was performed. Most patients who had large tissue defects postoperatively underwent immediate reconstruction, including free anterior lateral thigh flap, forearm free flap, lateral arm free flap, rectus abdominis free flap, and vascularized fibular flap. ND was performed for most patients with cN0 and all patients with cN^+ neck, as discussed below.

For patients with positive lymph nodes, pT4 tumors, or close margins ($\leq$4 mm), postoperative radiotherapy was advised.

STATISTICAL METHODS

The follow-up study continued until December 1, 2013. The median follow-up time was 54 months (range, 3 to 155 months). Commercial statistical software (SPSS 17.0; SPSS, Inc, Chicago, IL) was used for all statistical analyses. Variables that might have affected nodal status were analyzed using the χ^2 test. Survival time was calculated from the date of surgery using the Kaplan-Meier product-limit method, with the log-rank test for univariate analysis and a Cox regression model for multivariate analysis. Univariate and multivariate analyses were used to determine independent risk factors.

Results

PATIENTS

From June 1999 to September 2013, 168 consecutive patients (99 men and 69 women; median age, 62 yr; range, 35 to 87 yr) with BSCC who also met the predetermined eligibility criteria were included in this study. Demographic data of the 168 patents are presented in Table 1. In total, 34.5% of patients had a history of smoking and 22.0% had a history of alcohol use. The T-stage distributions were T1 in 20.2%, T2 in 43.5%, T3 in 10.1%, T4a in 24.4%, and T4b in 1.8%.

Table 1. CLINICAL CHARACTERISTICS OF 168 ENROLLED PATIENTS WITH SQUAMOUS CELL CARCINOMA OF THE BUCCAL MUCOSA

Characteristics	Patients, n (%)
Age (yr)	
35-87 (median 62)	
<65	89 (53.0)
≥65	79 (47.0)
Gender	
Male	99 (59.0)
Female	69 (41.0)
Subsites	
Cheek	118 (70.2)
Retromolar areas	50 (29.8)
Upper and lower bucco-alveolar sulci	21 (12.5)
Pathologic grade	
I	93 (55.3)
II	67 (39.9)
III	8 (4.8)
T stage	
T1	34 (20.2)
T2	73 (43.5)
T3	17 (10.1)
T4a	41 (24.4)
T4b	3 (1.8)
Growth pattern	
Exophytic	55 (32.7)
Ulcerative	47 (28.0)
Infiltrative	40 (23.8)
Unknown	26 (15.5)
Smoking history	
Smoker	58 (34.5)
Nonsmoker	106 (63.1)
Unknown	4 (2.4)
Alcohol history	
Drinking	37 (22.0)
Nondrinking	127 (75.6)
Unknown	4 (2.4)

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CLINICAL T STAGE AND NODE STATUS

The authors were most concerned with the pathologic node status of patients with cN0 neck; 89.6% (95 of 106) of those patients underwent ND. Eleven patients had a poor general condition; thus, these patients underwent only tumor excision at the primary site. Of patients with cN0 who underwent ND, 28.4% (27 of 95) were pathologically identified as nodal positive during primary surgery. The rates of pN^+ results by T stage were 13.0% (3 of 23) for T1, 31.8% (14 of 44) for T2, 18.2% (2 of 11) for T3, and 47.1% (8 of 17) for T4. Of those patients with cN0 and without ND, 1 patient developed recurrence in the neck. All patients with cN^+ neck were treated with ND. The rates of the pN^+ results by T stage were 40% (2 of 5) for T1, 60% (15 of 25) for T2, 40% (2 of 5) for T3, and 85.2% (23 of 27) for T4. Characteristics of the pathologic node states and clinical T stages of patients with cN0 and cN^+ and ND are presented in Table 2.

Table 2. PATHOLOGIC NODE STATES AND CLINICAL T STAGES OF PATIENTS WITH CN0 AND CN^+ NECK

Pathologic Node State	cN0 Neck (n = 95)				cN^+ Neck (n = 62)				
	T1	T2	T3	T4	T1	T2	T3	T4	Total
pN0	20	30	9	9	3	10	3	4	88
pN1	2	7	1	5	2	8	0	6	31
pN2b	1	6	1	3	0	7	2	15	35
pN2c	0	0	0	0	0	0	0	1	1
N skip	0	1	0	0	0	0	0	1	2

Abbreviations: cN0, clinically nodal negative; cN^+, clinically nodal positive; N skip, nodal skip metastasis.

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DISTRIBUTION OF PATHOLOGICALLY POSITIVE NODES

In total, 106 patients were preoperatively designated as having cN0, and 62 patients were designated as having cN^+. Ninety-six sides in 95 patients designated as cN0 and 65 sides in 62 patients with cN^+ underwent simultaneous ND. The distribution of pathologically positive nodes in the cN0 and cN^+ cases is listed in Table 3.

Of patients with cN0, 55 sides (57.3%) underwent supraomohyoid ND (SOND), 7 sides (7.3%) underwent extended supraomohyoid ND (ESOND), and 34 sides (35.4%) underwent modified or radical ND (MRND/RND). In the cN0 group, 1 patient was treated using bilateral SOND, but the pathologic node state was ultimately negative. Occult metastases were most common at level I. Level I metastasis was observed in 19 of 96 sides (19.8%), level II in 16 of 96 sides (16.7%), level III in 3 of 96 sides (3.1%), level IV in 1 of 75 sides (2.4%), and level V in 1 of 34 sides (2.9%). One case of skip metastasis was at level III, and no skip metastases of level IV or V alone were observed in patients with cN0 neck.

Of patients with cN^+ neck, 32 sides (49.2%) underwent SOND, 4 (6.2%) sides underwent ESOND, and 29 (44.6%) sides underwent MRND/RND. In the cN^+ group, 3 patients underwent bilateral ND. One underwent bilateral RND, 1 underwent bilateral SOND, and 1 underwent RND plus SOND. One patient diagnosed as having cT4aN2cM0 underwent bilateral RND and was found to have level I and level II neck metastases on the right side and level II metastasis on the left side.

Table 3. DISTRIBUTION OF PATHOLOGICALLY POSITIVE NODES IN PATIENTS WITH CN0 AND CN+ NECK

	cN0 Neck (n = 96 Sides)		cN+ Neck (n = 65 Sides)	
Lymph Node Level	n	%	n	%
MRND/RND + ESOND + SOND (n = 161)*	96	59.6	65	40.4
I	9	9.4	16	24.6
II	7	7.3	8	12.3
III	1	1.0	1	1.5
I + II	8	8.3	10	15.4
I + III	1	1.0	2	3.1
II + III	1	1.0	—	—
I + II + III	—	—	3	4.6
MRND/RND + ESOND (n = 74)†	41	55.4	33	44.6
Any (I to III) + IV	—	—	—	—
MRND/RND (n = 63)‡	34	54.0	29	46.0
I + IV + V	1	2.9	—	—
I + II + III + IV + V	—	—	1	3.4

Abbreviations: cN+, clinically nodal positive; cN0, clinically nodal negative; ESOND, extended supraomohyoid neck dissection; MRND, modified radical neck dissection; RND, radical neck dissection; SOND, supraomohyoid neck dissection.

* MRND/RND + ESOND + SOND, extension of neck dissection including below levels I to III (n = 161).

† MRND/RND + ESOND, extension of neck dissection including below levels I to IV (n = 74).

‡ MRND/RND, all patients underwent neck dissection at levels I to V (n = 63).

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Similarly, occult metastases were most common at level I. Level I metastasis was observed in 32 of 65 sides (49.2%), level II in 22 of 65 sides (35.4%), level III in 7 of 65 sides (10.8%), level IV in 1 of 62 sides (3.0%), and level V in 1 of 29 sides (3.4%). One patient in the cN+ group presented with skip metastasis at level III, and no skip metastases for level IV or V alone were observed in the cN+ group.

DISEASE-FREE SURVIVAL, OVERALL SURVIVAL, AND DISEASE-SPECIFIC SURVIVAL

During the follow-up period, 20 (11.9%) of the 168 patients were lost to survival analysis follow-up, and 52 (35.1%) of the remaining 148 patients died. Five patients died from causes unrelated to cancer: 3 from cardiac failure and brain stroke and 2 from respiratory failure.

Sites of the first recurrences and the treatment results are listed in Table 4. Overall, local recurrence was the most common disease progression, and the success rate of operative salvage in those cases was only 44.0%. A second primary carcinoma of the oral cavity was common postoperatively for patients with BSCC; fortunately, the success rate for operative salvage in these cases was 73.3%. The 3-year disease-free survival, overall survival, and disease-specific survival (DSS) rates were 60.6%, 74.6%, and 78.0%, respectively (Fig 1).

Univariate analysis suggested that gender, T stage, pathologic node status, and pathologic grade were significant factors in determining DSS length. Conversely, age, growth pattern, smoking history, and alcohol history were not associated with 3-year survival. Multivariate survival analysis suggested that pN status (hazard ratio = 1.956; 95% confidence interval, 1.286-2.975; $P = .002$) was the only independent predictive factor for 3-year DSS; details are presented in Table 5.

Discussion

BSCC is the third most common type of oral cavity SCC in North China and is the most common oral cavity cancer in Taiwan.[5,6] The literature on BSCC treatment in North China is limited. The present study sought to supplement the currently available data on China by showing the prognostic factors of

Table 4. SITES OF FIRST RECURRENCE AND TREATMENT RESULTS

	Patients With Recurrence (n = 74)		
Site of Recurrence	Patients, n	Treatment	Success Rate of Operative Salvage
Local	35	19 op; 6 op + RT; 5 RT; 5 quit	44.0%, 11/25
Local + node	5	3 op; 2 op + RT	40.0%, 2/5
Node only	10	4 op; 3 op + RT; 3 RT	57.1%, 4/7
Node + distant	2	1 CTRT; 1 quit	—
Distant	6	4 CT; 1 CTRT; 1 quit	—
SPM	16	12 op; 3 op + RT; 1 CT	73.3%, 11/15

Abbreviations: CT, chemotherapy; CTRT, concurrent chemoradiotherapy; op, operation; RT, radiotherapy; SPM, second primary malignancy.

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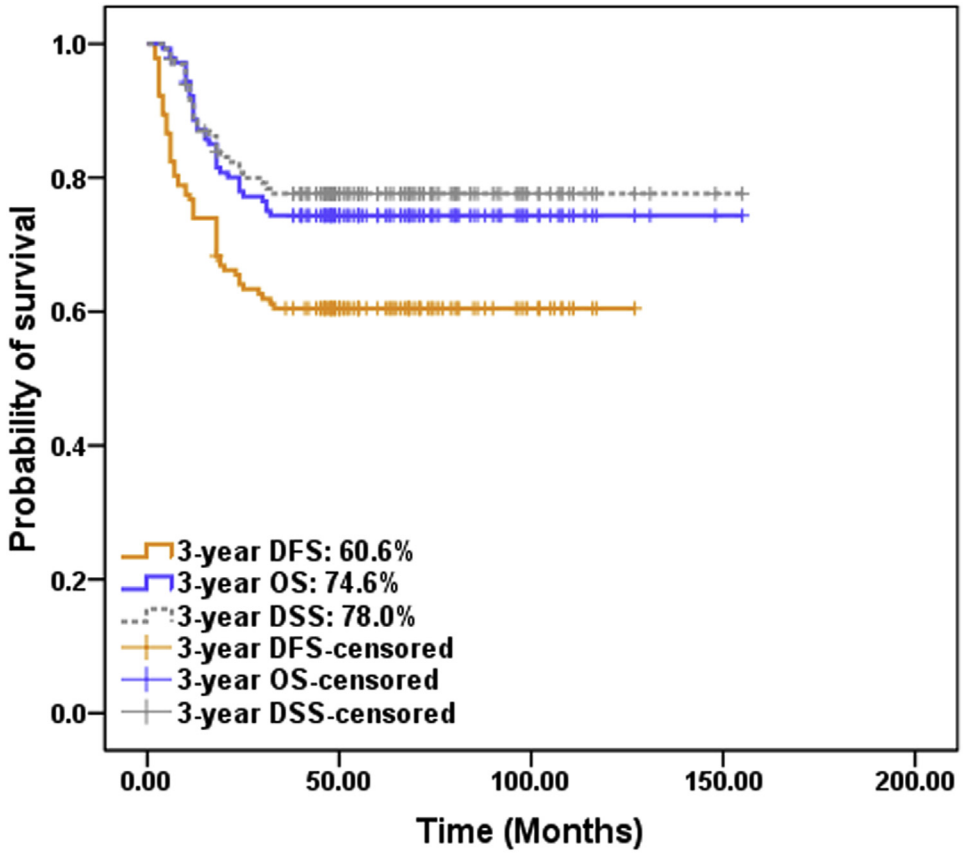

FIGURE 1. The 3-year DFS, OS, and DSS rates in patients with squamous cell carcinoma of the buccal mucosa. DFS, disease-free survival; DSS, disease-specific survival; OS, overall survival.

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BSCC and describing the treatment experiences at the authors' hospital in the past 14 years.

The present histopathologic findings are comparable to other available data on BSCC. The tumors the authors evaluated were differentiated as 55.3% well, 39.9% moderate, and 4.8% poor. These data are similar to those from studies of areas in which betel nut use is endemic, which have reported tumor differentiation rates of 41 to 44% well, 50% moderate, and 6% poor.[7-9] DeConde et al[10] obtained data from a population in North America and reported the following differentiation rates: 19% well, 48% moderate, and 21% poor. BSCC in the present North Chinese population tended to show more well-differentiated tumors.

The high rate of local BSCC recurrence is widely recognized and could be attributable to the absence of anatomic barriers that prevent the disease from spreading into the buccal space.[1] Once the tumor has invaded beyond the buccinator muscle and encroaches on the buccal fat, there is no effective anatomic barrier that can prevent the cells from spreading.[2] In the present study, the rates of local, regional, and locoregional recurrence were 47.3%, 13.5%, and 6.8%, respectively. Diaz et al[2] reported local, regional, and locoregional recurrence rates of 23%, 11%, and 9%, respectively, and noted that salvage therapy was successful in 22% of cases. However, they also reported that tumor location relative to the Stensen duct and buccinator muscle invasion had no statistically significant effect on locoregional recurrence, but that location was associated with decreased survival in patients with BSCC. Sieczka et al[11] reported that patients with negative margins and T1 to T2 disease had a 40% local failure rate when treated with surgical resection alone. They concluded that low T stage and negative margins are not adequate predictors of local control. The present results suggest that BSCC in North China also is a high-risk cancer type. Because of the high rate of local recurrence, the authors recommend undertaking extensive resection of the primary tumor.

A free flap-based reconstruction is the preferred "extensive resection" used in the authors' hospital. The free radial forearm flap, fibular flap, anterior lateral thigh flap, and rectus abdominis flap were most

Table 5. COX PROPORTIONAL HAZARD REGRESSION MODELS ESTIMATING 3-YEAR DISEASE-SPECIFIC SURVIVAL

Variable	HR	95% CI	*P* Value
Univariate analysis			
Age (<65 vs ≥65 yr)	0.727	0.405-1.303	.284
Gender (male vs female)	0.493	0.256-0.951	.035
T stage (T1, T2, T3, T4a, T4b)	1.643	1.274-2.120	<.001
pN status (N0, N1, N2b, N2c)	2.268	1.600-3.215	<.001
Pathologic grade (I, II, III)	1.810	1.166-2.811	.008
Growth pattern (exophytic, ulcerative, infiltrative)	1.388	0.895-2.154	.143
Smoking history (smoker vs nonsmoker)	1.259	0.689-2.298	.454
Alcohol history (drinker vs nondrinker)	1.545	0.818-2.919	.180
Multivariate survival analysis			
pN status (N0, N1, N2b, N2c)	1.956	1.286-2.975	.002
T stage (T1, T2, T3, T4a, T4b)	1.331	0.991-1.787	.058
Gender (male vs female)	0.669	0.330-1.357	.265
Pathologic grade (I, II, III)	1.036	0.582-1.844	.904

Abbreviations: CI, confidence interval; HR, hazard ratio.

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commonly used in the authors' department. The overall success rate was as high as 98.0%, and the technique has the advantage of providing adequate blood supply, strong anti-infective capacity, and radiation tolerance. Ratto and Ricci[12] concluded that the free flap is safe, reliable, and superior to the conventional pedicle flap technique. In addition, free flap reconstructions in buccal cancers do not interfere with re-examination after extensive lesion resection or conceal residual tumors or their recurrence. Furthermore, in cases of local recurrence or when reconstruction results in failure, a new free flap or an alternative pedicle flap can serve as the basis of a new reconstruction plan.

Regional lymph node metastases are generally considered less common in BSCC than are other subsites of the oral cavity,[13] but the present study includes novel data. Liao et al[8] reported that histologically proven lymph node metastasis occurred in only 38% of the 331 patients who underwent selective NDs. In another study of 121 Taiwanese patients by Lin et al,[9] BSCC with positive neck disease was reported in 38.8% of cases. Studies undertaken in India have reported neck disease rates of approximately 16 to 36%.[13,14] Other data in areas where chewing betel nuts is endemic have reported regional lymph node metastasis rates of 27 to 37%.[2,15] In the present study, the positive nodal metastasis rate (43.9%; 69 of 157) was higher than the rates obtained in the aforementioned studies. Elective treatment of cervical nodes in these patients was widely accepted when the risk of metastasis exceeded 15 to 20%.[16] In the present study, the rate of neck metastasis in patients with cN0 and ND was 28.4%, and patients with T2 to T4 cancer had an occult metastasis rate higher than 15%. The authors strongly believe that ND should be the preferred neck management treatment for T2N0 to T4N0 BSCC.

Lymphatic drainage from the oral cavity follows an orderly path, moving from the first echelon node to the next through simple overflow.[17] Dhawan et al[13] reported that pathologically identified level I neck metastasis occurred in 11.7% of patients with cN0 neck and 17.5% of patients with cN^+ neck, and they identified level II metastasis in 9% of patients with cN0 neck and 14% of patients with cN^+ neck. Pandey et al[14] reported that level II metastasis was identified in the first echelon of lymphatic spread in up to 20% of BSCC cases. In the present study, only 2 cases had skip metastasis to level III, and no skip metastasis to the lower levels was found. Based on these data and the results of the present study (in which metastases at levels III to V were rare), the authors believe that SOND is sufficient for the neck treatment of BSCC. ESOND and MRND/RND may not be indispensable for cN0 or even select cN^+ cases. The authors suggest selective ND for most cases of BSCC, except those with previous neck disease at levels IV to V. Overall, "selective ND" conforms to the oral SCC treatment concept in the authors' hospital, which provides high efficiency and minor morbidity.[18]

This study was retrospective and was restricted to patient subsets with samples; thus, all the results are to be considered exploratory. The study also can be criticized for the lack of a relation between the depth of invasion and thickness of the tumors and their locoregional recurrence, which the authors will present in full in future studies.

To the best of the authors' knowledge, this is the largest series study of patients with BSCC in North China. Their conclusion is that BSCC is a relatively rare but aggressive tumor that easily invades adjacent tissue and has a tendency to recur locoregionally. Elective SOND is recommended for patients with T2 to T4 cancers; for those with T1 cancer, a conservative approach with close observation should be used. The authors strongly suggest the following 3 principles for BSCC treatment: *1)* extensive resection of the primary tumor; *2)* SOND; and *3)* preferred free flap reconstruction. These principles have provided the preferred therapeutic concepts used for the past 10 years at the authors' hospital.

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