

Analysis of Clinical Data on 71 Patients with Salivary Gland Tumors

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Seventy-one patients treated for salivary gland tumors in our department during the past 25 years, from 1968 to 1993, were studied. This study included 33 males and 38 females with salivary gland tumors, indicating that tumors developed in females with a slightly higher frequency. The mean age of subjects was 46.2 years old for benign tumors and 56.3 for malignant. Of benign tumors, 25 were pleomorphic adenoma and one was a Warthin tumor. Of malignant tumors, 15 were adenoid cystic carcinoma, 13 mucoepidermoid carcinoma, 10 carcinoma in pleomorphic adenoma, 3 acinic cell carcinoma and the remainder were miscellaneous types. These tumors developed in the major salivary glands of 25 patients and in the minor salivary glands of 46 patients. Swelling was the most common symptom. Pain, ulcer, jaw trismus, and sensory nerve disturbance occurred with much greater frequency in cases of malignant tumors. Treatment results for previously untreated malignant tumors were analysed with respect to stage, treatment modality and histology: i) The 10-year cumulative survival rate was 95.0% for stages I and II and 23.0% for stages III and IV. ii) The surgical adjuvant therapy (S, S+C, S+C+R) had better prognosis than chemo- and radiotherapy (C+R). iii) The 5-year and 10-year cumulative survival rates were found to be as follows: mucoepidermoid carcinoma, 92.3% and 71.8%, respectively; adenoid cystic carcinoma, 83.0% for both intervals; carcinoma in pleomorphic adenoma, 57.1% and 45.7%, respectively.

key words: clinical stage; cumulative survival rate; histologic classification; salivary gland tumor; treatment modality

Salivary gland tumor is a relatively common disease in the oral and maxillofacial region. While this tumor often develops in the parotid gland, retrospective clinical analysis of patients referred to our oral surgery department revealed that symptoms frequently develop in the minor salivary gland and submandibular gland. Salivary gland tumors often follow a varied and complicated course, making diagnosis and treatment potentially complex.

We therefore have analysed the clinical findings, histopathological findings and treatment effectiveness for 71 cases of salivary gland tumor and report the results here along with a review of the relevant literature.

Patients and Methods

The subjects were 71 cases of salivary gland tumor examined and treated in our department over a 25-year interval from July 1968 to July 1993. They were reviewed histopathologically and classified according to World Health Organization criteria (Seifert and Sobin, 1991). Clinical staging was classified based on UICC (Hermanek and Sobin, 1987). Furthermore, we examined the cases in terms of age, sex, site, symptoms, signs at presentation, interval from onset to referral to our department, and treatment modality. Forty-five cases of malignant salivary gland tumor were analysed with respect

to histology, stage and treatment modality. To assess treatment effectiveness, cumulative survival rates were calculated for histological type, classification of stage and modality of treatment using Kaplan-Meier's method (Japan Society for Cancer Therapy, 1985).

Results

Age and sex (Fig. 1)

Subjects with benign tumors were composed of 11 males and 15 females, yielding a male to female ratio of 1:1.4. Average age was 46.2 years old, and subjects ranged in age from 22 to 71.

Subjects with malignant tumors were composed of 22 males and 23 females, yielding a male to female ratio of 1:1. Average age was 56.3 years old, and subjects ranged in age from 14 to 85.

Histological type and primary site (Table 1)

Of benign tumors, pleomorphic adenoma was the most common (25 cases). Among malignant tumors, adenoid cystic carcinoma developed most frequently, followed by mucoepidermoid carcinoma, and carcinoma in pleomorphic adenoma.

Among 25 tumors developing in the major salivary gland, 11 (44.0%) were found in the submandibular gland, 9 (36.0%) in the parotid gland and 5 (20.0%) in the sublingual gland.

The incidence of malignant tumor in the sublingual gland (100%) was higher than either the submandibular gland (72.7%) and parotid gland (44.4%).

Among 46 cases developing in the minor salivary gland, 27 (58.7%) were found primarily in the palate. The incidence of malignant tumor in the palate was 14 cases (51.9%); high incidences were also found in the retromolar region, the maxillary sinus and the mandible.

As for location by histological type, carcinoma in pleomorphic adenoma, pleomorphic adenoma, mucoepidermoid carcinoma and acinic cell carcinoma developed frequently in the minor salivary gland.

As for histological type by location, it was common to be seen pleomorphic adenoma and adenoid cystic carcinoma in the submandibular gland, pleomorphic adenoma in the parotid gland, pleomorphic adenoma, mucoepidermoid carcinoma and carcinoma in pleomorphic adenoma in the palate and adenoid cystic carcinoma in the buccal mucosa.

Clinical symptoms by histological type at initial diagnosis (Table 2)

At initial diagnosis, clinical symptoms such as swelling, pain, ulceration, trismus and sensory nerve disturbance were commonly noticed, especially swelling, which was seen in all 71 cases. Pain appeared in 3 cases (11.5%) of benign tumor, in contrast to 30 cases (66.7%) of

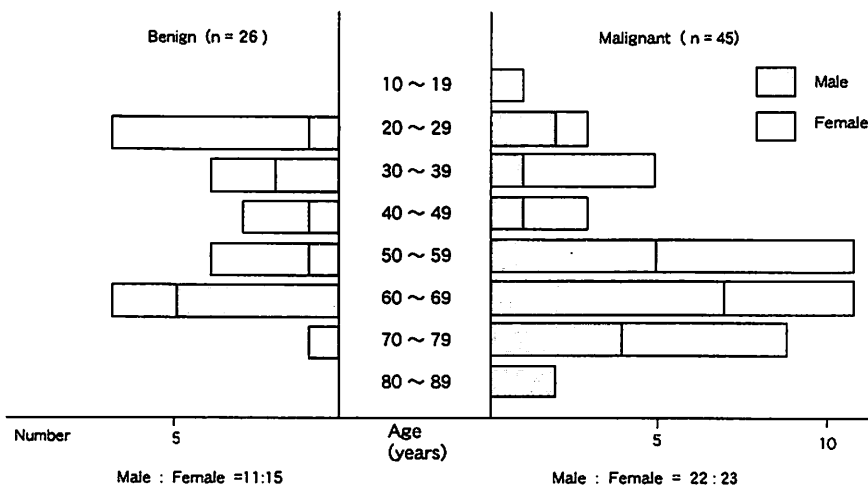


Fig. 1. Age and sex distribution of salivary gland tumor.

Salivary gland tumors

Table 1. The classification, location and frequency of salivary gland tumor

Histologic classification	No. of major salivary gland tumor				No. of minor salivary gland tumor							Total	
	Parotid	Submandibular	Sublingual	Total	Palate	Buccal mucosa	Retromolar	FM	Maxillary sinus	Lip	Man-dible*		Total
Pleomorphic AD	4	3		7	13	2		2		1		18	25
Warthin tumor	1			1									1
No. of Benign tumor	5	3		8	13	2		2		1		18	26
Adenoid cystic CA	1	3	2	6	4	3	1	1				9	15
Mucoepidermoid CA		2	2	4	5	1			2		1	9	13
CA in pleomorphic AD		2		2	5	1	2					8	10
Acinic cell CA	1			1		1	1					2	3
Squamous cell CA	1	1		2									2
Undifferentiated CA			1	1									1
Malignant melanoma	1			1									1
No. of malignant tumor	4	8	5	17	14	6	4	1	2		1	28	45
Total No.	9	11	5	25	27	8	4	3	2	1	1	46	71
%	12.7	15.5	7.1	35.3	38.0	11.3	5.6	4.2	2.8	1.4	1.4	64.7	100.0
% of malignant tumor	44.4	72.7	100.0	68.0	51.9	75.0	100.0	33.3	100.0	0	100.0	60.9	63.4

AD, adenoma; CA, carcinoma; FM, floor of mouth.

*Intrabony.

malignant tumor. Ulceration appeared in no cases of benign tumor, in contrast to 8 cases (17.8%) of malignant tumor. Trismus appeared in only one case of benign tumor, but 6 cases (13.3%) of

malignant tumor. Sensory nerve disturbance appeared in 5 cases of malignant tumor, but in none of the benign tumor cases.

Table 2. Symptoms and signs at presentation

Histologic classification	Total	Swelling	Pain	Ulcer	Jaw trismus	Change in sensation
Pleomorphic adenoma	25	25	3		1	
Warthin tumor	1	1				
No. of benign tumor	26	26	3	0	1	0
Adenoid cystic carcinoma	15	15	12	2	2	3
Mucoepidermoid carcinoma	13	13	7	3	2	
Carcinoma in pleomorphic adenoma	10	10	5	3	1	1
Acinic cell carcinoma	3	3	2			
Squamous cell carcinoma	2	2	2		1	1
Undifferentiated carcinoma	1	1	1			
Malignant melanoma	1	1	1			
No. of malignant tumor	45	45	30	8	6	5
Total	71	71	33	8	7	5

Table 3. Clinical staging of malignant tumors

Histologic classification	I	II	III	IV	Total
Adenoid cystic carcinoma	3 (1)	5 (4)	1 (0)	6 (4)	15 (9)
Mucoepidermoid carcinoma	3 (2)	4 (2)	5 (4)	1 (1)	13 (9)
Carcinoma in pleomorphic adenoma	1 (1)	2 (2)	1 (1)	6 (4)	10 (8)
Acinic cell carcinoma	1 (1)	2 (1)			3 (2)
Squamous cell carcinoma			1 (0)	1 (0)	2 (0)
Undifferentiated carcinoma	1 (0)				1 (0)
Malignant melanoma				1 (0)	1 (0)
Total	9 (5)	13 (9)	8 (5)	15 (9)	45 (28)

(), No. of minor salivary gland tumors.

Histological type and clinical stage (Table 3)

The number of stage I+II cases was nearly identical to that of stage III+IV. In terms of clinical stage by histological type, squamous cell carcinoma and carcinoma in pleomorphic adenoma developed frequently in late-stage cases; acinic cell carcinoma developed apparently in early-stage cases.

Duration of symptoms at presentation (Table 4)

The duration between appearance of initial symptoms and visit to our department ranged from 2 months to 30 years in benign tumors, and from one month to 64 years in malignant tumors. By histological type the interval from onset to referral was 2 years or less for 48.0% of benign tumors and one year or less for 60.0% of malignant tumors. Even in the malignant tumors, 3 cases (6.7%) developed over 10 years.

Table 4. Duration of symptoms at presentation

	Duration (year)							No. of patients diagnosed			
	≤0.5	0.5<	1.0<	2.0<	5.0<	10.0<	Total	within half a year	1 year	2 years	over 10 years
Pleomorphic AD	6 (5)	2 (2)	3 (1)	6 (3)	4 (3)	3 (3)	24 (17)	6 [25.0]	8 [33.3]	11 [45.8]	3 [12.5]
Warthin tumor		1 (0)					1 (0)		1 [100]	1 [100]	
Adenoid cystic CA	4 (4)	3 (2)	4 (2)	1 (1)	1 (0)	2 (0)	15 (9)	4 [26.7]	7 [46.7]	11 [73.3]	2 [13.3]
Mucoepidermoid CA	9 (5)	1 (1)	1 (1)	2 (2)			13 (9)	9 [69.2]	10 [76.9]	11 [84.6]	
CA in pleomorphic AD	4 (3)	1 (0)	1 (1)	1 (1)	2 (2)	1 (1)	10 (8)	4 [40.0]	5 [50.0]	6 [60.0]	1 [10.0]
Acinic cell CA		1 (1)	1 (0)	1 (1)			3 (2)		1 [33.3]	2 [66.7]	
Squamous cell CA	2 (0)						2 (0)	2 [100]	2 [100]	2 [100]	
Undifferentiated CA	1 (0)						1 (0)	1 [100]	1 [100]	1 [100]	
Malignant melanoma	1 (0)						1 (0)	1 [100]	1 [100]	1 [100]	
Total	27 (17)	9 (6)	10 (5)	11 (8)	7 (5)	6 (4)	70 (45)	27 [38.6]	36 [51.4]	46 [65.7]	6 [8.6]

(), No. of minor salivary gland tumors. [], %.

Table 5. Histologic classification and treatment modality

Histologic classification	S	S + C	S + C + R	R + C	Total
Adenoid cystic carcinoma	4 (1)	3 (1)	7 (6)	1 (1)	15 (9)
Mucoepidermoid carcinoma	6 (4)		5 (4)	2 (1)	13 (9)
Carcinoma in pleomorphic adenoma	2 (2)		3 (3)	5 (3)	10 (8)
Acinic cell carcinoma	2 (1)		1 (1)		3 (2)
Squamous cell carcinoma			1 (0)	1 (0)	2 (0)
Undifferentiated carcinoma		1 (0)			1 (0)
Malignant melanoma		1 (0)			1 (0)
Total	14 (8)	5 (1)	17 (14)	9 (5)	45(28)

C, chemotherapy; R, radiation therapy; S, surgical therapy. (), No. of minor salivary gland tumors.

Treatment modality

Histologic classification and treatment modality (Table 5)

In treating malignant tumors, surgery alone, surgery plus chemotherapy, a combination of surgery, chemotherapy and radiation therapy, and radiation plus chemotherapy were used. Treatment modalities including surgery accounted for 80.0% (36 cases) of all cases. This pattern was especially pronounced in the 15 cases of adenoid cystic carcinoma where only one case received no surgery. In 10 cases of carcinoma in pleomorphic adenoma, two cases were treated with surgery alone. Both cases of squamous cell carcinoma were treated in combination with radiotherapy.

Clinical staging and treatment modality (Table 6)

In stage I, surgical treatment alone was primarily used. In stages II and III, a combination of surgical treatment and other treatment was often seen. In stage IV, conservative treatment utilizing a combination of radiotherapy and che-

motherapy was used in 8 of 15 cases, and a combination of surgical treatment, chemotherapy and radiotherapy in 5 cases.

Treatment effect

Cumulative survival rates by histological classification (Fig. 2)

The 5-year and 10-year cumulative survival rates were notably high for adenoid cystic carcinoma and mucoepidermoid carcinoma.

Cumulative survival rates by clinical stage (Fig. 3)

The 5-year and 10-year cumulative survival rates in all cases amounted to 75.5% and 65.0%, respectively, and were high in early-stage group.

Cumulative survival rates by treatment modality (Fig. 4)

The 5-year and 10-year cumulative survival rates for all groups receiving surgical adjuvant therapy and the group receiving non-surgical treatment were 90.0% and 77.5%, respectively, for the former group while 5-year cumulative survival rate for the latter group was 0.0%.

Table 6. Clinical staging and treatment modality

Clinical staging	S	S + C	S + C + R	R + C	Total
I	7 (4)	1 (0)	1 (1)		9 (5)
II	4 (2)	2 (1)	6 (6)	1 (0)	13 (9)
III	3 (2)		5 (3)		8 (5)
IV		2 (0)	5 (4)	8 (5)	15 (9)
Total	14 (8)	5 (1)	17 (14)	9 (5)	45 (28)

C, chemotherapy; R, radiation therapy; S, surgical therapy. (), No. of minor salivary gland tumors.

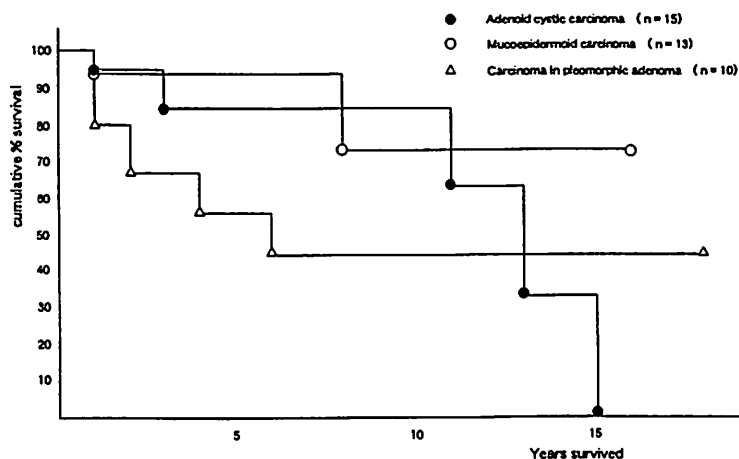


Fig. 2. Cumulative survival according to histologic classification.

tumor, fifty to seventy year olds accounted for about 70% of all cases, which nearly coincides with previously reported rates (Miyata et al., 1989). As for sex-related differences, benign salivary gland tumors occurred in females at a frequency 1.4 times greater than in males,

Discussion

Salivary gland tumors develop commonly and account for about 10% of all tumors in the oral and maxillofacial region, specific rates of 11.3% (Tamao et al., 1959), 7.1% (Terasaki et al., 1957), and 12.2% (Kajiyama and Kurokawa, 1983) have been reported.

The average age of subjects in our department was 46.2 years old for benign tumors and 56.3 years old for malignant tumors. According to some reviews (Chaudhry et al., 1961; Gore et al., 1964; Shirasuna et al., 1985; Spiro, 1986; Miyata et al., 1989), malignant tumors are generally considered to develop about a decade later than benign tumors, which coincides with our results. In terms of age distribution of malignant

but malignant tumors occurred at nearly the same frequency. According to previous reports, both benign and malignant tumors occur in females 1.1 to 2.4 times more frequently (Fujibayashi et al., 1972; Ogawa et al., 1981). Our results coincide with those reports.

In terms of incidence by histological type, most of previous reports (Yokoo et al., 1982; Shirasuna et al., 1985) suggest that in benign tumors pleomorphic adenoma occurs most frequently (Sakashita et al., 1988; Kameyama et al., 1989), and in malignant tumors mucoepidermoid carcinoma and adenoid cystic carcinoma occur most frequently, followed by carcinoma in pleomorphic adenoma. Our results showed a similar tendency.

In terms of incidence by location, 64.7% and 35.3% of all salivary gland tumors developed in the minor salivary gland and the major salivary gland, respectively. Some reports from the field of oral and maxillofacial surgery have emphasized that tumors in the minor salivary gland are more frequently reported as patients with major salivary gland tumors are

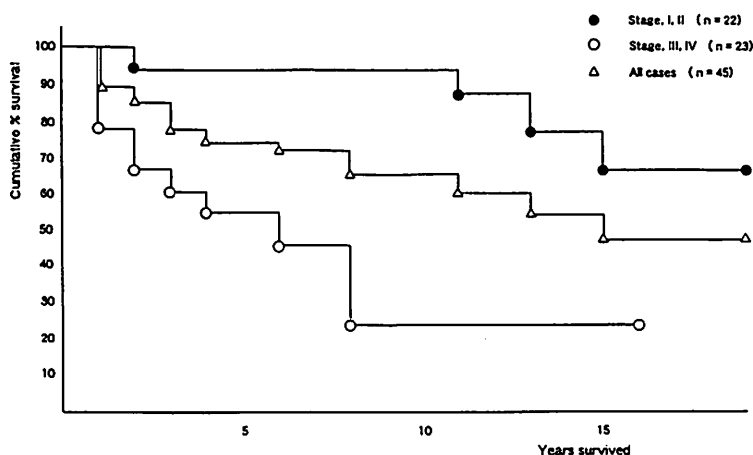
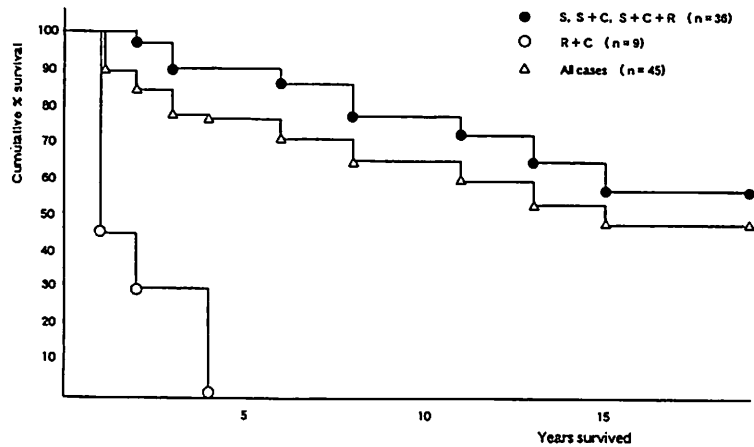


Fig. 3. Cumulative survival according to clinical stage.

Salivary gland tumors

Fig. 4. Cumulative survival according to treatment modality.



generally more apt to refer to other departments (Kameyama et al., 1989; Miyata et al., 1989). Generally speaking, major salivary gland tumors developed most frequently in the parotid gland (Eneroth, 1971; Eveson and Cawson, 1985a). In our results, tumors were seen mostly frequently in the submandibular gland, followed by the parotid gland. It was suggested that the lower incidence of tumors in the parotid gland implied more frequent referral to other departments. Of the minor salivary gland tumors seen in our department, 58.7% occurred in the palate. Other reports have indicated an incidence in the palate of around 50% to 60% (Saito et al., 1977; Eveson and Cawson, 1985b), ranging from a minimum of 41.7% (Chaudhry et al., 1984; Waldron et al., 1988) to a maximum of 74.6% (Isacsson and Shear, 1983). These results are nearly the same as our own. In terms of incidence of malignant tumors by location, values of 15% to 30% (Eneroth, 1971; Woods et al., 1975; Nagao, 1986), 40% to 55% (Eveson and Cawson, 1985a; Spiro, 1986) and 71% to 100% (Rankow and Mignogna, 1969; Ishikawa, 1982) have been reported for the parotid gland, submandibular gland and sublingual gland, respectively, while the incidence of such tumors in the minor salivary gland was a majority of 30% to 40% (Regezi and Lloyd, 1985; Chau and Radden, 1986; Waldron et al., 1988). The incidences we report for each salivary gland are slightly higher than these previous reports. Witten and others (1990) have suggested that the ratio of benign tumors to malignant tumors varies depending on the locality and is affected by nutritional status, endocrine, climatic factors and other causes. However no factors producing a higher frequency of malignant tumors in our results, compared to other reviews in Japan, could be detected.

The frequency of swelling as a clinical symptom at initial diagnosis has been reported as 100% in benign minor salivary gland tumors and 92% in malignant tumors of this type (Chau and Radden, 1986), and 87% in benign tumors of the parotid and submandibular gland and 69% for malignant ones (Spiro, 1986). Swelling was seen in all our cases of salivary gland tumors, suggesting that swelling is the most common symptom in salivary gland tumors. As for frequency of pain for benign and malignant tumors, the high incidence of pain in malignant tumors has been widely reported (Chau and Radden, 1986; Spiro, 1986; Tsuruta et al., 1986; Terakura et al., 1988; Kameyama et al., 1989). In our results, pain was frequently present as a symptom, especially in malignant tumor, with an incidence of 66.7%, as compared to 11.5% for benign tumors. In terms of histological type, pain was most frequent in squamous cell carcinoma cases. Looking at the incidence of ulcers, Chau and Radden (1986) reported 5 benign tumor cases (8%) of 61 and 8 malignant tumor cases (22%) of 37 with accompanying ulceration, suggesting that ulcers occur at a frequency several times greater in malignant tumor cases than benign ones. Our results thus support the opinion that ulceration can be helpful in differentiating benign from malignant tumors. In terms of frequency of ulceration by histological type, carcinoma in pleomorphic adenoma amounted to a plurality of 30.0% in our malignant salivary gland tumors. Chau and Radden (1986) and Fujibayashi and others (1972) have reported the

highest incidence of ulceration in carcinoma in pleomorphic adenoma, with frequencies of 100% (one of one case) and 50% (one of two cases), respectively. Sensory nerve disturbance was seen frequently in adenoid cystic carcinoma in our cases. Akimoto and others (1972) reported tumor infiltration to the surrounding nerves in 12 (41.4%) of 29 cases of adenoid cystic carcinoma. Such tumor infiltration was presumed to produce painful symptoms in the initial stage and neurological paralysis in the advanced stage.

The duration between the initial symptom and first visit was 2 years or less in 38.0% of benign tumors, according to a report by Chau and Radden (1986), but a figure of 50.0% was yielded by our study. Generally, the interval from the initial symptom to first visit is commonly reported to be long in benign tumors, but our study yielded an earlier visit pattern than those reports. We would suggest that this longer interval in benign tumors is due to painlessness, lack of symptoms other than swelling and the slow rate of expansion of the tumor. In our malignant salivary gland tumors, the interval from initial symptoms to visit was less than one year in 60.0% of cases and less than 2 years in 75.6%. Chau and Radden (1986) reported an interval of less than 2 years in 62.0% of cases (21 of 34). In addition, 6.7% of cases had a reporting interval longer than 10 years, which is similar to the result reported by Spiro (1986). With malignant tumors, the reporting interval was generally short, suggesting that the recognition of so longer cases implied the possibility of malignant change of benign salivary gland tumor. The interval from initial symptom to first visit by histological type was apparently short in cases of squamous cell carcinoma and mucoepidermoid carcinoma. This would suggest that rapid enlargement of such tumors prompted patients to visit a clinic. Chau and Radden (1986) reported a case of adenocarcinoma with a reporting interval of 24 years and we experienced a case of adenoid cystic carcinoma in the submandibular gland present for 64 years. In view of the above-mentioned results, it would appear that the salivary gland tumors varied from low grade to high

grade malignancy though of the same clinical diagnosis and a malignant change of benign tumor and so on affected the interval.

As for the survival rate by histological type, Hickman and Cawson (1984) investigated 52 abstracts (covering 2,298 cases) published from 1964 to 1982, and reported 5-year survival rates of 70.7% in mucoepidermoid carcinoma, 62.4% in adenoid cystic carcinoma and 55.7% in carcinoma in pleomorphic adenoma, along with 10-year survival rates of 50.0%, 38.9% and 31.0%, respectively. In our study, the cumulative 5-year and 10-year survival rate were higher than those reported by Hickman and Cawson (1984). In particular carcinoma in pleomorphic adenoma showed a lower survival rate than either adenoid cystic carcinoma or mucoepidermoid carcinoma, which agrees with previously reported results (Shidnia et al., 1980; Hickman and Cawson, 1984). Since mucoepidermoid carcinoma and acinic cell carcinoma are generally known as low-grade malignancies, it was considered necessary to strictly define grades of malignancy when individual treatment effectiveness was compared and evaluated. We therefore classified mucoepidermoid carcinoma by atypia, and classified varying proportions of mucous-secreting, epidermoid and intermediate-type cells and acinic cell carcinoma by nucleic atypia and infiltrative proliferation of tumor cells into low-grade malignancy and high-grade malignancy. This approach resulted in 11 of 13 cases of mucoepidermoid carcinoma and all 3 of the acinic cell carcinoma in our study being classified as low-grade malignancy approximately related to the treatment effectiveness. In terms of survival rate by clinical stage of salivary gland tumor both the cumulative 5-year survival rate and 10-year survival rate decreased as stage progressed, which corresponds to results from other reports (Witten et al., 1990). Our study yielded a 5-year survival rate of 90.0% in cases where surgical treatment was included, in contrast to 0.0% in other cases. In our study, surgical treatment was done performed on cases at every tumor stage, whereas radiotherapy was used in combination with chemotherapy in 8 of 9 cases classified as stage IV.

Therefore, effectiveness by individual treatment could not be definitely clarified. Shidnia and others (1980) have described the combination of surgical treatment and radiotherapy as useful in cases at stage III and stage IV. In consideration of those results along with our own, we would suggest that a combination of surgical and other treatment approaches provides enhanced treatment effectiveness in cases of malignant salivary gland tumor.

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