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Growth Rate of Head and Neck Tumors

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Abstract—*The actual doubling time for 17 local recurrences of head and neck tumors was calculated by use of the method of Philippe and LeGal. The median value of* 9.5 days *placed them in the class of fast-growing tumors. Site and age did not seem to influence their growth; instead, they seemed to grow faster in females than in males. Comparison between doubling times of local recurrences and pulmonary metastases collected from the literature showed a statistically significant difference: pulmonary metastases grow slower.*

INTRODUCTION

HEAD AND neck tumors represent a well-known group of tumors whose distinction is based on the site of the primary cancer rather than histologic type, which is almost always squamous cell carcinoma[1]. Their aggressiveness is mainly locoregional, and death usually results from local progression of the cancer rather than from distant metastasis. Prognosis depends on the size of the primary and on the degree of lymph node involvement: the worst prognosis is when the size of the primary is more than 4 cm and regional lymph nodes are extensively involved[1, 2]. The growth rate of these tumors has already been calculated on their pulmonary metastases[3–9]. Several studies on cell kinetics of the primary have been carried out[10–12], but no evaluation was made on their actual doubling time (DT).

The aim of this study was to investigate this biologic characteristic of head and neck tumors.

MATERIALS AND METHODS

Seventeen cases of local recurrences were selected from the case material of head and neck tumors of patients admitted to the Istituto Nazionale Tumori of Milan from 1971 to 1977 and previously treated with surgery alone. These were available for the study of DT, according to the criteria of Philippe and LeGal[13], because pathologic size of recurrences and date of previous treatment were precisely recorded. The actual DT was calculated by applying the formula of exponential growth:

$$DT = \frac{0.69315}{b}, \quad \text{and} \quad b = \frac{\ln V_1 - \ln V_0}{T_1 - T_0},$$

where V_0 is the volume of one cell, the first cell of the recurrence at time T_0 of previous treatment, and V_1 is the pathologic volume of the recurrence at time T_1 as measured on the specimen of the subsequent surgical treatment.

Table 1 shows the distribution of the 17 cases according to sex, age, site, histologic type and DT value. The male : female ratio of 3.5 : 1 and the range of ages (males, 34–73, and females, 45–81) are consistent with data reported in epidemiologic studies. The most represented sites were the lips (7 cases) and the tongue (4 cases).

From the literature 27 DT values of pulmonary metastases of head and neck tumors were collected, to which 4 personal observations were added. Table 2 reports the distribution of these cases according to site, authors and DT values. Age and sex are not mentioned because of the incomplete data reported by the different authors.

The histologic type of all but 2 recurrences (cases 3 and 11) was epidermoid carcinoma. Histology of the other 2 cases was adenocystic carcinoma. The histologic type of the pulmonary metastases is not mentioned because it was reported only by a few authors.

Comparisons were made between DT distribution according to site, sex and age, and

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Table 1. Characteristics of 17 local recurrences

	Site	Age	Sex	Histologic type	DT (days)
1	Lower lip	50	M	Squamous cell ca.	2.8
2	Lower lip	73	M	Squamous cell ca.	7.4
3	Upper lip	63	M	Adenocystic ca.	7.8
4	Lower lip	50	M	Squamous cell ca.	11.4
5	Lower lip	43	M	Squamous cell ca.	15.7
6	Lower lip	74	M	Squamous cell ca.	28.6
7	Lower lip	34	M	Squamous cell ca.	107.0
8	Tongue	45	F	Squamous cell ca.	4.7
9	Tongue	51	F	Squamous cell ca.	6.3
10	Tongue	83	F	Squamous cell ca.	7.1
11	Tongue	67	M	Adenocystic ca.	10.0
12	Floor of mouth	73	M	Squamous cell ca.	2.6
13	Floor of mouth	59	M	Squamous cell ca.	3.7
14	Floor of mouth	42	M	Squamous cell ca.	11.2
15	Gingiva	80	F	Squamous cell ca.	7.2
16	Retromolar trigon	67	F	Squamous cell ca.	9.7
17	Larynx	53	M	Squamous cell ca.	10.8

Table 2. DTs of pulmonary metastases from 31 head and neck tumors reported in the literature

Site	Reference	DT (days)
Lip	5	143
Floor of mouth	6, 23	22, 55
Tongue	2, 6, 7	20, 32, 220, 320
Hypopharynx	1, 6	15, 35, 40, 100
Oropharynx	6, 11	25, 270, 45, 45, 60, 70, 85
Larynx	5-7, 11, 12, 16	37, 44, 44, 41, 41, 60, 114, 157, 40, 40, 32, 48, 96

between DT of local recurrences and pulmonary metastases by use of the nonparametric test of Wilcoxon.

RESULTS

The comparison between DTs of cancer of the two most represented sites, lips and tongue, did not show any statistically significant difference (Table 3). Similarly, no statistically significant difference was found when DTs were distributed according to two age groups (Table 4), younger and older than 60 years. Instead, there was a statistically significant difference between the DTs distributed according to sex: females presented the smallest DT values (Table 5).

Finally, the comparison between DTs of local recurrences and pulmonary metastases showed a highly significant statistical difference: local recurrences had the smallest DT values (Table 6).

DISCUSSION

Local recurrences are like primary tumors in that they arise from the same anomalous clonogenic cells. Their behavior can thus be assumed as a useful mode to investigate the characteristics of primary cancer. It is not easy to carry out precise and successive measurements of primary localizations of head and neck tumors. Therefore, the method of Phillippe and LeGal[13] applied to local recurrences allowed us to overcome this obstacle.

Our study concerns a limited number of head and neck tumors, all but two of the same histologic type. However, their distribution according to sex and age was not different from that obtained in epidemiologic studies[1].

Table 3. Comparison between DTs of local recurrences of cancers of the lips and tongue

Site	No. of cases	DT (days) Range	DT (days) Median	Wilcoxon test
Lips	7	2.8 – 107.0	11.4	
				P > 0.1
Tongue	4	4.7 – 18.9	6.8	

Table 4. Comparison between DTs of local recurrences of head and neck tumors distributed according to 2 age groups

Age (yr)	No. of cases	DT (days) Range	DT (days) Median	Wilcoxon test
< 60	9	2.8 – 107.0	18.8	
				P > 0.05
> 60	8	2.5 – 28.6	8.5	

Table 5. Comparison of DTs of local recurrences of head and neck tumors distributed according to sex of patient

Sex	No. of cases	DT (days) Range	DT (days) Median	Wilcoxon test
Male	12	2.54 – 107.0	10.4	
				P < 0.05
Female	5	4.70 – 9.7	7.1	

Table 6. Comparison between DTs of 17 local recurrences and 31 pulmonary metastases of head and neck tumors

Localization	No. of cases	DT (days) Range	DT (days) Median	Wilcoxon test
Local recurrences	17	2.5 – 107.0	9.7	
				P < 0.001
Pulmonary metastases	31	15.0 – 320.0	45.0	

Their median DT value characterizes them as a fast-growing disease, and places them in the same group with soft tissue sarcomas[14], embryonal tumors[5, 15, 16] and hemato-sarcomas[17]. Cell kinetic studies confirm this interpretation. Tubiana and Malaise[12] studied 16 squamous cell carcinomas of the floor of the mouth with the technique of continuous labeling by the intra-arterial injection of 2 mCu/day for 6 to 20 days of tritiated thymidine. After 1 pulse the mean labeling index (LI) was 15%, and after 40 hr of continuous labeling the mean LI increased to 57%, but with individual cumulative LIs ranging from 25 to 97%. This means that the proportion of proliferating cells of these tumors during a short time is as high as we can expect in a fast-growing tumor. Apparently, site and age are not associated with growth rate; instead, these cancers seem to present a faster growth in females than in males.

The difference in growth rate between local recurrences and pulmonary metastases is noteworthy. Some criticisms can be made about different methods with which the two DT value groups were calculated, but the incidental over-evaluation of the method of Philippe and LeGal does not by itself explain these noticeable differences. We have to accept the existence of a real difference in growth characteristics between primary and secondary localizations of head and neck tumors. This difference is the same found between primary and pulmonary localizations of soft tissue sarcomas[18], which creates some doubt about previous conclusions on the relationship between growth rates of primary and secondary neoplasms[19]. Moreover, the potential DTs of 8.9 days for tongue cancer[11], 8.5 days for laryngeal cancer[11] and 6 days for squamous cell carcinoma[20] are not too different from the calculated values of actual DT of our case material of local recurrences.

It was not possible to evaluate the prognostic significance of DT on so small a case material. A prognostic significance of DT, in terms of survival, can be more easily assessed with reference to different classes of growth when the disease is no longer localized. However, Table 7 reports the distribution of DTs in 7 patients of our series who have died: the rank-

Table 7. Distribution of DTs and survival time of 7 deceased patients

Histologic type	DT (days)	Survival (months)
Squamous cell ca.	2.5	8
"	4.7	15
"	7.0	26
"	9.7	54
"	11.4	60
Adenocystic ca.	9.8	17
"	10.0	45

ing in terms of DT values within a histologic type corresponds exactly to the ranking by survival.

The review of DTs of pulmonary metastases from the literature offers another interesting observation: the median value of the 13 DTs of laryngeal metastases was about 40 days. This is very suggestive because it allows the characterization of laryngeal tumor metastases in quantitative terms and distinguishes them from primary lung cancers of identical histology[3, 8, 21–24] that arise in laryngeal cancer patients.

CONCLUSIONS

Because of the small size of our case material of head and neck tumors, our observations on their growth rate are only a stimulus to probe into the biologic characteristics of these tumors. We can thus conclude that head and neck tumors prevalently seem to be fast-growing, site and age evidently do not influence their growth, they seem to grow faster in females than in males and their pulmonary metastases grow much slower than local recurrences. The quantitative characteristics of pulmonary metastases of laryngeal tumors seem well-defined and permit them to be distinguished from primary epidermoid lung cancers.

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