Analysis of prognostic risk factors and treatment of parotid cancer

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Abstract. The aim of this study was to investigate the prognostic factors and therapeutic efficacy of parotid cancer (PC). A total of 135 patients with PC who received surgical treatment were recruited between January 1985 and January 2000. There were 47 patients with poorly differentiated PC and 88 with well-differentiated PC. In addition, PC of stage I, II, III and IV were found in 25, 47, 45 and 18 patients, respectively. Elective and therapeutic neck dissection was carried out in 46 and 39 patients, respectively, and 58 patients received post-operative radiotherapy. The Kaplan-Meier method was employed for survival analysis. The 5- and 10-year survival rates were 74.0 and 56.4%, respectively. A significant difference in the survival rates was observed between patients with poorly differentiated PC and those with well-differentiated PC (χ^2=5.72, P=0.016). Cox regression model analysis revealed that age, stage of PC, pathological grade of PC and post-operative radiotherapy were independent prognostic factors of PC. Early diagnosis, early treatment and post-operative radiotherapy may increase the survival rate of PC patients. Patients with PC should therefore receive neck lymph node dissection, the extent of which depends on the pathological grade of PC.

Introduction

Parotid cancer (PC) has a low incidence, long disease-course and numerous histological types. Moreover, the biological behaviors vary in different histological types (1), which results in complex therapy for PC. Few studies investigating PC have been conducted thus far (2,3). In the present study, 135 patients with PC were recruited from the Department of Head and Neck Surgery of Zhejiang Cancer Hospital, China, and the prognostic factors and therapeutic regimens of these patients were retrospectively analyzed.

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Patients and methods

Clinical information. A total of 671 patients with parotid tumors received surgical treatment in the Department of Head and Neck Surgery of Zhejiang Cancer Hospital, China, between January 1985 and January 2000. Of the 671 patients, 230 (34.3%) were diagnosed as having malignant tumors. There were 8 patients with malignant lymphoma, 2 with malignant melanoma, 4 with sarcoma and 63 patients with metastatic cancer. However, 18 patients with unresectable cancer were excluded. In the present study, 135 patients with primary PC were recruited with a median age of 57 years (range, 8-82), including 77 males and 58 females. Excluding 2 patients, a mass was found in the parotid gland region on palpation in the remaining patients. In addition, there were 42 patients with local pain (31.1%), 14 with facioplegia (10.4%), 6 with difficulty in opening the mouth (4.4%), and 39 with lymph node enlargement (28.9%).

The patients were pathologically diagnosed as PC and classified according to the criteria for PC classification developed by the World Health Organization (4): mucoepidermoid carcinoma (n=36; well-differentiated cancer in 10, moderately differentiated cancer in 9 and poorly differentiated cancer in 5), adenocarcinoma (n=19), acinar cell carcinoma (n=21), malignant pleomorphic adenoma (n=27), undifferentiated carcinoma (n=10), adenoid cystic carcinoma (n=12), salivary duct carcinoma (n=7), and squamous cell carcinoma (n=3). The cancer types were subgrouped into poorly differentiated cancer (poorly differentiated mucoepidermoid carcinoma, adenocarcinoma, squamous cell carcinoma, undifferentiated carcinoma, salivary duct carcinoma, and solid adenoid cystic carcinoma) and well-differentiated cancer. There were 47 patients with poorly differentiated and 88 with well-differentiated cancer. The clinical staging was based on the 1997 UICC classification system (5): stage I (n=25), II (n=47), III (n=45) and IV (n=18).

Superficial parotidectomy was performed in 30 patients, superficial parotidectomy plus neck lymph node dissection in 35, total parotidectomy in 15, total parotidectomy plus cervical lymph node dissection in 43 and palliative surgery in 12 patients (7 received cervical lymph node dissection). Moreover, 28 patients received facial nerve resection. Among the 85 patients who underwent cervical lymph node dissection, therapeutic lymph node dissection was performed in 39 patients and selective lymph node dissection in 46 patients.

Table I. Cox regression multivariate analysis of factors affecting the prognosis of PC patients.

Variables	Regression coefficient	Standard error	χ^2	P-value	OR	95% CI
Age	1.008	0.302	11.172	0.001	2.741	1.517-4.951
Stage	0.655	0.286	5.237	0.022	1.925	1.099-3.373
Grade	0.549	0.285	3.712	0.054	1.732	0.991-3.028
Radiotherapy	0.641	0.301	4.549	0.033	1.899	1.053-3.424

PC, parotid cancer; OR, odds ratio; CI, confidence interval.

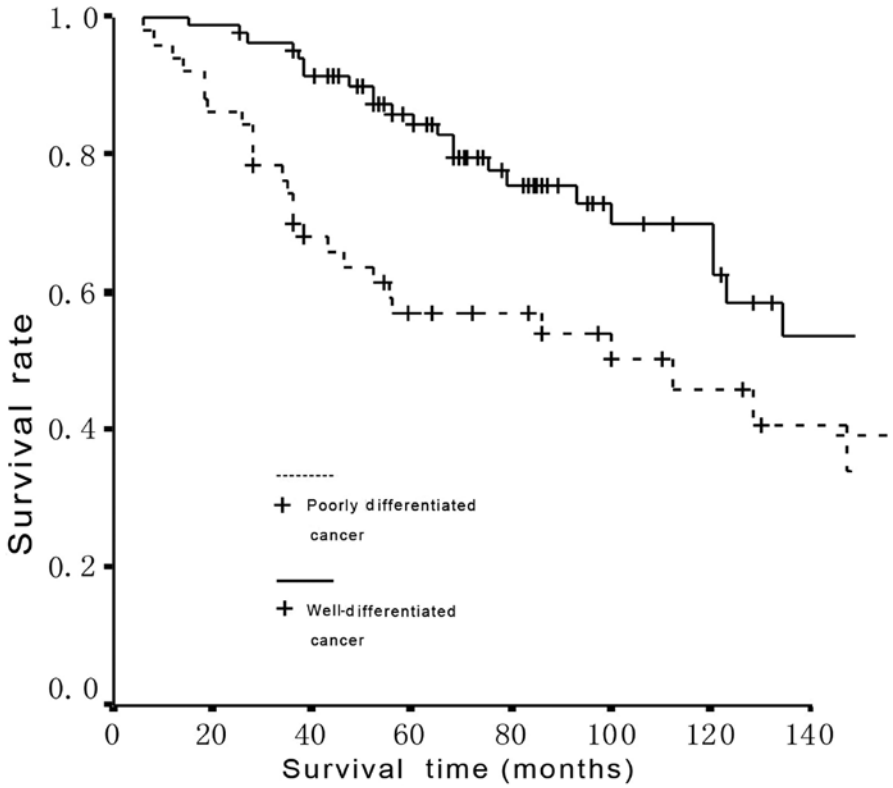

Figure 1. Survival curve of patients with well-differentiated and poorly differentiated PC. PC, parotid cancer.

There were 58 patients who received local radiotherapy following surgery, 31 of whom received cervical radiotherapy. The radiation dose was as follows: radiotherapy of the parotid gland region was performed at 1.8-2.0 Gy five times a week with a total dose of 40-65 Gy, and radiotherapy of the neck at 1.8-2.0 Gy five times a week with a total dose of 40-56 Gy. Follow-up was performed until January 2005. The study was approved by the ethics committee of Zhejiang Cancer Hospital. Informed concent was obtained from all patients involved.

Statistical analysis. Statistical analysis was performed with SPSS version 10.0. Qualitative data were analyzed using the Chi-square test and the survival rate was calculated using the Kaplan-Meier method and the log-rank test. Cox stepwise regression was employed for multivariate analysis. The P-value was defined as 0.1.

Results

Patient follow-up. Eighteen patients succumbed to the disease prior to follow-up and 86.7% of patients completed the follow-up. Survival time was counted from the day of treatment. The 5- and 10-year survival rates were 74.0 and 56.4%, respectively, and a significant difference was found in the survival between patients with well-differentiated and poorly differentiated PC (χ^2=5.72, P=0.0168) (Fig. 1). Results of the multivariate analysis revealed that age, stage and pathological grade of PC, and radiotherapy were independent factors affecting the prognosis of PC patients (Table I). Age <65 years, PC at an early stage, well-differentiated PC and post-operative radiotherapy predicted a good prognosis.

Lymph node metastasis. Among the 39 patients with clinical lymph node metastasis (CN1 and CN2), 25 had pathologically

proven lymph node metastasis. Of the 46 patients negative for clinical lymph node metastasis (CN0), who received selective lymph node dissection, lymph node metastasis was pathologically proven in 10 patients. In the 35 patients with lymph node metastasis, 19 had poorly differentiated PC (40.4%) and 16 had well-differentiated PC (18.2%). In addition, occult metastasis was found in 7 patients in the poorly differentiated PC group (7/28) and 3 patients in the well-differentiated PC group (3/18). Among the patients receiving selective lymph node dissection, there was no marked difference in the occult metastasis between the well-differentiated and the poorly differentiated PC groups (χ^2=0.447, P=0. 504).

Facial nerve involvement. There were 14 patients with symptoms of facial paralysis (14/135, 10.4%), of whom 10 had poorly differentiated PC. Among these 14 patients, 10 received resection of the facial nerve trunk and 4 received resection of the facial nerve branches. In the 14 patients without symptoms of facial nerve involvement (5 with poorly differentiated PC and 9 with well-differentiated PC), the facial nerve was enwrapped by the tumor or there was clear involvement of the tumor and thus, resection of facial nerve was performed. Of the 28 patients who received resection of the facial nerve, facial nerve involvement was pathologically confirmed in all patients. Furthermore, the proportion of patients with facial nerve involvement was significantly different between patients with poorly differentiated PC (15/47) and those with well-differentiated PC (13/88; χ^2=5.477, P=0.019).

Discussion

In the majority of studies (6-9), the poorly differentiated mucoepidermoid carcinoma, squamous cell carcinoma, undefined adenocarcinoma, undifferentiated carcinoma and salivary duct carcinoma were classified into poorly differentiated cancers. Certain studies classified all types of adenoid cystic carcinoma into well-differentiated cancer (10), whereas in other studies these types of carcinoma were classified as poorly differentiated cancer (6,8). According to our previous studies (11) on adenoid cystic carcinoma, the solid adenoid cystic carcinoma is more susceptible to facial nerve involvement and cervical lymph node metastasis. Thus, we classified solid adenoid cystic carcinoma into poorly differentiated cancer, which was consistent with the study of Pedersen *et al* (9). In the present study, the 5- and 10-year survival rates were 74.0 and 56.4%, respectively, and a significant difference was found in the survival between patients with well-differentiated and poorly differentiated PC (χ^2=5.72, P=0.0168).

Previous studies have demonstrated that pathological grade is a determinant of survival while in findings of other studies have suggested that disease stage is of greater significance as a prognostic factor (12,13). Pohar *et al* reported that the factors affecting the prognosis of PC were age and stage of disease. Multivariate analysis revealed that age <65 years, early disease and well-differentiated tumor predicted a good prognosis (13). These findings suggest it is necessary to investigate the age and severity of disease in further prospective studies.

In the present study, 25.9% of patients had lymph node metastasis. In patients in the CN0 stage receiving cervical lymph node dissection, the incidence of occult lymph node metastasis was 21.7%. Armstrong *et al* proposed that the treatment of metastatic cervical lymph nodes (including lymph node dissection during surgery and post-operative radiotherapy of cervical lymph nodes) should be selective for patients with PC (14). We consider that the cervical lymph nodes should be treated for patients with PC, as the incidence of occult lymph node metastasis is high in these patients. For patients negative for clinical lymph node metastasis, therapeutic cervical lymph node dissection is recommended. For patients in the CN0 stage, selective lymph node dissection can be performed according to the intra-operative pathological examination. For patients with poorly differentiated PC, removal of level II and III lymph nodes is recommended. A previous study demonstrated that the detection rate of metastatic lymph node was 90% following the removal of level II and III lymph nodes (14). For patients with well-differentiated PC, removal of the lymph nodes surrounding the parotid gland as the well-differentiated PC has a low incidence of local lymph node metastasis and PC mainly invades the surrounding lymph nodes directly. Our results also demonstrate that lymph node metastasis was closely correlated with the histological type. In patients with poorly differentiated PC, the incidence of cervical lymph node metastasis was 40.4%, but was only 18.2% in those with well-differentiated PC, demonstrating a significant difference (χ^2=7.893, P=0.005). In addition, the pathological grade following cervical lymph node dissection is also able to provide evidence for the radiotherapy of cervical lymph nodes.

In the surgical treatment of malignant parotid gland tumors, the balance between radical dissection of cancer and the preservation of the facial nerve has been a challenge for surgeons. Surgery for the parotid gland may in certain cases be regarded as surgery for the facial nerve. Dissection of the parotid gland tumor may occur close to the facial nerve. When cancer invades the tissues surrounding the facial nerve, it has the potential to involve the facial nerve. If separation of the facial nerve is complete in surgery, the facial nerve can be preserved. Post-operative radiotherapy can remove the minimal residual tumor. Thus, surgeons should pay attention to the preservation of the facial nerve in surgery, unless the nerve itself is involved in cancer. In the present study, dissection of the facial nerve was performed in 20.7% of patients, which was consistent with previous studies (6,15). Facial nerve dysfunction is a contributing factor of distant metastasis and also a predictive factor of recurrence (15). In the present study, among the 28 patients with pathologically proven facial nerve involvement, 13 patients developed local recurrence (46.4%). Of the 107 patients without facial nerve involvement, 20 patients had local recurrence (18.7%). A significant difference was revealed in the incidence of recurrence between patients with and without facial nerve involvement (χ^2=9.244, P=0.002).

In the past two decades, radiotherapy has become a significant component in the comprehensive treatment of PC. Although certain studies revealed that the survival rate following surgery plus post-operative radiotherapy was comparable to that following surgery alone, PC in the early stage, small PC and movable PC were not included in these studies for radiotherapy. Our results reveal that post-operative radiotherapy was an independent prognostic factor. Pohar *et al* retrospectively analyzed 163 patients with PC in two medical

centers in the USA between 1960 and 2000 (13). In 56 patients receiving surgery alone, the incidence of local recurrence was 37%. Among the 91 patients receiving surgery and post-operative radiotherapy, the incidence of local recurrence was 11%. Multivariate analysis demonstrated that post-operative radiotherapy did not improve the overall survival rate, but reduced the local recurrence and increased the recurrence-free survival rate. Recently, a study revealed that post-operative radiotherapy was also beneficial for patients with PC in stages T1 and T2. Zbaren *et al* (16) retrospectively analyzed 58 patients with PC in stages T1 and T2. Of the 34 patients receiving post-operative radiotherapy, only 1 developed recurrence (3%), while 8 had recurrence in 24 patients without post-operative radiotherapy (33%). In patients with and without recurrence, the 5-year survival rates were 93 and 83%, respectively, and the 5-year tumor-free survival rates were 92 and 70%, respectively. Thus, prospective studies are required to confirm these findings. For patients with recurrence following surgery, salvage surgery commonly causes dissection of the facial nerve, resulting in unacceptable disfigurement. Thus, we speculate that post-operative radiotherapy is necessary for patients with PC in stages T3 and T4, PC close to the surgical and positive margin, PC in combination with facial nerve involvement, deep lobe PC, poorly differentiated PC and PC with local lymph node metastasis.

In conclusion, our results have shown that the overall survival rate and incidence of cervical lymph node metastasis varied between the patients with poorly differentiated PC and well-differentiated PC. Facial nerve involvement is a significant factor affecting local recurrence. Multivariate analysis revealed that age, stage of PC, pathological grade and post-operative radiotherapy are independent prognostic factors. We recommend selective regional lymph node dissection in patients with primary PC, with the extent of lymph node dissection depending on the pathological grade. Post-operative radiotherapy is useful in improving the quality of life and survival. However, this is a retrospective study and a randomized control group was not included. Further clinical randomized trials are required to clarify which patients can benefit from post-operative radiotherapy.

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