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Postoperative Radiotherapy for Parotid Gland Malignancy

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Purpose: The aim of this study was to evaluate the clinical results of postoperative radiotherapy for parotid gland malignancy, and determine prognostic factors for locoregional control and survival.

Materials and Methods: Between 1980 and 2002, 130 patients with parotid malignancy were registered in the database of the Department of Radiation Oncology, Seoul National University Hospital. The subjects of this analysis were the 72 of these 130 patients who underwent postoperative irradiation. There were 42 males and 30 females, with a median age of 46.5 years. The most common histological type was a mucoepidermoid carcinoma. There were 6, 23, 23 and 20 patients in Stages I, II, III and IV, respectively. The median dose to the tumor bed was 60 Gy, with a median fraction size of 1.8 Gy.

Results: The overall 5 and 10 year survival rates were 85 and 76%, respectively. The five-year locoregional control rate was 85%, which reached a plateau phase after 6 years. Sex and histological type were found to be statistically significant for overall survival from a multivariate analysis. No other factors, including age, facial nerve palsy and stage, were related to overall survival. For locoregional control, nodal involvement and positive resection margin were associated with poor local control. Histological type, tumor size, perineural invasion and type of surgery were not significant for locoregional control.

Conclusion: A high survival rate of parotid gland malignancies, with surgery and postoperative radiotherapy, was confirmed. Sex and histological type were significant prognostic factors for overall survival. Nodal involvement and a positive resection margin were associated with poor locoregional control.

Key Words: Parotid gland malignancy, Postoperative radiotherapy, Prognostic factors

Introduction

Malignant tumors of the major salivary glands make up only approximately 0.4% of all cancers, and 3% to 4% of head and neck neoplasms.[1] The diversity in histologic appearance is well known and, in general, lymphatic spread is not frequent.[2] Currently surgery remains the primary treatment of parotid gland malignancies. Long-term surgical data revealing significant local failures has advocated the use of adjuvant radiotherapy for subclinical and microscopic residual disease.[3] Several studies have affirmed the efficacy of irradiation combined with surgery in improving local control of salivary gland tumors, and a 50~90% five-year local control rate has been reported.[3~9]

We previously reported the results of radiation therapy in 55 patients with parotid malignancies.[4] Among these 55 patients, 47 patients were treated postoperatively. The local control was affected by histologic grade, tumor size, and lymph node status.

The purpose of this study is to analyze clinical results of postoperative radiotherapy in newly diagnosed parotid gland malignancies, and to determine prognostic factors for locoregional control and survival.

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Materials and Methods

1. Patients

Between 1980 and 2002, 130 patients with parotid malignancy were registered in the database of the Department of Radiation Oncology, Seoul National University Hospital. Forty-two patients were diagnosed as having recurrent disease, 9 patients as having distant metastases, and definitive radiotherapy was given in 7 patients. The remaining 72 patients, who received surgery followed by radiotherapy, were the subjects of this study.

There were 42 males and 30 females, with a median age of 46.5 years (range: 5~72). All of the patients presented with a palpable mass in the parotid area accompanied by pain (10%) and facial nerve palsy (8%). Eastern Cooperative Oncologist Group performance status was: 0 in 10 patients, 1 in 57 patients, and 2 in 5 patients.

Mucoepidermoid carcinoma (36%) was most commonly seen, followed by adenoid cystic carcinoma (18%), malignant mixed tumor (14%), adenocarcinoma (14%), and squamous cell carcinoma (6%). Other several histologic types including salivary duct carcinoma were seen in 12% of patients. Pathologic T stages were T1 in 6 patients, T2 in 25 patients, T3 in 30 patients, and T4 in 11 patients. With regard to N stage, 51 patients were cN0 and 2 patients were pN0. For node positive patients, all but 4 patients received neck dissection. Five patients were N1, and 14 patients were N2. None of the patients had N3 nodal disease (Table 1). There were 6 patients in Stage I, 23 in Stage II, 23 in Stage III, and 20 in Stage IV.

2. Treatment

Total parotidectomy, superficial parotidectomy, wide excision, and mass excision were given in 38 (53%), 21 (29%), 5 (7%), and 8 (11%) of 72 patients, respectively.

Table 1. Distribution by Stage: TNM[15] (n=72)

Stage	N0	N1	N2a	N2b	Total
pT1	6	0	0	0	6 (8%)
pT2	23	1	0	1	25 (35%)
pT3	18	3	1	8	30 (42%)
pT4	6	1	0	4	11 (15%)
Total	53 (74%)	5 (7%)	1 (1%)	13 (18%)	72 (100%)

There were 53 patients with N0 neck. Among them, one patients received supraomohyoid neck dissection (SOHND), 3 patients received prophylactic neck irradiation, one patient received both SOHND and prophylactic neck irradiation, and 48 patients did not receive any neck treatment. In 19 patients with clinically palpable nodes, 13 patients received surgical neck dissection combined with radiotherapy, 2 patients received surgical neck dissection without radiotherapy, and 4 patients received radical neck irradiation only. Five patients received selective neck dissection, and 10 patients received radical neck dissection (RND) or modified radical neck dissection (MRND). Among 5 patients with N1 neck, 3 patients received SOHND and 2 patients did not receive neck dissection. Among 14 patients with N2 neck, SOHND was given in 2 patients and RND (or MRND) was given in 10 patients. Two patients did not receive neck dissection.

3. Radiotherapy

Radiotherapy was delivered through an ipsilateral paired wedge technique in 57 patients. A single ipsilateral field covering the entire parotid bed was applied in 8 patients, two bilateral fields covering the tumor bed and neck was applied in one patient, and multiple fields were applied in 6 patients. Radiotherapy was delivered with Co-60 or 4~6 MV photon beam with/without electron. Conventional fractionation schedule was used in all cases. Radiation doses for the subclnical disease were ranged from 45 Gy to 54 Gy, and additional boost dose was given to the tumor bed. The median dose to the tumor bed was 60 Gy (range: 49.5~70.0), with a median fraction size of 1.8 Gy (range: 1.5~2.0). More than 54 Gy (range: 50.0~70.0, median 60) was given to control microscopic (or macroscopic) residual disease. Radiotherapy was indicated in patients with involved resection margin or advanced T stage. Neck irradiation was done in most case of node positive patients. The median dose to the neck was 49.4 Gy (range: 44.0~71.6). The median time from date of surgery to initiation of radiotherapy was 32 days and the median duration of radiotherapy was 50 days. The median follow-up time was 95 months (range: 4~258).

4. Statistical Analysis

The statistical analysis was performed with the SAS pro-

gram, version 8.2. Survival data were calculated using the Kaplan-Meier method. The log rank test was used for comparison of the results. The Cox proportional hazards regression analysis was used for multivariate analysis.

Results

Five patients (7%) experienced local recurrence, another 5 patients (7%) did regional recurrence, and 10 patients (14%) did distant metastasis. One patient experienced both local recurrence and distant metastasis, and one patient did regional recurrence and distant metastasis. Among 6 patients with regional recurrence, 3 patients initially had N0 neck without any neck treatment. The other 3 patients initially had N2 neck and received both neck dissection and radiotherapy. Among 12 patients with distant metastases, 4 patients had adenoid cystic carcinoma and another 4 patients had malignant mixed tumor. The most common site of distant metastasis was the lung.

There were no significant acute side effects. Late complications of radiotherapy were seen in 13 patients: 5 patients had xerostomia; 4 patients had osteoradionecrosis; and 4 patients had chronic otitis media.

The overall survival (OS) rate was 85% at 5 years and 76% at 10 years. Disease-free survival (DFS) rate was 81% at 5 years and 73% at 10 years (Fig. 1).

In univariate analysis, age younger than 60 years, female sex, and initial presentation without facial nerve palsy were related to better overall survival. Histologic type was also associated with overall survival rate. Low-grade mucoepidermoid carcinoma achieved best overall survival rate. Other factors including stage (T stage, N stage), type of surgery, and radiation dose to the tumor bed were not statistically significant for overall survival rate (Table 2). In multivariate analysis, only sex and histologic type were significant prognostic factors for overall survival (Table 3).

The five-year locoregional control rate was 85%, and reached a plateau phase after 6 years. In univariate analysis, advanced T stage (T3-4), large tumor size (≥4 cm), positive resection margin, and presence of perineural invasion were

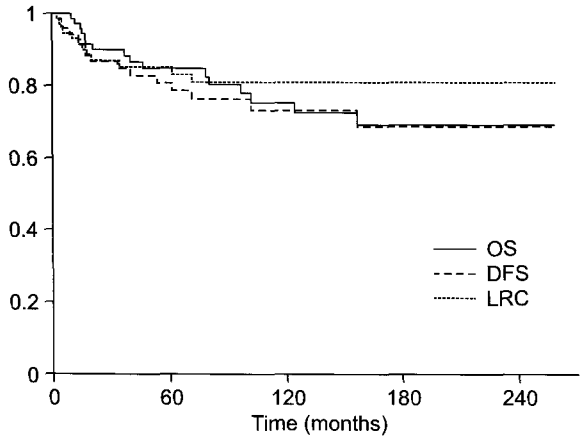

Fig. 1. Survival rate, disease-free survival rate, and locoregional control rate. Locoregional control rate reached plateau phase after 6 years, but overall and disease-free survival reached plateau phase after more than 10 years (OS: overall survival, DFS: disease free survival, LRC: locoregional control).

Table 2. Prognostic Factors Affecting Overall Survival (OS) by Univariate Analysis

Prognostic factor	5 yr OS* (%)	p-value
Age		
>60 vs. ≤60	60 vs. 90	0.022
Sex		
Male vs. Female	75 vs. 97	0.002
Initial symptom		
FNP† (—) vs. FNP (+)	87 vs. 53	0.011
Histologic type		0.047
Stage (T, N, stage)		NS‡
Resection margin		
Negative vs. Positive	97 vs. 69	NS
Perineural invasion		
Negative vs. Positive	100 vs. 83	NS
Type of surgery		
Total parotidectomy	83	
Superficial parotidectomy	90	NS
Wide excision	100	
Mass excision	66	
Radiation dose		
<60 Gy vs. 60~66 Gy vs. >66 Gy	84 vs. 91 vs. 50	NS

*overall survival, †facial nerve palsy, ‡statistically not significant

Table 3. Prognostic Factors Affecting Overall Survival (OS) by Multivariate Analysis

Prognostic factor	p-value
Age (>60 vs. ≤60)	NS*
Sex (Male vs. Female)	0.012
Facial nerve palsy (Negative vs. Positive)	NS
Histologic type	0.050
Resection margin (Negative vs. Positive)	NS
Stage (T, N)	NS

*statistically not significant

Table 4. Prognostic Factors Affecting Locoregional Control (LRC) by Univariate Analysis

Prognostic factor	5 yr LRC (%)	p-value
T stage		
T1-2 vs. T3-4	97 vs. 76	0.032
Tumor size		
≤4 cm vs. >4 cm	93 vs. 70	0.045
Resection margin		
Negative vs. Positive	97 vs. 69	0.002
Perineural invasion		
Negative vs. Positive	92 vs. 70	0.016
Facial nerve palsy		
Negative vs. Positive	87 vs. 67	NS*
Nodal status		
Negative vs. Positive	90 vs. 73	NS
Histologic type		NS
Type of surgery		
Total parotidectomy	81	NS
Superficial parotidectomy	95	
Wide excision	100	
Mass excision	73	
Radiation dose		
<60 Gy vs. 60~66 Gy vs. >66 Gy	81 vs. 91 vs. 83	NS

*statistically not significant

Table 5. Prognostic Factors Affecting Locoregional Control (LRC) by Multivariate Analysis

Prognostic factor	p-value
Tumor size (>4 cm vs. ≤4 cm)	NS*
Resection margin (Negative vs. Positive)	0.011
Perineural invasion (Negative vs. Positive)	NS
Facial nerve palsy (Negative vs. Positive)	NS
Nodal status (Negative vs. Positive)	0.008
Histologic type	NS
Type of surgery	NS
Radiation dose (<60 Gy vs. 60~66 Gy vs. >66 Gy)	0.069

*statistically not significant

associated with worse locoregional control (Table 4). The type of surgery and nodal involvement were not statistically significant but, in multivariate analysis, nodal involvement and positive resection margin were bad prognostic factors for locoregional control (Table 5).

Discussion

In our study, the overall survival rate was 85% at 5 years and 76% at 10 years, and this is comparable to the published range of 40% to 88%.[3~9] Several studies showed that tumor related prognostic factors such as histology, stage, and malignancy grade are important for overall survival.[9,10] Some of the authors reported age and sex as significant prognostic factors for overall survival.[7] We confirmed that sex and histologic type affect overall survival.

The locoregional control rate of our study was 85% at 5 years, and this result is comparable to the 50~90% locoregional control rate in many other studies.[3~9] Terhaard et al. reported that tumor size, bone invasion, facial nerve palsy, resection margin, and N stage were significant for locoregional control.[7] In our study, we confirmed several factors affecting locoregional control. In univariate analysis, T stage, tumor

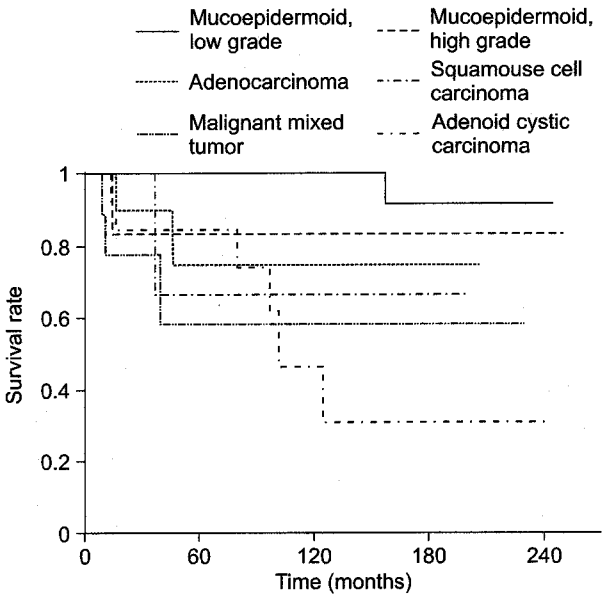

Fig. 2. Survival rate of each histologic type. Low-grade mucoepidermoid carcinoma showed highest overall survival rate compared with other histologic type and adenoid cystic carcinoma showed lowest 10 year overall survival rate.

size, resection margin status, and perineural invasion were statistically significant for locoregional control, but in multivariate analysis, nodal involvement and resection margin status were statistically significant.

After 6 years, the curve for locoregional control reached a plateau phase, but that of disease-free survival reached a plateau phase after more than 10 years. The overall survival rate curve of each histologic type was illustrated in Fig. 2. It revealed that low-grade mucoepidermoid carcinoma showed highest overall survival rate and adenoid cystic carcinoma

showed lowest overall survival rate. The overall survival rate of adenoid cystic carcinoma decreased steadily through 10 years. That of other histologic type reached plateau phase after 5 years. It implies that adenoid cystic carcinoma can metastasis after 5 years. We can find that, in case of adenoid cystic carcinoma, more than 10 year of observation is necessary.

Inadequate resection margin of parotid gland malignancy has been considered as an appropriate indication of postoperative radiotherapy. In our study, there were 30 patients (42%) with pathologically confirmed positive resection margins. Five of 30 patients had local failure. The relatively low incidence of local recurrence may be due to a large proportion of low-grade mucoepidermoid carcinoma with early T stage in patients with positive resection margins.

Hosokawa et al. reported that local control was dependent upon radiation dose.[6] Terhaard et al. showed clear dose-response relationship and recommended a dose of 66 Gy for primary radiotherapy and at least 46 Gy for postoperative neck treatment. In out study almost all of the patients received more than 46 Gy after neck dissection. Our study showed that the radiation dose to the tumor bed was borderline significant for locoregional control.

The benefit of elective surgical management of cervical nodes is debatable. Salvage rate was reported as low as 12~30% after neck recurrence.[10,11] Therefore it is important to determine the risk of nodal spread and to select the patient who will be a candidate for elective neck dissection before proceeding to surgical management. The size of the tumor ($\geq$ 4 cm) or high-grade histology have been regarded significantly as high risk factors for harboring occult metastases.[7,8,11~13] Kelly et al. reported that the clinical factors predictive of nodal involvement were pain, facial nerve palsy, advanced T stage, and high-grade of tumor.[13] Armstrong et al. proposed that prophylactic neck dissection was efficacious in patients with high-grade tumors, advanced T stage, or both.[2]

In our study, 48 patients with clinical N0 neck did not have any neck treatment, and 2 had neck failure. Among 48 patients, 23 had advanced T stage (T3-4), and only 2 of 23 patients (9%) had regional recurrence. One was in ipsilateral neck and the other was in contralateral neck. This result is discordant with the data from Armstrong et al, who reported that the incidence of neck failure was 9% in patients with pathologic N0 neck treated with elective neck dissection.[2] The data about histologic grade except mucoepidermoid carcinoma, was not available in most patients in our study; thus, this factor was not incorporated into our analysis. Based on our results, however, elective neck treatment would be unnecessary in patients without clinically involved node, even with advanced T stage.

In a review of our previous report[4] that was published in February 1994, there were 47 patients in the surgery-plus-radiotherapy group. Histologic grade and lymph node status were significant prognostic factors for locoregional control. Histologic grade was divided into low-grade and high-grade groups by histologic type. In this study, we confirmed that lymph node status affects locoregional control. The difference between this study and the previous study is the patient population which was analyzed. The previous study included both newly diagnosed patients and patients with recurrent disease, whereas this report included newly diagnosed patients only.

In conclusion, an 85% survival rate was seen after postoperative radiotherapy of parotid malignancies. Sex and histologic type were significant prognostic factors for overall survival. Nodal involvement and resection margin status were significant for locoregional control. It will be desirable to give a dose of 60 Gy or more to the tumor bed with microscopic disease, and to give 66 Gy or more with macroscopic disease.

Generally, more than 5 year of observation would be appropriate for the detection of locoregional recurrence and distant metastasis after postoperative radiotherapy. In the case of adenoid cystic carcinoma, more than 10 year of observation is necessary. A randomized study is needed to determine the necessity of elective neck treatment in patients with clinically uninvolved node.

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국문초록

귀밑샘 악성 종양의 수술 후 방사선 치료

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목 적: 귀밑샘 악성종양의 수술 후 방사선 치료 성적 및 예후인자를 분석하였다.
대상 및 방법: 1980년부터 2002년까지 130명의 귀밑샘 악성 종양 환자가 서울대병원 방사선 종양학과 데이터베이스에 등록되었고 이 중 수술 후 방사선 치료를 받은 72명의 환자에 대하여 후향적 분석을 실시하였다. 남자는 42명, 여자는 30명이었고, 나이의 중앙값은 46.5세였다. 점액표피양암종이 가장 흔한 조직학적 유형이었다. 병기에 따라서는 I, I, III, IV 병기에 각각 6, 23, 23, 20명이 해당되었다. 수술 부위의 방사선 조사량의 중앙값은 60 Gy였고, 일회 조사량의 중앙값은 1.8 Gy였다.
결 과: 5년 전체 생존율 및 10년 전체 생존율은 각각 85%와 76%였다. 5년 국소제어율은 85%였고 6년이 지나면서 변화가 없었다. 다변량분석을 하였을 때, 성별, 조직학적 유형이 생존율과 통계적 유의성이 있었다. 나이, 안면신경마비증상, 병기(T 병기, N병기, 병기)는 생존율과 관련된 통계적 유의성이 없었다. 국소제어율의 경우, 림프절 전이 및 절제연 침범여부가 의미있는 예후인자였다. 조직학적 유형, 종양의 크기, 신경침윤 여부 및 수술의 종류는 국소제어율의 예후인자가 아니었다.
결 론: 귀밑샘 악성종양에서 수술 후 방사선치료의 우수한 성적을 확인하였다. 성별 및 조직학적 유형이 생존율에 대한 의미있는 예후인자였고, 림프절 전이 및 절제연의 침윤이 있는 경우 국소제어율이 불량했다.

핵심용어: 귀밑샘 악성 종양, 수술 후 방사선치료, 예후인자