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Risk factors affect the survival outcome of hard palatal and maxillary alveolus squamous cell carcinoma: 10-year review in a tertiary referral center

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Objective. Hard palatal cancer is relatively rare in the head and neck region. Treatment outcome, risk factors that lead to poor survival outcome, and treatment strategy are still controversial.
Study design. Retrospective study in a tertiary medical center.
Results. Surgery is a better treatment strategy than concurrent chemoradiation therapy (CCRT) for achieving positive survival outcomes. We also found a higher surgical salvage rate in patients with hard palatal cancer who had local recurrence or neck relapse. Soft palate or infratemporal fossa involvement had poor outcomes. Ulcerative tumor features, tumor volumes larger than 10 mL, and local recurrent tumors that could not undergo salvage surgery also had poorer survival outcomes in our study.
Conclusion. Surgical management is still the first choice for patients with hard palate or alveolus squamous cell carcinomas even when patients had local or neck regional recurrence. **(Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2010;110:11-17)**

Squamous cell carcinomas (SCCs) of the hard palate and maxillary alveolus often have similar clinical presentations and management because of their adjacent anatomies. SCCs of both the hard palate and maxillary alveolar ridge are relatively uncommon.[1] Carcinomas of the maxillary alveolus and hard palate are classified as the same site by many investigators[1,2]; however, the risk factors that lead to poor survival outcome still need to be surveyed. Therefore, this study aimed to identify the risk factors for poor survival outcome and compare the treatment strategies of surgery and concurrent chemoradiation therapy (CCRT) in a retrospective setting in a tertiary head and neck center.

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MATERIALS AND METHODS

The records of 88 patients diagnosed with SCC of the hard palate and registered in the China Medical University Hospital from August 1997 to July 2007 were evaluated. All patients were followed for a minimum of 60 months or until death. Patients were excluded for the following reasons: incorrect site coding (n = 6), insufficient clinical data (n = 2), and other pathology (n = 1). There were 79 patients with biopsy-proven, previously untreated SCCs of the hard palate and maxillary alveolus. Staging was performed using clinical data recorded at the time of initial assessment of each patient according to the TNM (tumor stage, nodal stage, and distant metastasis) classification system of the American Joint Committee on Cancer (AJCC), sixth edition. The degree of bone involvement of the tumor was examined by extraoral projections (sagittal projection, lateral projection, and Waters' projection), panoramic film, and computed tomography (CT). The depth of palatal bony invasion of the tumor was measured with the coronal view of the preoperation CT scan and was later confirmed by

pathologic survey for every patient with palatal cancer who underwent an operation. The depth of palatal involvement of the tumors of nonoperated patients was also determined with a coronal view of the CT scan.[3] The gross tumor volume was summed and calculated by a 3-dimensional (3D) CT scan for every patient before treatment.

Tumor volume assessment was performed by transillumination of each CT image depicting the tumor at the primary site. The peripheral margins of the primary masses were outlined by an Eclipse IMRT Image Analyzer (Varian Eclipse planning system V7.1; Varian Medical Systems Inc., Palo Alto, CA, USA), and the tumor areas were calculated. This provided a cross-sectional area at multiple levels, separated by the distance between each slice. The distance between each slice (either 3 or 5 mm) was recorded and used to calculate the tumor volume. Primary tumor volume was determined by summing all measured tumor dimensions visible on the CT images.[4] The epicenter of tumor was also collected according to the chart review and reconfirmed by head and neck CT image study. Tumors that involved the soft palate or infra-temporal fossa were categorized as posterior hard palate tumor, otherwise they were categorized as anterior hard palatal tumor. After completing initial therapy, patients were enlisted in the oncology clinic outpatient follow-up program. The interval between visits during this follow-up was determined by the guidelines suggested by the American Cancer Society, according to which subjects are to be reviewed once a month during the first year after diagnosis, once every 2 months during the second year, every 3 months during the third year, and every 6 months during the rest of their lives. In addition, patients were subjected to a chest radiograph once every 6 months during the entire follow-up period, and a head and neck CT scan every year during the first 3 years of follow-up. Routine endoscopy was also part of this follow-up.

Patients who underwent CCRT were treated with cisplatin 100 mg/m^2 for 1 day every 3 weeks. Simultaneously, they also received radiation therapy (from 1.8 to 2.0 Gy/d, 5 days/week $\times$ 7, for a total dose of 68-74 Gy). After a complete CCRT course, patients underwent further chemotherapy with cisplatin 80 mg/m^2/d for 1 day and 5-fluorouracil 1000 mg/m^2 for 4 days for 2 courses.

After appropriate merges and data transformation, statistical analysis was performed using SPSS 15th edition software (SPSS Inc., Chicago, IL). Kaplan-Meier curves were used to compare time-to-success or survival probabilities among the different study groups using the log-rank test.

Table I. Distribution of tumor and nodal (T/N) stages and percentage of cervical nodal-positive patients for each tumor stage for hard palate and maxillary alveolar squamous cell carcinomas

T/N stage	*N0*	*N1*	*N2*	*N3*	*N+ (%)*	*Total*
T1	4	0	0	0	0	4
T2	28	0	0	0	0	28
T3	18	0	3	3	25	24
T4	12	4	5	2	47.8	23
Total	62	4	8	5		79

RESULTS

The tumor epicenter was found to involve the hard palate and maxillary alveolus in 79 patients from our center. The patients had a mean age of 56.3 years (SD 10.1). Four patients had stage I lesions, 28 had stage II lesions, 18 had stage III lesions, and 29 patients had stage IV lesions (Table I).

Surgery was used as the primary treatment modality in 55 patients, 18 of whom received postoperative radiotherapy. Twenty-four patients were treated with radiotherapy and chemotherapy. In the 55 patients treated with surgery, a transoral excision was used in 41 cases with no flap reconstruction. In 14 patients, a cheek flap with flap reconstruction was deemed necessary for adequate exposure and wound reconstruction. Margins on permanent section were found to be clear in 35 patients, close or within 2-5 mm in 19 patients, and involved in 1 patient.

Eleven cT4 and N-positive patients, 11 cT4 and nodal-negative patients, and 2 T3N3 patients received CCRT as an initial treatment with curative intent, with an average dose of 7000 cGy. In the other 51 node-negative and 4 cT3 nodal-positive patients who were treated with curative intent by surgery at the primary site, the neck was treated electively in 14 patients who were mainly stage IV (4 stage III, 10 stage IV); none of them experienced neck relapse. Among these 55 surgery-initiated patients, 10 nondissected neck patients had neck regional relapse at an average of 13.4 months (SD = 1.5 months). However, 9 of the 10 patients were salvaged by later neck dissection, giving a salvage rate of 90% (9/10) in our study.

Forty-seven patients experienced disease recurrence at an average of 11.4 months (SD = 3.3 months). Thirty-seven of them were categorized as having local tumor recurrence, and 27 of those could be salvaged by a second wide excision; thus, the surgical salvage rate for local recurrence was (27/37) 73.0%. The other 10 patients had neck regional relapse, 9 of whom could be salvaged by neck dissection; thus, the neck relapse salvage rate was 90%. Patients receiving surgery-initi-

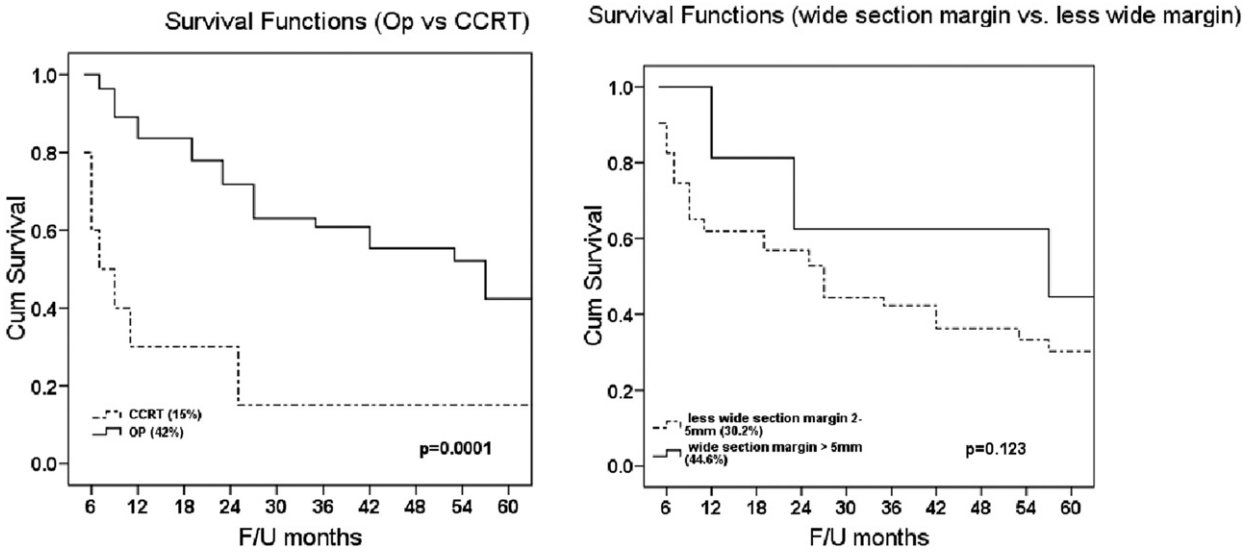

Fig. 1. Left, survival outcome between surgery-initiated or CCRT-initiated treatment. Right, wide section margin (>5 mm) versus narrower section margin (2-5 mm).

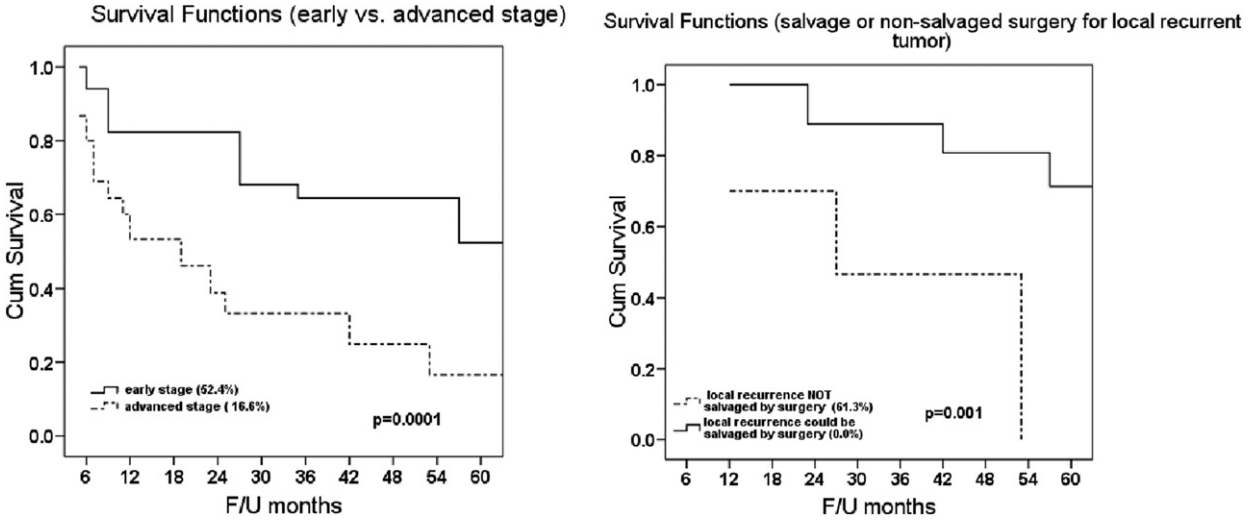

Fig. 2. Left, early stage hard palatal cancer had better survival outcome than advanced palatal cancer. Right, among all locally recurrent tumors, better survival outcome is observed in patients that could be salvaged surgically.

ated treatment, whether by tumor resection or a combination of tumor resection and neck dissection, had a significantly higher 5-year survival rate (42%) than those treated with the CCRT method (15%) (Fig. 1, left). The 5-year disease-free survival of a wide excision surgery with a safety margin over 5 mm with flap reconstruction was 44.6%, versus 30.2% for narrower margins (around 2-5 mm) with or without flap reconstruction; this difference, however, was not significant ($P = .123$) (Fig. 1, right). In our survey, patients with early-stage (stages I and II) hard palatal tumors had better survival outcomes than patients with tumors at advanced stages (stages III and IV) according to the AJCC sixth edition staging system (Fig. 2, left). Concerning the survival of patients with local recurrences, patients who could be salvaged by surgery had better survival results than patients who could not be surgically salvaged (Fig. 2, right).

Tumor feature analysis was performed to identify risk factors that could influence prognosis. The 5-year disease-free survival rate of ulcerative tumors was 0.0% and 59.5% in nonulcerative (mainly fungative protruding lesion) patients; in our analysis, this difference is significant (Fig. 3, left). The tumor pathologic

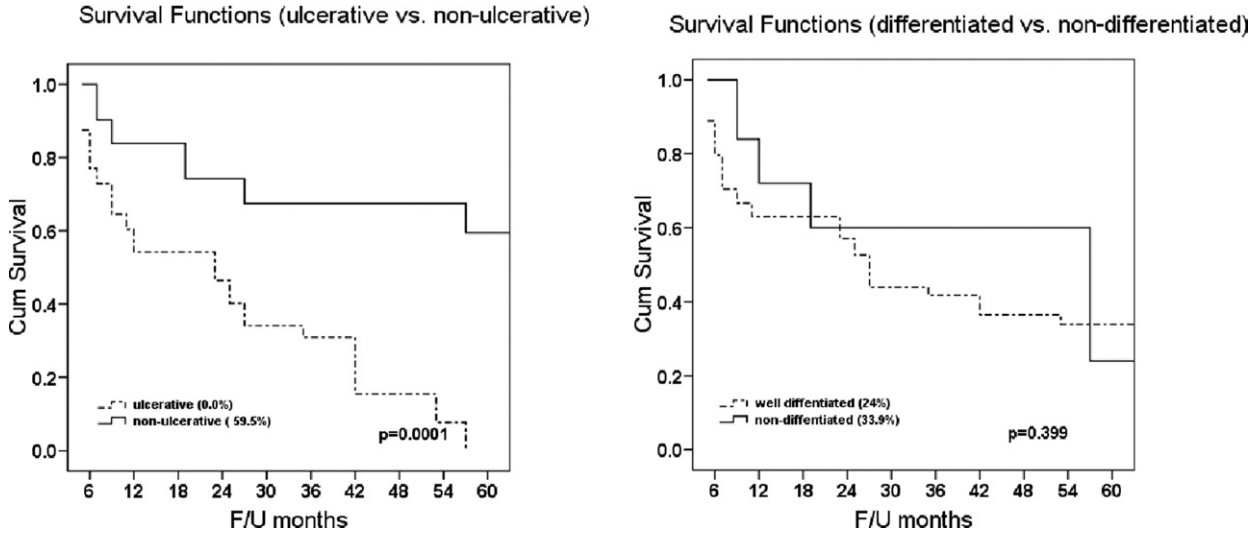

Fig. 3. Left, poor survival outcome is observed in patients with ulcerative tumor features. Right, tumor pathology differentiation resulted in no difference in survival outcome.

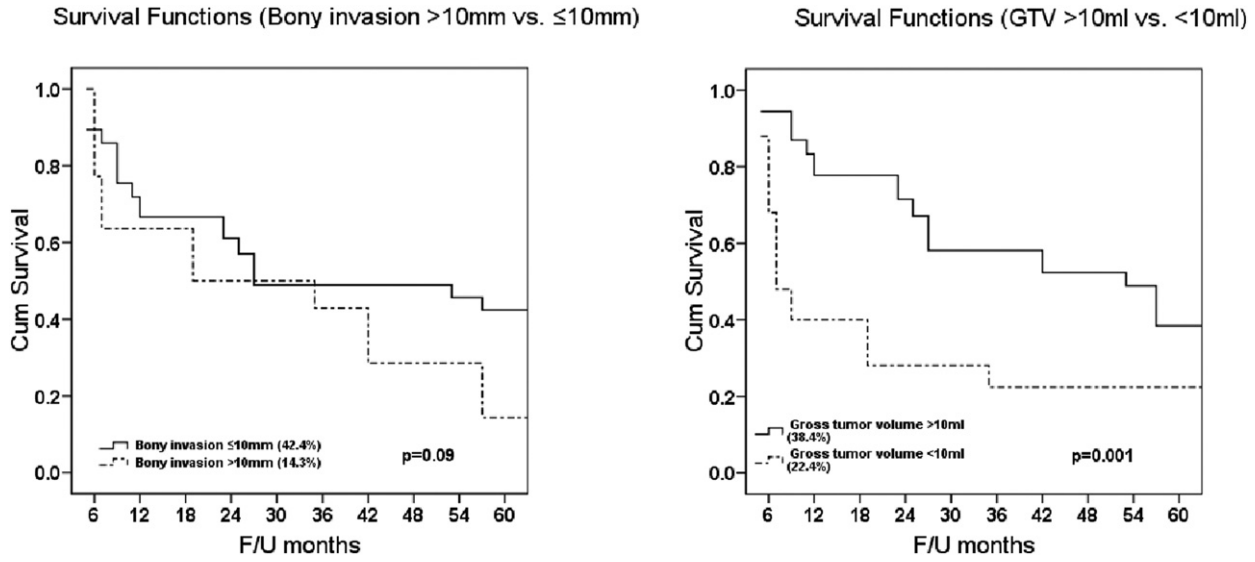

Fig. 4. Left, classification by depth of tumor invasion to the palatal bone results in no significant difference in survival outcome. Right, gross tumor volume, determined by 3D-CT, revealed that larger tumor volume (>10 mL) leads to poorer survival outcome.

differentiation grade did not significantly influence the 5-year survival rate (Fig. 3, right). We calculated the tumor vertical diameter (>10 mm invading into palatal bone or not) and calculated the gross tumor volume (GTV) with 3D-computed tomography (3D-CT) to analyze the relationship between prognoses and found that a tumor volume over 10 mL resulted in a different survival outcome, but the vertical tumor depth (10 mm depth of bone invasion or not) of the hard palatal bone did not (Fig. 4, left and right).

Although it is often difficult to determine the exact epicenter of an advanced tumor, we still defined a primary tumor with soft palate or infratemporal fossa involvement as posterior portion hard palate or alveolus tumor. The others were categorized into anterior portion hard palate or alveolus tumor. A worse survival outcome was found in patients with tumor involving the posterior portion of the hard palate or alveolus in our survey (Fig. 5, left). Composite resection combined with total maxillectomy or inferior maxillectomy resulted in no survival difference in our study (Fig. 5, right).

The 2-year survival outcome is not different between N0 patients with palatal cancer neck relapse salvage

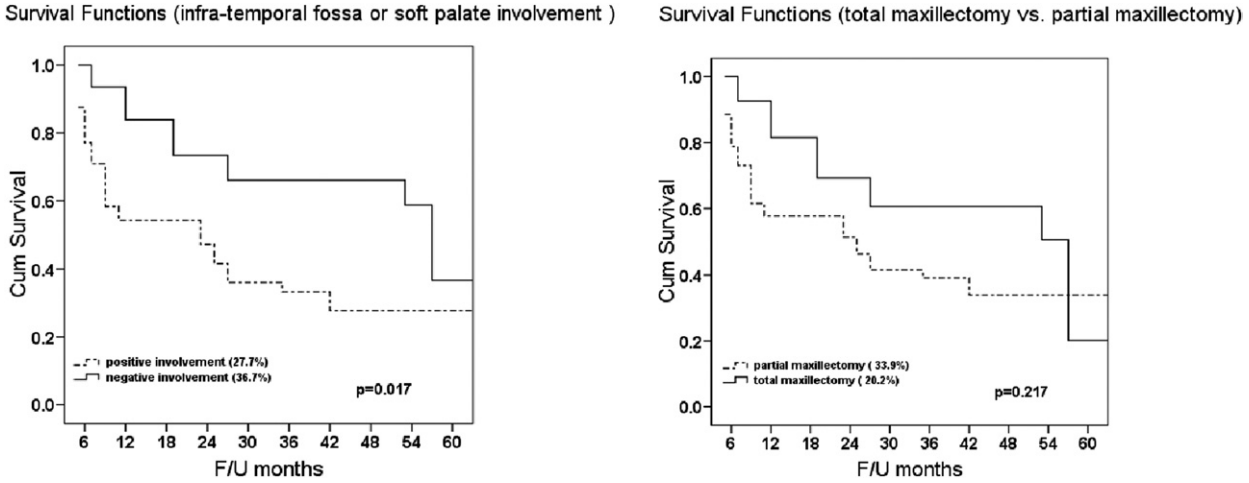

Fig. 5. Left, tumor with infratemporal fossa involvement or soft palate involvement leads to poor survival outcomes. Right, total or partial maxillectomy results in no different survival outcomes in our survey.

(27.8%) and N0 patients with palatal cancer with no neck relapse (41.8%) ($P = .072$).

DISCUSSION

SCCs of the hard palate and maxillary alveolus are relatively uncommon in Western societies.[2] These lesions appear to be considerably more common in India, accounting for 40% to 55% of oropharyngeal or oral cavity cancers.[5] The relatively low number of these tumors is the most likely reason that these lesions are often grouped and reported together with other sites, such as the buccal and soft palate, or are combined with salivary gland tumors. In contrast with most other reports,[5] this study examined treatment outcomes in a site that is anatomically specific and pathologically limited to SCC of the hard palate and maxilla alveolus (hard palatal portion) in a historical cohort.

A CT scan was performed for every patient to survey the palatal bony condition and to survey whether there was bony invasion or not, as well as to measure the depth of bony invasion.[3] MRI helped to survey the infratemporal fossa or soft palatal involvement; not all patients received MRI in our study.[6]

The overall or absolute 5-year survival of 33.9% reported in this study is relatively low. Reported survival rates for these sites range from 24% to 80% and are difficult to interpret, as they are often grouped to include other sites and other pathological entities, such as salivary gland tumors.[7]

Whether the patients could be treated by surgery-initiated therapy as the procedure with curative intent is still the main factor in survival outcome. Although Yorozu et al.[7] reported that CCRT was a safe, well-tolerated, effective treatment method for patients with hard palate cancer, survival outcome was only 24% in cT3-4 patients, and that study included not only SCCs but also palatal salivary gland carcinomas.

Margin status did not affect survival outcome in any of the cases with involved margins; there were no survival differences between cases using a narrow (2-5 mm) or wide resection margin (>5 mm) in our survey. However, Binahmed et al.[8] found the status of the surgical margin is an important predictor of outcome in oral cavity cancer, and Nason et al.[9] suggested an adequate resection in oral cancer should provide a margin of greater than 3 mm on permanent pathology section. Because most of our patients had clear section margin over 3 mm, we could not find the survival difference in our study. The salvage operation could be performed in most cases of palatal recurrence, and the salvage neck dissection could even be performed when neck relapse occurred later, after composite resection of the palatal cancer. This result was not similar to a study reported by Simental et al.[2] and Mourouzis et al.[10] They found hard palatal or maxillary alveolus cancer frequently have occult neck metastasis; thus, neck dissection was suggested routinely performed during initial treatment. However, is was not difficult to manage neck relapses after primary tumor treatment in our study.[2,10,11]

In this report, there was a trend toward worsened survival outcome in advanced disease stages, as observed in other series.[1] However, Yokoo et al.[12] and Sasaki et al.[13] were unable to correlate disease stage with prognosis. In their series, 50% to 80% of patients had stage IV tumors. They proposed a new classification system dependent on maxillary sinus or nasal floor involvement. However, we observed bet-

Fig. 6. Computed tomography (coronal and sagittal view) revealed infratemporal fossa involvement (*black arrow*) that resulted in poor survival outcome.

ter survival in patients treated with a surgical method with curative intent, as reported by Petruzzelli and Myers.[14]

There seemed to be worse prognoses when the soft palate was involved compared with when there was no soft palate involvement. This trend was confirmed in other series. The reason for this is probably related to the increased incidence for the development of regional and distant metastases when the posterior portion of the hard palate or alveolus is involved. Another possible explanation may be that there are differences in lymphatic drainage routes at palatal sites compared with other oropharyngeal sites.[15] Therefore, anatomic location of the epicenter of cancer has a considerably important affect on survival outcome. In our survey, patients with posterior portion of hard palate or alveolus cancers indeed had worse prognoses than anterior portion cancers. We also found that tumors with infratemporal fossa involvement resulted in poor outcomes. Infratemporal fossa involvement was observed by CT scan (Fig. 6); Yu et al.[16] also reported that tumors of the maxillofacial region have different pathways of infiltration into the pterygopalatine or infratemporal fossas. CT examination is very important for the evaluation of lesions involving pterygopalatine and infratemporal fossas, and it is an important tool for determining the depth of tumor invasion and the tumor volume of palate cancers.[4,16] Tumor stage was still correlated with survival outcome in this study; initial surgical treatment with curative intent was also still the most important factor for better survival outcome.[1,2,7] There was a high salvage rate in patients with local recurrence or neck regional recurrence. Neck regional relapse could also be treated by salvage neck dissection. Therefore, neck dissection might not need to be performed in the N0 neck of patients with palatal cancer.[10,11]

Concerning features of tumor appearance, we found that patients with ulcerative-type tumors had poor survival outcomes; we also found a positive correlation of survival with the higher rate of bony invasion in patients with ulcerative-type palatal cancers. In our survey, tumor volume was still a good prognostic factor for disease treatment outcome and could be used as a tool supporting the tumor staging systems currently in use.

No difference was noted in survival outcomes between total and partial maxillectomy for patients with palatal bony invasion in our study, similar to a report by Truitt et al.[17] However, a free resection margin of at least 2 mm is still considered.

CONCLUSION

In conclusion, SCCs of the hard palate and maxillary alveolus differ from other oral cancers in several respects. Initial surgery for hard palatal cancers is still the main strategy for patients with hard palatal cancer. A higher surgical salvage rate was also noted among patients with hard palatal recurrence or neck regional relapse. Patients with tumors that extended into the oropharyngeal soft palate or infratemporal fossa had poor survival outcomes. In addition, patients with ulcerative tumor features (higher bony destruction rate), tumor volumes of over 10 mL, and local recurrent tumors that could not receive salvage surgery also had poorer survival outcomes in our study.

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