Virchows Arch [Pathol Anat] (1982) 396:19–39

Virchows Archiv A

Papillary Thyroid Carcinomas

Morphology and Prognosis

Jacqueline Tscholl-Ducommun and Chr. E. Hedinger
Department of Pathology, University of Zürich, University Hospital, CH-8091 Zürich, Switzerland

Summary. It is generally believed that the histological pattern of papillary thyroid carcinomas has no influence on the course of the disease. However, we were puzzled by the evident differences in the clinical course of these tumours and decided to re-examine all microscopic specimens available at the Institute of Pathology of the University of Zürich. These had been obtained from 169 surgical cases operated on between 1962 and 1977. We classified the material according to precise morphological criteria and matched it with a number of clinical and catamnestic data in order to determine which parameters correspond best with the development of the disease. Although the fate of patients below 50 years of age is slightly more favourable than that of older subjects, age is by no means the most important factor. In fact, the prognosis correlates significantly better with the initial local extension of the primary tumour (occult, intrathyroid or extrathyroid). Furthermore, this parameter is closely related to the histological pattern of our various papillary carcinoma subtypes which we graded according to differentiation. All factors considered, the morphological pattern appears to offer a rewarding approach to the provision of an accurate prognosis.

Key words: Papillary thyroid carcinoma – Morphology – Prognosis

Although the so-called papillary thyroid carcinomas, according to the nomenclature of the World Health Organization (Hedinger and Sobin 1974), are usually characterized by a remarkably favourable prognosis, they are not always as harmless as is generally believed. In some cases the patient dies from local tumour infiltration (trachea, oesophagus, major blood vessels), in other instances from generalized metastatic growth. Unlike anaplastic carcinomas, however, papillary tumours are generally not fulminant. Frequently, their development

Offprint requests to: Chr. E. Hedinger at the above address

0340-1227/82/0396/0019/$04.20

takes years or even decades and therefore requires a particularly long follow-up, as pointed out by Frazell and Foote (1958).

In a study published in 1961, Hirabayashi and Lindsay demonstrated that tumours behaved significantly more favourably in patients who were younger than 40 at the time of diagnosis than in patients who were over 40 when first seen. Subsequently a number of studies have confirmed the prognostic significance of age (Frazell and Foote 1958; Woolner 1971; Cady et al. 1976, 1979; Mazzaferri et al. 1977; Harwood et al. 1978; Byar et al. 1979; Frauenhoffer et al. 1979; Mazzaferri and Young 1981). Nevertheless, according to Franssila (1975), age has minor effect on survival within any particular histological type and stage of the disease.

The course of the disease correlates well with the extension stages (occult carcinoma, intrathyroid carcinoma and extrathyroid carcinoma) described by Woolner (1971) and Woolner et al. (1960, 1961) and later adopted by various other workers (Franssila 1971, 1978; Beaugié et al. 1976; Cady et al. 1976; Mazzaferri et al. 1977; Byar et al. 1979; Frauenhoffer et al. 1979; Hubert et al. 1980; Mazzaferri and Young 1981). Occult carcinomas are often sclerosing, and their diameter must not exceed 1.5 cm (Woolner et al. 1960; Sobrinho Simões 1978; Sobrinho Simões et al. 1979; Hubert et al. 1980). As a rule they are detected during histological examination of the specimen removed after thyroid surgery for goiter or because of metastatic cervical adenopathies. Intrathyroid tumours which are larger than 1.5 cm are confined to the parenchyma, i.e. the thyroid capsule remains intact. Extrathyroid tumours grow beyond the confines of the thyroid, invading surrounding tissue, cervical muscles and adjacent structures, such as the trachea and oesophagus. Their prognosis is relatively poor. On the other hand, as Woolner et al. (1960), Franssila (1971), Sobrinho Simões (1978), Sobrinho Simões et al. (1979), Georgii and Lang (1979), Hubert et al. (1980), and Mazzaferri and Young (1981) demonstrate, occult papillary carcinomas appear to have biologically different behaviour from other extension types. In spite of the high incidence of numerous and bulky nodal metastases, the authors did not record a single death due to primary disease. Some workers go as far as to suggest that metastatic adenopathies may act as a protection against distant metastases (McKenzie 1971) and improve (possibly by some immunological mechanism) survival especially in patients above 40 (Cady et al. 1976; Harwood et al. 1978).

Some authors feel that histological data concerning papillary carcinoma are prognostically irrelevant (Frazell and Foote 1958; Woolner et al. 1961; Ibanez et al. 1966; Beaugié et al. 1976; Mazzaferri et al. 1977; Harwood et al. 1978; Cady et al. 1979). Meissner and Adler (1958) and Selzer et al. (1977) note a more favourable course for pure papillary carcinomas than for the mixed papillary-follicular type. Others make directly contradictory assessments (Gérard-Marchant et al. 1970). Lindsay (1960, 1969), Woolner (1971), and Franssila (1975, 1978) conclude that the proportion of papillae and follicles is irrelevant for prognosis. Furthermore, it is generally agreed that dedifferentiation of papillary thyroid tumours into the epidermoid or anaplastic type is associated with high mortality (Tollefsen et al. 1964; Hutter et al. 1965; Wychulis et al. 1965; Silverberg et al. 1970; Harada et al. 1977; Byar et al. 1979). Most authors, however, do not classify dedifferentiated tumours (i.e. anaplastic tumours containing papillae) as papillary lesions but as undifferentiated growths. It would

appear therefore that the patient's age and the local extension stage of papillary tumours at the time of diagnosis constitute meaningful and universally recognized criteria that correlate well with the long-term clinical behaviour of the disease. However, the importance of the histological pattern alone remains to be clarified.

We therefore attempted to discover why some papillary carcinomas take an unfavourable clinical course, and, by comparison of exactly defined morphological subgroups, to determine whether the histological features of the primary tumour can be prognostically useful.

Material and Methods

We re-examined the slides of surgical and biopsy specimens of the 547 cases of thyroid carcinoma that were available at the Institute of Pathology of the University of Zürich for the period 1962–1977. For our study we selected exclusively those tumours with papillary excrescences (regardless of the appearance of the nucleus) and some cancers with pure follicular architecture and a characteristic "ground glass" appearance of the nucleus. These constituted 169 papillary carcinomas altogether, or 30.9% of the original material. Preliminary results were published in a thesis by Jeanneret (1978).

Virtually all of this material had been obtained from the primary tumour, the remainder from nodular metastatic lesions, or from distant metastases of undisputed thyroid origin. On the whole the usual staining methods were adequate (haematoxylin eosin and van Gieson). Only some of the paraffin-embedded blocks had to be resectioned to enable us to trace colloid (PAS staining) or elastic fibres (elastin staining) during our search for vascular invasion.

We deliberately refrained from dividing our cases into pure papillary carcinomas, predominantly papillary and predominantly follicular tumours, because a quantitative evaluation of this criterion is problematical. In fact, the distribution of these structures may vary considerably in different parts of the tumour. A reasonably exact picture could be obtained only by serial sectioning. Furthermore, adenopathies often reveal a higher proportion of papillary excrescences and comparatively fewer follicles than the actual thyroid tumour. However, in some cases this relationship may be reversed.

On the basis of these considerations we applied broader differentiation criteria to define the following subgroups:

A. Non-Eosinophilic Carcinomas

I. Well-Differentiated Papillary Carcinomas

a) Classical Type (Fig. 1). Characteristic structure of fine papillae with delicate conjunctivo-vascular axis, which are covered by mono-stratified prismatic epithelium. In the apical region, cell contours are blurred, frayed or indented. Nuclei are arranged like tiles on a roof and display the distinctive "ground glass" appearance which is caused partially by peripherally located chromatin (particularly fine-grained) and by pseudo-inclusions within the nucleus which are, in reality, cytoplasmic evaginations. Common findings include central stellate sclerosis with retraction effect, cystic lesions (especially in nodal metastases) and lymphoplasmacytic inflammatory infiltrations. In some cases the pure follicular sheets are very large.

b) Non-Classical Type (Fig. 2). Unlike the classical type, the nucleus is chromatin-rich and lacks the "ground glass" appearance. The cells show well-defined contours and juxtaposed nuclei. However, the growth pattern is still papillary, stellate sclerosis, cystic structures and chronic inflammation are still frequent.

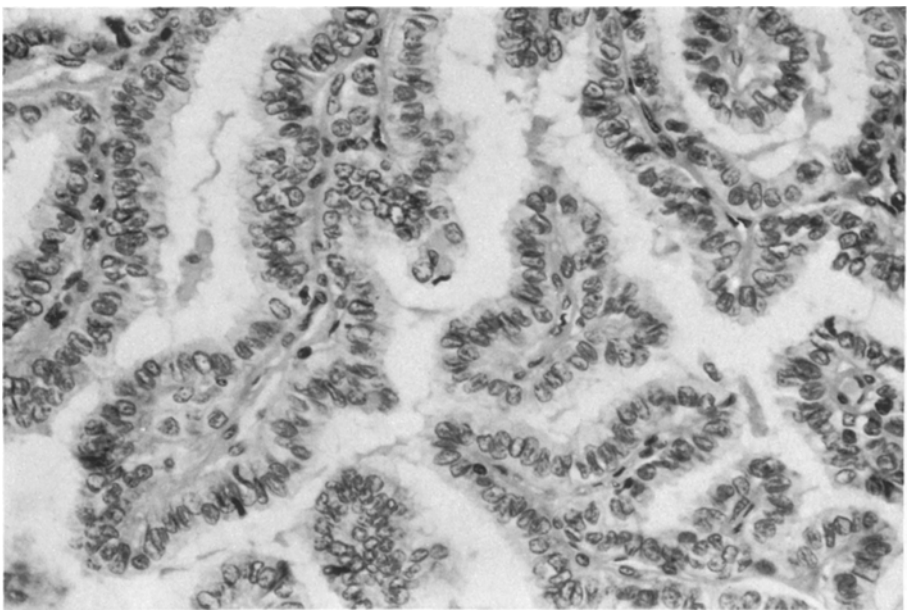

Fig. 1. Well-differentiated papillary carcinoma, classical type. 42 year old woman, HZ 17674/76, HE × 300

c) Lindsay's Tumour (Fig. 3). This well-differentiated tumour consists virtually wholly of follicles of which the cells contain nuclei of the characteristic "ground glass" type. Neither psammoma bodies nor stellate sclerosis are present, and as a rule the tumour is well encapsulated (Lindsay 1960; Franssila 1973).

II. Moderately Differentiated Papillary Carcinomas (Figs. 4 and 5)

The predominant papillary architecture is easy to identify, but there are obvious changes suggesting poorer differentiation: extensive solid sheets resembling epidermoid metaplasia (Fig. 5a) (polygonal cells, occasionally with intercellular bridges, and sometimes laminated concentric cell clusters), detached cell islets infiltrating the adjacent parenchyma, the capsule, and even the muscle (Fig. 5b). We were struck by the polymorphic appearance of cell and nucleus: "ground glass" nuclei alternate with round or oval chromatin-rich nuclei; some cell contours are well-defined, others frayed, and there are sometimes sheets of clear cells. Thus, the histological pattern is much less uniform.

Depending on the presence or absence of certain typical features found in highly differentiated papillary carcinomas, we distinguished between two types:

a) Presence of retractive stellate sclerosis, well-defined cystic changes and/or extensive lymphoplasmacytic inflammatory infiltrations at peritumoral or intrapapillary sites.

b) No evidence of the above.

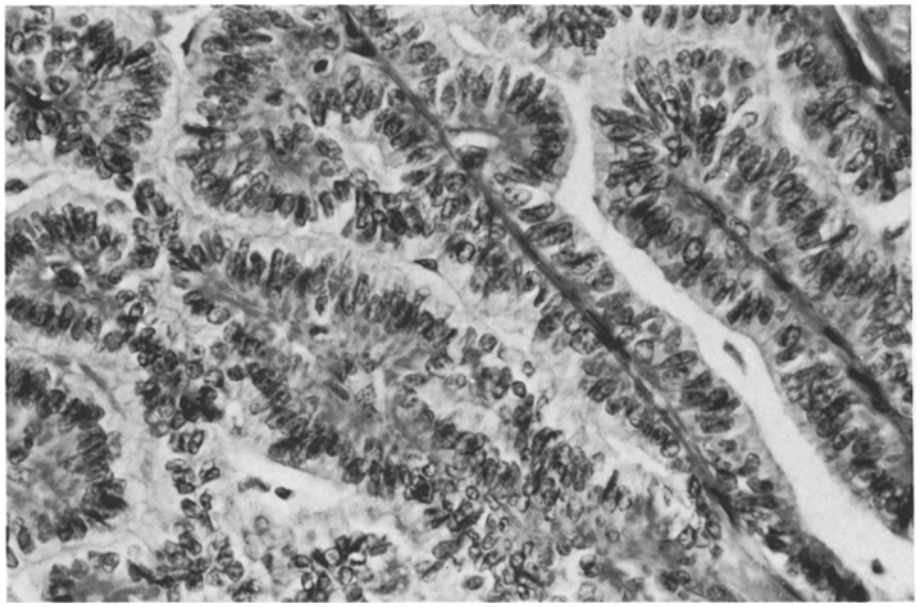

Fig. 2. Well-differentiated papillary carcinoma, non-classical type. 33 year old woman, MB 14623/68, HE ×300

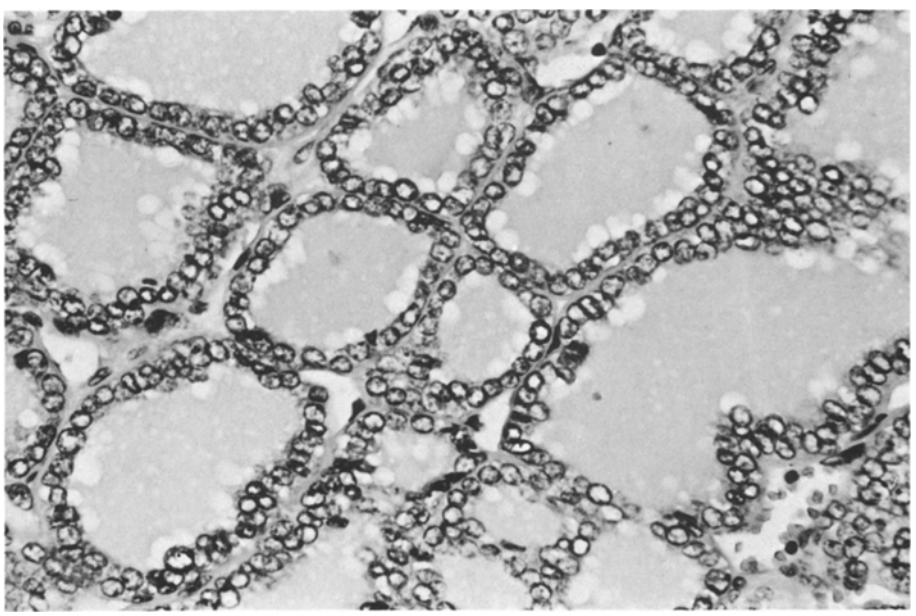

Fig. 3. Well-differentiated papillary carcinoma, predominantly follicular, so-called Lindsay's tumour. 34 year old woman, HZ 1627/76, HE ×300

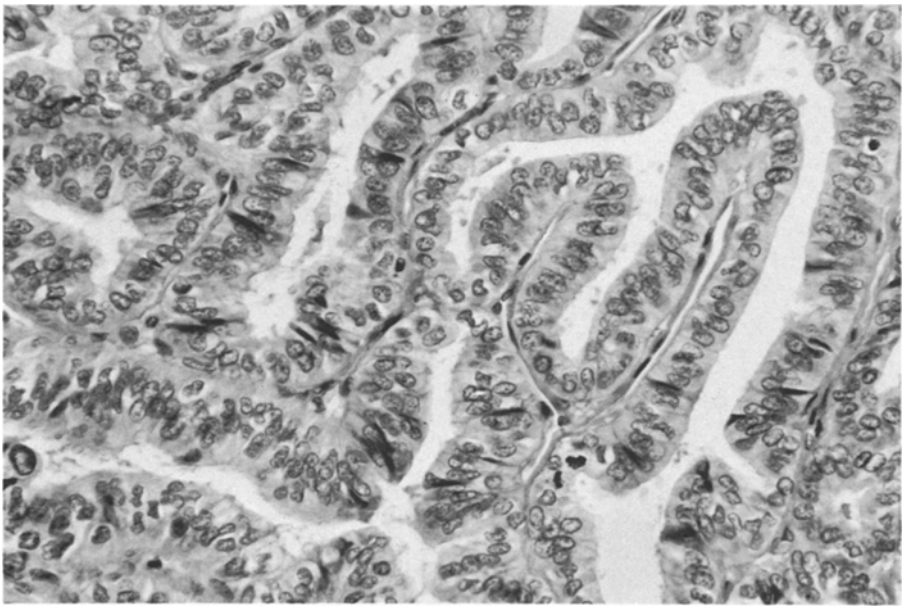

Fig. 4. Moderately differentiated papillary carcinoma. 66 year old woman, HZ 10953/77, HE × 300

III. Poorly Differentiated Papillary Carcinomas (Figs. 6 and 7)

In addition to unequivocal papillary structures this type displays large, essentially microfollicular foci. The epithelium in these areas often consists of clear cells (Fig. 6). Other follicles are larger, tumour cells flatter, colloid is absent. The very characteristic cribriform histological picture resembles the so-called "proliferating Langhans' goiter" (Fig. 7). The nuclei are frequently polymorphic; whereas vascular invasion is rarely encountered in the previous categories, it is now a frequent and evident finding.

IV. Undifferentiated Papillary Carcinomas (Fig. 8)

Conspicuous carcinomatous epidermoid and anaplastic growth (giant and spindle cells) makes the diagnosis easy. Mitosis is common and often pathological. Vascular invasiveness seems to be the rule. In spite of their evident undifferentiated and anaplastic features, these carcinomas display some typical and clearly detectable digitiform excrescences; we therefore classified them as papillary tumours.

Laminated intrapapillary calcaneous structures termed "psammoma bodies" can be observed in all of the above subgroups with the exception of Lindsay's tumour, but do not occur in all of the cases under study. Also isolated sheets of clear cells and/or eosinophilic cells are a relatively common finding in all these categories. Histologically at least, however, tumours containing exclusively such cell types, should be considered as a separate group.

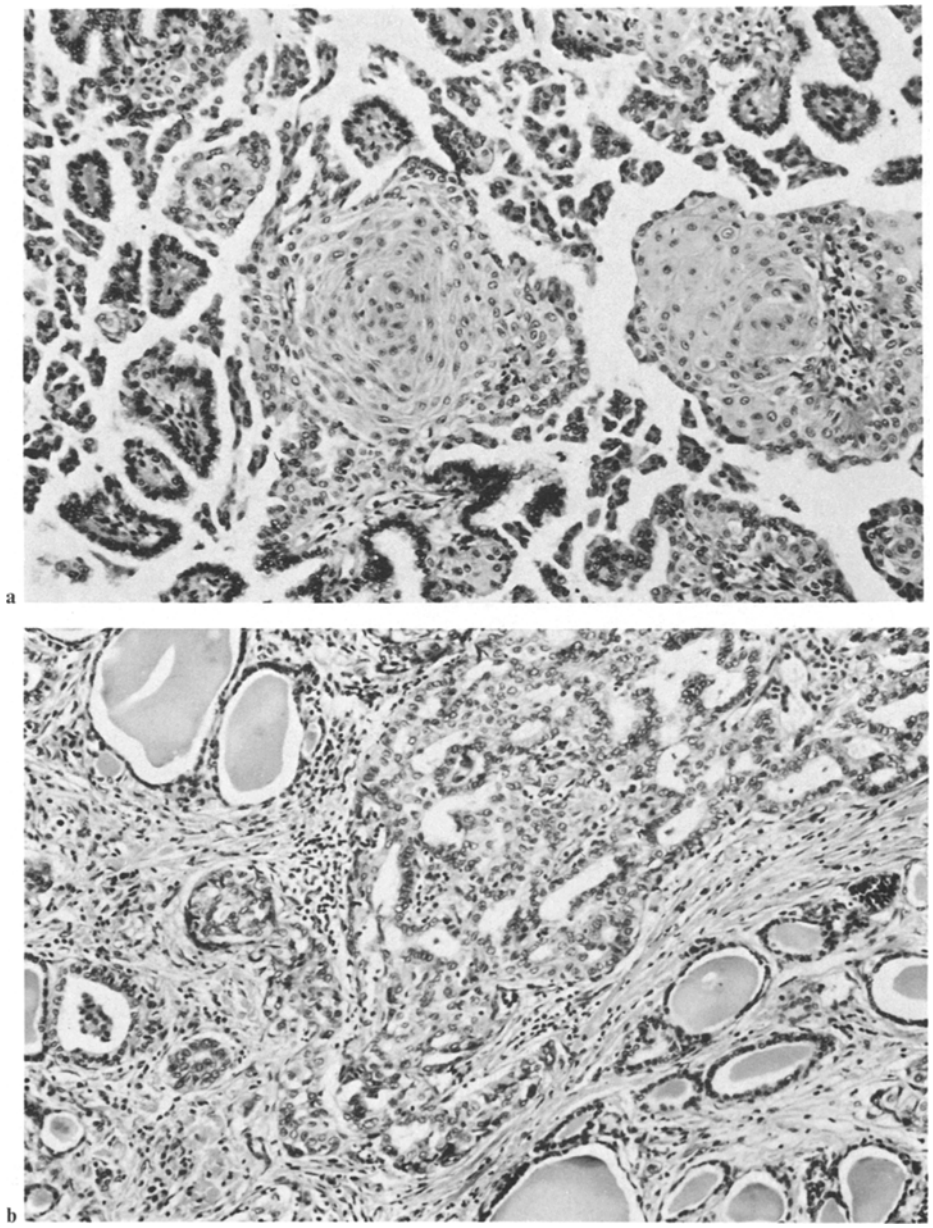

Fig. 5a, b. Moderately differentiated papillary carcinoma. **a** With epidermoid metaplasia. **b** Infiltrating the adjacent thyroid tissue. $14^{6}/_{12}$ year old boy, MB 17343/69, HE $\times 125$

B. Eosinophilic Carcinomas (Hürthle Cells)

The large tumour cells are round. The cytoplasm is highly acidophilic, containing numerous mitochondria. Colloidal calcific structures are frequent, but not of the laminated or intrapapillary type, and should therefore not be confused

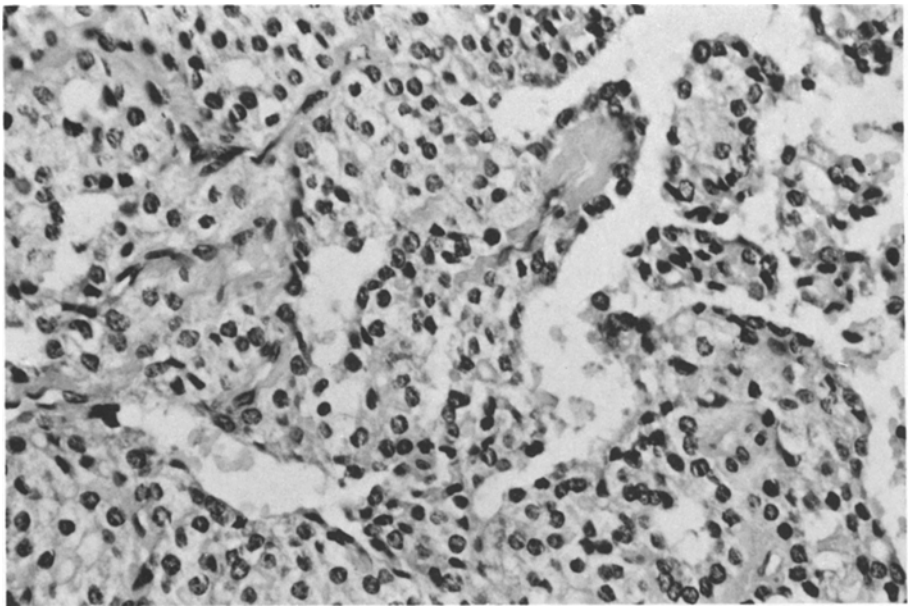

Fig. 6. Poorly differentiated papillary carcinoma, polymorphic appearance of tumour cells, clear cells. 69 year old man, HZ 9407/64, HE × 300

with psammoma bodies. As a rule these tumours are follicular in structure and have a compact appearance. We distinguished three types:

a) Eosinophilic Papillary Carcinomas. Usually follicular architecture with unquestionable evidence of digitiform structures (Fig. 9).

b) Eosinophilic Tumours With Equivocal Structure (Papillary or *Follicular*). The friable and compact tumour tissue might be mistaken for papillae (Fig. 10).

c) Undifferentiated Eosinophilic Tumours displaying giant cells, occasionally multinuclear, with atypical mitoses (Fig. 11).

In the light of the histological and clinical data, we analysed our patients in terms of sex, age, Woolner's extension stages of the primary tumour (occult, intrathyroid, extrathyroid) (Woolner et al. 1960; Tollefsen et al. 1964), multifocality of the disease, and by initial lymph node involvement or distant metastases. Secondly, we reviewed the catamnesis of these patients. We used the chi square test to compare various distributions with each other, and the student t test to analyse the mean values. We obtained valuable information from the case histories available in surgical, otorhinolaryngological and nuclear medicine departments. A large number of physicians also kindly contributed information on their patients[1].

1 The authors gratefully acknowledge these valuable contributions

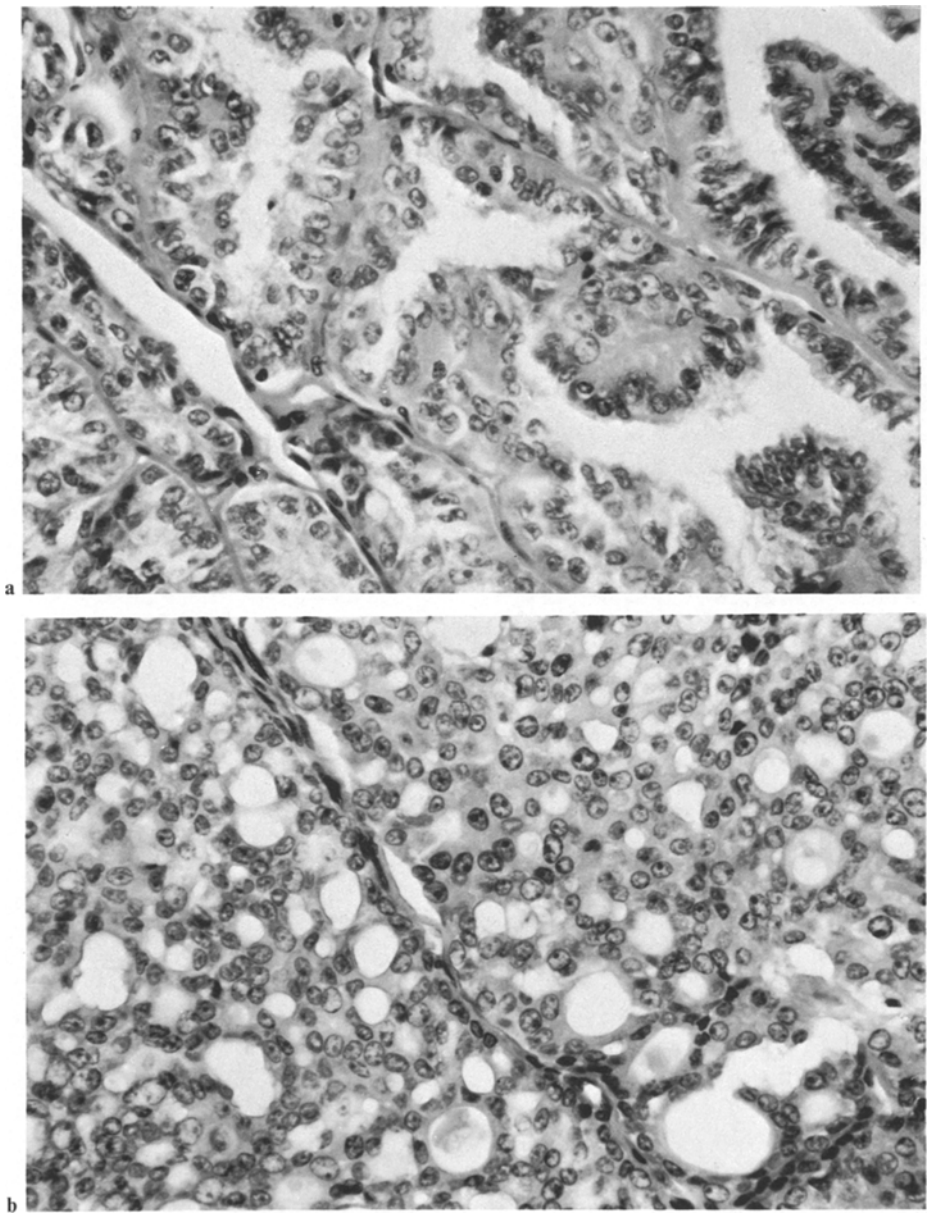

Fig. 7a, b. Poorly differentiated papillary carcinoma. **a** Papillary structures. **b** Cribriform histologic picture. 49 year old woman, HP 10194/65, HE ×300

Results

Our group comprises 169 patients with a *mean age* of 48 $^{4}/_{12}$ years, including 123 women, i.e. 72.8% (mean age 47 years and 9 months) and 46 men (mean age 50 years) (Table 1). Figure 12 shows their distribution by age and sex. The

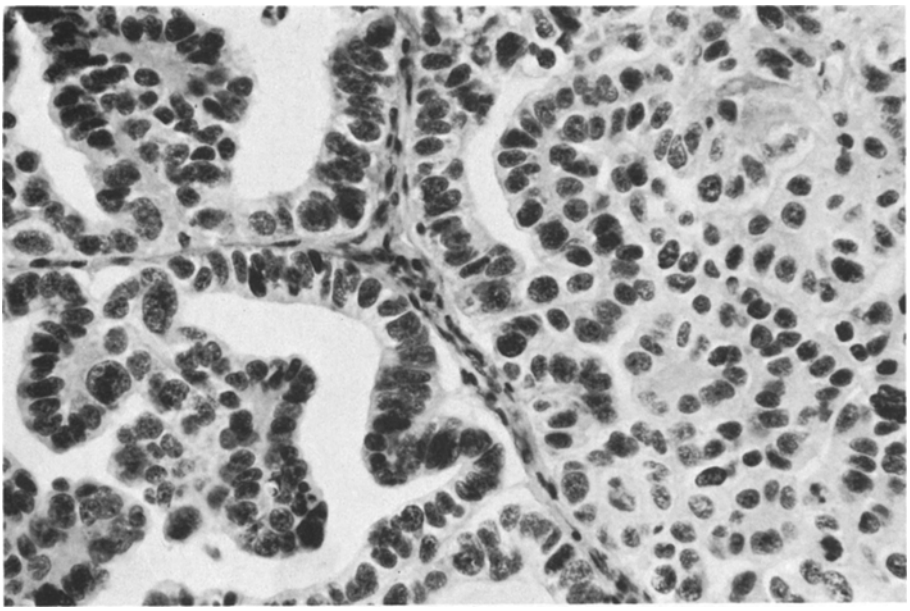

Fig. 8. Undifferentiated papillary carcinoma. 51 year old woman, MB 9503/64, HE ×300

papillary carcinomas are fairly evenly distributed among the various age ranges between 20 and 70 years. The peak at age 60–70 includes a relatively large number of male subjects.

In one case it was impossible to classify the *local tumour stage* because of lack of clinical data and inconclusive histology. Occult carcinomas (diameter max. 1.5 cm) are found in 23 patients (13.7% of our series) (average age 44 years and 4 months), including 17 women and 6 men. Intrathyroid tumours are the most common type, occurring in 108 cases (64.3%) (mean age 47 years and 9 months), including 85 women and 23 men. Extrathyroid cancer was diagnosed in 37 cases (22%) (average age 52 years and 4 months) and concerned 21 female and 16 male patients. Despite the association of greater age with more aggressive invasion, the values do not differ significantly: for example $p > 0.05$ when mean age of patients with occult and extrathyroid stages are compared. Of the 23 occult lesions, 9 were revealed because of cervical node involvement. The remaining 14 patients underwent surgery for an apparently innocuous goiter, and their tumours were discovered during the subsequent histological examination. Two of them presented nodal metastases in addition.

In 37 patients, 21 women and 16 men (22% of all patients) (mean age 42 years and 9 months), we found *multiple cancerous foci* in the same or the opposite lobe. 13.5% of the tumours were graded as occult, 51.5% as intrathyroid, and 35% as extrathyroid.

Initial Lymph Node Involvement at the time of surgery or diagnosis was discovered in 43 patients (25.6% of our cases) (mean age 40 years and 11 months), including 25 women and 18 men. When graded by invasiveness, 25% of these papillary carcinomas are occult, 43% intrathyroid and 32% extrathyroid. Here,

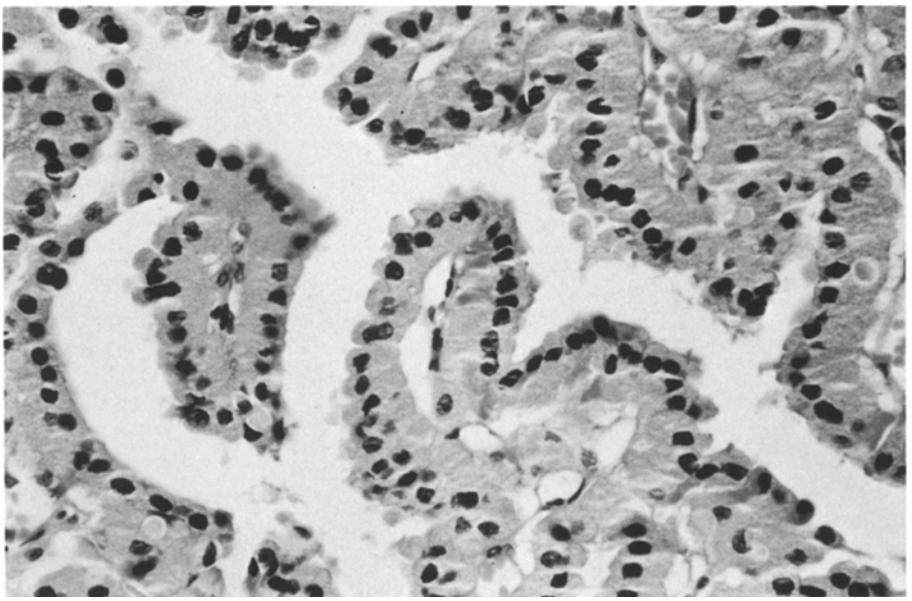

Fig. 9. Eosinophilic papillary carcinoma. 63 year old man, HP 9714/63, HE ×300

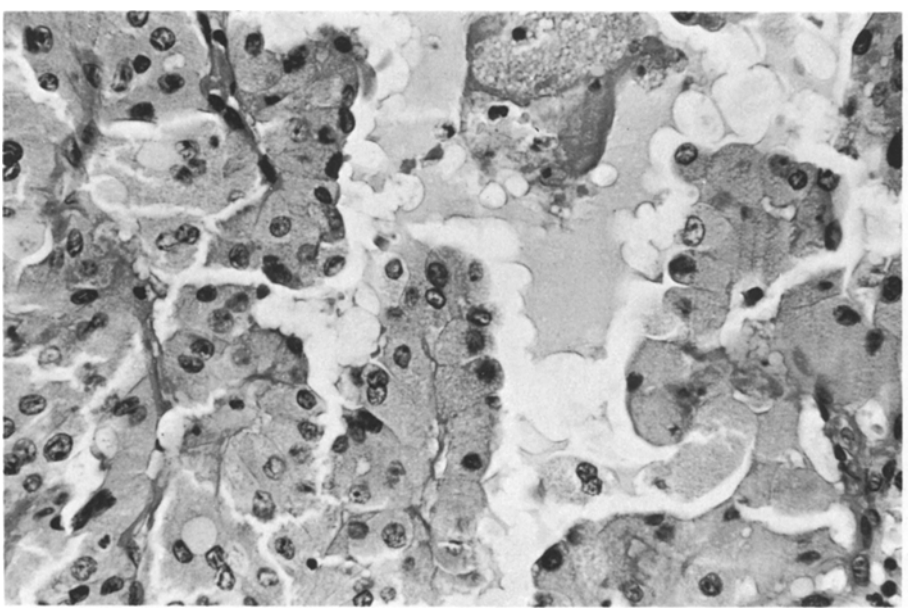

Fig. 10. Eosinophilic tumour with equivocal structures (papillary or follicular). 21 year old woman, HP 485/70, HE ×300

primary tumours grow through the glandular capsule more frequently (32%) than in cases without nodal involvement (18%) ($p < 0.05$). Furthermore, regional node involvement is clearly associated with multifocal thyroid carcinoma (39%), whereas multifocal disease occurs in only 16% of nonmetastazizing tumours ($p < 0.005$).

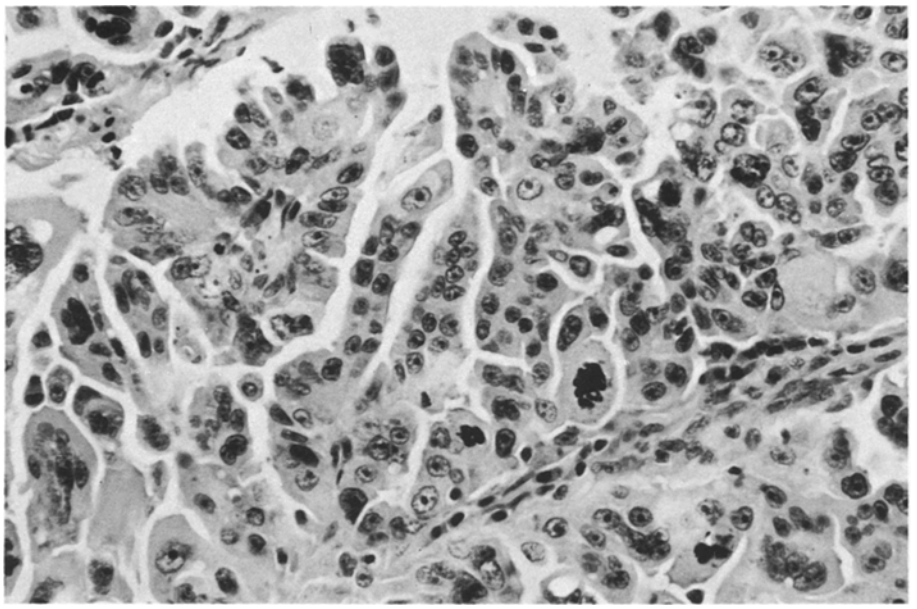

Fig. 11. Undifferentiated eosinophilic tumour. 70 year old man, HZ 9374/75, HE ×300

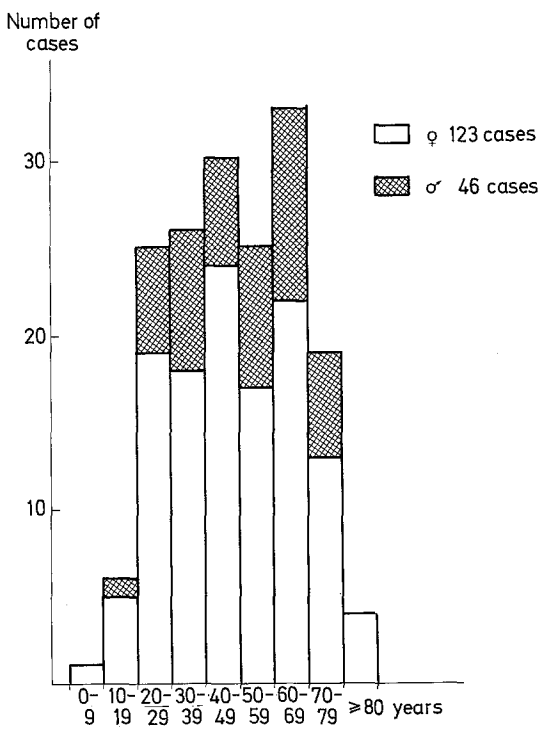

Fig. 12. Papillary carcinomas (169 cases). Distribution by age and sex

Table 1. Papillary carcinomas of the thyroid (169 cases). Distribution by histology at time of initial diagnosis

Histologic subgroup	Ia	Ib	Ic	IIa	IIb	III	IV	Ba	Bb	Bc	Total
Number of cases	20	16	7	60	11	28	8	12	6	1	169
female	14	13	6	42	9	21	4	9	5	–	123
male	6	3	1	18	2	7	4	3	1	1	46
Average age	$40^{1}/_{12}$	$44^{8}/_{12}$	$41^{9}/_{12}$	$44^{2}/_{12}$	$55^{3}/_{12}$	$57^{1}/_{12}$	$61^{6}/_{12}$	$51^{9}/_{12}$	55	70	
Occult	6	3	–	14[a]	–	–	–	–	–	–	23[a]
Intrathyroid	13	12	7	28	6	20	3	12	6	1	108
Extrathyroid	1	1	–	17	5	8	5	–	–	–	37
Multifocal tumour	7	3	1	12	2	5	2	4	–	1	37
Initial lymph node involvement	8	4	1	20	2	4	2	1	–	1	43
Initial distant metastases	1	1	–	1	2	4	2	–	–	–	11

[a] 1 patient excluded while unknown initial extension stage

Initial Distant Metastases are found in 9 women and 2 men (6.5% of our series) (average age 53 years and 8 months). With regard to tumour extension, we did not discover any occult lesions among these subjects. 73% had intrathyroid carcinomas and 27% extrathyroid invasion. Apparently, extrathyroid disease does not promote the development of distant foci. In fact, 26% of the patients without metastases also present tumours infiltrating the surrounding structures. Multifocal primary disease, which affects 18% of these patients, shows no statistical correlation with the incidence of distant metastases. Equally, no relationship could be demonstrated between the latter and regional lymph node involvement ($p > 0.1$), although these two parameters are recorded more often together than separately.

Table 1 shows the distribution of the different histologically defined subgroups. Distribution by sex is uniform ($p > 0.9$); in contrast, increasing average age is related to decreasing histological differentiation, but these data are not significantly correlated when adjacent subgroups are compared.

However, in spite of scattered isolated values, subgroup I (well-differentiated) is clearly younger (average age 42 years and 1 month) than subgroups III and IV (poorly differentiated and undifferentiated) (average age 58 years and 1 month) ($p < 0.001$). The correlation persists ($p < 0.001$) when subgroup IV (undifferentiated) is left out. Histologically and by age (average age 45 years and 11 months), tumours in category II range from well- to poorly differentiated lesions. However, a closer analysis shows that subgroup II a (some histological characteristics as in well-differentiated cancers) is on the average younger (44 years and 2 months) than subgroup II b (55 years and 3 months), although the difference remains non-significant ($p > 0.05$).

With regard to primary tumour extension, there exists an excellent correlation between morphology and occult disease ($p < 0.0005$), the latter occurring exclusively in subgroups I and IIa. Conversely, the incidence of invasive tumours is significantly higher in categories IIb, III and IV ($p < 0.025$). However, if subgroup IV is left out, this difference is not significant ($p > 0.05$). The incidence of intraglandular lesions is approximately the same in all histological categories ($p > 0.7$).

Multifocality is not related to the histological differentiation ($p > 0.6$). The corresponding rates in the different subgroups vary between 17.9 and 35%. Initial lymph node involvement is more frequent in categories I and IIa (32%) than in subjects under IIb, III and IV (17%). Statistically, however, the difference is not significant ($p > 0.05$). On the other hand, there is a good correlation for initial distant metastases, which affect only 3% of the patients in groups I and IIa, but 17% in groups IIb, III and IV ($p < 0.025$). In this respect, therefore, subgroup IIa appears to approach the behaviour of well-differentiated tumours (I) more than does subgroup IIb, despite the morphological similarity of the two former subgroups.

Results Based on Catamnestic Data

Case histories were available for 142 patients (100 women and 42 men), i.e. 84.0% of our initial collective. Follow-up periods vary between 6 months and 28 years (median duration 6 years). 49 patients had recurrences, while 93 patients can be regarded as disease-free. The distribution of local recurrences, nodal metastases, distant foci and deaths is represented in Table 2. Of 41 deaths, 24 are due to the primary tumour (all with distant metastases). The remaining 17 patients died of the following causes: breast cancer 2, carcinoma of the rectum 1, cancer of the choledochus 1, leukaemia 1, cardiovascular disease 3, infections 3, craniocerebral trauma 1, postoperative complications 1, complications following irradiation 1, 3 died of unknown causes.

Table 3 shows the variation of the clinical course in relation to primary tumour extension. The remarkably favourable prognosis for occult carcinomas is evident. We find neither recurrent disease, distant metastases, nor death due to primary disease in these cases. In contrast, extrathyroid tumours have the lowest cure rate, and their clinical behaviour differs significantly from that of the other lesions ($p < 0.0005$). The incidence of recurrent disease ($p < 0.0005$), distant metastases and death due to tumour ($p < 0.0005$) is markedly higher in extrathyroid papillary carcinomas than in intrathyroid lesions. When intra- and extrathyroid disease is compared for the incidence of nodal metastases, we find that the difference reaches the significance limits ($p < 0.05$).

No correlation can be demonstrated between sex and clinical course ($p > 0.1$), but patients considered to have been cured are definitely younger (mean age 45 years and 10 months) than those who died of distant metastases (mean age 60 years and 10 months) ($p < 0.001$).

Furthermore, patients with local recurrences and/or cervical satellite adenopathies are significantly younger (average age 54 years and 3 months) than those who developed or died of distant disease (average age 60 years and 10 months)

Table 2. Catamnestic data (142 cases)

1. Cure	Total	93 cases
death not due to thyroid carcinoma		11 cases
2. Local recurrences	Total	27 cases
alone	6	
with lymph node metastases	6	
with distant metastases	9	
with both involvement	6	
death due to thyroid carcinoma		14 cases
death not due to thyroid carcinoma		3
3. Lymph node metastases	Total	22 cases
alone	7	
with local recurrence	6	
with distant metastases	3	
with both involvement	6	
death due to thyroid carcinoma		8 cases
death not due to thyroid carcinoma		3
4. Distant metastases	Total	30 cases
alone	12	
with local recurrence	9	
with lymph node metastases	3	
with both involvement	6	
death due to thyroid carcinoma		24 cases
death not due to thyroid carcinoma		none

Table 3. Clinical course by initial extension stages of the thyroid tumour (141 cases). (1 patient excluded while unknown initial extension stage)

	Occult (19 cases)	Intrathyroid (88 cases)	Extrathyroid (34 cases)	Total (141 cases)
Local recurrences	0%	13.6% (12)	41.2% (14)	18.4% (26)
Lymph node metastases	0%	17.1% (15)	20.6% (7)	15.6% (22)
Distant metastases	0%	13.6% (12)	50.0% (17)	20.6% (29)
Death due to thyroid tumour	0%	10.2% (9)	44.1% (15)	17.0% (24)
Cure	100% (19)	69.3% (61)	38.2% (13)	66.0% (93)
Death not due to thyroid tumour	5.3% (1)	13.6% (12)	11.8% (4)	12.1% (17)

($p < 0.02$). On the other hand, there is no age difference between the "cured" group and the group with "recurrence with or without node involvement".

Among the other parameters studied, initial regional node involvement and multifocal primary tumour reveal no correlation with the clinical development, while initial distant metastases are clearly associated with a more ominous course ($p < 0.0005$).

Table 4. Papillary carcinoma of the thyroid (eosinophilic tumours excluded). Distribution by histology and catamnestic data (126 cases)

	Well differentiated I+IIa (82 cases)	Less differentiated IIb+III+IV (44 cases)	Total (126 cases)
Local recurrences	10.9% (9)	34.1% (15)	19.0% (24)
Lymph node metastases	12.2% (10)	22.7% (10)	15.9% (20)
Distant metastases	7.3% (6)	47.7% (21)	21.4% (27)
Death due to thyroid carcinoma	3.7% (3)	45.5% (20)	18.3% (23)
Cure	79.3% (65)	40.9% (18)	65.9% (83)
Death not due to thyroid carcinoma	8.5% (7)	13.6% (6)	10.3% (13)

Table 4 shows the distribution of the different clinical behaviour patterns over our histologically defined subgroups. No statistical difference is found between categories I and IIa, which contain the highest cure rates. But there is a marked difference between these and subgroups IIb, III and IV with regard to cure rates ($p < 0.0005$), local recurrence ($p < 0.001$), distant metastases ($p < 0.0005$), and death due to thyroid tumour ($p < 0.0005$). No correlation can be established between lymph node involvement occurring in the later course of the disease and the morphology. As already pointed out, subgroups IIa and I are strikingly alike in respect of initial age as well as initial and longterm tumour behaviour. In fact, patients in IIa have a much better prognosis than those in IIb, despite the very similar histological pattern (recurrence $p < 0.005$; distant metastases and death due to disease $p < 0.0005$). Thus, the morphological features which are displayed both by subgroup IIa and subgroup I, but not by subgroup IIb (retractive stellate sclerosis, cystic lesions, peritumoral or intrapapillary lymphoplasmacytic infiltration) may indeed represent favourable factors for the clinical prognosis. In order to illustrate more precisely the value of the histological features, Table 5 shows the catamnestic data of the papillary carcinomas (well- and less differentiated) in relation to the extension stages, i.e. occult, intrathyroid and extrathyroid. All the occult tumours are cured, but they are without exception, included within the well-differentiated carcinomas. In contrast, if we consider separately the intrathyroid and extrathyroid extension, the well-differentiated tumours behave more favourably than the less differentiated ones (less local recurrences, fewer distant metastases and deaths due to carcinomas). The lymph node metastases are less frequent, too, but the difference is significant for the extrathyroid carcinomas only if the subgroup IV is included. For the well-differentiated tumours, the percent cure is higher than for the less differentiated tumours, although this is not so statistically evident if the subgroup IV is excluded.

Patients with eosinophilic tumours are on average older than those with papillary carcinomas figuring in subgroups I and younger than those classified in subgroups III–IV (Table 1). All of these tumours are intrathyroid, including our only eosinophilic papillary carcinoma with anaplastic foci. Tumours with large acidophilic cells, clearly papillary, seem to manifest some tendency towards multifocality, but show little evidence of nodal and distant metastases. In the clinical course, these neoplasms behave much like well-differentiated papillary tumours of subgroup I, i.e. their development is characterized by local recurrence and satellite adenopathies rather than by distant foci, and the cure rate is high. In view of the particularly short follow-up period of this group (2 years and 8 months), however, a closer analysis is problematical[2].

2 The cooperation of our documentation group PADOK is gratefully acknowledged

Table 5. Papillary carcinomas of the thyroid (eosinophilic tumours excluded). Clinical course by histologic differentiation for each initial extension stage (125 cases, 1 patient excluded while unknown initial extension stage)

Histologic subgroup	a) Occult		b) Intrathyroid		c) Extrathyroid	
	Well differentiated I+IIa (19 cases)	Less differentiated IIb+III (no case)	Well differentiated I+IIa (46 cases)	Less differentiated IIb+III+IV (26 cases)	Well differentiated I+IIa (16 cases)	Less differentiated IIb+III+IV (18 cases)
Local recurrences	0		8.7% (4)	19.2% (5)*[4]	25.0% (4)	55.6% (10)*[5]
Lymph node metastases	0		17.4% (8)	19.2% (5)*[1]	12.5% (2)	27.8% (5)*[2]
Distant metastases	0		4.3% (2)	26.9% (7)*[5]	18.8% (3)	77.8% (14)*[5]
Death due to thyroid carcinoma	0		2.2% (1)	26.9% (7)*[5]	12.5% (2)	72.2% (13)*[5]
Cure	100% (19)		76.1% (35)	61.5% (16)*[3]	68.8% (11)	11.1% (2)*[5]
Death not due to thyroid carcinoma	1		6.5% (3)	19.2% (5)	18.8% (3)	5.6% (1)

*[1] non significant; [2] $p<0.05$; [3] $p<0.01$; [4] $p<0.005$; [5] $p<0.0005$

Discussion

In our introduction we referred to the criteria which most authors believe to be helpful in predicting the probable clinical course of papillary thyroid carcinomas. Many workers feel that the patient's age when first seen and treated is of overriding importance (Hirabayashi and Lindsay 1961; Woolner 1971; Cady et al. 1976, 1979; Mazzaferri et al. 1977; Harwood et al. 1978; Böcker 1979; Frauenhoffer et al. 1979; Mazzaferri and Young 1981). The younger the patient the greater the chance that he will be "cured". However, the distinctive biological behaviour of papillary tumours calls for particularly long, possibly life-long, follow-up. Our findings show a significant difference between the mean age of cured patients (45 years and 10 months) and that of subjects who eventually develop distant metastases (60 years and 10 months). On the other hand, the correlation is less significant when the mean age of patients with local recurrent disease and/or lymph node involvement (54 years and 3 months) is compared to that of patients with distant metastases (average age 60 years and 10 months). No clear age difference is found between the groups with the most favourable clinical development.

In a study published in 1976, Cady et al. conclude that recurrences are more frequent in men than in women. Frauenhoffer et al. (1979) found lower survival rates in males with papillary carcinoma than in females. Our own study does not indicate such a correlation between sex and prognosis. On the other hand, our data corroborate previous findings regarding the close relationship between extent of the primary tumour and clinical course (Woolner et al. 1960, 1961; Woolner 1971; Franssila 1971, 1975, 1978; Beaugié et al. 1976; Mazzaferri et al. 1977; Böcker 1979; Hubert et al. 1980; Mazzaferri and Young

1981). All occult lesions can be considered as cured, and their distinctive biological behaviour clearly sets them apart from the two other invasion stages. The highest rates of recurrence, distant metastases and death due to thyroid tumour clearly occur among subjects with extrathyroid carcinomas. Intrathyroid lesions seem to be a transitional type with variably favourable and unfavourable behaviour. Vascular invasion is considered as a bad prognostic sign by Frauenhoffer et al. (1979), an opinion not shared by Hofstädter and Unterkircher (1980).

According to some authors (McKenzie 1971; Cady et al. 1976; Harwood et al. 1978), initial lymph node involvement is associated with benign clinical development. We have not been able to confirm this assertion. On the other hand, patients with initial distant metastases definitely have a less favourable long-term prognosis than those without. However, it is interesting to note that initial pulmonary involvement in three patients disappeared completely in two of them who received radioactive iodine (the third patient underwent total resection). Histologically, these patients (who remained free of later disease) are included in subgroups I and IIa respectively. The other 8 patients with initial distant disease are subsummed morphologically under types IIb, III and IV. None of them were cured, and 7 died of generalized disease.

This brings us to the controversial issue of the relationship between the histological pattern of papillary thyroid carcinomas and their clinical course. Numerous and often contradictory studies have been published on this subject. While some authors maintain that histological findings have no prognostic value (Woolner et al. 1961; Ibanez et al. 1966; Woolner 1971; Beaugié et al. 1976; Mazzaferri et al. 1977; Cady et al. 1979), others are convinced that the papillae/follicle ratio is decisive (Meissner and Adler 1958; Selzer et al. 1977), but not always in the same sense (Gérard-Marchant et al. 1970). As some workers point out, the mixture of these structures may vary considerably in the actual tumour and in metastases (Frazell and Foote 1958; Franssila 1971 and 1978; Woolner 1971).

In order to determine whether the markedly varying patterns of the clinical course correspond to clearly defined histological differences, we opted for the broader differentiation criteria outlined above. As we have seen, tumours in categories Ia and Ib are highly differentiated, fairly monomorphous and uniform. In view of the high incidence of retractive stellate sclerosis, cystic structures and lymphoplasmacytic inflammatory infiltration in these groups, we felt that these features might be associated with a favourable prognosis. To test our hypothesis we divided the distinctly polymorphic subgroup II into two categories, i.e. the above factors are present in IIa but not in IIb. This division may at a first glance appear arbitrary, but is in fact of both practical and prognostic relevance. Patients in category IIa have an entirely different prognosis from those in IIb: the generally favourable course of the disease in the former group conforms statistically with that encountered in highly differentiated tumours. It should be mentioned, however, that according to Hofstädter and Unterkircher (1980) the presence or absence of lymphocytic infiltration and psammoma bodies is not valuable in establishing a prognosis.

Patients in category IIb show a significantly more ominous tendency towards recurrence, distant metastases and death due to disease. Analysing the complete

catamnestic data of some patients in category IIb, we found furthermore definite evidence that the histological pattern of these tumours may change gradually, and progressively develop the typical morphology of the lesions in subgroups III and IV, which – unlike typically papillary carcinomas – tend to invade veins and produce distant metastases. Because of their poor histological differentiation, such tumours could closely mimic clear cell carcinomas or certain follicular cancers (formerly known as "Langhans' proliferating goiter"). However, the occasional papillary structures are unquestionable. Incidentally, the regionally striking resemblance of some tumours to haemangioendothelioma seems to justify the speculation as to whether the transformation noted might be caused by successive haemorrhage episodes within a moderately differentiated papillary tumour.

The patient's age is not the most important factor, but definitely plays a role. Our study shows that the poorly differentiated papillary carcinomas are found in notably older people. One may assume that the differentiation stage is related partially to age. The possibility that the disease may have progressed for such a long time in older people that an extrathyroid extension stage of the carcinoma is shown more frequently has to be kept in mind.

Histologically, and in its favourable clinical course, the "Lindsay's tumour" subgroup (Ic) approximates to the behaviour of well-differentiated papillary carcinomas. Our group of eosinophilic cancers is too small for a conclusive statistical evaluation, although tumours containing papillae seem to be less agressive than those without papillae: in fact, the former behave much like well-differentiated papillary tumours with regard to recurrence, lymph node involvement and dissemination via the bloodstream.

In addition, the series under study revealed a conspicuous correlation between histological pattern and the extension of the primary tumour: while occult lesions are restricted to the differentiated categories (I and IIa), extrathyroid tumours occur mainly in the less-differentiated subgroups (IIb, III and IV). Therefore, the notion of intrathyroid tumour is not sufficient in itself to predict the clinical development. The observation of the histological patterns is of great value in making a prognosis in these cases.

With this study we have attempted to rehabilitate the value and the significance of morphological features for the prognosis of papillary thyroid carcinomas. Confirming earlier findings in this field, our results indicate that the age of the patient at the time of diagnosis correlates well with the catamnestic data and that there is a still more pronounced relationship between extension of the primary tumour and long-term disease behaviour. In particular, we are convinced that even in the group of papillary thyroid carcinomas the histological pattern is a helpful prognostic parameter. Thus, it may prove useful to refine the histological criteria so as to permit discrimination between the various morphological patterns of papillary carcinoma. More particularly, we should study whether the functional behaviour of tumour cells and their ultrastructural features, both in transmission and scanning electron microscopy, allow a more reliable assessment of prognosis (see Böcker 1979; Böcker et al. 1980; Johannessen and Sobrinho Simões 1981).

References

Beaugié JM, Brown CL, Doniach I, Richardson JE (1976) Primary malignant tumours of the thyroid: The relationship between histological classification and clinical behaviour. Br J Surg 63:173–181

Böcker W (1979) Funktionelle Pathomorphologie der menschlichen Schilddrüsentumoren. Immunhistochemische und elektronenmikroskopische Untersuchungen. Veröffentlichungen aus der Pathologie, Heft 110. Gustav Fischer Verlag, Stuttgart, New York

Böcker W, Dralle H, Hüsselmann H, Bay V, Brassow M (1980) Immunohistochemical analysis of thyroglobulin synthesis in thyroid carcinomas. Virchows Arch (Pathol Anat) 385:187–200

Byar DP, Green SB, Dor P, Williams ED, Colon J, van Gilse HJ, Mayer M, Sylvester RJ, van Glabbeke M (1979) A prognostic index for thyroid carcinoma. A study of the E.O.R.T.C. Thyroid cancer cooperative group. Eur J Cancer 15:1033–1041

Cady B, Sedgwick CE, Meissner WA, Bookwalter JR, Romagosa V, Werber J (1976) Changing clinical, pathologic, therapeutic, and survival patterns in differentiated thyroid carcinoma. Ann Surg 184:541–553

Cady B, Sedgwick CE, Meissner WA, Wool MS, Salzman FA, Werber J (1979) Risk factor analysis in differentiated thyroid cancer. Cancer 43:810–820

Franssila KO (1973) Is the differentiation between papillary and follicular thyroid carcinoma valid? Cancer 32:853–864

Franssila KO (1975) Prognosis in thyroid carcinoma. Cancer 36:1138–1146

Franssila KO (1978) Outcome in papillary carcinoma of the thyroid. Ann Chir Gynaecol 67:49–57

Frauenhoffer CM, Patchefsky AS, Cobanoglu A (1979) Thyroid carcinoma. A clinical and pathologic study of 125 cases. Cancer 43:2414–2421

Frazell EL, Foote FW (1958) Papillary cancer of the thyroid. A review of 25 years of experience. Cancer 11:895–922

Georgii A, Lang W (1979) Frühe neoplastische Veränderungen in der Schilddrüse. Verh Dtsch Ges Pathol 63:203–218

Gérard-Marchant R, Flamant R, Sancho H (1970) Nomenclature et classification histopathologique des épithéliomas primitifs du corps thyroïde. (A propos de 306 observations). J Chir (Paris) 100:61–66

Harada T, Ito K, Shimaoka K, Hosoda Y, Yakumaru K (1977) Fatal thyroid carcinoma. Anaplastic transformation of adenocarcinoma. Cancer 39:2588–2596

Harwood J, Clark OH, Dunphy JE (1978) Significance of lymph node metastasis in differentiated thyroid cancer. Am J Surg 136:107–112

Hedinger Chr, Sobin LH (1974) Histological typing of thyroid tumours. International Histological Classification of Tumours Nr. 11. World Health Organization, Geneva

Hirabayashi RN, Lindsay S (1961) Carcinoma of the thyroid gland: A statistical study of 390 patients. J Clin Endocrinol Metab 21:1596–1610

Hofstädter F, Unterkircher S (1980) Histologische Kriterien zur Prognose der Struma maligna. Pathologe 1:79–85

Hubert JP jr, Kiernan PD, Beahrs OH, McConahey WM, Woolner LB (1980) Occult papillary carcinoma of the thyroid. Arch Surg 115:394–398

Hutter RVP, Tollefsen HR, De Cosse JJ, Foote FW, Frazell EL (1965) Spindle and giant cell metaplasia in papillary carcinoma of the thyroid. Am J Surg 110:660–668

Ibanez ML, Russell WO, Albores-Saavedra J, Lampertico P, White EC, Clark R Lee (1966) Thyroid carcinoma – biologic behavior and mortality. Postmortem findings in 42 cases, including 27 in which the disease was fatal. Cancer 19:1039–1052

Jeanneret M (1978) Carcinomes papillaires de la thyroïde. Thèse, Zürich

Johannessen JV, Sobrinho-Simões M (1981) Papillary carcinoma of the human thyroid gland. An ultrastructural study with emphasis on scanning electron microscopy. In: Fenoglio CM, Wollf M (eds) Progress in Surgical Pathology. Vol 3. Masson, New York, pp 111–128

Lindsay S (1960) Carcinoma of the thyroid gland. A clinical and pathologic study of 293 patients at the University of California Hospital. Charles C. Thomas, Springfield, Ill

Lindsay S (1969) Papillary thyroid carcinoma revisited. In: Hedinger ChrE (ed) Thyroid cancer. UICC Monograph Series Vol 12. Springer, Berlin Heidelberg New York, p 29

Mazzaferri EL, Young RL (1981) Papillary thyroid carcinoma: A 10 year follow-up report of the impact of therapy in 576 patients. Am J Med 70:511–518

Mazzaferri EL, Young RL, Oertel JE, Kemmerer WT, Page CP (1977) Papillary thyroid carcinoma: The impact of therapy in 576 patients. Medicine (Baltimore) 56:171–196

McKenzie AD (1971) The natural history of thyroid cancer. A report of 102 cases analyzed 10 to 15 years after diagnosis. Arch Surg 102:274–277

Meissner WA, Adler A (1958) Papillary carcinoma of the thyroid. Arch Pathol 66:518–525

Selzer G, Kahn LB, Albertyn L (1977) Primary malignant tumors of the thyroid gland. A clinicopathologic study of 254 cases. Cancer 40:1501–1510

Silverberg SG, Hutter RVP, Foote FW jr (1970) Fatal carcinoma of the thyroid: histology, metastases, and causes of death. Cancer 25:792–802

Sobrinho Simões MA (1978) Carcinoma oculto da tireóide. Proposta de interpretação biopatológica. Thesis, Porto

Sobrinho-Simões MA, Sambade MC, Gonçalves V (1979) Latent thyroid carcinoma at autopsy. A study from Oporto, Portugal. Cancer 43:1702–1706

Tollefsen HR, DeCosse JJ, Hutter RVP (1964) Papillary carcinoma of the thyroid. A clinical and pathological study of 70 fatal cases. Cancer 17:1035–1044

Woolner LB, Lemmon ML, Beahrs OH, Black BM, Keating FR jr (1960) Occult papillary carcinoma of the thyroid gland: A study of 140 cases observed in a 30-year period. J Clin Endocrinol Metab 20:89–105

Woolner LB, Beahrs OH, Black BM, McConahey WM, Keating FR jr (1961) Classification and prognosis of thyroid carcinoma. A study of 885 cases observed in a thirty year period. Am J Surg 102:354–387

Woolner LB (1971) Thyroid carcinoma: pathologic classification with data on prognosis. Semin Nucl Med 1:481–502

Wychulis AR, Beahrs OH, Woolner LB (1965) Papillary carcinoma with associated anaplastic carcinoma in the thyroid gland. Surg Gynecol Obstet 120:28–34

Accepted January 26, 1982