Radiation Therapy in Malignant Tumors of the Parotid Gland

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A retrospective analysis was performed on 55 patients with malignant parotid tumor who were treated with radiation therapy between March, 1979 and July, 1989. Of these patients, 8 patients received radiation therapy(RT) alone and 47 patients were treated with combined operation and radiation therapy(OP+RT). The follow-up period of the survivors ranged from 1 to 129 months with a median of 48 months. The common histologic types were mucoepidermoid carcinoma (25 cases), malignant mixed tumor(12 cases), adenoid cystic carcinoma(6 cases).

The 5 and 10 year local control rate were 69.8% and 65.7% in all patients. In OP+RT group, prognostic factors related to local control were histologic grade, tumor size, lymph node metastasis. Resection of facial nerve did not affect the local control rate significantly($p=0.129$). Distant metastasis developed in 23.6% of patients, mostly to the lung. Actuarial overall survival rate was 72.2% at 10 years and formed plateau after 5 years. Disease-free (NED) survival rate was 49.4% at 10 years and was better achieved in OP+RT group and low grade lesions. Based on our result, a well planned postoperative RT following parotidectomy is highly efficacious in controlling malignant tumors of the parotid gland and preservation of facial nerve.

Key Words : Malignant parotid tumor, Radiation therapy, Prognostic factor, Facial nerve

INTRODUCTION

Salivary gland tumors account for approximately 3% of all head and neck tumors and one of three parotid tumors are malignant. The biologic behavior of malignant parotid tumors was quite variable according to histologic grade[1]. Traditionally they were considered as radioresistant possibly because of relatively slow regression rate after radiation therapy and poor results of treating locally advanced and recurrent tumors. Thus most of malignant salivary gland tumors have been treated by a surgical resection[2,3]. But analysis of long term surgical data revealing significant local failures has prompted use of adjuvant radiation therapy for subclinical, microscopic disease[4]. In recent years, some study showed that radiosensitivity of malignant parotid tmors was same as squamous cell carcinoma and there have been many reports indicating that radiation therapy can indeed contribute to cure rates in the disease[4-9].

We reviewed our experience in managing malignant parotid gland tumors and analyzed prognostic factors that influence the control of local

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disease.

MATERIALS AND METHODS

Sixty patients with malignant parotid tumors treated at the Seoul National University Hospital (SNUH) between March, 1979 and July, 1989 were retrospectively reviewed. Five patients who received incomplete treatment or were treated palliatively excluded from the analysis. Of the evaluable 55 patients, there were 32 males and 23 females with a median age of 49 years(range: 5–76 years). Median follow-up for all survivors was 48 months with range of 1–129 months. Based on American Joint Committee on Cancer(AJCC) staging system, the tumors were restaged retrospectively from the data in patient's chart: 21 were stage I; 15 stage II; 10 stage III; 9 stage IV. The common histologic types were mucoepidermoid carcinoma(25 cases), malignant mixed tumor(12 cases) and adenoid cystic carcinoma(6 cases). The histologic grade was high in 33 patients, low in 18 patients and 4 patients had a unknown grade with unspecified histologic type. Table 1 shows details of distribution of patients by stage and histologic types.

Table 1. Distribution by Stage and Histologic Type

Histology	Stage				Total
	I	II	III	IV	
Low grade					18
Acinic cell	0	1	0	0	1
Mucoepidermold	10	4	3	0	17
High grade					33
Mucoepidermoid	1	1	1	5	8
Adenoid cystic	3	2	1	0	6
Malignant mixed	3	4	2	3	12
Squamous cell	0	1	1	1	3
Adenocarcinoma	2	1	0	0	3
Undifferentiated	0	0	1	0	1
Unspecified	2	1	1	0	4
Total	21	15	10	9	55

Table 2. Treatment Modalities

Surgicl procedure	No.(%)
RT alone(biopsy)	8(15)
OP+RT	47(85)
Excision	11
Parotidectomy with nerve preservation	27
Parotidectomy with nerve resection	9

8 patients whose tumors were inoperable or unresectable received RT alone and 47 patients received OP+RT which is the standard treatment of parotid cancer in SNUH. The most common surgical procedure was parotidectomy with facial nerve preservation(Table 2). Postoperative RT was indicated if there were risk factors as following[6,10]: high grade tumor; invasion of muscle, bone, skin, nerve, extraparotid tissue; regional node metastasis after neck dissection; gross or microscopic residual disease; close surgical margin particularly if the deep lobe is involved.

Radiation field extended from the zygomatic arch superiorly to below the mandible to cover the first echelon nodes. The anterior border was on the anterior edge of masseter and posterior border covered the mastoid. Multiple fields, frequently ipsilateral paired wedged, were applied to spare the opposite salivary gland. The lower neck was electively irradiated in 11 patients who had a cervical lymph node metastasis after neck dissection(6-radical neck dissection, 5-modified neck dissection). Radiation therapy was delivered with ^{60}Co unit or 6MV linear accelerator and sometimes high energy en face electron beam was used. The median tumor dose was 6750 cGy(range: 5000–7650 cGy) in RT alone group, 6000 cGy(range: 3800–7200 cGy) in the OP+RT group. Radiation was delivered in single daily fraction of 180–200 cGy, five times per week.

Survival period was measured from the date of treatment to the date of last follow-up or death certificates and Kaplan-Meier method was used for the calculation of survival rate. Differences and trends of results were tested by using Logrank test.

RESULTS

In all 55 patients, the local control rate was 69.8% at 5 years and 65.7% at 10 years. In the RT alone group, the 10 year local control rate was 28.6% and we found 5 established local recurrences among these 8 patients. In OP+RT group, the 10 year local control rate was 71.8% and we found 11 local recurrences among these 47 patients. The favoring result of OP+RT group was translated to statistical significance(p=0.005) (Fig. 1).

We next analyzed the influence of facial nerve resection on local control rate(Fig. 2). Sparing of the nerve was not associated with a higher failure rate than with nerve resection. At 10 years the local control rate did not show any significant differences between groups(nerve preservation, 80.2% versus nerve resection, 59.3%, p =0.129).

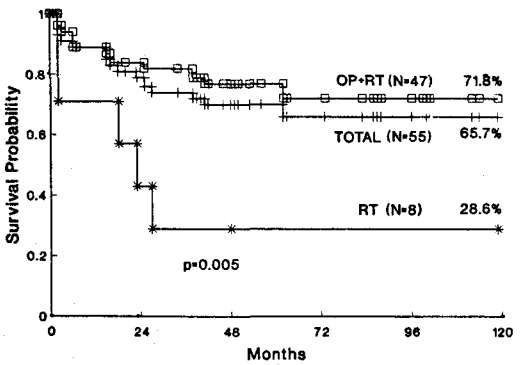

Fig. 1. Local control rate by treatment modality.

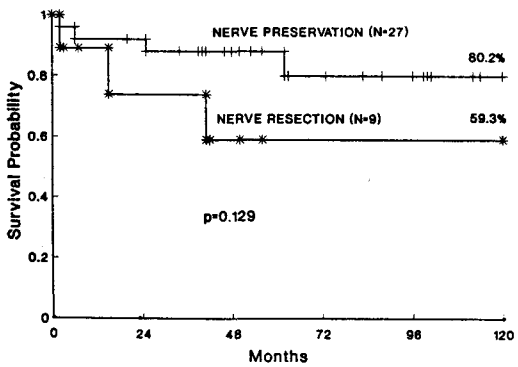

Fig. 2. Local control rate by operation type.

Then to find out prognostic factors affecting local control in postoperative RT group, univariate analysis was performed for the following variables: histologic grade, tumor size(T stage), lymph node metastasis(N stage), preservation or resection of facial nerve, RT dose, resection margin status. There were several factors that appeared to be predictive for local failures. The high grade, T3 & T4 stage(>4㎝), positive node at presentation greatly increased the risk of local failures and p values between each compared groups were 0.018, 0.021 and 0.015, respectively. As we stated previously facial nerve resection did not affect the local control rate significantly and dose-response relationship could not be demonstrated. Resection margin involvement also did not correlated with local control(Table 3).

The actuarial overall survival rate was 72.2% at 10 years and formed plateau after 5 years.

Table 3. Prognostic Factors Affecting Local Control (OP+RT, N=47)

Factors	No. of control /No. of pts,	10-year local control	p-value
Histology			
Low grade	15/16	88.9	0.018
High grade	18/28	59.9	
Tumor size			
≤ 4㎝	29/34	80.0	0.021
> 4㎝	7/13	50.8	
Lymph node			
Positive	6/11	43.0	0.015
Negative	30/36	79.4	
Facial nerve			
Preservation	23/27	80.2	0.129
Resection	6/9	59.3	
RT dose			
< 6000	17/23	71.9	0.501
≥ 6000	19/24	73.6	
Margin			
Positive	8/9	88.9	0.326
Negative	28/38	67.1	

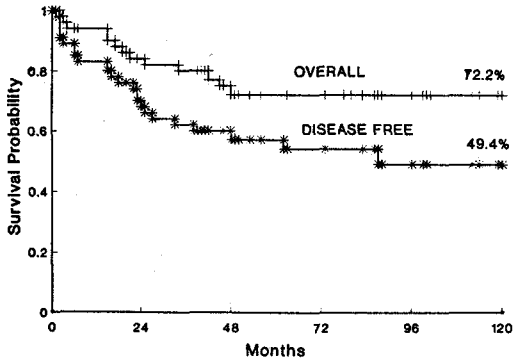

Fig. 3. Overall and disease free survival rate(N=55).

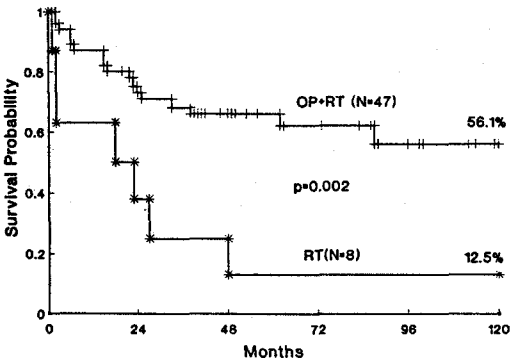

Fig. 4. Disease free survival rate by treatment modality.

The NED survival rate at 10 years was 49.4% for all patients and 56.1% for the OP+RT group, 12.5% for the RT alone group(p=0.002)(Fig. 3, 4). There was also a significant differnece in 10 year NED survival rate depending upon histologic grade(low grade, 63% versus high grade, 39%, p=0.01).

Among 55 patients, 24 patients(44%) ultimately failed. Table 4 demonstrated failur pattern according to the histologic types. The highest failure rate(75%, 9/12) occurred in malignant mixed tumor and all of the failure were within the radiation field in squamous cell carcinoma and distant metastases in adenocarcinoma. Local recurrences were documented in 16 patients(29%, 16/55). 11 patients had a local failure only and the other 5 patients had a distant metastasis, too. An isolated lymph node failure occurred in 3 cases, of which one case had received a radical neck dissection and lower neck irradiation. Distant metastasis developed in 13 patients(24%, 13/55), mostly to the lung(Table 5,6). 85% of distant metastasis occurred in high grade lesion

Table 4. Failure Pattern by Histologic Type (N =55)

Histology	Failure		Total
	LRF	DM	
Low grade	3	1	4/18
Acinic cell	0	1	1/1
Mucoepidermoid	3	0	3/17
High grade	13	11	19/33
Mucoepidermoid	3	2	4/8
Adenoid cystic	1	2	2/6
Malignant mixed	7	5	9/12
Squamous cell	2	0	2/3
Adenocarcinoma	0	2	2/3
Undifferentiated	0	0	0/1
Unspecified	0	1	1/4
Total	16	13	24/55

LRF: locoregional failure
DM: distant metastasis

Table 5. Failure Pattern

Treatment	No. of pts.	Pattern		
		LRF	DM	LRF+DM
RT alone	8	5	2	0
OP+RT	47	6	6	5
Total	55	11	8	5

LRF: locoregional failure
DM: distant metastasis

Table 6. Failure Site

Site	No. of pts.(%)
LRF	16(100)
Primary	11(69)
Neck node	3(19)
Primary+node	2(12)
DM	13(100)
Lung	10(77)
Bone	2(15)
Axillany node	1(8)

LRF: locoregional failure
DM: distant metastasis

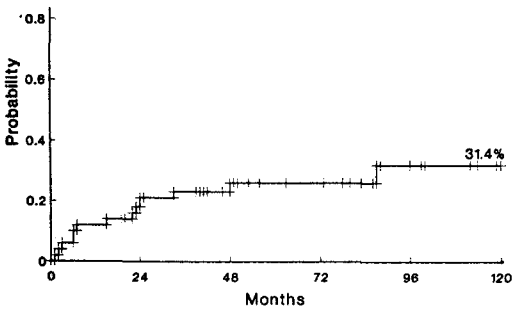

Fig. 5. Cumulative risk of distant metastasis after treatment(N=55).

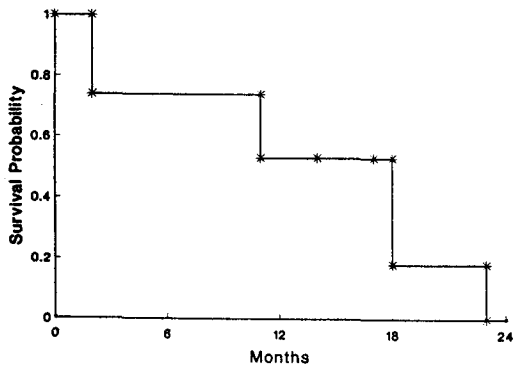

Fig. 6. Survival rate after appearance of distant metastasis(N=13).

and 62% of the distant metastasis developed in spite of local control. The cumulative risk of distant metastasis was 31.4% at 10 years(Fig. 5). The actuarial survival rate after appearance of distant metastasis was abruptly dropped and all the patients with distant metastasis expired within 2 years(Fig. 6). So that, the factor which most strongly determines the survival is the appearance of distant metastasis.

DISCUSSION

Malignant parotid tumors is known to be not a radiocurable tumor and radiation therapy is seldom employed curatively as the initial therapy of choice. Still now surgery remains the primary treatment[2,3]. But complex surgical problems owing to intricate relationship of the facial nerve is frequently met[11] and the tumors, adenoid cystic carcinoma in particular, infiltrate outside of confines of the parotid gland, spread the surrounding soft tissue along the facial, auriculotemporal nerve[12]. Hence radical surgery does not prevent high local recurrent rates[13]. Wood et al[14] reported that 28% of patients who received radical procedures including more frequent sacrifice of the facial nerve ultimately failed. Spiro et al[15] also reported a local recurrent rate of 7, 21, 58% for his own stage I, II, III disease respectively and Hodgkinson[16] showed a 38% local recurrent rate at 5 years occurred despite aggressive surgery that sacrificed the facial nerve in 64% of the patients. Recently postoperative radiation therapy is often used for parotid tumors and it has proved to be an effective measure in the management of the disease[4,6]. In the Fitzpatrick's series[8], 74% of the patients obtained locoregional control with the combined surgery and radiation achieving statistically significant improvements over surgery alone(24%). Matsuba et al[7] also described that the overall rate of 70% local control with surgery plus radiation is significantly better than the 20% achieved with surgery alone($p<0.005$). In a series from the M.D. Anderson Hospital, King and Fletcher[17] reported a local control of 93.5% in 46 patients who received postoperative RT of 6000cGy and in McNaney's experience[10] all 77 patients referred for postoperative RT had a high risk of developing local recurrence, locoregional control was obtained in 87% of the patients. In our study the 10 year local control rate was 71.8% in postoperative RT group and this figure is similar to results obtained with other comparable studies[4,7,18,19]. The local control rate with postoperative RT showed no significant difference regardless of whether the facial nerve was resected. The patients who did not undergo resection of the facial nerve had a lower incidence of local failure than those who underwent nerve resection, but this difference could be explained by the fact that those patients requiring sacrifice of the facial nerve generally had more extensive tumor.

The 10 year local control rate for patients with RT alone was 28.6% in our study and the figure was consistent with Park's experience[19]. There are many literatures which analyzed factors that influence the local control[10,15,20,21]. In the McNaney's series[10], radiation response seems to be similar among different histologic types. Spiro et al[15, 21] emphasized the importance of clinical staging at the time of treatment rather than the extent of surgical procedures and observed that patients who had a recurrent disease or facial nerve involvement tended toward decreased local control. Poulsen et al[22] identified age greater than 60 years, involved nodes, postsurgical residual disease and poor differentiation as a bad prognostic factors. In our study, univariate analysis of variables showed that high grade, large tumor(>4cm, T3, T4), node metastasis were bad prognostic indicators. This may be caused by either increased chance of regrowth form residual disease, positive lymph node or its own inherent radioresistance. But facial nerve resection, high radiation dose(≥6000 cGy), negative resection margin did not influence the local control. In our study, most of locoregional failures were primary site failures and nodal failures occurred in 9%(5/55) of cases. Spiro et al[15] found occult neck disease in only 18 of 288(6%) patients and nodal failure rates in the literature vary between 12% to 25%[7,8]. The general treatment policy of nodal area was not to irradiate the second echelon nodes electively except in the case of positive cervical node at presentation or very high grade lesions.

The local control of primary site ultimately uncovers the remaining problem of distant metastasis. Distant metastasis is especially common with high grade lesion and may occur quite later in the course of disease. Incidence of distant metastasis of 12% to 25% are quoted in the literature[7,8,10]. In our series, relapse at distant sites occurred in 24% of cases and most of distant metastasis developed irrespective of local control. The cumulative risk of distant metastasis was 31.4% at 10 years and the appearance of distant metastasis portend a worse prognosis. Thus further improvement in survival can only be achieved by virtue of more effective systemic chemotherapy.

Some authors presented very high local control rate of a patients with inoperable and unresectable salivary gland tumors using fast neutron radiation therapy[23,24]. Catterall et al[25] reported a local control of 72% and 5 year survival rates of 50% in 65 patients with locally advanced or recurrent parotid tumor. Although the numbers in these series were small and follow-up was relatively short, these new methodology might be a guide for a future trials.

In conclusion, our data confirm the efficacy of the approach using meticulous surgical technique with intent on preserving facial nerve followed by postoperative RT and can be summarized as follows:

1) local control was significantly improved with postoperative RT as compared to either modality alone.

2) high grade, large tumor(4> c m) and node metastasis were poor prognostic factors.

3) local control rates with RT showed no difference regardless of facial nerve resection, so that the operating surgeon should preserve the facial nerve unless it is grossly involved.

4) further therapeutic measures using effective chemotherapy should be explored in the hope of improving survival rate.

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=국문초록=

이하선 악성종양에 대한 방사선 치료의 효과

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1979년 3월부터 1989년 7월사이에 서울대학교병원 치료방사선과에서 55명의 환자가 이하선에 생긴 악성종양으로 치료를 받았다. 이 환자들을 대상으로 방사선 치료의 효과를 알아보기 위해 저자들은 후향성조사를 하였으며 다음과 같은 결과를 얻었다. 8명의 환자는 수술이 불가능하거나 재발한 경우로 방사선 치료만 받았으며 나머지 47명에게는 수술후 방사선 치료를 추가하였다. 이 환자들의 중앙추적기간은 48개월이었다. 조직학적으로는 mucoepidermoid ca가 25명으로 제일 많았으며 malignant mixed tumor와 adenoid cystic ca가 각각 12명, 6명이었다.

모든 환자에 있어서 국소치유율은 10년에 65.7%였으며 수술과 방사선 치료를 병합한 군이 방사선 단독 치료군보다 양호한 결과를 나타내었다(71.8% 대 28.6%). 조직학적 grade 및 종양의 크기, 임파절의 전이 여부가 국소치유율을 결정하는 요인이었으며 안면신경의 절제유무는 국소치유율에 영향을 주지 못했다. 원격전이는 환자의 23.6%에서 일어났으며 주로 high grade 병변에서 폐를 침범하였다. 전체생존율은 10년에 72.2%였으며 5년이후에는 plateau를 이루었다. 무병생존율은 10년에 49.4%였으며 수술과 방사선 치료를 병합한 군과 low grade 병변에서 좀 더 양호한 결과를 나타내었다.

결론적으로 이하선 악성종양의 치료에 있어서 이하선 절제술과 적절한 방사선치료를 병합함으로써 수술 혹은 방사선 단독 치료군보다 국소치유율의 향상 및 안면신경의 기능유지를 도모할 수 있으며 환자의 생존율을 높이기 위해서는 원격전이시 보다 효과적으로 작용하는 항암제의 개발이 시급하다 하겠다.