

# Salivary Gland Tumors among Atomic Bomb Survivors, 1950–1987

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**BACKGROUND.** Malignant and benign tumors of the salivary glands have been associated with exposure to ionizing radiation from various sources, including the atomic bombings in Hiroshima and Nagasaki. However, questions remain unanswered regarding the nature and size of the risk and specific types of tumors involved.

**METHODS.** The incidence and pathology of malignant and benign tumors of the salivary glands was studied in the Life Span Study cohort of atomic bomb survivors followed by the Radiation Effects Research Foundation (RERF) in Hiroshima and Nagasaki, Japan. Incident cases diagnosed during the period 1950–1987 were ascertained from the tumor and tissue registries of Hiroshima and Nagasaki and supplemented by additional case findings from autopsy, biopsy, and surgical specimens maintained at RERF and other institutions. Pathology slides and medical documents were reviewed by a panel of four pathologists who classified tumors using the World Health Organization classification scheme. Analyses were performed of histologic features associated with radiation exposure.

**RESULTS.** Of 145 tumors of the salivary glands identified (119 of the major and 26 of the minor salivary glands), 120 (83%) were histologically confirmed by the current investigators. Among 41 malignant tumors, the frequency of mucoepidermoid tumor was disproportionately high at high radiation doses ( $P = 0.04$ ); among 94 benign tumors, the frequency of Warthin's tumor increased with increasing radiation dose ( $P = 0.06$ ). The nature of the tumor was undetermined for the remaining ten cases. Mortality from malignant tumors of the salivary gland was inversely related to radiation dose, reflecting the predominance of mucoepidermoid carcinoma at high dose levels in this series. In one case with high radiation exposure, mucoepidermoid carcinoma of the parotid gland was accompanied by a preexisting or coexisting Warthin's tumor.

**CONCLUSIONS.** These findings, supported by population-based analyses in a companion study reported elsewhere, suggest a causal role for ionizing radiation in salivary gland tumorigenesis, particularly for mucoepidermoid carcinoma, and in the induction of one type of benign tumor (Warthin's tumor). *Cancer* 1997; 79:1465–75. © 1997 American Cancer Society.

**KEYWORDS:** salivary gland tumor, ionizing radiation, atomic bomb survivors, mucoepidermoid carcinoma, Warthin's tumor.

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Salivary gland tumors are relatively rare, with the world age-adjusted incidence rates being 1 per 100,000 people per year in various populations around the world.<sup>1</sup> The mechanism for the development of salivary gland tumors is not well understood, but medical radiation exposures have been associated with these tumors. An increased occurrence of salivary gland tumors has been observed in individuals treated with X-rays for benign lesions of the head and neck or chest,<sup>2-11</sup> children treated with scalp X-rays for tinea capitis,<sup>12,13</sup> patients treated with <sup>131</sup>I for hyperthyroidism,<sup>14</sup> and patients given repeated diagnostic radiography to the oral cavity.<sup>15,16</sup> One ecologic study also suggested an association between ultraviolet radiation exposure and salivary gland carcinoma.<sup>17</sup>

Tumors of the salivary gland have been the subject of much interest in the follow-up studies of the atomic bomb survivors. Belsky et al. first investigated the incidence of this tumor in the Life Span Study (LSS) sample, a cohort of survivors who were exposed to radiation from the atomic bombs in Hiroshima and Nagasaki in 1945 and who have been followed by the Atomic Bomb Casualty Commission and later by the Radiation Effects Research Foundation (RERF). They reported a significantly elevated incidence of salivary gland tumors for the period 1957-1970 in persons exposed to high radiation doses (3 gray (Gy) or more).<sup>18,19</sup> A similar tendency was observed when malignant tumors alone were considered. More recently, comprehensive analyses of the LSS cancer incidence for the period 1958-1987, including 22 cases of salivary gland carcinoma cases, demonstrated a remarkably high risk of this carcinoma associated with radiation exposure; the cases were limited to those with carcinoma of the major salivary glands and benign tumors were not included.<sup>20</sup> In a separate study, Takeichi et al. investigated salivary gland tumors in the general population of Hiroshima and identified 211 cases during the period 1953-1971.<sup>21-23</sup> The incidence of salivary tumors was increased in people exposed to the atomic bombing within 5 kilometers of the hypocenter.

The current study was undertaken to update and expand the salivary gland tumor incidence data in the LSS cohort. As with the earlier study by Belsky et al.,<sup>18,19</sup> both benign and malignant tumors were included. The follow-up observation was from October 1, 1950 through December 31, 1987 for a total of 37 years, extending the earlier series by 17 years. This article describes the case series, with particular emphasis on case ascertainment and characterization of histologic features of the tumors; a companion article<sup>24</sup> concerned mainly population rates and risk analysis.

## **MATERIALS AND METHODS**

### **Case Ascertainment**

Following the RERF guidelines for the conduct of cancer incidence studies,<sup>25</sup> cases in the LSS cohort were ascertained by linkage to the tumor and tissue registries in Hiroshima and Nagasaki. The Hiroshima and Nagasaki tumor registries are population-based registries established in 1957 and 1958, respectively. Reportable tumors for the tumor registries are malignant and selected benign tumors; until recently, the latter have included benign salivary gland tumors. The tissue registries, started in 1973, are pathology-based registries that collect diagnostic data and tissue slides for histologically diagnosed tumor cases, both malignant and benign.<sup>26</sup> Through these registries, relevant autopsy and surgical records at major medical institutions were also accessed for this study. Also available for the current study were clinical and pathology records maintained at RERF and death certificates for deceased members of the LSS cohort, which has been followed since 1950.

The International Classification of Diseases for Oncology (ICD-O) rules dictate that neoplasms of minor salivary glands be classified and coded to their anatomic sites.<sup>27</sup> This practice does not allow minor salivary gland tumor cases to be identified based on ICD-O codes that are routinely used in the tumor/tissue registry database. It was also suspected that salivary gland tumors, both major and minor, might be misclassified and miscoded to other tumors in the oral and head/neck regions. Therefore, initial screening was very wide, including: 1) cases diagnosed as neoplasms in the anatomic sites in which the salivary glands are located (i.e., lip, oral cavity, pharynx, middle ear, nasal cavity, and accessory sinuses); 2) primary and metastatic tumors of the lymph nodes in the head, face, and cervical regions; and 3) carcinoma in situ and neoplasms of unknown or unspecified morphology of the larynx, digestive system, and respiratory system. All cases with any of the above diagnoses coded under relevant ICD codes were identified and their source documents accessed for review. To find cases missed by the regular tumor and tissue registry activities, especially before the inception of the registries, special case-finding efforts were undertaken using pathology log books and other documents kept at the university and other area hospitals.

The total number of potential cases subjected to the initial screening was 1837. A considerable number of these potential cases were excluded because, upon close inspection of case records, diagnoses were clearly inconsistent with salivary gland tumors. Also excluded at this stage were cases whose dates of tumor diagnosis were outside the current follow-up observation period. The number of cases thus eliminated was

450, leaving 1387 cases for further diagnostic confirmation.

A pathology review, as described later in this article, was then conducted for 136 cases for which relevant tissue slides and/or pathology reports were obtained. These cases were selected by one of the study pathologists and were considered likely to be salivary gland tumors and in need of a detailed review. For 917 cases, clinical records were available for review; for 334 cases, only death certificates were available. Specific diagnosis of salivary gland tumor was mentioned in a very small fraction of cases with clinical or death certificates only.

### Pathology Review

Each case was first reviewed and histologic diagnosis given independently by one of the four pathologists (T.S., Y.H., O.T., or H.M.) who comprised the panel. Tumor types were grouped using the World Health Organization classification.<sup>28</sup> When the four investigators did not agree on histologic diagnosis or type, or when diagnosis given by the panel did not agree with the diagnosis previously given by a hospital pathologist, the four pathologists met again to discuss and review the materials to reach a final consensus diagnosis. When pathology records were available but tissue slides of the primary salivary gland tumor were not available for review, pathology diagnoses made by hospital pathologists were adopted. Cases with clinical records only or those with death certificates only were also reviewed by the panel.

### Statistical Analysis

The emphasis of the current analysis, unlike that of the related article reported elsewhere,<sup>24</sup> is with the case series rather than with the tumor incidence rates in the underlying population. However, both types of analyses are presented. Inferences regarding proportional frequencies of different types and sites of neoplasm are made with respect to variation by city, gender, age at the time of the bombings (age ATB), age at diagnosis, calendar year, and radiation dose. The relevant analyses were performed by modeling the binomial odds, fitted by maximum likelihood, according to the GMBO (General Models for Binomial Outcomes) program from the EPICURE package of statistical programs for analyses of epidemiologic data.<sup>29</sup> Analyses in terms of population rates, abstracted from the companion article,<sup>24</sup> used the AMFIT program for Poisson regression, from the same package. Survival time after diagnosis of salivary neoplasm was evaluated as a function of tumor type or radiation dose, by proportional hazards<sup>30</sup> methods using the PEANUTS program, also from the EPICURE package. Here, survival time was defined as time from tumor diagnosis to

**TABLE 1**  
Salivary Gland Tumor Incident Cases in the Life Span Study, 1950–1987: Demographic and Other Characteristics of the Case Series

	Total cases	145	Percent
Diagnostic confirmation	Histology review by panel	120	83
	Histologic diagnosis; no histology review by panel	2	1
	Clinical diagnosis	22	15
	Death certificate only	1	1
Tumor behavior	Malignant	41	28
	Benign	94	65
	Undetermined	10	7
City	Hiroshima	98	68
	Nagasaki	47	32
Gender	Male	62	43
	Female	83	57
Mean age at diagnosis (yrs)	Malignant tumor cases	55.3	
	Benign tumor cases	55.7	

death, without regard to cause, occurring during the follow-up period through 1987. For malignant cases only, a similar analysis was performed in which the endpoint was death from salivary gland cancer. All reported *P* values are two-tailed, based on likelihood ratio tests. Point estimates are presented with two-sided, equi-tailed, likelihood ratio confidence intervals (CI), at confidence level 0.95.

### Radiation Dose Estimates

The DS86 system provides individual dose estimates of gamma rays and neutron exposure based on individual exposure history information. Radiation dose to the salivary glands, which are relatively superficial organs compared with other cancer sites, was approximated by DS86 tissue kerma in Gy, that is, shielding by buildings and terrain was taken into consideration, but not shielding by tissue.<sup>31</sup> Dose-related comparisons were made with respect to categories defined in terms of exposure and dose intervals (nonexposed, exposed with 0–0.09, 0.10–0.99, and  $\geq 1.00$  Gy, and exposed with unknown dose). However, following the usual RERF practice trend tests were performed with respect to equivalent dose in Sievert (Sv), with neutrons assigned a biologic effectiveness factor of 10 relative to gamma rays.<sup>20</sup>

### RESULTS

In all, 145 salivary gland tumors were identified. Of these, 120 (83%) were accepted on the basis of review of histologic materials by the current panel of pathologists (histologically confirmed), and 2 (1%) on the basis of pathologists' reports for which the original materials were unavailable to the panel (Table 1). In the absence

of histologic information, 22 cases with clinical diagnoses and 1 case with a death certificate diagnosis only were accepted as salivary gland tumors. No multiple tumors were observed among the 120 histologically confirmed cases, except for 1 case in which histologic evidence suggested that an originally benign tumor had been replaced largely by a malignant counterpart. This case was included as a malignant tumor case.

Less than one-third (41) of the 145 salivary gland tumors were malignant; for 10 cases, the tumor behavior could not be determined (Table 1). The slightly higher percentage of female cases and the 2:1 ratio of Hiroshima to Nagasaki cases are consistent with the distribution of subjects within the LSS population. The mean age at diagnosis for malignant tumors of salivary gland (55.3 years) was similar to that of benign tumor cases (55.7 years).

There appeared to be some differences in case ascertainment between Hiroshima and Nagasaki during the early years. Before 1961, 20 tumors (8 malignant and 12 benign) were observed but they were all in Hiroshima. All the malignant tumors during this period and 50% of the benign tumors were diagnosed after the inception of the Hiroshima Tumor Registry in 1957; no malignant or benign tumors were observed in Nagasaki until 1961, even though the Nagasaki Tumor Registry began in 1958. Thereafter, the tumor distribution between the two cities was approximately what would be expected given the 2:1 ratio of Hiroshima to Nagasaki survivors in the LSS sample.

More than two-thirds (119 [82%]) of the tumors occurred in the major salivary glands, mainly the parotid gland, and 26 (18%) in the minor salivary glands, half of them in the palate (Table 2). The preponderance of major salivary gland tumors was more pronounced for benign tumors. All tumors of unknown behavior were of the major salivary glands. There were no significant differences in male/female ratio by tumor behavior or site (data not presented).

Detailed histologic classification is presented for the 120 histologically confirmed tumors by tumor behavior and site in Table 3. Mucoepidermoid carcinoma and adenoid cystic carcinoma were the preponderant types of malignant tumor, together accounting for 23 (or approximately two-thirds) of the 35 malignancies; 11 of the 23, or nearly half, were derived from minor salivary glands. For benign tumors, pleomorphic adenoma was the most common type, comprising 75% of all benign tumors. Warthin's tumor, with 16 cases (19%), was the second most common type of benign tumor.

#### **Salivary Gland Tumors by Exposure Group and Radiation Dose**

DS86 radiation dose estimates were available for 101 exposed cases (31 malignant, 64 benign, and 6 of un-

**TABLE 2**  
**Salivary Gland Tumors by Tumor Site and Behavior: Life Span Study Cohort, 1950-1987**

Tumor site	Tumor behavior			Total
	Malignant	Benign	Undetermined	
Major salivary gland	27	82	10	119
Parotid gland	16	69	7	92
Submandibular gland	10	12	3	25
Sublingual gland	1	—	—	1
Site unknown	—	1	—	1
Minor salivary gland	14	12	—	26
Oral cavity	—	2	—	2
Palate	7	6	—	13
Floor of mouth	4	1	—	5
Gum	1	—	—	1
Tongue	2	1	—	3
Pharynx	—	2	—	2
Total	41	94	10	145

known behavior) but were unavailable for 13 cases (2 malignant, 10 benign, and 1 of unknown behavior); 31 patients who provided cases (8 malignant, 20 benign, and 3 of unknown behavior) were not exposed, i.e., were not in the cities at the time of the bombings (NIC).

Table 4 shows the distribution by specific morphologic type for histologically confirmed cases. The frequency of malignant relative to benign tumors increased significantly with radiation dose ( $P = 0.032$  for linear trend using equivalent dose in Sv). Among the malignancies, adenoid cystic carcinoma was most common, especially in the nonexposed group and among those exposed to doses  $<1$  Gy. However, in the  $\geq 1$  Gy group, there was not a single case of adenoid cystic carcinoma, whereas mucoepidermoid carcinoma accounted for six of the eight malignant cases. The proportion of mucoepidermoid carcinomas relative to other malignant tumors increased strongly with increasing dose ( $P = 0.004$  for linear trend), with an odds ratio of 6.1 at 1 Gy (95% CI, 1.4- $\infty$ ). Although pleomorphic adenoma was the most frequent type of benign tumor for all dose groups combined followed by Warthin's tumor, in the  $\geq 1$  Gy group only one of the four benign tumors was pleomorphic adenoma and the other three were Warthin's tumor. The proportion of Warthin's tumor increased with increasing dose, although not significantly ( $P = 0.061$  for linear trend), with an odds ratio of 3.2 at 1 Sv (95% CI, 0.97-16.5).

In the population-based analysis abstracted from the companion article<sup>24</sup> (Table 5) the incidence rate (indirectly standardized to those at 0-99 milli-

**TABLE 3**  
**Distribution of 120 Histologically Confirmed Salivary Gland Tumors by Tumor Site, Behavior, and Histologic Type:**  
**Life Span Study Cohort, 1950–1987**

Tumor behavior and histology	Parotid gland	Submandibular gland	Minor salivary gland	Total
Malignant tumors	12	10	12	35 <sup>a</sup> (100%)
Mucoepidermoid carcinoma	6	1	5	12 (34)
Adenoid cystic carcinoma	1	3	6	11 <sup>a</sup> (31)
Polymorphous low grade adenocarcinoma	—	—	1	1 (3)
Adenocarcinoma	1	2	—	3 (9)
Carcinoma in pleomorphic adenoma	1	4	—	5 (14)
Squamous cell carcinoma	2	—	—	2 (6)
Undifferentiated carcinoma	1	—	—	1 (3)
Benign tumors	63	11	11	85 (100%)
Pleomorphic adenoma	46	7	11	64 (75)
Basal cell adenoma	2	1	—	3 (4)
Warthin's tumor	14	2	—	16 (19)
Canalicular adenoma	1	—	—	1 (1)
Nonepithelial tumor	—	1	—	1 (1)
Total	75	21	23	120

<sup>a</sup> Includes one case of malignant tumor of the sublingual gland.

**TABLE 4**  
**Histologically Confirmed Salivary Gland Tumors by Radiation Dose and Histologic Type: Life Span Study Cohort, 1950–1987**

Histologic type of tumor	NIC	Radiation dose (Gy)			Unknown
		0–0.09	0.10–0.99	≥ 1.00	
Malignant tumor	8	12	5	8	2
Mucoepidermoid carcinoma	2	2	1	6	1
Adenoid cystic carcinoma	3	4	3	—	1
Polymorphous low grade adenocarcinoma	—	1	—	—	—
Adenocarcinoma	1	1	—	1	—
Carcinoma in pleomorphic adenoma	1	3	—	1	—
Squamous cell carcinoma	1	1	—	—	—
Undifferentiated carcinoma	—	—	1	—	—
Benign tumor	19	38	14	4	10
Pleomorphic adenoma	16	31	9	1	7
Basal cell adenoma	1	1	1	—	—
Warthin's tumor	2	6	3	3	2
Canalicular adenoma	—	—	—	—	1
Lymphangioma	—	—	1	—	—
Total	27	50	19	12	12

NIC: Nonexposed persons who were not in Hiroshima or Nagasaki City at the time of the bombing; Gy: gray.

gray) increased significantly with increasing dose, using a linear dose-response model and Poisson regression as described earlier, for both malignant ( $P < 0.001$ ) and benign ( $P = 0.024$ ) tumors. The rate for mucoepidermoid carcinoma increased significantly with dose ( $P < 0.001$ ), whereas that for all other malignant tumors combined did not ( $P = 0.11$ ). The incidence rate increased significantly with dose for Warthin's tumor ( $P = 0.008$ ), but not for all other

benign tumors combined ( $P = 0.29$ ). No significant variation with respect to malignancy was observed by gender, city, age at diagnosis, or age at the time of the bombing (ATB). There was no evidence that the distribution by site of either benign or malignant tumors varied consistently by radiation dose or by exposure group. The analysis of the data presented in Table 5 is based on all tumors with diagnoses as to behavior and subtype, parallel analyses confined

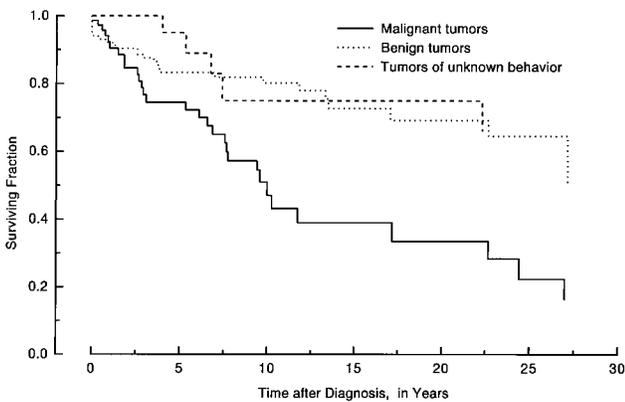
**TABLE 5**  
Tumor Cases and Rates by Exposure Group and Tumor Type: Life Span Study Cohort, 1950–1987

		Exposed, with dose estimates (Kerma interval, in Gy)					<i>P</i> value for trend)	Unknown dose
		NIC	0–0.09	0.10–0.49	0.50–0.99	1.00+		
Mean sievert <sup>a</sup>		0	0.015	0.264	0.831	2.607		
Malignant neoplasms	Cases	8	18	2	3	8	(<0.001)	2
	Rate <sup>b</sup>	12.1	11.1	6.5	32.5	98.0		11.6
Mucoepidermoid carcinoma	Cases	2	4	0	1	6	(<0.001)	1
	Rate	2.6	2.5	0	9.4	67.3		6.1
Other cancer	Cases	6	14	2	2	2	(0.11)	1
	Rate	9.9	8.7	7.2	23.3	25.9		5.6
Benign neoplasms	Cases	20	44	10	5	5	(0.024)	10
	Rate	28.0	27.2	31.0	51.6	56.0		50.0
Warthin's tumor	Cases	2	6	2	1	3	(0.008)	2
	Rate	2.9	3.7	6.5	10.3	31.9		10.2
Other benign tumors	Cases	18	38	8	4	2	(0.29)	8
	Rate	25.4	23.5	24.6	41.1	22.6		39.7

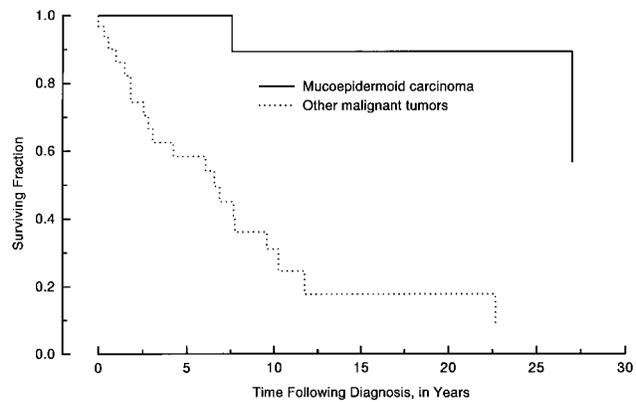
Gy: gray; NIC: nonexposed persons who were not in Hiroshima or Nagasaki City at the time of the bombing.

<sup>a</sup> Neutron-weighted Kerma.

<sup>b</sup> Rates per 10<sup>6</sup> per year indirectly standardized to the city, gender, and age distribution of the 0–0.09-gray kerma group.



**FIGURE 1.** Survival curves for death from any cause, adjusted for city, gender, age at the time of the bombings and (age ATB), and attained age. Curves were standardized to represent individuals 30 years of age ATB and 55 years of age at diagnosis. Tumors are of malignant, benign, and unknown behavior.



**FIGURE 2.** Survival curves for death from salivary gland carcinoma adjusted for city, gender, age at the time of the bombings (age ATB), and attained age. Curves were standardized to represent individuals 30 years of age ATB and 55 years of age at diagnosis. Shown are curves for mucoepidermoid carcinoma versus other malignant tumors.

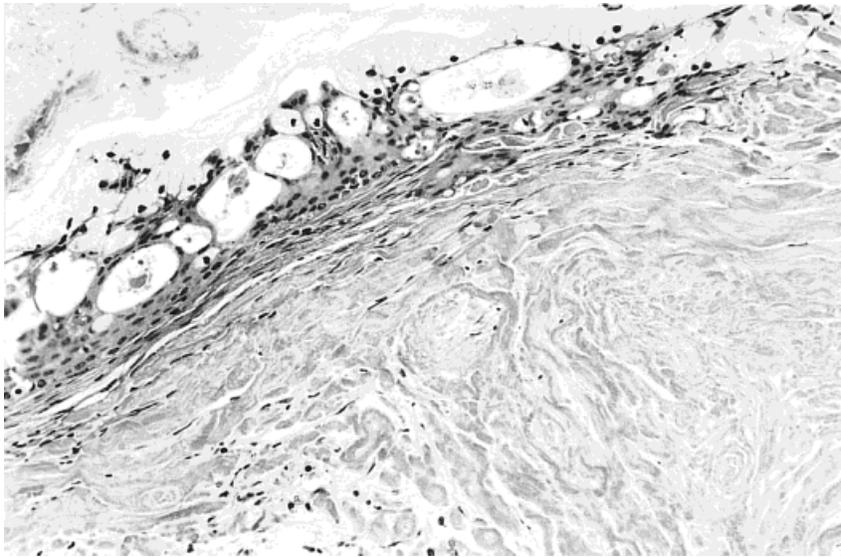
to histologically confirmed diagnoses gave similar results (data not shown).

**Survival Analysis**

Figure 1 shows survival curves for death from any cause, adjusted for city, gender, age ATB, and attained age and standardized to 30 years of age ATB and 55 years of age at diagnosis. Separate curves are given for benign and malignant tumors, and for tumors of unknown behavior. Significant variation in all-cause mortality was observed by behavior (*P* = 0.001), with the greatest mortality for malignant tumors. Estimated

median survival was 9 years for malignant tumors and >27 years for other neoplasms.

There was a marked, and significant (*P* = 0.002), survival difference (all causes of death) between mucoepidermoid carcinomas (median, 25 years) and other malignant tumors (median, 6 years; data not shown). The difference was especially marked in analysis restricted to mortality from salivary gland carcinoma (Figure 2), for which there were only two deaths from salivary gland carcinoma among the 14 mucoepidermoid cases (including 2 diagnoses based on pathology reports without examination of tissue by the



**FIGURE 3.** Mucoepidermoid carcinoma of the left parotid gland seen in a 66-year old female, exposed at 29 years of age in Hiroshima (radiation dose 2.23 gray). (H & E, original magnification  $\times 215$ ) (Courtesy of Hiroshima Chuden Hospital, Dr. K. Nakamura, Director).

present investigators) versus 20 among the 27 other malignant cases. By contrast, for benign tumors there was little evidence of survival differences by histologic type. In particular, there was no statistically significant survival difference between Warthin's tumor and other benign tumors ( $P = 0.65$ ; analysis not shown).

#### Case Report

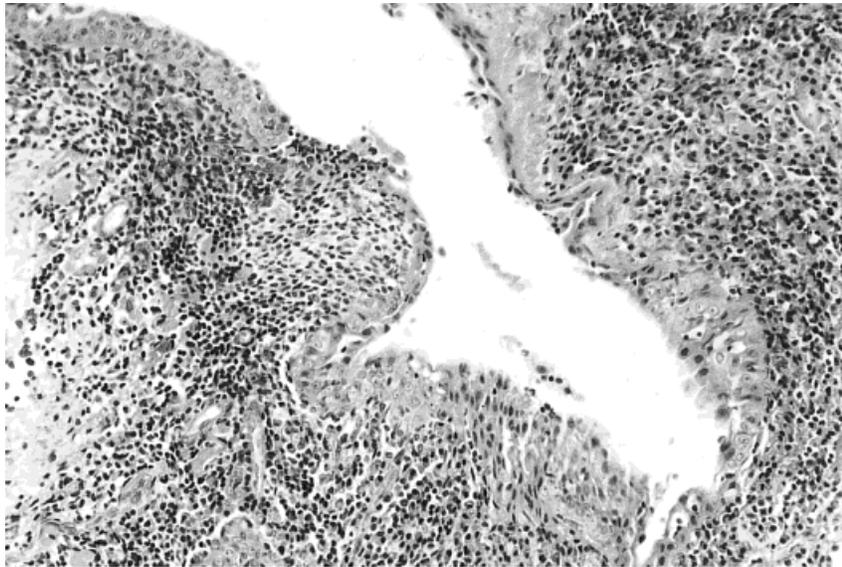
Of special interest for the current study was a case of the 66-year-old female (exposed in Hiroshima at age 29, estimated dose of 2.23 Gy). A mucoepidermoid carcinoma of the parotid was observed in an extensive stromal hyaline degeneration and dense lymphocytic infiltration in the tumor periphery, suggesting that a preexisting or coexisting Warthin's tumor had been largely replaced by the carcinoma. Figure 3 shows the tumor, located in the left parotid gland, that had persisted for as long as 20 years without increasing in size. When surgically removed, it measured approximately 2.0 cm in greatest dimension and enclosed a concrete nodule in the tumor. There were mucous and intermediate tumor cells proliferating along a cystic lumen of the mucoepidermoid tissue. Figure 4 shows a Warthin's tumor-like lesion at the periphery of the same specimen shown in Figure 3. There is a cystic space lined by several rows of oncocytic epithelial cells in the lymphoid stroma.

#### DISCUSSION

The current study was intended to provide an extended ascertainment of salivary gland tumor cases

beyond those regularly reported to the tumor and tissue registries in Hiroshima and Nagasaki. Comparison of the current findings with previous series is useful for understanding the significance of the newest data. The previous case series reported by Belsky et al.<sup>18,19</sup> included 30 cases (9 malignant and 21 benign) of salivary gland tumors for the period 1957–1970. For the same period, the current study identified 55 cases (16 malignant, 30 benign, and 9 of unknown behavior), almost as twice as many cases as reported by Belsky et al. This reflects the recent rebuilding and improvement of the tumor registries that served as the primary source of the cases for the current study. Of the 55 cases in the current study, 7 malignant and 11 benign tumors were included in the series by Belsky et al.<sup>18,19</sup> Two of the nine malignant tumors in the series by Belsky et al. were rejected because of a metastatic nature, and one tumor previously classified as benign was judged to be of unknown behavior, whereas no tissues or relevant records were available for review for ten of the benign tumor cases in the previous series. (After the completion of the study, two cases with pleomorphic adenoma from the series by Belsky et al.<sup>18,19</sup> were confirmed, both with exposure of  $<0.10$  Gy).

The most recently published tumor registry incidence report<sup>20</sup> covered the period 1958–1987 and was limited to malignant tumors of the major salivary glands. For the same period, the current study identified two cases of malignant tumor of the major salivary glands that were not included in the tumor registry



**FIGURE 4.** Warthin's tumor-like lesion seen at the periphery of the tumor shown in Figure 3 (H & E, stain original magnification  $\times 205$ ) (Courtesy of Hiroshima Chuden Hospital, Dr. K. Nakamura, Director).

report. In the tumor registry, one of these cases was coded as having a benign (fibrous mixed) tumor of the parotid gland whereas the pathology panel's diagnosis was that of mucoepidermoid carcinoma; the other case was registered as pending due to insufficient information but proved to be a malignant tumor case based on additional data obtained from the hospital. Conversely, the current pathology panel concluded that seven cases included in the tumor registry series did not have a malignant tumor of the major salivary gland. According to the panel's diagnoses, six cases had malignant tumors in the major salivary regions but with no clear evidence that the primary was in the salivary gland, or with evidence suggesting a metastatic lesion from nonsalivary tissues. One case had a squamous carcinoma of the tongue and another had an adenocarcinoma of the head/neck region. Some of the discrepancies between the tumor registry and panel diagnoses, even though relatively minor, indicate the value of site specific studies of this kind for the continuing refinement of the registries. Comparison of the current series in the fixed LSS cohort with those reported by Takeichi et al.<sup>21-23</sup> is not relevant because the latter cases were derived from the open general population of Hiroshima.

Compared with other published case series of salivary gland tumors, the current series has a lower proportion of parotid gland tumors and higher proportions of submandibular and minor salivary gland tumors (Table 6). The distribution of the present salivary gland tumor cases differs significantly from that of the

other three, as a group, with respect to each of these three proportions ( $P < 0.005$  for each comparison using a simple fourfold contingency table analysis). The literature also indicates that common types of malignant salivary tumors are mucoepidermoid carcinoma, acinic cell carcinoma, and adenoid cystic carcinoma whereas the majority of benign tumors are of a mixed tumor type.<sup>2,8,11,15</sup> Table 7 presents the distribution by specific histologic types, limited to parotid gland tumors, for the current and other published series. The ratio of malignant to benign tumors was 12:63 (1:5.3) for these tumors in the current series, which is comparable to the range observed by the other series, from 1:4.7 (Stockholm)<sup>32</sup> to 1:7.9 (Edinburgh).<sup>33</sup> The relative frequencies of mucoepidermoid carcinoma and Warthin's tumor are remarkably higher in the LSS series than in the others, a finding of special interest in view of the results regarding variation with respect to radiation dose (Table 4).

The statistically significant tendency in the current series for mucoepidermoid carcinomas to predominate among malignant tumors at higher radiation dose levels lends considerable weight to the impression gained from other irradiated series that it is the principal histologic type of radiation-related salivary gland carcinoma. The increasing trend with increasing dose in the ratio of Warthin's tumor to other benign tumors suggests that, if benign tumor risk is associated with radiation dose, Warthin's tumor may be the predominant radiation-related type.

Schneider et al.<sup>8,9</sup> reported on eight malignant sali-

**TABLE 6**  
Salivary Gland Epithelial Tumor Cases: Current Series versus Three Large International Series

Tumor site	Current study <sup>a</sup>	Stockholm <sup>b</sup>	New York <sup>c</sup>	London <sup>d</sup>
Parotid gland	92 (64)	2158 (86)	315 (86)	1756 (73)
Submandibular gland	24 (17)	170 (7)	23 (6)	257 (11)
Sublingual gland	1 (1)	—	1 (0.3)	7 (0.3)
Minor salivary glands	26 (18)	185 (7)	27 (7)	336 (14)
Others	1 (1)	—	—	54 (2)
Total	144 (100)	2513 (100)	366 (100)	2410 (100)

<sup>a</sup> One case of nonepithelial tumor of the submandibular gland was excluded.

<sup>b</sup> Patients treated at the Radiumhemmet and Karolinska sjukhuset during 1919–1969; histologically reclassified cases, Eneroth.<sup>32</sup>

<sup>c</sup> Patients seen at the New York Hospital during 1948–1968; histologically verified cases, Sharkey.<sup>33</sup>

<sup>d</sup> Cases registered with the British Salivary Gland Tumor Panel from 1975–1984; histologically verified cases, Eveson and Cawson.<sup>34</sup>

<sup>e</sup> Major salivary gland tumor, site unknown.

**TABLE 7**  
Parotid Gland Tumors by Histologic Type: Current Series versus Three Large International Series

Histologic type of tumor	Current study	Stockholm <sup>a</sup>	Edinburgh <sup>b</sup>	London <sup>c</sup>
Malignant tumor	12 (100)	378 (100)	33 (100)	258 (100)
Acinic cell carcinoma		66 (17)	5 (15)	44 (17)
Mucoepidermoid carcinoma	6 (50)	88 (23)	13 (39)	26 (10)
Adenoid cystic carcinoma	1 (8)	49 (13)	3 (9)	35 (14)
Adenocarcinoma	1 (8)	52 (14)	9 (27)	46 (18)
Carcinoma in pleomorphic adenoma	1 (8)	32 (8)	1 (3)	56 (22)
Malignant mixed tumor			2 (6)	
Squamous cell carcinoma	2 (17)	7 (2)		19 (7)
Undifferentiated carcinoma	1 (8)	84 (22)		32 (12)
Benign tumor	63 (100)	1780 (100)	261 (100)	1498 (100)
Pleomorphic adenoma	46 (73)	1658 (93)	223 (85)	1111 (74)
Basal cell adenoma	2 (3)			125 (8)
Myoepithelioma			3 (1)	
Oxyphilic adenoma		21 (1)	1 (0.4)	16 (1)
Warthin's tumor	14 (22)	101 (6)	34 (13)	246 (16)
Canalicular adenoma	1 (2)			
Total	75	2158	294	1756

<sup>a</sup> Patients treated at the Radiumhemmet and Karolinska Sjukhuset during 1919–1969, histologically reclassified cases, Eneroth.<sup>32</sup>

<sup>b</sup> Cases seen or treated at the South East Scotland Radiotherapy Service from 1950 to 1965; histologically confirmed cases, Main et al.<sup>35</sup>

<sup>c</sup> Cases registered with the British Salivary Gland Tumor Panel from 1975–1984; histologically verified cases, Eveson and Cawson.<sup>34</sup>

vary gland tumors among patients who had received radiation therapy to the tonsils and nasopharynx; seven were mucoepidermoid carcinomas. There were also 19 benign tumors, including 17 mixed tumors, 1 Warthin's tumor, and 1 ductal adenoma. Observed numbers of both malignant and benign tumors were very high compared with expectation based on population rates, although a case-finding effort may have been responsible for some of this difference, as it apparently was for thyroid tumors in the same group of patients. Katz and Preston-Martin<sup>11</sup> identified 11 salivary gland carcinoma patients with a history of radiation treatment; there were 6 mucoepidermoid carcinomas, 3 adenoid cystic carcinomas, 1 lymphoma,

and 1 unspecified malignant tumor. Nineteen of the 20 benign tumors were mixed tumors.

Several other reports suggested the preponderance of mucoepidermoid carcinoma among radiation-related salivary gland carcinoma cases.<sup>36–41</sup> Spits et al.<sup>37</sup> found 25 cases of mucoepidermoid carcinoma among 57 salivary gland carcinomas after medical irradiation. Twelve of the cases of mucoepidermoid carcinoma had histories of previous benign salivary gland tumors. Warthin's tumor was one of the more common tumors of the salivary gland, and showed bilaterally synchronous as well as metachronous development or unilateral multiple development.<sup>42</sup> The possibility of reactive histogenesis, including delayed

hypersensitivity or inflammation, has been the subject of debate for this particular tumor in relation to frequent multiple tumor development.<sup>43,44</sup> It is of interest to note that approximately 1% of Warthin's tumors can transform to malignant tumors including mucoepidermoid carcinoma,<sup>43</sup> and some reports describe patients with mucoepidermoid carcinoma of the parotid gland, arising in or simultaneously with Warthin's tumor.<sup>45-47</sup>

The two tumor types singled out in the current series by the analyses with respect to radiation dose were associated in one high dose case with a long-standing clinical history of a left parotid tumor. It appeared from histologic evidence that a preexisting or coexisting Warthin's tumor had been replaced largely by a mucoepidermoid carcinoma and had remained a lesion of cystic space lined by eosinophilic epithelial cells, surrounded by lymphoid stroma.

Five-year survival rates for salivary gland carcinoma are neither high nor low relative to other sites (e.g., 47.8% compared with 56.3% for all sites except basal and squamous cell carcinomas of the skin among U.S. residents<sup>48</sup>), but the likelihood of eventual mortality from this disease is fairly high. The mortality consequences of benign salivary gland tumors are far less serious. Survival analyses by tumor behavior and histologic type suggest that, in the current series, survival for the predominant radiation-related carcinoma, mucoepidermoid carcinoma, is significantly higher than that for other malignant salivary gland tumors, and not much less than that for benign tumors.

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