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The Differentiation of Atypical Adenomas and Encapsulated Follicular Carcinomas in the Thyroid Gland

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Summary. From 1968 to 1977 a total of 1,394 follicular neoplasms were seen in surgical material containing 4,612 thyroid glands. 1,159 tumors were obviously benign adenomas. All remaining follicular tumors with equivocal histological appearances were extensively re-examined, together with all apparently invasive follicular carcinomas. Thereby, 125 atypical adenomas, 55 encapsulated and 55 widely invasive follicular carcinomas were diagnosed. In 102 tumors a definite diagnosis was reached after excision and histological examination of ten tissue blocks from preserved wet material. In each case the number of blood vessel invasions and penetrations of tumor capsule was recorded. Among these tumors, 17/36 (47%) encapsulated carcinomas proved to be only slightly invasive. All their tissue blocks were cut into sequential sections and in 6/17 cases additional vascular invasions found. It was shown by this study that the proof of vascular invasion is more often successful than the proof of capsular penetration and therefore a better indication of malignancy in encapsulated follicular tumors. Examination of 10 tissue blocks represents the minimum effort to estimate the invasive capability of a follicular tumor, whereas sequential sections through less than 10 blocks are of little help in most cases. A follow-up study of all patients included here seems to justify the distinction we have made between atypical adenomas and encapsulated follicular carcinomas.

Key words: Follicular carcinoma of thyroid – Atypical adenoma – Encapsulated follicular carcinoma – Vascular invasion.

Zusammenfassung. In den Jahren 1968–1977 wurden insgesamt 1394 follikuläre Tumoren der Schilddrüse in einem Operationsgut von 4612 Strumen diagnostiziert. 1159 follikuläre Tumoren waren zweifelsfrei als Adenome einzuordnen. Alle übrigen follikulären Tumoren mit zunächst unklarer Dignität

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aber auch solche mit eindeutig invasivem Wachstum wurden histologisch eingehend nachuntersucht. Daraus resultierten 125 atypische Adenome, 55 weitgehend abgekapselte follikuläre Carcinome und 55 ausgedehnt invasive Carcinome. Bei 102 Tumoren stützte sich die endgültige Diagnose auf die histologische Nachuntersuchung von 10 Gewebsentnahmen aus dem kapselnahen Bereich. Dabei wurde die Zahl der Tumoreinbrüche in prae- oder postcapilläre Blutgefäße und die Zahl der kompletten Kapseldurchbrüche registriert. Bei 17/36 (47%) abgekapselten Carcinomen waren jeweils nur ein oder zwei Gefäßeinbrüche festzustellen. In diesen Fällen wurden die vorhandenen 10 Gewebsblöcke pro Tumor in 20 weiteren Schnittstufen aufgearbeitet und bei 6/17 zusätzliche Gefäßeinbrüche gefunden. Die quantitative Auswertung hat ergeben, daß der Nachweis von Gefäßeinbrüchen häufiger gelingt als der von Kapseldurchbrüchen und damit ein besserer Hinweis für die Malignität eines abgekapselten follikulären Tumors ist. Allerdings ist die Untersuchung von 10 Entnahmestellen das Minimum für eine zuverlässige Diagnose und mit Sicherheit nicht durch Schnittstufen mit weniger Gewebsblöcken zu erreichen. Der bisherige postoperative Verlauf aller in dieser Studie erfaßten Patienten rechtfertigt die nach den angegebenen Kriterien vorgenommene Unterscheidung zwischen atypischen Adenomen und abgekapselten follikulären Carcinomen.

The essential purpose of any tumor classification is to define morphological entities showing specific biological behaviourism. For this reason the WHO classification of thyroid neoplasms (Hedinger and Sobin, 1974; Hedinger, 1975) makes no distinction between simple, fetal or embryonal adenomas. All non-invasive encapsulated tumors without papillary structures are designated 'follicular adenomas' and all invasive tumors with histological patterns characteristic of adenomas are defined as 'follicular carcinomas'. Within the adenoma group this classification also includes tumors exhibiting a pronounced proliferative activity and some irregularity of architecture. These particular features were described in detail by Hazard (1954b). Especially American authors (Meissner and Warren, 1969; Woolner, 1971) used the term 'atypical adenoma'. The distinction of atypical adenomas from follicular carcinomas often poses real problems to even experienced thyroid pathologists and therefore needs a thorough search for vascular invasion (Hedinger, 1978). Comparable diagnostic problems do not appear in the usual type of adenoma. Thus, as long as a progression of atypical adenomas into malignancy has not been excluded by sufficient follow-ups, there are arguments regarding these tumors as a separate group of follicular adenomas. A further subdivision might be indicated with follicular carcinomas without regard to their histological differentiation. There are encapsulated tumors whose malignant potentiality is demonstrated by the proof of vascular invasion and/or capsular penetration to a minimal, sometimes moderate extent, opposed to widely invasive carcinomas. Several authors found a different clinical course of both types of tumor (Crile and Hawk, 1971; Hazard and Kenyon, 1954a; McKenzie, 1971; Woolner, 1971). Our own results support this view (Georgii, 1977).

The difficulties in differentiating atypical adenomas and encapsulated follicular carcinomas have often been discussed (Graham, 1924; Habermel, 1934; Warren, 1931; Zimmermann et al., 1950). It is still a matter of debate how extensive the histological examination should be for a reliable distinction.

Experienced authors have recommended various quantities of tissue blocks to be examined (Hazard and Kenyon, 1954b; Warren, 1956). However, there is no clear analysis showing the probability of correct diagnosis depending on the quantity of tissue blocks examined. For this purpose we have evaluated our material.

Material and Methods

Surgical specimen of thyroids containing adenomas and follicular carcinomas were studied. Among 4,612 thyroids subtotally or totally resected during 1968 to 1977 were 1,159 adenomas (25%), 125 atypical adenomas (2.7%) and 110 follicular carcinomas (2.4%) comprising 55 encapsulated carcinomas and 55 widely invasive carcinomas (see also Table 1). These numbers are related to revised diagnoses – see below.

1. Tumor size was measured in the surgical specimen, the largest diameter has been given in mm.

2. The original diagnoses were reviewed in all follicular tumors of equivocal histological nature and in all follicular carcinomas by examination of additional sections from the paraffin-embedded tissue blocks after staining them with hematoxylin-eosin and elastic-van Gieson. If needed, further staining was carried out such as Gomori-silver-impregnation, PAS-reaction or Congo-red.

3. Additional examination was carried out in 102 cases by excision of 10 tissue blocks from each tumor including the capsular region.

The thyroids had been preserved in slices of 5–10 mm in thickness kept in equal volumes of formalin (10%) and ethanol (70%). The usual paraffin technique has been applied for the histological procedure. On average, the tumor tissue within the paraffin block measured 20–25 × 15 mm in diameter and 3–4 mm in thickness. From each block 4 histological sections were prepared, one stained with hematoxylin-eosin and three with elastic-van Gieson. In this sequence, these histological sections were called 'routine sections'.

The following criteria were recorded by microscopical evaluation:

a) number of vascular invasions
b) number of capsular penetrations
c) principal and associated histological pattern.

Table 1. Follicular tumors (final diagnoses) in resected thyroid glands from 1968 to 1977

Follicular tumors	Number	(%)	Percentage of 4612 thyroids
Simple adenomas	1,159	83.0%	25.0%
Atypical adenomas	125	9.0%	2.7%
Follicular carcinomas	110	8.0%	2.4%
Encapsulated	55	4.0%	1.2%
Widely invasive	55	4.0%	1.2%
Total	1,394	100.0%	

4. Clinical data from the patients' histories were collected including age at time of diagnosis, sex, interval between the onset of presenting symptoms and surgical treatment, recurrences, metastases and death.

Results

Macroscopy

A macroscopic distinction between atypical adenoma and encapsulated follicular carcinoma in most cases was impossible. The cut surface of both types of tumor appeared parenchymatous, grey-red to whitish in color. Degenerative changes, especially hemorrhage, were found in both atypical adenoma and encapsulated follicular carcinoma in about 40%.

In exceptional cases of encapsulated follicular carcinoma, capsular breakthrough was suggested by small satellite-like tumor nodules adjacent to the capsule.

Of 125 atypical adenomas, tumor size was recorded in 78 cases and in 46 cases of 55 encapsulated follicular carcinomas. The mean diameter of atypical adenoma was 37.9 mm and of encapsulated follicular carcinoma 40.7 mm which presents a non-significant difference. The distribution of tumor size is given in Fig. 1. It appears that larger tumors are more often encountered in encapsulated follicular carcinomas than in atypical adenomas, although this difference was statistically also insignificant.

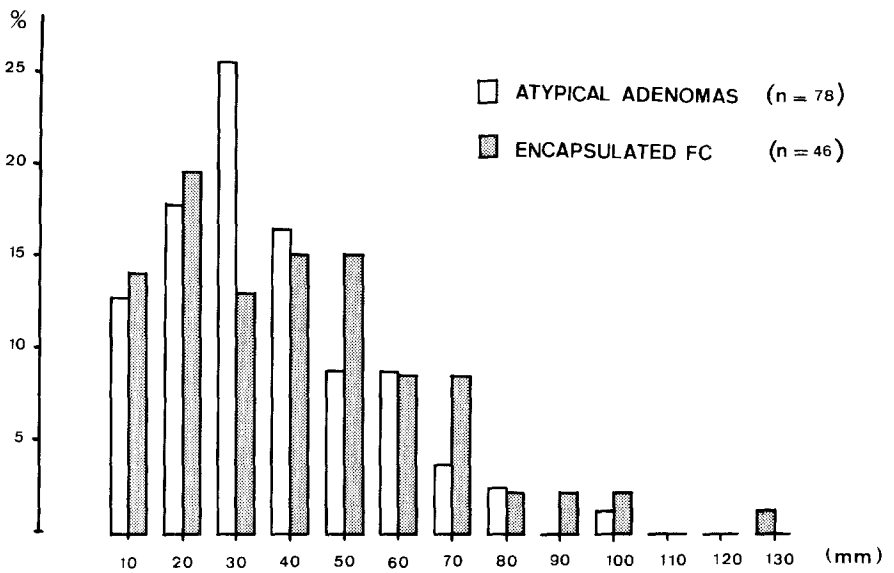


Fig. 1. Comparison of tumor size in 78 atypical adenomas and 46 encapsulated follicular carcinomas. Columns indicate frequency of tumors in classes of 10 mm in range, middle of each class is written on abscissa

Table 2. Preliminary versus final diagnosis after evaluation of 10 tissue blocks from 102 tumors

		Final diagnosis							
		A	AA	EFC	WIFC	AC	PC	Total	Accordance
Preliminary diagnosis	A	0	3	1	0	0	1	5	–
	AA	3	27	3	0	0	0	33	82%
	EFC	1	18	32	0	0	0	51	63%
	WIFC	0	0	0	11	1	0	12	(88%)
	AC	0	0	0	1	0	0	1	–
	Total	4	48	36	12	1	1	102	69%

A = 'simple adenoma, AA = atypical adenoma, EFC = encapsulated carcinoma, WIFC = widely invasive carcinoma, AC = anaplastic carcinoma, PC = papillary carcinoma

Histology

The principal histological pattern of atypical adenoma was microfollicular or mixed microfollicular and trabecular and/or solid in 80%. These patterns were found in 75% of encapsulated follicular carcinomas. The rest was either purely trabecular or completely solid. 19 encapsulated follicular carcinomas (17%) were normo-macrofollicular with a high colloid content. 8/125 (16.4%) atypical adenomas and 7/110 follicular carcinomas (6.4%) were purely oncocytic.

Examination of 10 extra blocks from each of 102 tumors resulted in 4 adenomas, 48 atypical adenomas, 36 encapsulated and 12 widely invasive carcinomas, 1 papillary and 1 anaplastic carcinoma (Table 2). 19/51 (37%) tumors originally diagnosed as encapsulated carcinomas were now classified into the adenoma group (18 atypical and 1 'simple' adenoma). 4/38 (10.5%) adenomas consisting of 33 atypical and 5 'simple' adenomas following the preliminary diagnosis were actually invasive and therefore classified into the encapsulated carcinoma group.

21/48 (44%) atypical adenomas had one or more pseudo-infiltrations of their capsule. In the 36 encapsulated follicular carcinomas vascular invasions were found in variable numbers (Fig. 2). 9/36 (25%) encapsulated follicular carcinomas had only one vascular invasion in 10 tissue blocks. Another 8/36 (22%) had two invasions in 10 blocks. The rest of encapsulated follicular carcinomas had three to nine vascular invasions. On average, 3 vascular invasions out of 10 tissue blocks were demonstrated for the whole group of encapsulated carcinomas. By contrast, the 12 widely invasive carcinomas had 6–7 invasions on average. The number of capsular penetrations in encapsulated carcinomas was still less, 14/36 (39%) encapsulated carcinomas had none at all (Fig. 2). A single tumor had no vascular invasion but did have one unequivocal capsular penetration and was thus accepted as encapsulated follicular carcinoma. More than 10 blocks could not be taken in this case.

The above mentioned 17 encapsulated carcinomas showing only one or two vascular invasions in routine sections from 10 tissue blocks have been further examined. Each block was completely cut into serial sections out of which

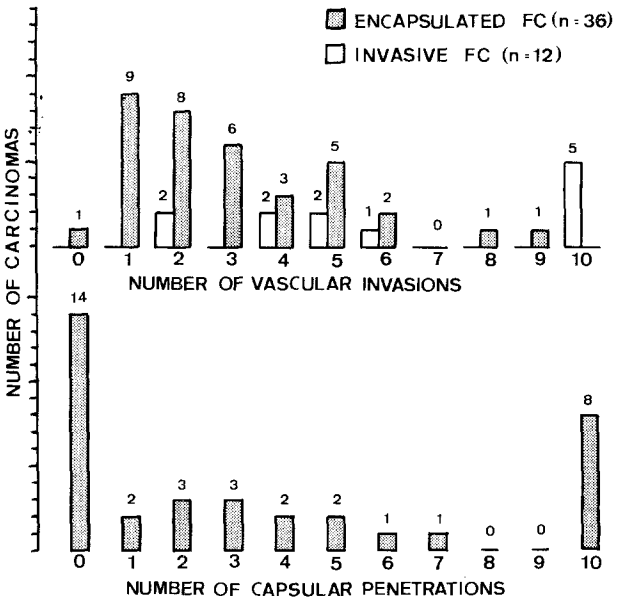


Fig. 2. Upper half: number of vascular invasions found in 36 encapsulated follicular carcinomas and 12 invasive follicular carcinomas. Lower half: number of capsular penetrations in 36 encapsulated follicular carcinomas. In each tumor 10 tissue blocks were examined

Table 3. Number of vascular invasions found in 10 tissue blocks of encapsulated follicular carcinomas with minimal invasiveness by routine sections[a] and 20 additional sequential sections

Tumor (Case No.)	I	II	III	IV	V	VI	VII	VIII	IX
Number of vascular invasions found in 10 blocks per tumor									
by routine sections[a]	1	1	1	1	1	1	1	1	1
by following 20 sections	1	1	0	0	0	0	0	0	0
Total	2	2	1	1	1	1	1	1	1
Tumor (Case No.)	X	XI	XII	XIII	XIV	XV	XVI	XVII	
Number of vascular invasions found in 10 blocks per tumor									
by routine sections[a]	2	2	2	2	2	2	2	2	
by following 20 sections	3	2	1	1	0	0	0	0	
Total	5	4	3	3	2	2	2	2	

[a] Routine sections: 4 histological sections (1 HE, 3 Ev Gieson) from each block

20 steps have been examined and additional vascular invasions counted. The result is shown in Table 3. In 9 tumors that originally showed a single invasion we could demonstrate one additional invasion each. Of the remaining 8 carcinomas, routine sections showing 2 invasions each, we could establish one to three additional invasions. One of two widely invasive follicular carcinomas

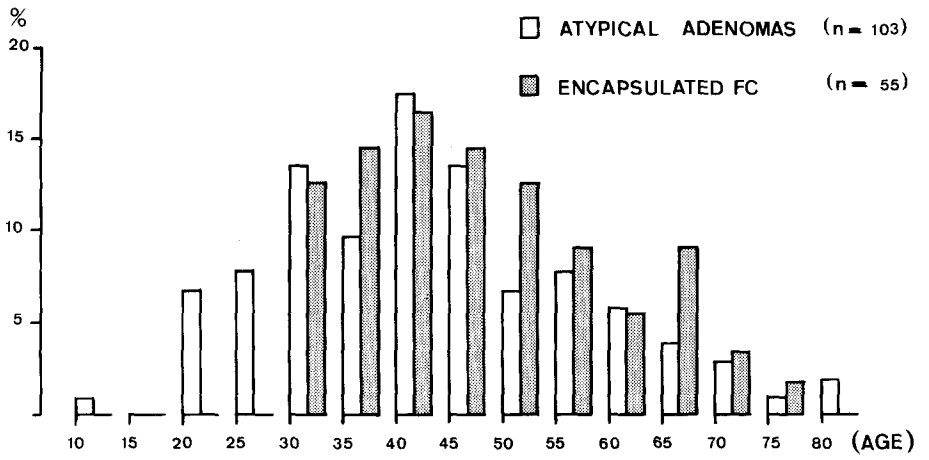


Fig. 3. Age distribution of 103 patients with atypical adenomas and 55 patients with encapsulated follicular carcinomas at time of operation. Age of patients in classes of 5 years with first year of each class written on abscissa

(not recorded in Table 3) with 2 invasions in routine sections showed 5 additional invasions.

All in all 7/19 (37%) tumors furnished additional proof of invasiveness, 12/19 (63%) revealed no further vascular invasion.

Clinical Data

The age-specific incidence of patients bearing an atypical adenoma or encapsulated follicular carcinoma at time of surgery differed by 4.6 years (Fig. 3). The mean age of patients with an atypical adenoma was 44.9 years, with encapsulated follicular carcinoma it was 49.5 years. This difference was statistically significant (t-test; $P < 0.05$). The male to female ratio was 1:7.4 for atypical adenomas and 1:5.9 for encapsulated follicular carcinomas. For 'simple' adenomas the ratio was 1:5 and for all follicular carcinomas 1:4.2.

In 36/125 atypical adenomas and 35/55 encapsulated follicular carcinomas reliable information was found in patients' histories as to the presenting symptoms and their duration up to surgery. The mean interval between the onset of symptoms and surgery was 9.5 months in patients with atypical adenomas and 10.1 months in encapsulated follicular carcinomas. This difference was not significant.

Follow-up was possible in 88/125 (70%) patients bearing an atypical adenoma. All 55 patients with encapsulated follicular carcinomas have been followed up until 1978. Meanwhile, one atypical-adenoma-patient has died without clinical evidence of local tumor recurrence or metastases. Out of the encapsulated follicular carcinoma-patients one died without signs of tumor recurrence. During a mean period of follow-up amounting to 2.9 years in atypical-adenoma-patients no local recurrence or metastasis was observed.

In encapsulated follicular carcinoma-patients the mean follow-up was 3.7 years. 2/55 (3.6%) had regional lymph-node metastases.

Discussion

Morphologically there is no clear cut boundary between atypical adenomas and 'usual' adenomas and their clinical significance may be largely identical. No local recurrences or distant metastases have been observed in atypical adenomas after complete surgical removal (Hofstädter et al., 1979). In a single report such as the one of Silverberg (1966), a fetal adenoma has caused metastases. This was unusually large tumor and the author did not give any information concerning the extent of histological examination that had been undertaken to exclude its invasiveness.

The most important difference between atypical adenoma and 'usual' adenoma is the increased proliferative activity. Following Hazard (1954b), the mitotic rate is significantly raised in atypical adenoma and is about equal to that of encapsulated follicular carcinoma. Since the mitotic activity and also the DNA-content of cells in atypical adenoma and encapsulated carcinoma are indistinguishably high (Haemmerli et al., 1968; Lindsay, 1970) the proof of invasiveness remains the only distinctive feature. Even though invasiveness cannot be established in atypical adenoma its histological and cytological appearance suggests that a later transformation into carcinoma might be possible. Therefore we believe that a distinction between 'usual' adenoma and atypical adenoma should be maintained at least until long-term follow-up studies have brought a definite decision. Also as follow-up is concerned, the classification into encapsulated follicular carcinoma and widely invasive carcinoma seems to be justified (Hazard and Kenyon, 1954b; McKenzie, 1971; Warren, 1931; Woolner, 1971). The main point is that encapsulated follicular carcinomas may actually be prone to metastasize and even fatal cases have been reported – however seldom – (Batsakis et al., 1960; Crile and Hawk, 1971; Woolner, 1971). Our own results appear to confirm this view in spite of a relatively short follow-up period of about three to four years on average (Georgii, 1977; Lang et al., 1977). However, Hazard (1954a) has concluded from his extensive material that recurrences and metastases by follicular carcinomas have usually been observed during the first five-year period following surgery.

The mean age of our patients with atypical adenoma and encapsulated follicular carcinoma differs by five years. This too gives reason to conclude that encapsulated follicular carcinoma could originate from atypical adenoma. Such a possibility is not accepted unanimously (Clark et al., 1966; Iida, 1973; Silverberg and Vidone, 1966).

In our material the frequency of atypical adenoma (9.8% of all adenomas) is relatively high. A still higher percentage has been found by Hofstädter (1979). In a survey published by Neracher and Hedinger (1975) a frequency of only 3% was reported. The reason for this discrepancy may be that we are rather prone to diagnose an atypical adenoma where there is increased proliferative activity. The frequency of encapsulated follicular carcinoma among our surgical

Table 4. Criteria for the distinction of atypical adenoma and encapsulated follicular carcinoma by histological examination. These are based on the first description of Hazard and Kenyon (1954b) and consecutive discussions (Warren, 1956; Woolner, 1971)

Diagnostic criteria	Atypical adenoma	Encapsulated carcinoma
I Growth pattern	Suggesting malignancy: – high cellularity plus increased mitotic rate – (increased nuclear size) – disturbed architecture	Resembling atypical adenoma: e.g. indistinguishable from atypical adenoma
II Tumor capsule	Questionable infiltration[a]: – focal attenuation of capsule – cellular lump within capsule – splitting of capsule	Unquestionable penetration: one ore more complete disruptions of capsule
III Blood vessels	Questionable invasion[a]: – tumor cells intruding into space without clearly identifiable vascular wall – isolated cellular aggregates within vascular space	Unquestionable invasion: – one or more disruptions of distinct vascular wall by tumor cells – tumor thrombus filling vascular space

[a] Facultative diagnostic criterion

specimen (1.2%) is comparable to that found in the literature (Batsakis et al., 1960; Hazard and Kenyon, 1954b; Neracher and Hedinger, 1975; Warren, 1931).

The diagnostic criteria we have used to distinguish atypical adenomas and encapsulated carcinomas are summarized in Table 4. In the microscopical evaluation of vascular invasion and capsular penetration the following points have been observed: capsular penetration was only assumed to have occurred if complete disruption of the fibrous capsule and infiltration of adjacent normal tissue could be demonstrated in the elastic-van Gieson-stained section (Fig. 4a). Splitting of tumor capsule or incomplete infiltration and attenuation of capsule was not taken as proof of invasiveness (Fig. 4b). The latter findings were called 'pseudoinfiltration' because a reliable distinction between this and the sclerosing process often found in the capsular region might be impossible. Blood vessel invasion was mainly searched for near the tumor capsule since vascular invasion might be obscured or simulated in central parts of tumor by hemorrhage and regressive changes. Thereby we followed the opinion given by Hazard (1954a) and the fact is that unquestionable vascular invasion has not been found very often in central parts of tumors. Invasion was only assumed if elastic-van Gieson-stained sections or Gomori's silver-stain showed disruption of the vascular wall or complete stuffing of the vascular space by a tumor thrombus (Fig. 5a). A few tumor cells or even small groups of tumor cells within a vascular space (Fig. 5b) were regarded as artifacts (Horn, 1960). Infiltration of sinusoids or capillaries was only accepted if the disrupted endothelial layer could be demonstrated without any doubt (Fig. 5c). Groups of tumor cells intruding into sinu-

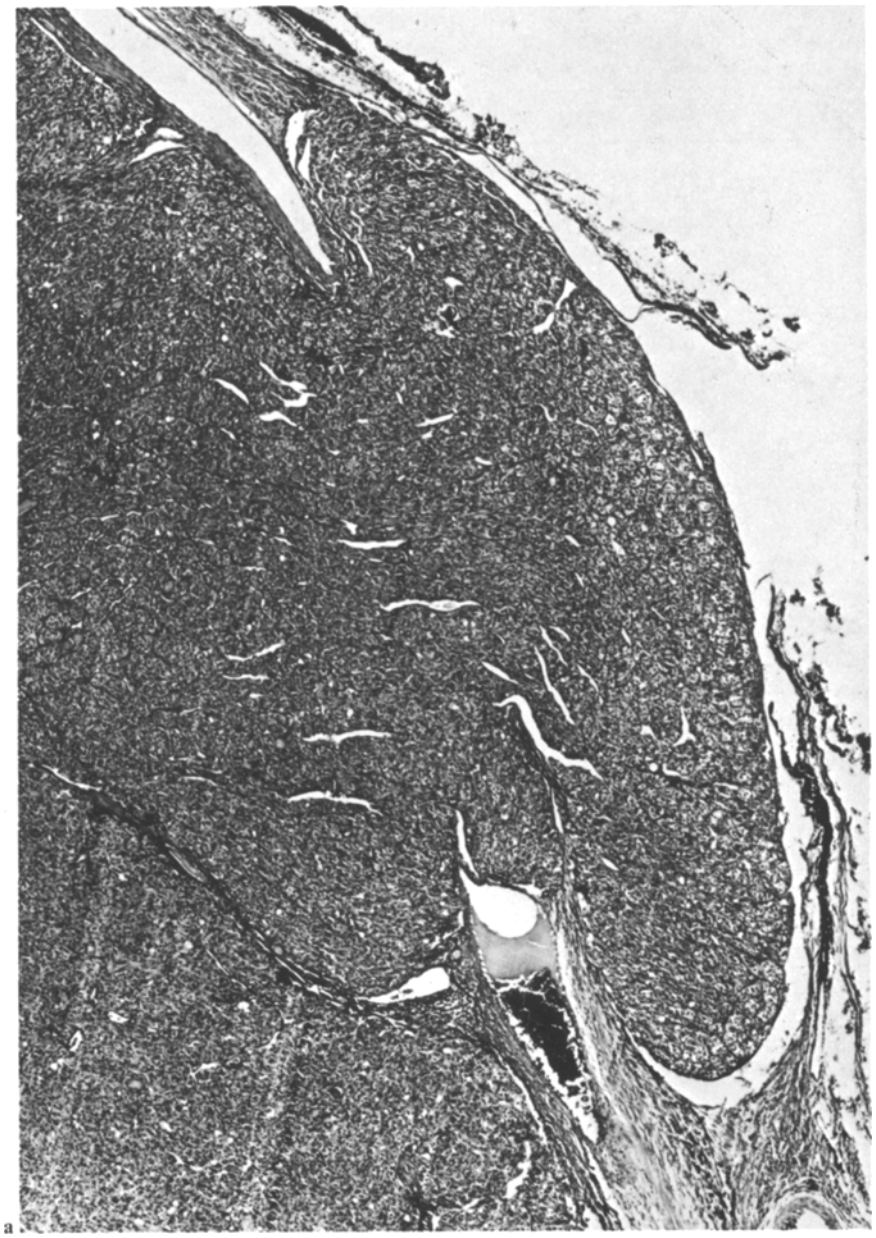
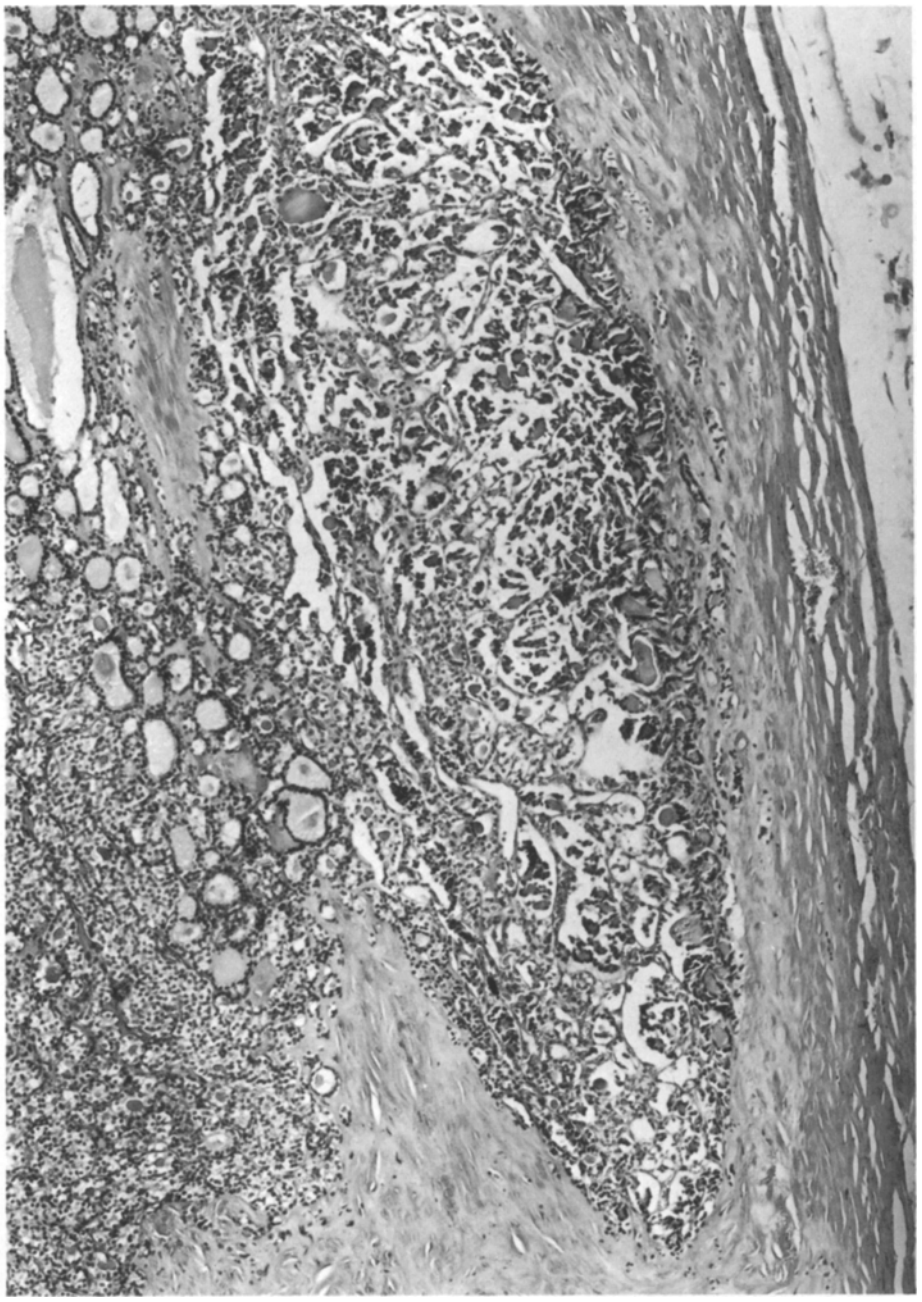


Fig. 4. a Capsular penetration by an otherwise encapsulated follicular carcinoma. 70-year old female (EvG, ×63). **b** Pseudo-infiltration of tumor capsule with atypical adenoma probably caused by process of irregular scarring or sclerosis. 45-year old female (EvG, ×125)



b

soid-like spaces which present a frequent finding in trabecular of solid tumors (Fig. 5d) sometimes give rise to misinterpretation.

Applying these criteria of invasiveness we had to revise a number of diagnoses of 'encapsulated carcinomas' (37% – see Table 2) where often equivocal situations had been overestimated as vascular invasion. In a smaller number of

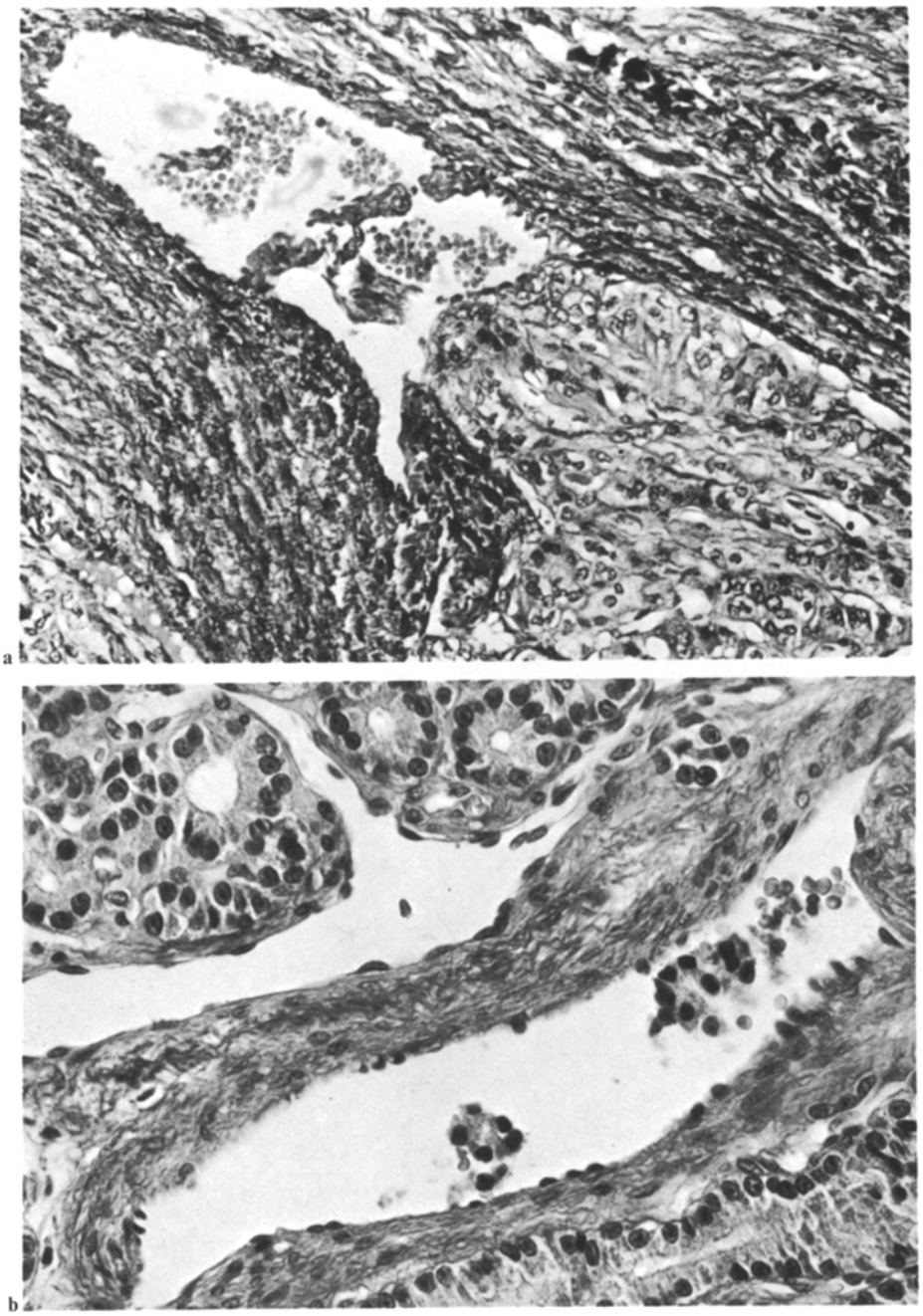
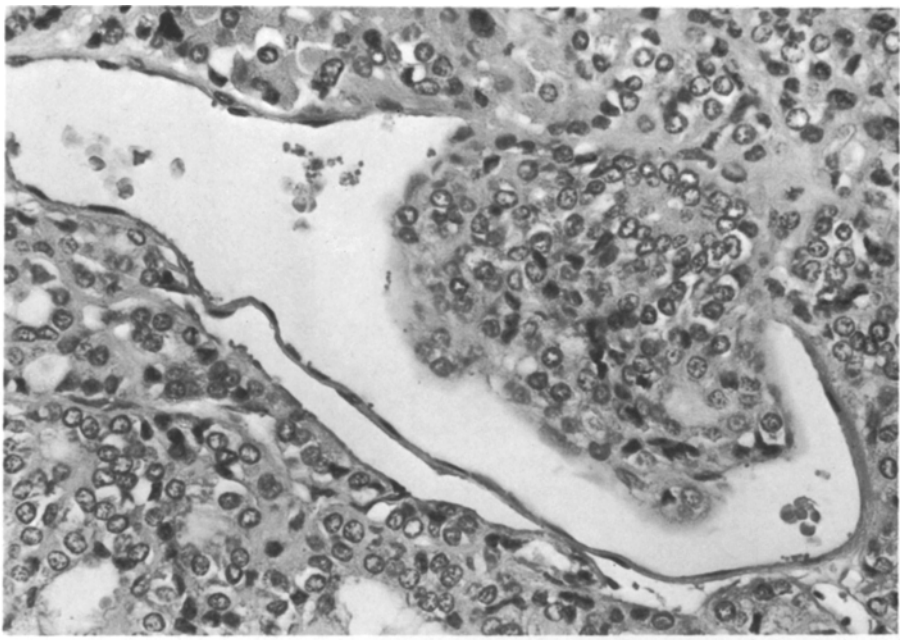


Fig. 5. a Vascular invasion with tumor mass intruding into vessel space. Encapsulated follicular carcinoma in a 33-year old female (EvG, ×250). **b** Pseudo-invasion of vessel with small groups of tumor cells within vascular space. Atypical adenoma in a 19-year old female (EvG, ×390). **c** Invasion of thin walled blood vessel by an encapsulated follicular carcinoma showing disruption of endothelial layer. 45-year old female (EvG, ×390). **d** Pseudo-invasion simulated by protrusion of tumor cells into sinusoid-like space. Encapsulated follicular carcinoma in a 65-year old male (Ag, ×390)



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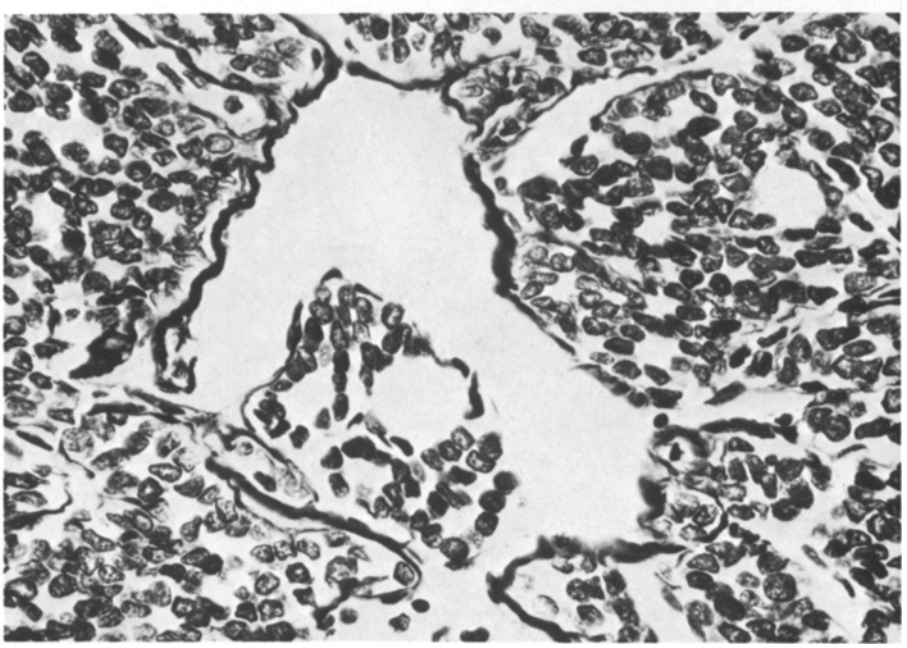

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'atypical adenomas' following the preliminary diagnosis (10.5%) unquestionable invasion was found. However, the 102 adenomas and carcinomas, re-examined in extra blocks, consisted mainly of tumors whose diagnosis appeared already difficult at the time of first examination. Within the total group of follicular neoplasms which have been reviewed the diagnosis was revised in 24%.

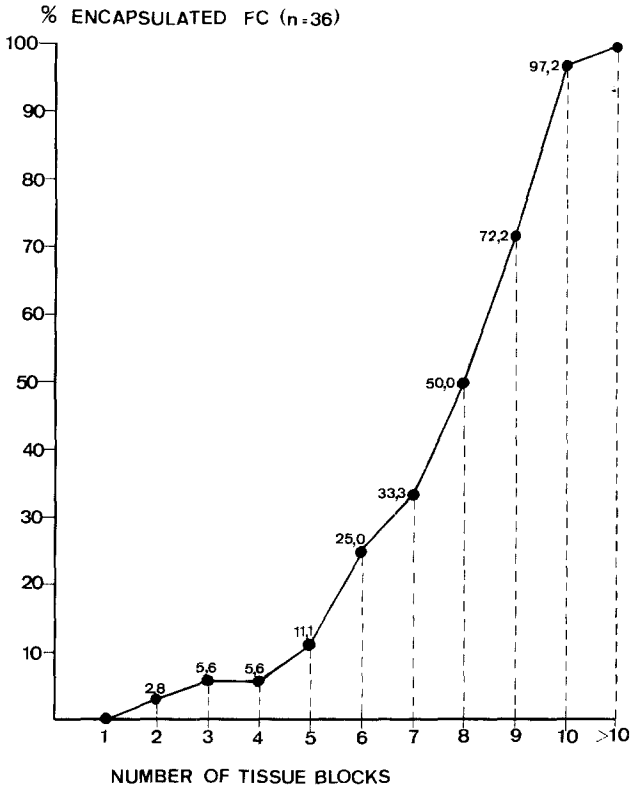

Fig. 6. The dependence of detecting a carcinoma on the number of tissue blocks examined: percentage of 36 encapsulated follicular carcinomas detectible by examination of the respective number of tissue blocks

A quantitative histological study concerning the differentiation of atypical adenomas and encapsulated follicular carcinomas gives the most important information. In contrast to some statements in the literature (Hazard and Kenyon, 1954b; Warren, 1956) we have shown that histological examination of 10 tissue blocks of an encapsulated follicular tumor is the minimum necessary to assess its true nature. A still more extensive search might possibly reveal some further tumors whose invasive capability was not detected by examination of 10 tissue blocks. This conclusion may be supported by the fact that a great part of our encapsulated follicular carcinomas had only one or two vascular invasions in 10 blocks. However, the diagnostic effort proposed was based mainly on practical grounds. Most tumors under consideration were relatively small so that no more material was available for examination. In addition we found no significant correlation between tumor size and number of vascular invasions. Furthermore, the two encapsulated follicular carcinomas which gave rise to regional lymph node metastases did not exceed average tumor size.

On the other hand we did not see recurrent diseases or metastases within the group of tumors diagnosed as atypical adenomas.

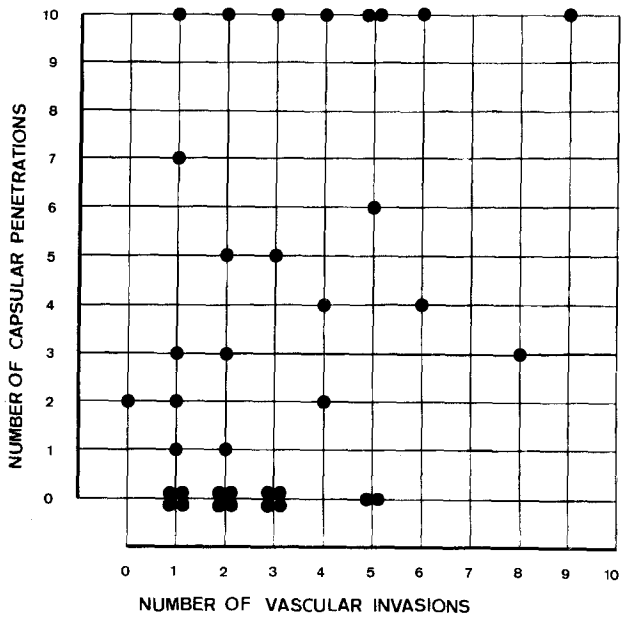

Fig. 7. Vascular invasion versus capsular penetration in 36 encapsulated follicular carcinomas. Each tumor (represented by a black dot) is entered into the grid according to its number of vascular invasions and capsular penetrations found in 10 tissue blocks

The great advantage in sampling a series of histological sections is that strict criteria may be applied to exclude every artifact simulating vascular invasion. Furthermore, the chance of detecting vascular invasion is greater from sampling many different areas of the whole circumference of a tumor than from looking for it in a few blocks with sequential histological sections. In Fig. 6, the probability of correct diagnosis is shown to be dependent on the number of tissue blocks excised. In none of the 36 encapsulated follicular carcinomas vascular invasion could be found in every tissue block, i.e., in no case the diagnosis could be reached with certainty from a single block. Only 1/36 tumors (2.8%) had one invasion in each of 9 blocks, i.e., 2 blocks would have been sufficient for diagnosis instead of 10. Using 8 blocks only 50% of all tumors were diagnosed, whereas using 10 blocks practically all tumors could be diagnosed.

In agreement with Warren (1956) vascular invasion appears to be of greater importance for diagnosis than capsular penetration. This conclusion is supported when the number of vascular invasions and capsular penetrations found in each encapsulated follicular carcinoma are compared with each other (Fig. 7). Thereby, no correlation is found between the frequencies of these two diagnostic criteria. As might be seen in Fig. 7, where each tumor is represented by a black dot, 14/36 encapsulated follicular carcinomas (39%) are found in the lowest row indicating that there is no capsular penetration in spite of one or more vascular invasions.

All other morphological criteria for differentiation of atypical adenomas and encapsulated follicular carcinomas are less reliable. Examination of ultrastructure or chromosomal analyses (Beierwaltes and Al-Saadi, 1966; Lupulescu and Boyed, 1972) do not give prompt and clear results. Karyometric studies using histological sections of those tumors (Lang et al., 1977; Ostertag et al., in preperation) are of limited value. Standardization of the distribution of nuclear size for both tumors has not yet been established.

The value of cytological differentiation of adenomas and encapsulated carcinomas by fine needle aspiration smears or direct imprint from fresh surgical material has been discussed in a separate study (Lang et al., 1978).

References

Batsakis, J.G., Nishiyama, R.H., Rich, C.R.: Microlithiasis (calcospherites) and carcinoma of the thyroid gland. Arch. Pathol. **69**, 493–498 (1960)

Beierwaltes, W.H., Al-Saadi, A.A.: Chromosome abnormalities in human thyroid disease. J. Clin. Endocrinol. Metab. **26**, 729–734 (1966)

Clark, R.L., Ibanez, M.L., White, E.C.: What constitutes an adequate operation for carcinoma of the thyroid. Arch. Surg. **92**, 23–26 (1966)

Crile, G., Hawk, W.A.: Carcinomas of the thyroid. Cleve. Clin. Q. **38**, 97–104 (1971)

Georgii, A.: Die epithelialen Tumoren der Schilddrüse. Verh. Dtsch. Ges. Path. **61**, 191–208 (1977)

Graham, A.: Malignant epithelial tumors of the thyroid with special reference to invasion of blood vessels. Surg. Gynecol. Obstet. **39**, 781–790 (1924)

Habermel, J.F.: Relation of fetal adenoma to malignancy of the thyroid gland. Am. J. Surg. **25**, 97–101 (1934)

Haemmerli, G., Sträuli, P., Schlüter, G.: Deoxyribonucleic acid measurements on nodular lesions of human thyroid. Lab. Invest. **18**, 675–680 (1968)

Hazard, J.B., Kenyon, R.: Encapsulated angioinvasive carcinoma (angioinvasive adenoma) of thyroid gland. Am. J. Clin. Pathol. **24**, 755–766 (1954a)

Hazard, J.B., Kenyon, R.: Atypical adenoma of the thyroid. A.M.A. Arch. Pathol. **58**, 554–563 (1954b)

Hedinger, Chr., Sobin, L.H.: Histologic typing of thyroid tumours. International Histological Classification of Tumours. Nr. 11. Geneva: WHO 1974

Hedinger, Chr.: Klassifizierung der Schilddrüsentumoren. Schweiz. med. Wschr. **105**, 997–1000 (1975)

Hedinger, Chr.: Pathologie der Schilddrüsengeschwülste. In: Diagnostik und Therapie der Schilddrüsentumoren. Stuttgart-New York: Schattauer 1978

Hofstädter, F., Schistek, R., Ladurner, D.: Morphologie und klinischer Verlauf des „atypischen Adenoms" der Schilddrüse. Verh. Dtsch. Ges. Path. **63**, (1979) (in press)

Horn, R.C.: Problems in the pathologic diagnosis of carcinoma of the thyroid. A.M.A. Arch. Pathol. **69**, 481–492 (1960)

Iida, F.: The fate and surgical significance of adenoma of the thyroid gland. Surg. Gynecol. Obstet. **136**, 536–540 (1973)

Lang, W., Georgii, A., Atay, Z.: Differentialdiagnose zwischen atypischen Adenomen und follikulären Carcinomen der Schilddrüse. Verh. Dtsch. Ges. Path. **61**, 275–279 (1977)

Lang, W., Atay, Z., Georgii, A.: Die cytologische Unterscheidung follikulärer Tumoren in der Schilddrüse. Virchows Arch. A Path. Anat. and Histol. **378**, 199–211 (1978)

Lindsay, S.: Microspectrophotometric measurements of deoxyribonucleic acid in human thyroid carcinomas. Surg. Gynecol. Obstet. **131**, 905–913 (1970)

Lupulescu, A.P., Boyd, C.B.: Follicular adenomas – an ultrastructural and scanning electron microscopic study. Arch. Pathol. **93**, 492–502 (1972)

McKenzie, A.D.: The natural history of thyroid cancer. Arch. Surg. **102**, 274–277 (1971)

Meissner, W.A., Warren, S.: Tumors of the thyroid gland. In: Atlas of tumor pathology. Second series, fascicle 4, p. 46. Washington: AFIP 1969

Neracher, H., Hedinger, Chr.: Klassifizierung der Schilddrüsenmalignome nach der Nomenklatur der WHO 1974. Schweiz. med. Wschr. **105**, 1000–1006 (1975)

Ostertag, H., Choritz, H., Lang, W., Georgii, A.: Karyometric investigations in follicular tumours of the thyroid by image analysis. (in preparation)

Silverberg, S.G., Vidone, R.A.: Adenoma and carcinoma of the thyroid. Cancer **19**, 1052–1062 (1966)

Warren, S.: Significance of invasions of blood vessels in adenomas of the thyroid gland. Arch. Pathol. **11**, 255–257 (1931)

Warren, S.: Invasion of blood vessels in thyroid cancer. Am. J. Clin. Pathol. **26**, 64–65 (1956)

Woolner, L.B.: Thyroid carcinoma: pathologic classification with data on prognosis. Semin. Nucl. Med. **1**, 482–502 (1971)

Zimmermann, L.M., Wagner, D.H., Perlmutter, H.M., Amromin, G.D.: Benign and malignant epithelial tumors of the thyroid gland. A.M.A. Arch. Surg. **60**, 1183–1198 (1950)

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