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Prognosis of salivary adenocarcinomas

A retrospective study of 52 cases with special regard to cytochemically assessed nuclear DNA content* **

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Summary. 52 salivary adenocarcinomas of the years 1965–1980 from the files of the Salivary Gland Registry, Institute of Pathology, University of Hamburg, were evaluated retrospectively with regard to clinical follow up and cytochemically assessed nuclear DNA content. The age distribution showed a peak from the 6th to 8th decade (range 3 to 87 years). The m:f ratio was 1:1.36, the mean age was 59.3 years. Over 80% of the tumours were located in the major salivary glands. The clinical course was characterized by metastases present at initial diagnosis (16 cases), subsequent development of metastases (9 cases), local recurrence (15 cases) or death from tumour (10 cases) and was related to differentiation, grade 3 tumours showing the worse clinical courses. In 37 cases, nuclear DNA content was determined by a single scanning cytophotometry device. 28 cases were diploid, 9 were atypical. The clinical course was significantly related to the histogram type, atypical tumours showing a dismal prognosis.

Key words: Adenocarcinomas – Nuclear DNA content – Prognosis – Salivary glands

Introduction

Adenocarcinomas of the salivary glands are a poorly defined group of neoplasms that include papillary, mucus producing, tubular, trabecular and solid tumours (Main et al. 1976; Seifert and Schulz 1985; Seifert et al. 1980; Spiro et al. 1982; Stene and Koppang 1981). They differ from mucoepidermoid carcinomas, acinic cell carcinomas and adenoid cystic carcinomas (Seifert et al. 1986; Stene and Koppang 1981). As many of the gland forming salivary carcinomas cannot be separated into categories, some authors refer to them simply as adenocarcinomas and regard histological and cytological grading as more important for prognosis than morphological architecture of subtypes (Spiro et al. 1982). Other criteria that have been used for grading of malignancy are invasive and non-invasive growth patterns (Blanck et al. 1971). Prognosis is in general related to differentiation, although this is not acknowledged by all authors (Stene and Koppang 1981; Seifert et al. 1986).

As general prognostic criteria obtained from evaluation of tumour collections cannot be easily applied to individual cases, further information on the biological behavior of individual neoplasms is desirable for the choice of an adequate therapy. A further method for determining the clinical aggressiveness of tumours is the cytochemical assessment of nuclear DNA content. A better clinical course for malignant disease is often associated with a nuclear DNA content comparable to normal diploid cells, whereas clinically more aggressive tumours often show an atypical DNA distribution pattern (Auer et al. 1989; Sandritter et al. 1966). For salivary gland tumours, this is true for mucoepidermoid carcinomas, but not for acinic cell carcinomas or epithelial-myoepithelial carcinomas (Hamper et al. 1989a, b, c).

In the present investigation, the salivary adenocarcinomas documented in the files of the Salivary Gland Registry in Hamburg were used for a retrospective study in order to determine the correla-

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** Dedicated to John James Frost of Baltimore, Maryland on the occasion of his 50th birthday

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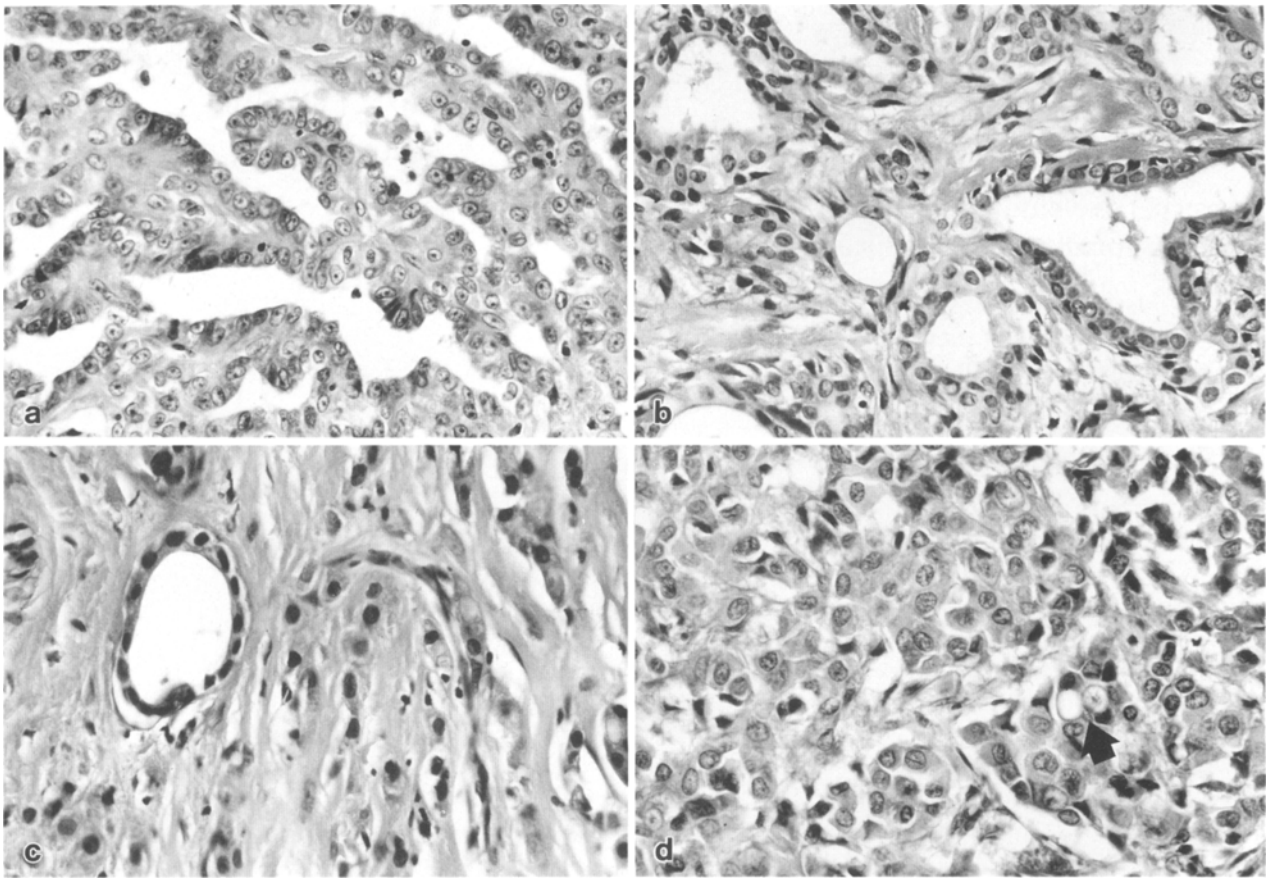


Fig. 1. Histology of adenocarcinomas. **a** papillary type with highly differentiated papillary proliferations and relatively uniform cells and nuclei (grade 1), HE, ×210. **b** tubular type with duct like proliferations of varying shape and a higher degree of cellular anaplasia (grade 2), HE, ×210. **c** tubular type with primitive ductular proliferations and pronounced hyperchromasia and pleomorphism (grade 3), HE, ×210. **d** solid type with only residual lumina with scanty mucus production (*arrow*) and marked cellular pleomorphism (grade 3), PAS, ×210

tion between epidemiological, histomorphological and in particular cytochemically assessed nuclear DNA parameters, in the prognosis of these rare neoplasms.

Materials and methods

Slides of salivary adenocarcinomas from the Salivary Gland Registry at the Institute of Pathology, University of Hamburg, FRG, were reviewed and reclassified. When paraffin blocks were available, additional sections were cut. Tumour material was stained by haematoxylin and eosin, periodic acid – Schiff, and astrablue. Papillary, tubular, trabecular and solid forms were distinguished (Seifert et al. 1986; Fig. 1). In accordance to Bloom and Richardson (1957) tumours were graded into high differentiation (grade 1), intermediate differentiation (grade 2) and poor differentiation (grade 3), groups depending on differentiation of glandular structures, cellular anaplasia and mitotic rate. Tumours were regarded as highly differentiated when there were well marked tubular or papillary growth patterns with more or less regular arrangements of cells, when cellular pleomorphism was mild, and when only a slight increase of mitotic rate could be noted. Conversely, tumours were regarded as poorly differentiated when glandular structures were only primitively developed with highly irregular arrangements of cells, when pleomorphism was marked and mitotic rate was high. Of the 4068 salivary gland tumours documented from 1965 to 1987 in the registry, 101 were adenocarcinomas, representing 2.5% of all tumours and 9.1% of malignant tumours. For reasons related to clinical follow up only adenocarcinomas received during the years 1965 to 1980 were included in the study. 52 cases were thus available.

Letters were sent to clinicians and pathologists having contributed cases during the time period mentioned above in order to assess the clinical course. Tumour size, localization, date of primary diagnosis, tumour recurrences, metastases, deaths from tumour or from other causes, and therapy were questions of interest. In some cases, no information was available, in other cases, there was only incomplete information since numerous cases had been contributed from physicians all over Germany and other European countries.

Feulgen staining was performed in the following manner: From the tissue blocks, sections of 8 µm were cut on a Reichert microtome. Deparaffination and rehydration was done in xylene and descending alcohol concentrations, followed by acid hydrolysis (1 M hydrochloric acid [HCl], 60° C for 6 min), after which sections were washed in distilled water. Slides were incu-

bated in Schiff's reagent (90 min, room temperature) and washed again, first in distilled water, then three times in sulfide washing solution (10 ml sodium disulfite [$Na_2S_2O_5$], 10 ml 1 M HCl, 180 ml distilled water), rinsed under running tap water, dehydrated in ascending alcohol concentrations and xylene and finally mounted in Eukitt (Kindler, Freiburg, FRG, refractory index 1.494).

A single cell scanning cytophotometry device was chosen for the cytochemical nuclear DNA assessment of tumour cell nuclei (MPV Compact Scanning Microscope Photometer [Leitz, Wetzlar, FRG], combined with a Eurocos Microcomputer [EES-GmbH, Munich, FRG]). By this procedure, it was possible to identify tumour cells by their morphological appearance before measuring their DNA content (Auer and Tribukait 1980; Caspersson et al. 1983). In all but two cases, 100 tumour cell nuclei were evaluated. For technical reasons only 50 nuclei could be evaluated in two cases. The clinical course of the disease was not known to the examiner. The histograms were standardized by the mean diploid DNA value of 100 salivary duct epithelium nuclei (Hamper et al. 1987) and interpreted graphically. Additionally, the nuclear size parameters calculated by the computer program were evaluated.

Results

The age distribution diagram showed a peak from the 6th to 8th decade (Fig. 2). At primary diagnosis, the youngest patient was 3 years, the oldest 87 years old. There was a female preponderance with a m:f ratio of 1:1.36, 22 patients (42.3%) being male and 30 (57.7%) being female. The mean age was almost equal in males (59.3 years) and females (59.2 years).

Most of the tumours were located in the major salivary glands, the parotid being the most frequent site (Table 1). The histological differentiation showed distributional differences with regard to localization (Table 2). While grade 3 tumours were more common in the major salivary glands, they were absent in the minor glands. Most tumours measured between 2 and 4 cm at primary diagnosis (Table 3). Almost every tumour larger than 4 cm was grade 3, the other sizes showed no striking correlation with differentiation.

Table 4 demonstrates the clinical course. Local recurrences occurred in fifteen cases, metastases were present at initial diagnosis in sixteen cases, and developed in the course of the disease in nine cases. Distant metastases were located in lung, bone, brain and liver. Four patients had no evidence of disease after treatment of local recurrence and two patients were alive with tumour at the end of follow up. Ten other patients died of their tumour. The clinical course was defined as "favorable" when there was no tumour manifestation besides the primary and no recurrence, and as unfavorable when there were metastases at primary diagnosis, or the development of metastasis during the course of the disease, or local recurrences. Kaplan-Meier curves (Kaplan and Meier 1958) regarding overall survival and occurrence of recurrences and metastasis arising as late as 80 months after primary diagnosis, are shown in Fig. 3. Mean time of follow up was 78 months (range 2–204 months).

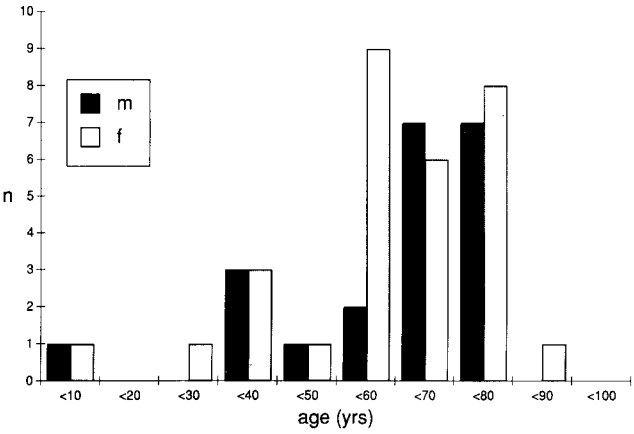


Fig. 2. Age and sex distribution of salivary adenocarcinomas ($n = 52$)

Table 1. Localization of tumours ($n = 52$)

Localization	*n*	%
Major salivary glands	43	82.7
Parotid gland	34	65.4
Submandibular gland	8	15.4
Sublingual gland	1	1.9
Minor salivary glands	9	17.3

Table 2. Tumour differentiation and localization ($n = 52$)

Grade	1 %	2 %	3 %
Major salivary glands	11 (25.6)	12 (27.9)	20 (46.5)
Parotid gland	10 (29.4)	9 (26.5)	15 (44.1)
Submandibular gland	1 (12.5)	3 (37.5)	4 (50.0)
Sublingual gland	–	–	1 (100.0)
Minor salivary glands	2 (22.2)	7 (77.8)	–
Total	13 (25.0)	19 (36.5)	20 (38.5)

Table 3. Tumour size and histological grade ($n = 52$)

Grade	1	2	3	Total
–1 cm	1	1	2	4
–2 cm	5	7	5	17
–4 cm	5	8	4	17
>4 cm	1	–	7	8
No information	1	3	2	6
Total	13	19	20	52

Table 4. Tumour grade and clinical course (multiple appearance of cases possible, for example Recurrence and Death from tumour)

Grade	1		2		3		Total	
	n	%	*n*	%	*n*	%	*n*	%
No recurrence	5	41.7	10	62.5	1	6.25	16	36.4
Recurrence	6	50.0	3	18.8	6	37.5	15	34.1
Initial metastasis	2	16.7	4	25.0	10	62.5	16	36.4
Late metastasis	2	16.7	–		7	43.8	9	20.5
No evidence of disease after recurrence	3	25.0	1	6.25	–		4	9.1
Alive with tumour	–		–		2	12.5	2	4.5
Dead from tumour	2	16.7	1	6.25	7	43.8	10	22.7
Dead from other causes	3	25.0	2	12.5	–		5	11.4
Favorable	5	41.7	10	62.5	1	6.3	16	36.4
Unfavorable	7	58.3	6	37.5	15	93.7	28	63.6
Total	12		16		16		44	

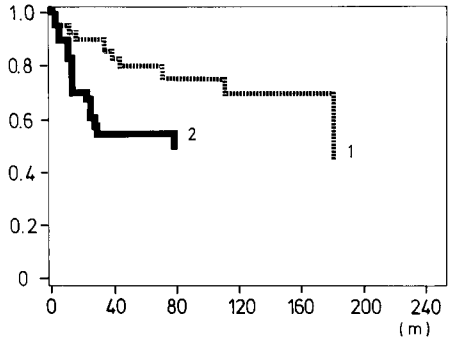
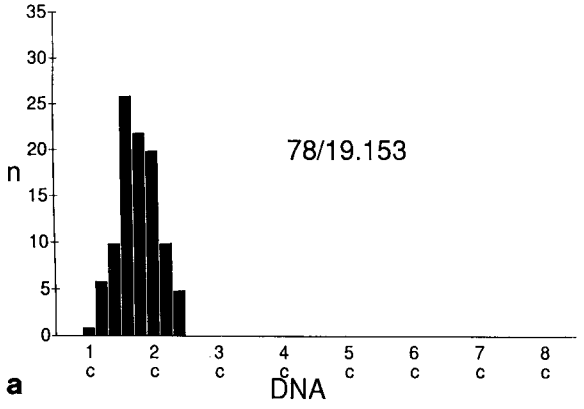


Fig. 3. Kaplan-Meier-Curves of adenocarcinoma collective. (1. Survival. 2. Incidence of recurrences or metastases)



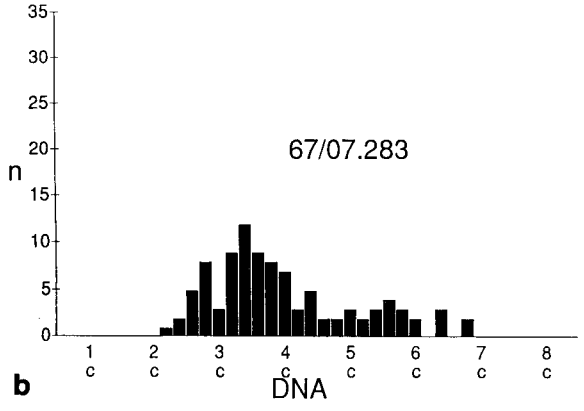


Fig. 4. Typical histograms. **a** diploid type with high peak in the 2c region. **b** atypical type with flattening and spread to the right

In 37 tumours, nuclear DNA content was determined as described above. In one case, material was only available from a recurrence, which should not have affected the result (see Auer et al. 1984). Two different types of histogram were observed (Fig. 4). One showed a single peak in the diploid or neardiploid region or additional single small peaks in the triploid to tetraploid range. Mean values were between 1,6 c and 2,5 c. This type of histogram corresponds to "diploid" nonneoplastic tissue (28 cases). The other showed a distinct flattening of the 2c peak and a considerable spread to the right side of the histogram with important additional peaks in the triploid, tetraploid, pentaploid, hexaploid up to the heptaploid region. Mean values of this group were between 2,12 c and 3,54 c. This type of histogram is regarded as atypical due to high proliferative rates and/or aneuploid stemlines (9 cases).

It was possible to correlate certain tumour characteristics with the clinical course. In 46 cases, the exact tumour size was known and in 39 cases, information on tumour size and clinical course was available (Table 5). The correlation between tumour size and clinical course was not striking, but tumours larger than 4 cm showed an unfavorable course in all cases and the highest percentage of

Table 5. Tumour size and clinical course (divergent case numbers due to incomplete information concerning tumour size)

Tumour size (cm)	−1		−2		−4		>4	
	n	%	*n*	%	*n*	%	*n*	%
No recurrence	1	25.0	6	42.9	8	61.5	–	
Recurrence	1	25.0	6	42.9	3	23.1	2	25.0
Initial metastasis	1	25.0	4	28.6	4	30.8	5	62.5
Late metastasis	2	50.0	2	14.3	2	15.4	2	25.0
No evidence of disease after recurrence	1	25.0	3	21.4	–		1	12.5
Alive with tumour	–		1	7.1	1	7.7	–	
Dead from tumour	1	25.0	4	28.6	1	7.7	3	37.5
Dead from other cause	–		2	14.3	2	15.4	–	
Favorable	1	(25.0)	6	(42.9)	8	(61.6)	–	
Unfavorable	3	(75.0)	8	(57.1)	5	(38.4)	8	(100.0)
Total	4		14		13		8	

deaths from tumour. Differences in clinical course between grade 1 and 2 tumours were not impressive, on the contrary, grade 2 tumours seemed to have a better prognosis in many instances. Grade 3 tumours, however, were prone to metastasis (both initially and late) and to a fatal outcome (alive with tumour present at the end of follow up or dead from tumour) in comparison with grade 1 and 2. The overall prognosis for grade 3 tumours was poor (Table 4). Architectural appearance (e.g. papillary, tubular or solid) showed no apparent relation to prognosis.

50% of the tumours located in the minor glands showed a primarily favorable clinical course and 75% of patients were free of disease at the end of follow up. In contrast, only 33.4% of tumours located in the major salivary glands had a primarily favorable course, and only 58.3% of patients were free of disease at the end of follow up. Comparing histogram type and tumour grade, most, but not all grade 1 tumours were diploid and all grade 2 tumours were diploid whereas only half of the grade 3 tumours had atypical histograms (Table 6a). There was no correlation between histograms and tumour size. The clinical course was significantly related to the histogram type (Table 6b) as 8 tumours with an atypical histogram all showed unfavorable courses and no favorable one (no follow up in the ninth case). The 28 tumours with a diploid histogram showed a heterogeneous clinical behavior (15 favorable and 13 unfavorable courses). Differences between the two cytophotometric groups were significant ($p<0.01$; Fisher's Exact Test). In the diploid group, multiple cases with initial metastasis or no evidence of disease after treatment of a recurrence accounted for the high incidence of unfavorable courses. This becomes evident when comparing the final outcome with histogram type. In eight cases with atypical histograms, all patients died of their tumours, while in 17 diploid cases, all patients were free of disease at the end of follow up (Table 6c). Nuclear size parameters given by the computer program did not yield additional information.

Table 6. Histogram and histological grade (a), clinical course (b), and final outcome (c; divergent case numbers due to incomplete follow up)

	Diploid	Atypical
(a)		
Grade 1	6	2
Grade 2	15	–
Grade 3	7	7
Total	28	9
(b)		
Favorable	15	–
Unfavorable	13	8
No information	–	1
Total	28	9
(c)		
No recurrence	17	–
Dead from tumour	–	8

Discussion

All surgical pathologists occasionally encounter salivary gland tumours. The rarity of these lesions in routine diagnostic practice, however, makes a correct diagnosis often difficult. Prognostic evaluation is even more difficult, as only special reference

centers accumulate series large enough to make reliable statements (Thackray and Lucas 1974; Thackray and Sobin 1972; Seifert et al. 1986). Since histology is sometimes an uncertain variable for the estimation of prognosis, other factors have been sought that might be helpful in obtaining additional information on the biological behavior of malignant tumours. For this purpose, a particularly valuable investigation is the cytochemical DNA assessment of tumour cell nuclei (Auer et al. 1989).

The adenocarcinomas of salivary glands are a heterogeneous tumour group that includes neoplasms of glandular differentiation which differ from mucoepidermoid carcinomas, acinic cell carcinomas and adenoid-cystic carcinomas (Stene and Koppang 1981; Fried 1986). Because of their rarity, the importance of a simple subclassification, for example into tubular, papillary and solid neoplasms, has been stressed (Seifert and Schulz 1985). However, according to other authors, histological subtypes of adenocarcinomas are not different in biological behavior (Chaudhry et al. 1961; Thackray and Lucas 1974), but invasive and non-invasive growth patterns are important criteria for prognostic evaluation (Blanck et al. 1971), and grading (Spiro et al. 1982). In the last years, rarely occuring tumour entities have been recognized, like salivary duct carcinoma, which tends to have a worse prognosis (Araujo et al. 1987; Chen 1983; Chen and Hafez 1981; Fayemi and Toker 1974; Fried 1986; Gal et al. 1985; Garland et al. 1984; Hui et al. 1986), glycogen-rich adenocarcinoma (Lattanzi et al. 1985; Mohamed and Cherrick 1975), oncocytic adenocarcinoma (Goode and Corio 1988) and polymorphous low grade or terminal duct adenocarcinoma of minor salivary glands (Aberle et al. 1985; Allen et al. 1974; Batsakis et al. 1983; Dardick and van Nostrand 1988; Evans and Batsakis 1984; Freedman and Lumerman 1983; Frierson et al. 1985; Gnepp et al. 1988; Mills et al. 1984) and epithelial-myoepithelial duct carcinoma (Donath et al. 1972; Hübner et al. 1969; Corio et al. 1982; Daley et al. 1984; Hamper et al. 1989c; Luna et al. 1985; Palmer 1985). Adenocarcinomas have been classified further by their site of genesis in the ductal system (Luna et al. 1986). These various forms, however, are not yet included in the WHO classification (Thackray and Sobin 1972).

Very little is known about nuclear DNA content of salivary adenocarcinomas. Flow cytometric studies of 2 cases of salivary duct carcinoma, which is regarded by some authors as a distict type of adenocarcinoma, yielded aneuploid histograms compatible with the aggressive clinical behavior of the tumours (Hui et al. 1986). In a case of low grade papillary adenocarcinoma, the histogram was found to have a diploid stemline and small triploid and tetraploid peaks compatible with the usual biological behavior of these tumours (occasional recurrences), although no precise clinical data for this case were given (Olinici and Ecke 1986). Three other cases of adenocarcinoma were studied in 1974, and it was stated that the modal DNA values of the histograms were in keeping with the biological degree of malignancy, although precise clinical data were not given (Eneroth and Zetterberg 1974). It is obvious that these are too few cases with lack of clinical data to establish significant relations between histogram and prognosis.

The epidemiologic data given in other studies are comparable with the present study (Blanck et al. 1977; Main et al. 1976; Spiro et al. 1982; Stene and Koppang 1981). It became evident that a distinction between grade 1 and grade 2 tumours with regard to prognosis is academic, because both groups showed a relatively mild clinical course, although there were quite a few unfavorable courses and even deaths from tumour occured. Grade 2 tumours had a better prognosis than grade 1 tumours which might be explained, by the fact that primary therapy in grade 1 tumours was inadequate due to the relatively benign histological appearance with consequent recurrences and eventual uncontrollable spread of the disease. Grade 3 tumours, however, were characterized by a dismal prognosis with more than 90% of unfavorable courses and multiple deaths from tumour, in contrast to grade 1 and 2. A favorable course and cases without evidence of disease after treatment of local metastases were observed, however. While histological grading can thus be regarded as a good prognostic factor, separating a group of low grade malignancies, corresponding to grade 1 and 2, from a group of high grade malignancy, corresponding to grade 3, the architecture of the tumours is of no apparent use for prognosis.

A correlation of clinical course with tumour size could not be observed, except that tumours larger than 4 cm showed an unfavorable course in all cases, which is in keeping with other observations that attributed a worse prognosis to tumours larger than 3 cm (Hui et al. 1986). Deaths from tumour were also commonest in this group. Localization of tumours showed an influence on prognosis, as those located in the minor salivary glands more often had a favorable course and the patients were more often free of disease at the end of follow up which is consistent with other studies (Seifert et al. 1980).

In this study, the cytophotometric data on a large collection of adenocarcinomas are presented for the first time. The histograms of 37 tumours showed "diploid" patterns in 28 cases and "atypical" patterns in 9 cases. While most of grade 1 and 2 tumours were of the diploid type, corresponding to the relatively benign clinical courses, only 2 grade 1 tumours were atypical. These two were the only two in the grade 1 tumour group that caused the death of patients. In the grade 3 tumours, however, there were 7 diploid and 7 atypical tumours. Of the latter, 6 tumours caused the death of patients (death of unknown origin in the seventh case). No patient with a diploid tumour died of his or her lesion in this group, although two patients were alive with tumour at the end of follow up. The most striking finding arises when comparing the ratio of patients with no evidence of disease (even after treatment of recurrences or local metastases) at the end of follow up and those dead from tumour. In seventeen patients that were free of disease all tumours showed diploid patterns, and in eight patients that died from their tumour, all lesions showed atypical patterns. This is possibly due to a generally less aggressive behavior of diploid tumours that occasionally recur or metastasize, especially after inadequate primary therapy, but never kill the patient. Therapy in these cases should be aggressive, but its extent could depend on other data, such as clinical staging. In contrast, an atypical histogram pattern is an ominous sign which should give rise to a maximal therapeutic effort. In order to determine the prognosis on morphological grounds, a distinction between low and high grade malignancy (corresponding to grade 1 and 2 and grade 3 tumours respectively) should be made and should be completed by DNA assessment.

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