

## Primary Radiation Therapy of Malignant Salivary Gland Tumors by Conventional Megavoltage Irradiation

—Korea Cancer Center Hospital—

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Retrospective analysis of survival rates was undertaken in the patients of 58 cases treated with conventional radiation therapy for malignant salivary gland tumors between January 1975 and December 1984 in Korea Cancer Center Hospital (KCCH). They were patients whose long-term follow-up was possible and who had refused surgery or had had recurrences postoperatively. Out of 58 patients, 25 patients (43.1%) had mucoepidermoid carcinomas and 24 patients (41.3%) adenoid cystic carcinoma.

Total actuarial survival rates at 5 years and 10 years were 68.2% and 31.8% respectively, but disease-free survival rates, 43.2% and 13.0%, respectively.

According to TNM stage, the survival rates at 5 years were 86.5% in T<sub>1</sub>, 40.0% in T<sub>2</sub> + T<sub>3</sub>, and 0% in T<sub>4</sub>. In terms of histologic types, 5 years disease-free survival rate of adenoid cystic carcinomas (40.1%) was lower than that of mucoepidermoid carcinomas (49.8%) but overall survival rate (77.3%) was much higher than that of mucoepidermoid carcinomas (51.5%). Therefore, we concluded that the patients, who had had disease after failure of treatment, could survive during a certain period of time and their alive times were 2 years on the average. There was a difference in survival rates in the mucoepidermoid carcinomas in terms of histological grade of differentiation and it was a arbiter in prognosis: 5 YSR of low-grade was 78.8% and higher 2 times than that of high-grade. There was no difference in survival rates according to location and sex. The number of patients having minor salivary gland tumors was 6 cases and their actuarial 5 YSR was 32.3%. Consequently, prognostic factors which influence the survival rates of patients with malignant salivary gland tumors are thought to be 1) histological subtypes 2) T and N staging (AJCC) 3) histological grade, especially in mucoepidermoids.

**Key Words:** Postoperative recurrent and inoperable salivary gland tumors, Conventional megavoltage irradiation, Neutron therapy, Survival rates by prognostic factors, Adenoid cystic carcinomas, Mucoepidermoid carcinomas

### INTRODUCTION

Malignant salivary gland tumors comprise less than 1% of head and neck cancers and have a variety of histological subtypes. Although the treatment modality may be somewhat different among diverse institutes, there is no doubt that the surgery has been a traditional mainstay of treatment.

Local recurrence rate, however, was considerably high even though complete resection. Of course, it depended upon the histologic subtypes, grade of differentiation, and extent of disease. Rosenfield et al<sup>1)</sup> reported that the local recurrence rate was 53% in adenoid cystic carcinoma and squamous cell carcinoma, 58% in high-grade

mucoepidermoid carcinoma, 50% in undifferentiated, and 26% in low-grade mucoepidermoid carcinoma. Spiro et al<sup>2)</sup> reported that the local recurrence rate was about 27%, on the average, in all stages of parotid gland tumors. In spite of high local recurrence postoperatively, radiation therapy had not been admitted to be a postoperative adjuvant treatment modality, because malignant salivary gland tumors had been known to be radioresistant by Frazell et al<sup>3)</sup>. Fletcher and King<sup>4)</sup>, Guillaumondegui<sup>5)</sup>, and Matsuba<sup>6)</sup>, however, found that the survival rate could be considerably enhanced with radiation therapy in cases of positive resection margin and small size of residual gross tumor. Especially in case of adenoid cystic carcinoma, its survival rate was a match for that of

initial treatment with aggressive radiation therapy, although it was a recurrent case after surgery. Complete local control could be anticipated only in cases that tumor size was less than 3 cm in diameter, but in case of more than 3 cm, the control rate was very poor.

Recently malignant salivary gland tumors were known to be treated effectively with fast neutron in the clinical practice and so especially in case of locally advanced tumors (stage III and IV).

We, authors, began to treat patients having postoperative recurrent tumors and inoperable ones with fast neutron from October 1986.

Consequently, this retrospective study was carried out to define the role of conventional radiation therapy in the treatment of malignant salivary gland tumors, to evaluate our treatment results with respect to stage (AJCC, 3rd edition 1988<sup>7)</sup>, histology and differentiation grade of the disease, and to determine further the effectiveness of fast neutron therapy in the near future by comparing with the results of conventional radiation therapy.

## MATERIALS AND METHODS

This series consisted of 58 patients with postoperative recurrent and inoperable tumors originating from the major and minor salivary glands, each having received the conventional megavoltage irradiation at KCCH for 10 years between January 1975 and December 1984.

Median follow-up period was 7.5 years and minimum follow-up period was 5 years.

### 1. Patient Characteristics

#### 1) Age and Sex

Fifty eight patients consisted of 37 males and 21 females for a male: female ratio of 1.7 : 1. The median age of the males was 56.2 years and that of

females was 54.8 years. There was no difference in peak age incidence between males and females.

#### 2) Location

Fifty two patients had major salivary gland carcinomas (33 in the parotid gland, 19 in the submandibular gland), and 6 patients had minor salivary gland carcinomas (2 in soft palate, 2 in the maxillary antrum, 1 in the nasal cavity, 1 in the buccal mucosa).

#### 3) Pathology

Most common histological subtypes were encountered in our patients (Table 1). Mucoepidermoid carcinoma was the tumor encountered most frequently (25 patient, 43.1%) and adenoid cystic carcinoma was the next (24 patients, 41.3%). The other histological subtypes were infrequently encountered.

#### 4) Patients Distribution by TNM staging

Table 2 categorizes the patients distribution according to the T stage classification based on AJC. Most patients (39 patients, 67.2%) were in T<sub>1</sub>+T<sub>2</sub> stage and only 19 patients (32.8%) in T<sub>3</sub>+T<sub>4</sub>

**Table 1.** Distribution of Patients by Histology

Histology	No. of patients			
	Major	Minor	Total	
Mucoepidermoid	High	10	1	25
	Low	14	0	
Adenoid cystic carcinoma	19	5	24	
Malign. mixed carcinoma	2	0	2	
Adenocarcinoma	3	0	3	
Squamous cell carcinoma	1	0	1	
Acinic cell carcinoma	1	0	1	
Undifferentiated carcinoma	2	0	2	
<b>Total</b>	<b>52</b>	<b>6</b>	<b>58</b>	

**Table 2.** Patients Distribution by T Stage

T stage*	Parotid	Submandibular	Minor	Total
	No. of patients			
T 1	10	8	0	18 (31.0%)
T 2	13	7	1	21 (36.2%)
T 3	4	2	1	7 (12.1%)
T 4	6	2	4	12 (20.7%)
<b>Total</b>	<b>33 (56.9%)</b>	<b>19 (32.7%)</b>	<b>6 (10.4%)</b>	<b>58</b>

\* Classified by AJC staging

**Table 3.** Distribution by N Stage

N status	Parotid	Submandibular	Total
	No. of patients		
Positive (N 1)	5*	3**	8
Negative (N 0)	28	16	44
Total	33	19	52

\* 5 cases of L/N metastases included 2 cases of mucoepidermoid, 1 case of adenoid cystic carcinoma, 1 case of adenocarcinoma, and 1 case of squamous cell carcinoma.

\*\* 3 cases of L/N metastases included 2 cases of adenoid cystic carcinoma and 1 case of mucoepidermoid.

stage.

Out of 33 patients with tumors involving parotid glands, only 5 patients (15.1%) had cervical lymph nodes involvement. In cases of submandibular gland tumors, only 3 patients (15.7%) had lymph nodes metastases (Table 3).

#### 5) Status of Patients

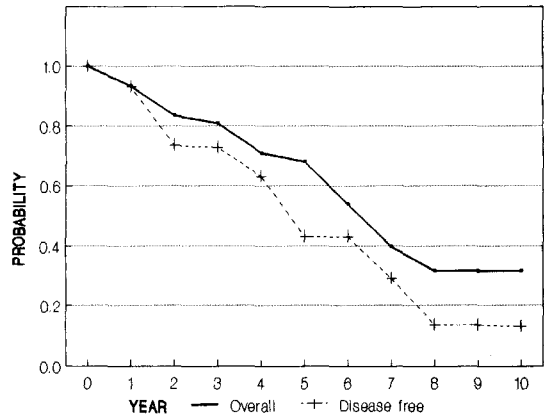
Out of 58 patients, 36 patients were postoperative recurrent cases and numbers of inoperable cases (including the cases that patients refused surgery or surgery not indicated on account of medical problems) were twenty two.

## 2. Techniques of Treatment

Treatment plans were individualized for patients, keeping in mind the anatomy of the gland and the behaviour of various pathological subtypes.

The first echelon of lymph node drainage was always included in the treatment volume. In tumors of high-grade histology, the entire neck on the ipsilateral side was included within the treatment field.

With clinically positive or palpable nodes, supraclavicular anterior single port was added to treatment field up to 4500 cGy/25 fractions or 5040 cGy/28 fractions. The total doses to the primary sites were 6500 to 7000 cGy with daily fraction size of 180 or 200 cGy and to neck nodes, more than 6000 cGy/6 to 7 weeks. We chose a single lateral electron beam (11 MeV to 15 MeV) oppositional to contour or a pair of back-to-back wedged fields (30-degree or 45-degree), with only photon (Co-60) or electron beams, and angled the field (about 5-degree) posteriorly to avoid radiation to the eye



**Fig. 1.** 10 years survival rate of malignant tumors of salivary glands.

and other salivary gland and to include the surgical scar. Especially, in cases of adenoid cystic carcinomas, the base of skull was included in the treatment field.

## RESULTS

### 1. Total Survival Rates of Malignant Salivary Gland Tumors, Including Major and Minor Salivary Glands

The 5 years overall survival rate was 68.2% and disease-free survival rate was 43.2%. The difference of survival rates between overall and disease-free status was small during the first 4 years, but diverged after 4 years. The total survival rates declined progressively even after 5 years' follow-up and reached the plateau at 8 years, implying that at least 10 years' follow-up period will be necessary to determine the survival pattern in patients having the malignant salivary gland tumors (Fig. 1).

### 2. Survival Rate According to Sex

Fig. 2 and Fig. 3 showed that the difference of survival rates according to sex was very small and insignificant statistically in the parotid and submandibular gland tumors. Therefore, sex did not have an influence on the survival rate as a prognostic arbiter.

### 3. Survival Rate According to TNM Stage

#### 1) Parotid Glands

In  $T_1+T_2$  group patients, overall survival rate was 81.2% at 5 years and 78.6% at 10 years. In  $T_3+T_4$  group patients, overall survival rate was 38.0% at 5 years and 0 at 10 years. the survival rates of

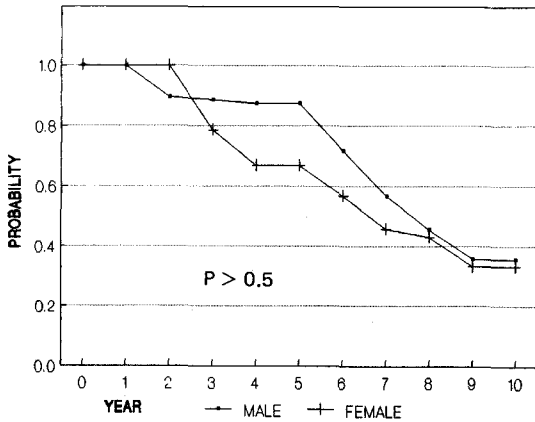


Fig. 2. Survival curve of submandibular tumors by sex.

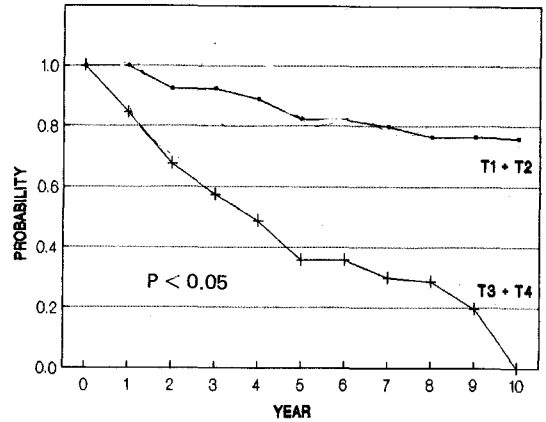


Fig. 4. Survival curves of parotid tumors by T stage.

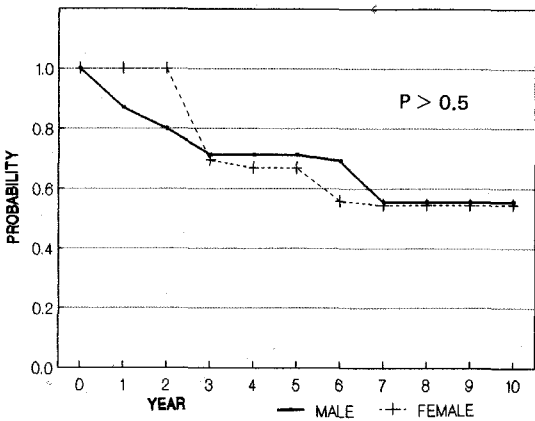


Fig. 3. Survival curve of parotid tumors by sex.

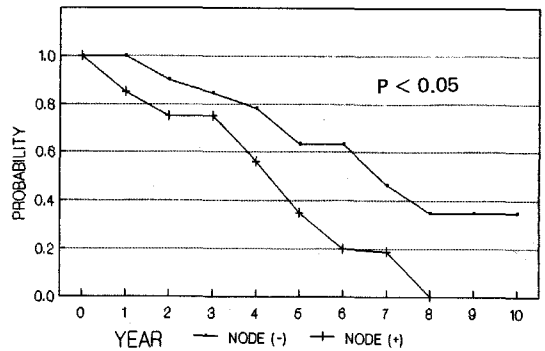


Fig. 5. Survival curve of parotid tumor nodal by status.

the T<sub>3</sub>+T<sub>4</sub> group were much lower than those of T<sub>1</sub>+T<sub>2</sub> group, and declined progressively to reach zero percent at 10 years. Therefore, photon therapy did not have an influence on increase in survival rates of the advanced stage of malignant parotid tumors effectively (Fig. 4).

In terms of nodal status, the overall survival rates of node-positive group were 38.2% at 5 years and 0 at 10 years respectively. On the other hand, the survival rates of node-negative group at 5 years and 10 years were 62.1% and 38.1% respectively (Fig. 5).

### 2) Submandibular Glands

In T<sub>1</sub>+T<sub>2</sub> group, actuarial survival rates were 80.2% at 5 years and 60.0% at 10 years. In T<sub>3</sub>+T<sub>4</sub> group, actuarial survival rates were 38.2% at 5 years and 0 at 10 years. (Fig. 6).

The survival rates of patients with negative nodes were 78.3% at 5 years and 21.0% at 10 years

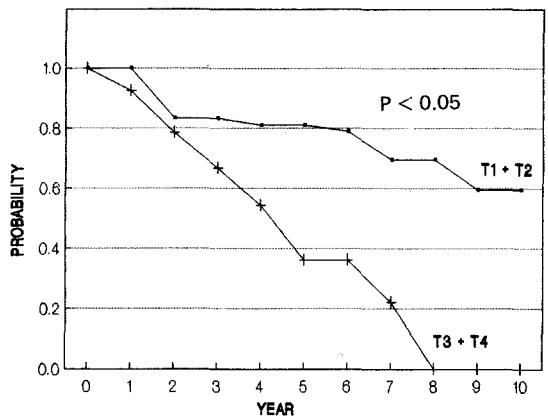


Fig. 6. Survival curves of submandibular tumors by T stage.

(Fig. 7). The patients numbers of node-positive group were very small (3 cases) and we excluded them from analysis of survival rate.

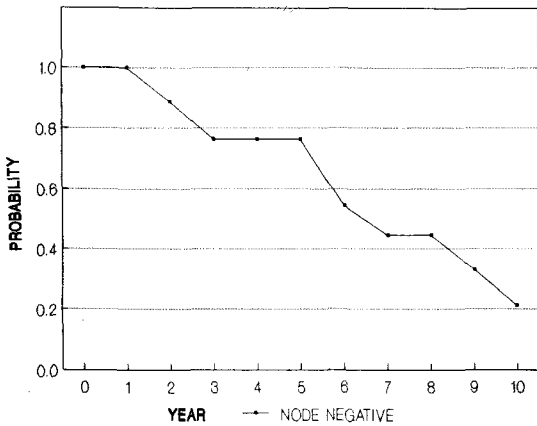


Fig. 7. Survival curve of submandibular tumor nodal by status.

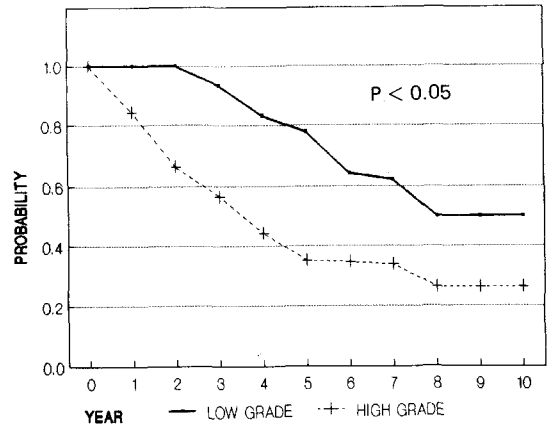


Fig. 9. 10 years survival curve of mucoepidermoid carcinoma.

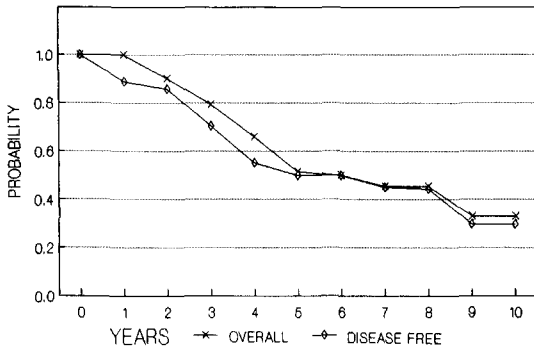


Fig. 8. 10 years survival rate of mucoepidermoid carcinoma.

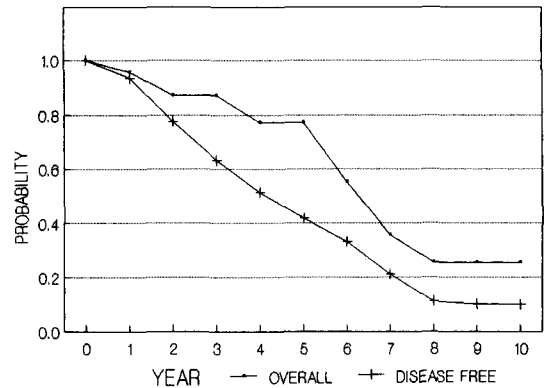


Fig. 10. 10 years survival rate of adenoid cystic carcinoma.

**3) Minor Salivary Gland**

Actuarial survival rate was 32.3% at 5 years.

**4. Survival Rate According to Histological Subtypes**

**1) Mucoepidermoid Carcinoma**

Overall survival rates were 53.5% at 5 years, 38.6% at 10 years and disease-free survival rates were 52.5% at 5 years, 37.2% at 10 years.

Therefore, the difference between the overall survival rate and disease-free survival rate was not significant (Fig. 8).

From the standpoint of histologic grade of differentiation, the survival rate of low-grade mucoepidermoid carcinomas (5 YSR and 10 YSR: 78.5% and 55.0% respectively) was much higher than that of high-grade mucoepidermoid carcinomas (5 YSR and 10 YSR: 38.8% and 24.5% respectively) (Fig. 9).

**2) Adenoid Cystic Carcinoma**

In contrast to the survival pattern of muco-

epidermoid carcinoma, there was a significant difference between the overall survival rate and disease-free survival rate of adenoid cystic carcinoma. Overall survival rates at 5 years and 10 years were 78.5% and 22.3% respectively and disease-free survival rates at 5 years and 10 years were 41.2% and 10.0% respectively (Fig. 10). These facts show that patients with adenoid cystic carcinomas could be alive during some periods in the state of having disease. Fig. 11 shows the average alive time with disease after recurrence was 2 years.

**5. Pattern of Failure after Radiation Therapy**

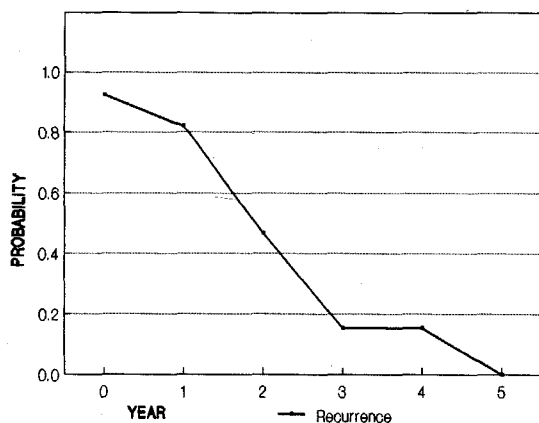
Out of 58 patients, 23 patients recurred after completion of radiation therapy: 10 patients recurred in the primary site, 4 patients in the regional lymph node, and 9 patients developed distant

**Table 4.** Pattern of Failures after RT by Histologic Types

Histology	No. of Pts	Site of failure (%)		
		Primary site*	Neck	Distant metastasis**
Adenoid cystic	19	4 (21)	1 (5)	5 (26)
Mucoepidermoid	24	5 (21)	1 (4)	3 (12)
Squamous cell	1	0	1	0
Malign. mixed	2	0	0	0
Adenocarcinoma	3	1	1	0
Acinic cell	1	0	0	0
Undifferentiated	2	0	0	1
<b>Total</b>	<b>52</b>	<b>10</b>	<b>4</b>	<b>9</b>

\* Failure in the primary site included residual disease after completion of RT

\*\* All of cases of distant metastasis included lung, with the exception of 1 case of temporal lobe metastasis in adenoid cystic carcinoma.



**Fig. 11.** Alive time with disease after recurrence of adenocystic carcinoma.

metastases. Of 9 patients having developed distant metastases, all of the cases with the exception of 1 case of temporal lobe metastasis in adenoid cystic carcinoma had distant metastases to the lung. The proportion of distant metastases was much higher in the patients with adenoid cystic carcinomas (26%) than in those having mucoepidermoid carcinomas (12%). This fact shows that adenoid cystic carcinoma had a higher probability of distant metastasis than mucoepidermoid carcinoma (Table 4).

## DISCUSSION

Malignant salivary gland tumors are relatively rare, comprising less than 1% of all head and neck malignancies. They can arise in a variety of different

sites and consist of diverse histological subtypes having various potentials for aggressive local behaviours and distant metastases.

Although the parotid glands are involved in 70 to 80 percent of all tumors of salivary glands, the percentage of malignant tumor involvement is lowest in the parotid glands (20 to 30 percent). In our cases, 56.9 percent of malignant tumors occurred in the parotid glands and 32.7 percent in submandibular glands. However, our cases were not randomized, but retrospectively selected for evaluation of survival patterns of postoperative recurrent and inoperable tumors, thus not reflecting the natural history and epidemiology of salivary glands tumors.

There was no significant differences in the incidence between mucoepidermoid carcinomas and adenoid cystic carcinomas (43.1% vs 41.3%) in our cases.

The incidence of lymph node metastasis was very low in our cases. In cases of parotid tumors, the incidence was 15.1 percent, and 15.7 percent in submandibular tumors. These data were consistent with other studies.

The initial treatment for malignancies of the salivary glands has been almost exclusively surgical, because these tumors were known to be radioresistant. I have no doubt that surgery has a definitive effect in controlling the early stage of malignancies, but it has a limited role in controlling the locally advanced tumors (stage III and stage IV) without sacrifice of facial nerve<sup>9</sup>.

In patients with stage III lesions, the local recurrence rate approached 60 percent. Local recurrences after surgery are frequent, particularly in

patients with aggressive high-grade tumors or those in whom known microscopic disease was left at or near the resection margin. Therefore, postoperative radiation therapy is mandatory in these cases.

The role of radiation therapy in the management of malignant salivary gland tumors was highlighted by Fletcher<sup>4)</sup>, Guillaumondegui<sup>5)</sup>, and McNaney et al<sup>9)</sup>.

Particularly, Guillaumondegui<sup>5)</sup> at M.D. Anderson Hospital proposed the indications for postoperative irradiation: 1) highly malignant tumors 2) invasion of muscle, bone, skin, temporomandibular joint, nerves or perineural lymphatics 3) regional lymph node metastases 4) after resection of recurrent tumors 5) tumors of the deep lobe 6) gross residual tumor after surgical resection 7) the tumor is adjacent to facial nerve.

The survival rate of recurrent tumors after surgical resection has been reported infrequently and as very low, if reported, by some authors.

Up to date, reported series tend to be small and difficult to compare with each other. Moreover, the series tend to cover many years of treatment with changes both in treatment equipment and technique occurring over the time span in question.

We, therefore, chose the patients with recurrent disease after surgery or inoperable disease (excluding postoperative adjuvant radiation therapy) in order to obtain the survival rate and the failure pattern of postoperative recurrent tumors after radiation by using the photon and take them as a baseline study for the neutron therapy.

Out of 89 patients who had undergone the complete resection and had not received postoperative radiation therapy, 36 patients (40.4%) recurred.

The rest of objects of our analysis (22 patients) were inoperable cases due to medical problems or difficulty in surgical technique. Fu et al<sup>10)</sup> reported a local recurrence rate of 54 percent for all histological types and in another<sup>11,12)</sup>, a 38 percent local recurrence rate at 5 years occurred. These results are similar to ours.

Although postoperative recurrent tumors have more aggressive behaviour than initial status of original tumors, they are thought to be relatively responsive to the aggressive radiation therapy (6500 cGy to 7000 cGy).

Total overall 5 and 10 year survival rates of recurrent tumors or inoperable tumors were 68.2% and 36.5% respectively, and thus this fact showed that aggressive radiation therapy had been effective

even in the treatment of postoperative recurrent tumors. Another fact judging from our results was that five years results could be quite misleading in patients with salivary glands tumors because the five years cure rate decreased progressively until ten years follow-up. These facts were much alike in the various histological subtypes of salivary glands tumors. Long-term follow-up period (at least 10 years), therefore, is necessary to determine the survival pattern in the malignant salivary glands tumors.

Other interesting feature was that there was a significant difference between the overall and disease-free survival rate, especially in the adenoid cystic carcinomas. For example, the overall 5 years survival rate in patients with adenoid cystic carcinoma was 78.5% while the disease-free 5 year survival rate was 41.2%. Judging from the above-mentioned data, we knew that the patients with malignant salivary gland tumors could be alive during some periods in the state of having disease, especially with adenoid cystic carcinomas. According to paper reported by Matsuba<sup>6)</sup> and Thawley<sup>13)</sup>, half of the patients with metastases were alive more than 3.5 years later, although distant metastases developed in one half of the cases.

In our cases, 23 patients out of 52 patients (excluding 6 cases in the minor salivary gland tumors) recurred within average 4 years after completion of radiation therapy and survived 2 years, on the average, in the state of having disease.

These facts may be related to biological behaviours of salivary gland tumors, such as slow growth (relatively long doubling time and long cell-cycle time) and spread pattern.

Consequently, the disease-free survival rate is much more meaningful than the overall survival rate in estimating the survival pattern of malignant salivary gland tumors.

In spite of improvement in both radiotherapy technique and equipment of low-LET irradiation over the several decades, the survival rates and/or local control rates for inoperable lesions remain less than for combined surgery and radiation therapy. Most series including our data showed 5 years disease-free survival rates of more or less than 40 percent, although they were dependent on the residual tumor size (T status), nodal status, histological subtypes, and histological grade (especially in mucoepidermoid carcinomas). There had been an extensive world-wide effort studying the use of high-LET radiation (including neutron) in lieu of conventional radiation therapy to obtain the

improved survival rate. Neutron offers several advantages over the low-LET irradiation: 1) reduced OER (~1.6) compared with 2.5~3.0 for high energy photons to overcome the problem of hypoxic cells, 2) little or no repair of SLD or PLD, 3) less variation of sensitivity through the cell cycle.

The potential role of fast neutrons exploiting these biological advantages in the treatment of malignant salivary gland tumors was first discovered in 1975 when Catterall<sup>14)</sup> reported control rates as high as 90 percent.

From reviews of many articles for fast neutron therapy<sup>14~20)</sup>, we knew that the local control rate was about 71 percent (38 percent to 85 percent) and neutron therapy was superior to conventional low-LET irradiation.

We have treated 14 patients having malignant salivary gland tumors in the state of locally advanced disease (stage III and IV) with fast neutron since October 1986.

Out of 14 patients, 12 patients showed complete responses at the completion of radiation therapy (85.7%). Out of 12 complete responders, 3 patients succumbed to their diseases due to distant metastases and 2 years survival rate was, therefore, 64.3% (9/14). Out of 10 patients (more than 4 cm in diameter of tumor) with the exception of 4 postoperative adjuvant cases, 6 patients survived 2 years. Consequently, 2 years disease-free survival rate of postoperative recurrent and inoperable cases was 60% (6/10).

In our hospital, the disease-free survival rate at 2 years of fast neutron therapy in T<sub>4</sub> stage was much higher than that of conventional photon therapy in the same stage (60% versus 38%). Our data appear to be superior to other series reported by Henry et al<sup>21)</sup> from University of Washington and Ornitz et al from MANTA (quoted from Laramore)<sup>17)</sup>. But, the number of eligible patients is statistically small in estimating the effectiveness of fast neutron therapy and longer follow-up periods will be required.

We have chosen a fast neutron therapy as a primary radiation treatment in a locally far-advanced stage of malignant salivary gland tumors since installation of cyclotron (producing 50 MeV neutron) in our hospital in 1986, October and the results of fast neutron therapy will be reported more precisely further in the near future.

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= 국문초록 =

### 악성 타액선 종양의 방사선 치료 성적에 대하여

—원자력 병원의 10년 경험 (1975.1~1984.12)—

원자력병원 치료방사선과 · 이비인후과\*

조철구 · 고경환 · 류성렬 · 박영환 · 박우윤 · 심운상\* · 오경균\*

1975년 1월부터 1984년 12월까지 원자력병원 치료 방사선과에서 악성 타액선 종양으로 방사선 치료를 받은 58명의 환자를 대상으로 하여 이들의 생존율을 후향적으로 분석하였다. 이들은 수술후 재발했거나, 수술이 불가능한 환자들이었다. 58명의 환자중 mucoepidermoid carcinoma를 가진 환자가 43.1%, adenoid cystic carcinoma를 가진 환자는 41.3%였다.

주 타액선 종양의 5년 보험생존율은 68.2%, 10년 생존율은 31.8%였으나, 무병생존율은 각각 43.2%, 13.0%로써 치료 후 재발된 상태에서도 비교적 오래 산다는 것을 알 수 있었다. TNM staging에 의한 생존율도 T<sub>1</sub>의 5년 생존율이 86.5%, T<sub>2</sub>+T<sub>3</sub>가 40.0%, T<sub>4</sub>가 0%로, T stage가 높아지면 질수록 생존율도 현저히 감소하였다. 병리조직학적 관점에서 볼 때, adenoid cystic carcinoma의 5년 무병생존율은 40.1%로써, mucoepidermoid ca.의 49.8%보다 낮았으나, 전체적인 생존율은 77.3%로써, mucoepidermoid ca.의 51.5%보다 현저히 높았다. 따라서, adenoid cystic carcinoma는 치료실패후 병을 가진 상태에서도 상당 기간 생존할 수 있다는 것을 알았으며, 평균 생존기간은 2년이였다.

또한 mucoepidermoid ca.인 경우에는 세포의 분화정도에 따라 생존율이 달라졌는데, 저등도 분화세포의 5년 생존율이 78.8%로 고등도 분화세포의 38.2%보다 거의 2배나 높았다. 암의 위치와 성별에 따른 생존율의 차이는 없었다.

Minor salivary gland tumor는 6명으로 5년 보험생존율은 32.3%였다. 따라서 주 타액선 종양의 생존율에 영향을 끼칠 수 있는 예후 인자는 1) 병리조직학적 세포종류, 2) T와 N stages (AJCC), 3) mucoepidermoid carcinoma에 있어서 분화 정도였다.