Book PUB: 01/2012

Clinical approach to well-differentiated thyroid cancers

Edited by

Frederick L. Greene
Andrzej L. Komorowski

BYWORD BOOKS™

Contents

Foreword

Differentiated thyroid cancer belongs to the small group of human malignancies with very good prognosis. Excellent outcomes result from the unique tumour biology and constantly improving treatment options. This book was constructed as a concise clinical guide to the current management of this tumour.

The authors come from 9 countries and 4 continents. The wide geographical distribution and different clinical background of each author result in a unique perspective on a clinical problem. As a rule, the commentaries are written by specialists based in a country other than the country of the author of the chapter.

Some topics are covered by more than one chapter. This is because we believe that each part of the book should be "functionally" complete to avoid browsing through the pages in search of information that should logically appear also in the chapter the reader is currently reading.

We do hope that this book will help our readers to treat their patients better. We will be more than happy to receive feedback (z5komoro@cyf-kr.edu.pl). This way, the editors can also do better in the future.

Frederick L. Greene
Andrzej L. Komorowski

Dosage schedules are being constantly revised and new side-effects recognized. The reader is thus strongly urged to consult the printed instructions of drug companies before administering any of the drugs recommended in this book. It is possible that errors might have crept in despite our best efforts to check drug dosages.

First published 2012

10 9 8 7 6 5 4 3 2 1

ISBN 978-81-8193-082-8

Cover design: Netra Shyam
Typesetting: Jacob Thomas

Published by
Byword Books Private Limited
GF-15, Virat Bhavan
Mukherjee Nagar Commercial Complex
Delhi 110009, India; Phone: 011-47038040
email: bywordbooks@gmail.com
website: www.bywordbooks.in

Printed at Replika Press Limited, India

Dedicated to the memory of my grandfathers

Władysław Roman Bochenek, engineer, prisoner of the Gross Rosen and Mittelbau-Dora German Concentration Camps, who taught me the love for the unspoiled nature

and

Adam Ignacy Komorowski, master in goldsmithery, soldier of the Polish First Army, who taught me the meaning of the word Katyń

ALK

List of contributors

Marcin Barczyński
Department of Endocrine Surgery,
3rd Chair of General Surgery
Jagiellonian University, Medical College, Kraków,
Poland

Tahar Benhidjeb
Department of General,
Visceral and Thoracic Surgery
University Medical Center Hamburg-Eppendorf, Hamburg,
Germany

Carmine De Bartolomeis
Department of Surgery, University of Pisa
Ospedale Santa Chiara, Pisa,
Italy

Istvan Gal
Department of Surgery
Telki International Private Hospital, Telki,
Hungary

Frederick L. Greene
Chairman, Department of General Surgery
Carolinas Medical Center,
Charlotte, North Carolina,
USA

Stephen J. Gwyther
Consultant Radiologist
East Surrey Hospital, Redhill, Surrey,
UK

Daria Handkiewicz-Junak
Department of Nuclear Medicine and Endocrine Oncology
Maria Sklodowska-Curie Memorial Cancer Center
and Institute of Oncology, Gliwice Branch, Gliwice,
Poland

Pietro Iacconi
Department of Surgery,
University of Pisa
Ospedale Santa Chiara, Pisa,
Italy

Barbara Jarząb
Department of Nuclear Medicine and Endocrine Oncology
Maria Skłodowska-Curie Memorial Cancer Center
and Institute of Oncology, Gliwice Branch, Gliwice,
Poland

R. Kalyani
Sri Devaraj Urs Medical College
Sri Devaraj Urs Academy of Higher education and
Research Consultant Pathologist,
Sri R.L. Jalappa Hospital and Research Centre,
Kolar, Karnataka
India

Stanislaw Kłęk
Department of General Surgery
1st Chair of General Surgery
Jagiellonian University, Medical College
and Nutrimed Medical Corporation, Kraków,
Poland

Andrzej L. Komorowski
Department of General Surgery
Hospital Virgen del Camino,
Sanlúcar de Barrameda,
Spain

2

Pathology of differentiated thyroid cancers

Janusz Ryś and Joanna Wysocka

This chapter discusses briefly the pathological aspects of differentiated thyroid cancers. The authors explain the histological features of thyroid cancers and possible approaches for making a firm diagnosis. The prognosis of different subtypes of differentiated thyroid cancer is also discussed.

Introduction

Thyroid cancers represent a heterogeneous group of neoplasms that comprise ~1% of all human malignancies. They constitute the bulk of cancers of the endocrine system and are responsible for the majority of deaths associated with malignant endocrine neoplasms. On the basis of their morphology, clinical features and molecular characteristics of the tumour cells, these tumours have traditionally been divided into major categories of well-differentiated (papillary or follicular), medullary, and undifferentiated carcinomas. Almost 90% of all thyroid malignancies are well-differentiated carcinomas (WDTC) that originate from the follicular epithelial cells and possess the ability to produce and release thyroid hormones. This category includes both papillary and follicular carcinomas. According to the WHO classification, the Hürthle-cell carcinoma is recognized as a variant of follicular carcinoma.

Most of the WDTCs behave like indolent tumours and have an excellent prognosis; the 5-year survival rate of patients exceeds 90%.

Fine-needle aspiration cytology of thyroid nodule

Fine-needle aspiration biopsy (FNAB) is a basic, common test that is considered the method of choice for diagnosis in the current recommendations for management of thyroid nodules. It is a minimally invasive procedure with enough sensitivity and specificity, which protects as many as 75% of patients with clinically solitary nodules, thereby eliminating the need for further tests and unnecessary surgical treatment.

To minimize any disparity in diagnoses by cytopathologists/pathologists

Table 2-1. The Bethesda System for Reporting Thyroid Cytopathology; recommended diagnostic categories and risk of malignancy (according to SZ Ali and ES Cibas—modified)

Diagnostic categories of FNA of thyroid gland	Risk of malignancy (%)
I. Non-diagnostic or unsatisfactory	
II. Benign – Consistent with a benign follicular nodule (includes adenomatoid nodule, colloid nodule, etc.) – Consistent with lymphocytic (Hashimoto) thyroiditis in the proper clinical context – Consistent with granulomatous (subacute) thyroiditis – Others	0–3
III. Atypia of undetermined significance or follicular lesion of undetermined significance	5–15
IV. Follicular neoplasm or suspicious for a follicular neoplasm – Specifying of oncocytic type of neoplasm is recommended	15–30
V. Suspicious for malignancy – Suspicious for papillary carcinoma – Suspicious for medullary carcinoma – Suspicious for metastatic carcinoma – Suspicious for lymphoma	60–75
VI. Malignant – Papillary thyroid carcinoma – Poorly differentiated carcinoma – Medullary thyroid carcinoma – Undifferentiated (anaplastic) carcinoma – Squamous cell carcinoma – Carcinoma with mixed features – Metastatic carcinoma – Non-Hodgkin lymphoma	97–99

FNA fine-needle aspiration

and clinicians, the Bethesda System for Reporting Thyroid Cytopathology (BSRTC) recommends that each thyroid FNAB report should begin with a general diagnostic category. The six BSRTC diagnostic categories are depicted in Table 2-1. Adequate smears are divided into four groups: (i) benign, (ii) undetermined, (iii) suspicious (groups IV–V, Table 2-1), and (iv) malignant. The benign category includes a normal thyroid, nodular goitre or hyperplastic/adenomatoid nodule, as well as lymphocytic or granulomatous thyroiditis. The group of malignant smears includes papillary carcinoma, medullary carcinoma, poorly differentiated and undifferentiated carcinoma, lymphoma, and metastatic or secondary malignant neoplasm. The suspicious category concerns mainly follicular neoplasms because the cytological features of follicular carcinoma and follicular adenoma are undistinguishable. It also refers to oncocytic tumours (which are included in the group of follicular neoplasms). This category applies also to smears of papillary and medullary carcinomas and/or lymphomas, which lack the specific cytological features required for diagnosing a malignant lesion.

In the case of thyroid cancer, the sensitivity and specificity of FNAB ranges from 65% to 98% and from 72% to 100%, respectively. The rate of false-negative results is estimated to vary from 1% to 11% and the false-positive results from 0% to 7%.

Cytological features that are diagnostic of papillary thyroid carcinoma

Papillary thyroid carcinoma (PTC) presents characteristic cytological features that can be recognized easily in aspirates. Typical aspirates from PTC contain an abundance of cells that may be grouped in three-dimensional clusters (Fig. 2-1) and syncytial-like flat sheets ('monolayers') or formed papillary arrangements. Crowding, overlapping and molding of the cancer cells are important features that distinguish them from benign follicular cells (Figs 2-2 and 2-3). However, the defining and diagnostic features of PTC are seen in the nuclei of the cancer cells. They are typically enlarged and contain dusty-to-powdery chromatin (so-called 'ground-glass nuclei'). Furthermore, the nuclear membrane has characteristic irregularities that look like intranuclear pseudoinclusions and grooves (Table 2-2 and Figs. 2-4, 2-5). Other typical features of PTC

Table 2-2. Principal nuclear features of papillary carcinoma

1.	Nuclear enlargement
2.	Nuclear crowding and overlapping
3.	Chromatin clearing
4.	Irregularity of nuclear contours
5.	Intranuclear pseudoinclusions
6.	Intranuclear grooves

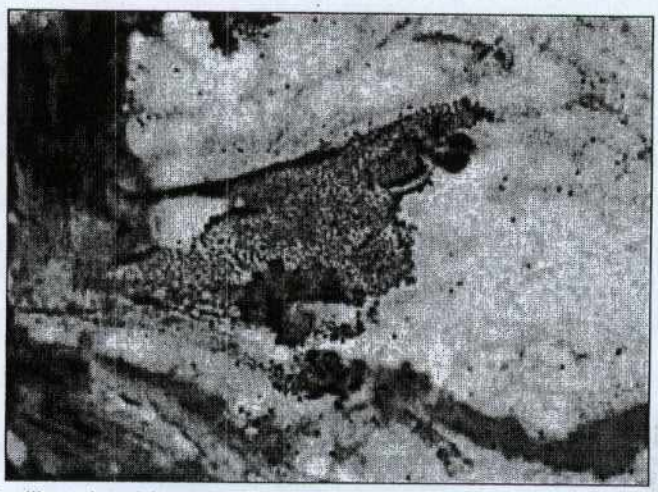

Fig. 2-1. Papillary thyroid carcinoma. Three-dimensional clusters of neoplastic cells (smear, HE stain)

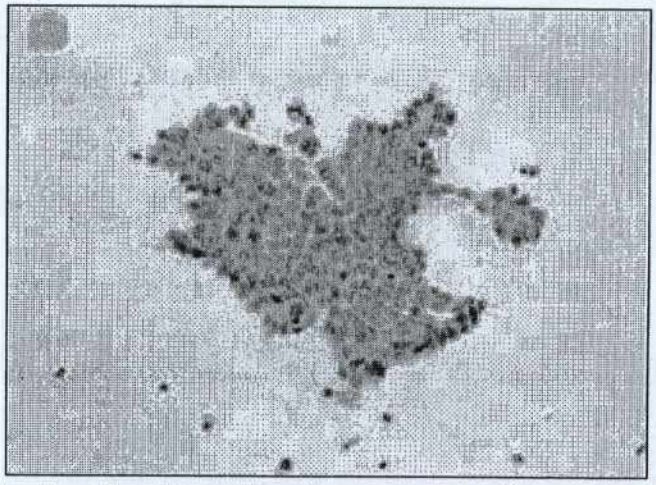

Fig. 2-2. Papillary thyroid carcinoma. Monolayer sheet of neoplastic cells with syncytial-like appearance. Notice the clearing of nuclear chromatin as well as crowding, overlapping, and molding of the cancer cells typical for papillary carcinoma (smear, HE stain)

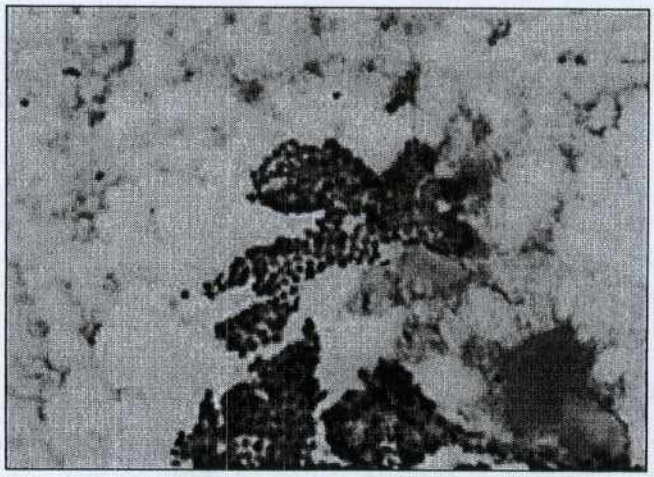

Fig. 2-3. Papillary thyroid carcinoma. Papillary-like arrangements of cancer cells (smear, HE stain)

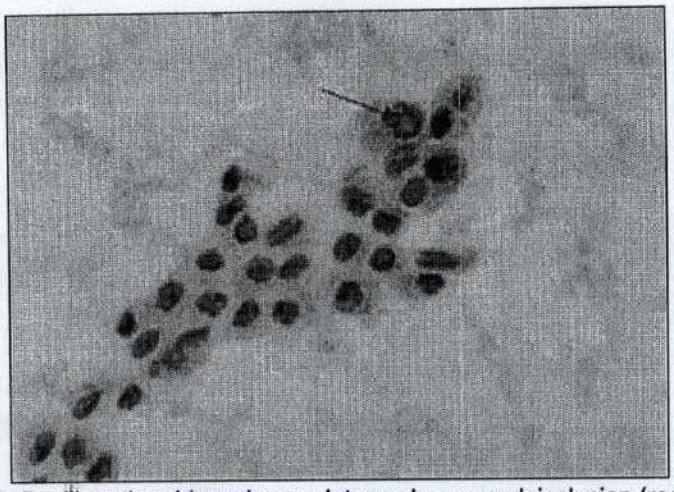

Fig. 2-4. Papillary thyroid carcinoma. Intranuclear pseudoinclusion (red arrow) (smear, HE stain)

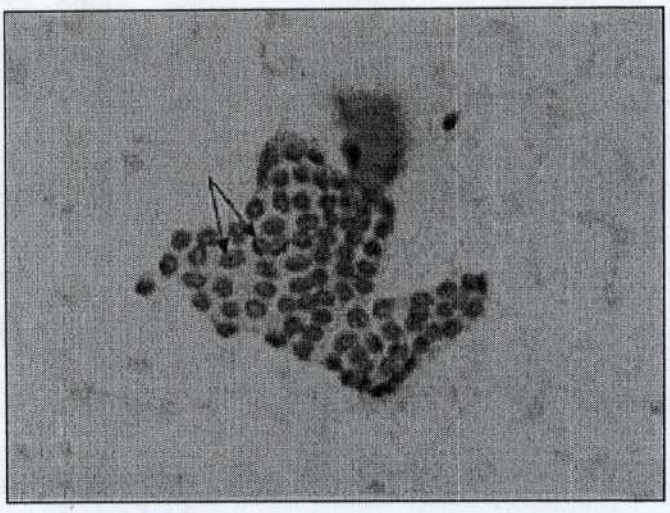

Fig. 2-5. Papillary thyroid carcinoma. The nuclear grooves (red arrows) (smear, HE stain)

are multinucleated cells and bodies (rounded and lamellated calcifications). Additionally, specimens also contain droplets of ropy (or 'chewing gum') colloid.

In selected cases, the cytological picture of PTC may be confused with aspirates from papillary structures of Grave disease or papillary hyperplastic nodules. The differential diagnosis must also include hyalinized trabecular adenoma—the rare tumour of follicular cell origin characterized by trabecular growth, marked hyalinization and nuclear changes imitating completely those of PTC (nuclear inclusions and grooves, psammoma bodies).

Cytological aspirates from the follicular variant of PTC may be sometimes confused with smears from follicular neoplasms. This is because some features may be absent, such as papillary arrangements of cells, multinucleated giant

cells and psammoma bodies. Instead of papillary structures, the tumour cells form syncytial-like sheets and dispersed multifollicular clusters. However, the nuclear features of the cancer cells are typical of PTC.

Cytological characteristics of follicular thyroid carcinoma

Contrary to PTC, cytological diagnosis of follicular thyroid carcinoma (FTC) is more difficult or even impossible because of microscopic similarities in aspirates from FTC and adenoma. Smears of both FTC and follicular adenoma usually contain numerous clusters of glandular cells, often arranged in ring-like (follicular) or rosette-like acinar structures (Figs 2-6, 2-7 and 2-8). Some of them contain inspissated colloid. Single follicular cells and nuclei stripped of cytoplasm are also visible. The presence of nuclear atypia does not reflect the malignant behaviour of tumours. Hence, the diagnosis of malignancy of a follicular tumour depends on the histological features of the neoplasm—capsular and/or vascular invasion (*see* section on Follicular carcinoma). It is for this reason that the cytological diagnosis of 'follicular neoplasm' requires an obligatory surgical excision and microscopic examination of the tumour.

In the case of oncocytic thyroid tumours (Hürthle-cell lesions), the cytological analysis of smears also does not distinguish benign from malignant lesions. For a definitive diagnosis, a histological examination is required that can demonstrate capsular and/or vascular invasion. The cytological features of oncocytic tumours are similar to those of follicular

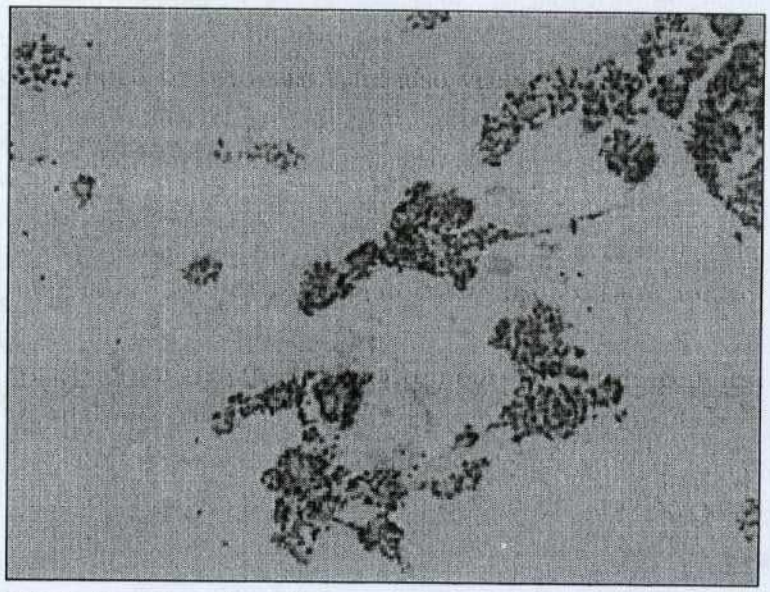

Fig. 2-6. Follicular thyroid neoplasm. Numerous clusters of glandular cells (smear, HE stain)

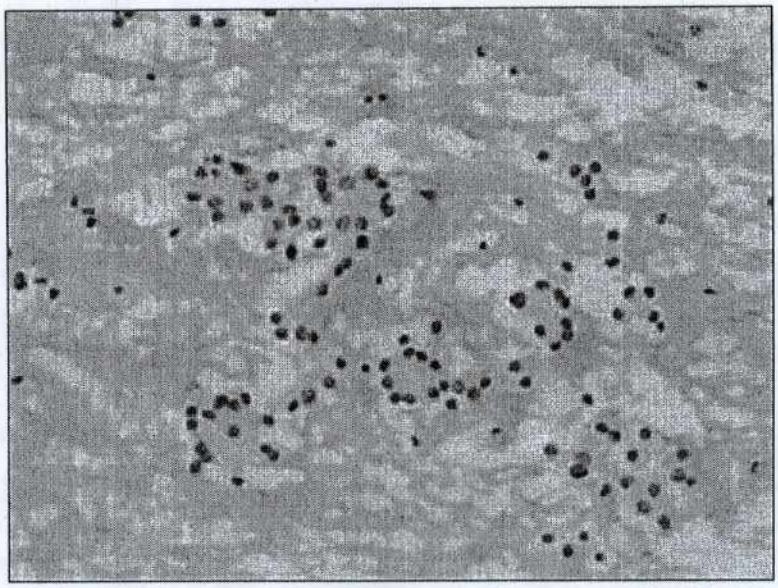

Fig. 2-7. Follicular thyroid neoplasm. Glandular cells arranged in ring-like (follicular) structures (smear, HE stain)

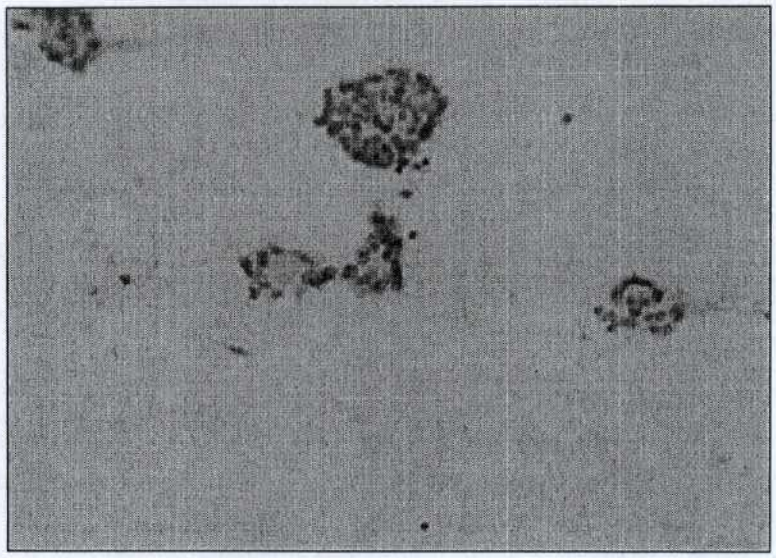

Fig. 2-8. Follicular thyroid neoplasm. Glandular cells arranged in ring-like (follicular) structures. Some of them contain inspissated colloid (smear, HE stain)

neoplasms. However, Hürthle cells are characterized by deeply eosinophilic and granular cytoplasm, and round, large, hyperchromatic nuclei with prominent nucleoli.

Why not a frozen section?

The frozen section procedure is a popular and very important diagnostic method in oncological surgery; it often decreases the extent of the surgery

and establishes an initial morphological diagnosis ('benign tumour' versus 'malignant tumour') during the operation. However, in the context of thyroid surgery, a practical application of this method is very limited. First, so-called 'freezing artefacts' are seen in the slides. These artificial changes in the microscopic appearance of the cells make the assessment of nuclear features impossible. Essentially, it hinders the diagnosis of PTC. Although this limitation can be excluded by the use of touch imprints (cytological preparations taken directly from the fresh specimen), the diagnostic (cytological) criteria employed here are the same as those for FNAB.

The second important issue is difficulties in differentiating between benign and malignant follicular neoplasms, as well as Hürthle-cell lesions. In these cases, a diagnosis of malignancy depends mainly on the findings of capsular and/or vascular invasion. It requires evaluation of the whole tumour capsule with extensive sampling of the specimen, which is impossible with the frozen section procedure. This limitation often is called a 'sampling error' because it is associated with an inadequate number of slices available during this rapid pathological examination.

To summarize, most authors do not recommend the use of the frozen section procedure during thyroid surgery.

Histopathology of well-differentiated thyroid carcinomas

Papillary carcinoma

Papillary thyroid carcinoma (PTC) accounts for 80%–85% of all cases of malignant epithelial tumours of the thyroid. Most PTCs occur in adults (20–50 years of age), especially among women (female-to-male ratio 4:1). PTC also represents the most common paediatric malignancy of the thyroid gland. Multifocality is a frequent finding in these neoplasms; this phenomenon may be associated with intraglandular metastases but data from studies of the clonal rearrangements or X chromosome inactivation patterns support somewhat the simultaneous growth of multiple primary tumours in most patients.

Pathogenesis. Various environmental, hormonal and genetic factors play a role in the development of PTC. The link to radiation of the thyroid gland (derived from either external or internal sources, e.g. exposure to radioactive iodine) is well documented. The carcinogenic effect of radiation is seen particularly in young children. A clear increase in the incidence of thyroid cancer in children has been noted in Belarus after the Chernobyl disaster in 1986 (100-fold higher compared with the worldwide incidence). PTC

is also considered to be associated with substantial dietary iodine intake. This type of thyroid carcinoma is three times more common in women compared to men, which suggests a hormonal influence on the pathogenesis of PTC. The rearrangements of the *RET* gene, leading to the formation of various types of *RET/PTC* oncogenes, is believed to be specific to PTC. The second most popular genetic change in PTC is point mutations of the *BRAF* and *RAS* genes.

Gross examination. PTCs present a variety of macroscopic patterns. However, most of them are grey–white masses with irregular or sharply circumscribed margins. Sometimes, calcifications can be noticed on gross examination within the tumours. PTC can present as a solid and/or cystic tumour; entirely cystic papillary carcinomas are rare. The size of the tumour ranges from a tiny nodule (<1 mm) to a mass that is several centimetres in diameter. PTC can even involve the whole lobe of the thyroid gland and infiltrate into fat, skeletal muscle and adjacent organs (oesophagus, larynx and trachea). On the contrary, when the carcinoma's dimension is <1 cm in diameter, it is called a 'papillary microcarcinoma' (*see* later part of this section).

Microscopic examination. The WHO classification of thyroid tumours specifies 16 histological types of PTC (including classic/conventional variants) (Fig. 2-9). The histological division is based on the growth pattern,

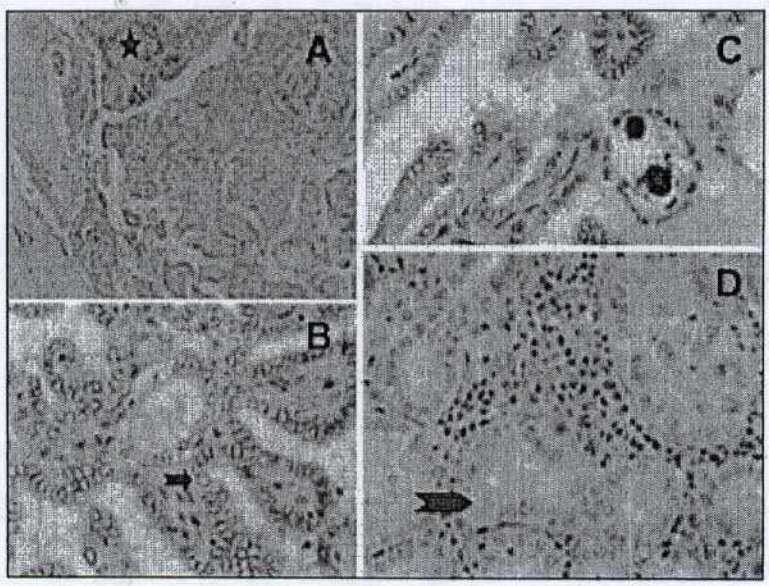

Fig. 2-9. Papillary thyroid carcinoma. A–C: Classic type with the branching papillae covered by cells with characteristic 'ground glass' nuclei (red arrow on Fig. C) and microcalcifications (asterisks).
D: Follicular variant built of ring-like structures. The diagnosis is based on nuclear features of the cancer cell. Notice nuclear pseudoinclusion (red arrow) typical for papillary carcinoma (histological slide, HE stain)

Table 2-3. Histological variants of papillary thyroid carcinoma (PTC) and their different prognoses. (Note the types with an unfavourable prognosis.)

Variants of PTC	Prognosis
Classic	Good
Follicular*	Similar to classic type Good ['Similar=Good']
Macrofollicular	Similar to other follicular variants, with lymph node metastases present in ~20% and distant metastases in 7% of cases
Oncocytic	Not known
Clear cell	Not known
Diffuse sclerosing	Similar to classic type (despite high incidence of regional lymph node and distant metastases)
Tall cell	Poor
Columnar cell	Poor
Solid	Poor**
Cribriform	Not known (usually associated with FAP [Gardner syndrome])
With fasciitis-like stroma	Similar to classic type
With focal insular component	Not known
With squamous cell or mucoepidermoid carcinoma	Poor
With spindle and giant cell carcinoma	Not known
Combined papillary and medullary carcinoma	Not known
Papillary microcarcinoma	Good (but in ≤11% cases lymph node metastasis can be present)

* It is a special variant of PTC built exclusively or predominantly of follicular growth patterns. The differential diagnosis from follicular carcinoma is based on the typical nuclear features of follicular PTC, which are similar to those observed in a classical variant of papillary carcinoma.
**Although some studies have revealed a slightly higher recurrence and mortality associated with the solid variant, most reports have shown a prognosis similar to that of classic papillary carcinoma. FAP familial adenomatous polyposis

cytological features of tumour cells, and the type of tumour stroma. All papillary carcinomas present with the typical nuclear features (Table 2-2) that are required for diagnosing PTC. Histological subtypes of PTC are listed in Table 2-3; they differ either morphologically or clinically. Some of them may have an aggressive clinical course.

The most frequent type of PTC is the classic variant, which presents a typical papillary architecture. The papillae consist of a fibrovascular core and usually demonstrate complex branching (Figs 2-10 and 2-11). Apart from the papillary structures, psammoma bodies and multinucleated cells

Fig. 2-10. Papillary thyroid carcinoma. Classic type with typical papillary arrangements (histological slide, HE stain)

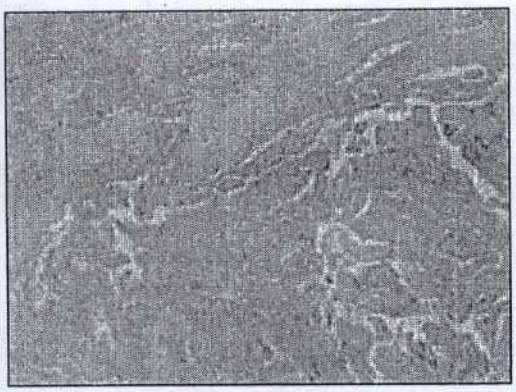

Fig. 2-11. Papillary thyroid carcinoma. Classic type with typical papillary arrangements (histological slide, HE stain)

can be observed.

A special variant of PTC, which requires a separate description because of its clinical importance, is a papillary microcarcinoma. This term is reserved for an incidentally found neoplasm measuring ≤10 mm in diameter. Typically, this type of PTC is characterized by a benign clinical course; however, in children it can behave more aggressively.

Irrespective of the size of the tumour, ≤11% of papillary microcarcinomas can be lymph node positive (according to other authors this rate is even higher and reaches 14%–44%). Ito and Miyauchi distinguish the selected clinico-morphological (high-risk) features of papillary microcarcinoma, which identify patients who need immediate surgical treatment. These features include the following: tumours located near the trachea or on the dorsal surface of the thyroid (these carcinomas show dorsal extension and invade the adjacent organs), features of a high-grade tumour in cytological material (from an FNAB), presence of regional lymph node or distant metastasis, increase in the size of tumour, and/or appearance of node metastasis. Patients with such tumours should undergo surgery.

Prognosis. Most PTCs are characterized by an excellent prognosis—the 10-year survival rate is >90%; in the case of young patients it can even be >98%.

Follicular carcinoma

By definition it is a malignant epithelial tumour which shows a follicular differentiation (follicle formation) and lack of the characteristic nuclear features of papillary carcinoma. FTC accounts for 10%–15% of thyroid malignancies. It is more common in women and usually occurs in patients who are older than those with PTC. This kind of neoplasm has a much

Table 2-4. Histological variants of follicular thyroid carcinoma (FTC) and their different prognoses. Note the types with an unfavourable prognosis (based on Nikiforov *et al.*).

Variants of follicular carcinoma	Prognosis
Encapsulated FTC with microscopic capsular invasion (no vascular invasion is present) = minimally invasive follicular carcinoma	Very low probability (<5% of cases) of metastases, recurrence or tumour-associated mortality
Encapsulated FTC with angioinvasion (capsular invasion is present or absent)	Metastases, recurrences or tumour-associated mortality in 5%–30% of cases
Widely invasive follicular carcinoma	Metastases, recurrences or tumour-associated mortality in 50%–55% of cases
Oncocytic	Nodal metastases in approximately 30% of cases
Clear cell	Not known
Mucinous variant	Not known
FTC with signet-ring cells	Not known

lower frequency of lymph node metastasis compared with PTC (<5%), but distant metastases (mainly to the lung and bone) are more often present at the time of diagnosis (from 20% to 33%, according to different authors).

Pathogenesis. Environmental and genetic factors affect the development of FTC, which is associated with dietary iodine deficiency. In this type of tumour, *RAS* mutations and *PAX8-PPARγ* (peroxisome proliferator-activated receptor-gamma) rearrangement often can be observed.

Gross examination. Usually follicular carcinomas are encapsulated solid tumours and their size is >1 cm. The colour of the neoplasm on cross-section varies from grey–tan to brown. In the case of widely invasive tumours, involvement of the tumour capsule can be easily seen or the capsule is altogether absent, whereas the appearance of minimally invasive carcinomas is practically identical with this type of follicular adenoma.

Microscopic examination. The morphology of FTC is variable and includes tumours with follicles filled with colloid, and neoplasms that have solid and trabecular growth patterns (Fig. 2-12). However, the criteria for malignancy depend on the presence of vascular and/or capsular invasion; features of tumours, such as architecture or cytological atypia, are not essential for diagnosis. Generally, FTC is divided into two main groups according to the extent of tumour invasiveness—minimally invasive (with limited infiltration of the tumour capsule or through the tumour capsule and/or vascular invasion; [Fig. 2-13]) and widely invasive follicular carcinoma (Fig. 2-14). The latter category includes carcinoma with distinct and wide infiltration of thyroid tissue and/or blood vessels (Table 2-4). Because of the many

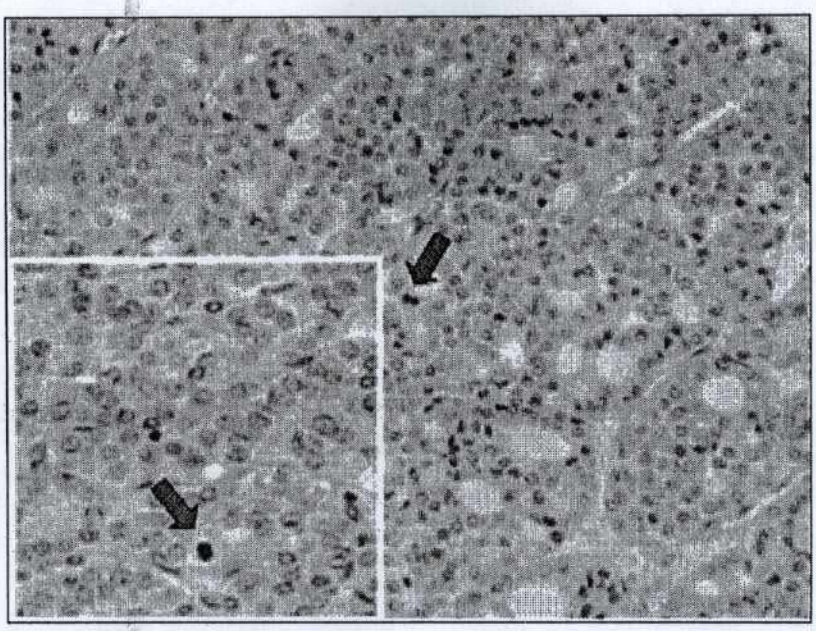

Fig. 2-12. Follicular thyroid carcinoma. Neoplastic glandular cells forming the follicles filled with colloid or the solid and trabecular patterns. Numerous mitotic figures (red arrows) (histological slide, HE stain)

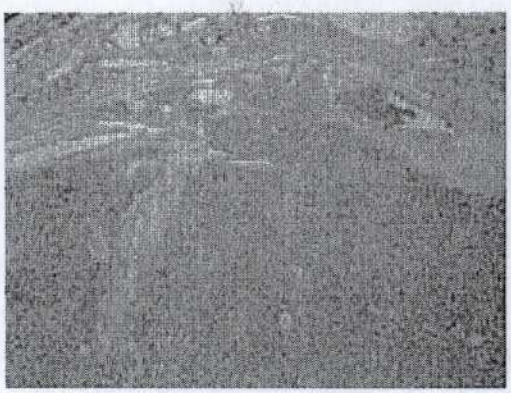

Fig. 2-13. Minimally invasive follicular thyroid carcinoma. Notice the infiltration of normal thyroid tissue outside the tumour capsule (histological slide, HE stain)

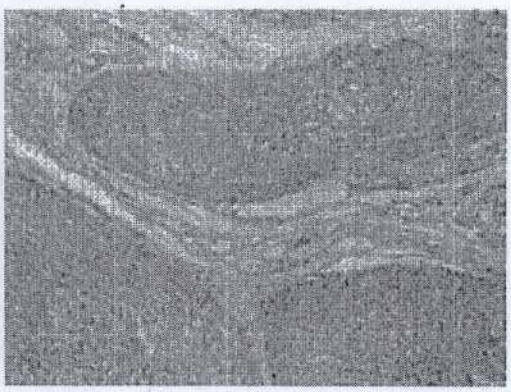

Fig. 2-14. Widely invasive follicular thyroid carcinoma. Distinct and wide infiltration of thyroid tissue (histological slide, HE stain)

opinions regarding this issue, the WHO classification has defined the term 'capsular invasion' and 'vascular invasion'. A 'capsular invasion' should be recognized only when tumour cells penetrate through the capsule and this cannot be linked with the site of a previous FNAB. 'Vascular invasion' means the presence of intravascular tumour cells covered by endothelium or associated with a thrombus; it refers only to the vessels within or beyond the capsule. Some authors also use the term 'grossly encapsulated angio-invasive follicular carcinoma' to describe a tumour in which both capsular and vascular invasion is present (as opposed to minimally invasive carcinoma with only capsular invasion).

The important issue is differentiation between minimally invasive FTC and follicular adenoma and nodular goitre. Therefore, a diagnosis of this type of carcinoma can be made only after a thorough microscopic examination of the tumour.

The two histological variants of FTC according to the WHO classification are oncocytic and clear-cell types. Oncocytic follicular carcinoma is also called oxyphil or Hürthle-cell carcinoma and is discussed below.

Prognosis. In the case of FTC, the 10-year survival rate varies from 70% to 95% and for PTC it is a little lower. Prognostic factors that are related to an unfavourable prognosis include age >45 years, oncocytic variant of FTC, neoplasmatic infiltration beyond the thyroid, tumour size >4 cm, and the presence of distant metastases.

Hürthle-cell carcinoma

The WHO classification lists Hürthle-cell carcinoma as a variant of FTC, but many authors think that it is a separate pathological entity characterized by a distinct microscopic appearance and clinical behaviour. The oncocytic variant of follicular carcinoma comprises ~5% of malignant thyroid tumours and, in contrast to FTC, the frequency of nodal metastases in this neoplasm is ~30%.

Pathogenesis. There is no evidence that the pathogenesis of Hürthle-cell carcinoma is different from conventional FTC, although *H-ras* mutations are found more frequently in this type of tumour than in FTC.

Gross examination. Macroscopically, Hürthle-cell tumours are characteristically brown–mahogany in colour (different from other thyroid tumours) and are encapsulated. The morphological changes within the tumour, such a haemorrhage, cystic areas, infarction, fibrosis and cellular atypia, can be associated, but not exclusively, with a previous FNAB. These changes can also develop independently.

Microscopic examination. The tumour comprises oncocytic cells, which are the only or the main (at least 75%) component of the neoplasm. The architecture of this carcinoma can be varied—follicular or solid/trabecular growth patterns. The Hürthle cells have deeply eosinophilic and granular cytoplasm; their nuclei are round and hyperchromatic with prominent nucleoli. Similar to FTC, the differentiation between Hürthle-cell adenoma and carcinoma is based on the same criteria of capsular and/or vascular invasion (*see above*). The malignant tumours are divided into minimally invasive and widely invasive variants.

Prognosis. Patients with Hürthle-cell carcinoma are considered to have

a worse prognosis than patients with FTC and PTC. The frequency of lymph node metastases, as well as distant metastases, is higher than in non-Hürthle follicular carcinoma. The lower uptake of radioactive iodine makes treatment of the oncocytic variant of FTC more problematic.

Suggested reading

Amos KD, Habra MA, Perrier ND. Carcinoma of the thyroid and parathyroid glands. In: Feig BW, Berger DH and Fuhrman GM (eds). *The MD Anderson surgical oncology handbook*. Philadelphia; 2006.

Boerner SL, Asa SL. Biopsy interpretation of the thyroid. In: *Biopsy interpretation series*. Philadelphia: Wolters Kluwer/Lippincott Williams & Wilkins; 2010.

Ito Y, Miyauchi A. Prognostic factors and therapeutic strategies for differentiated carcinomas of the thyroid. *Endocrine Journal* 2009;**56:**177–192.

Koss LG, Melamed MR. *Koss' diagnostic cytology and its histopathologic bases*. Philadelphia: Lippincott Williams & Wilkins; 2006.

Nikiforov YE. Thyroid carcinoma: Molecular pathways and therapeutic targets. *Modern Pathology* 2008;**21:**37–43.

Nikiforov YE, Biddinger PW, Thompson LDR. *Diagnostic pathology and molecular genetics of the thyroid*. Philadelphia: Wolters Kluwer/Lippincott Williams & Wilkins; 2009.

DeLellis RA, Lloyd RV, Heitz PU, Eng C (eds). *Pathology and genetics of tumours of endocrine organs*. (IARC WHO Classification of tumours). IARC Press, Lyon, 2004.

Silverberg SG. Silverberg's Principles and practice of surgical pathology and cytopathology. 4th ed. Churchill Livingstone: Elsevier; 2006.

Syed Z Ali, Cibas ES (eds). *The Bethesda system for reporting thyroid cytopathology. Definitions, criteria and explanatory notes*. Springer Science+Business Media; 2010.

Commentary

R. KALYANI

The chapter on pathology of differentiated thyroid cancers is well structured: the introduction, scope of fine-needle aspiration cytology (FNAC) of thyroid nodules, diagnostic categories, cytological features of papillary carcinoma and follicular neoplasm; the role of frozen section and its limitations are adequately described. However, one should be aware of histological changes after pre-operative FNAC, such as areas along the needle tract of haemorrhage, granulation tissue, cholesterol crystals, adjacent follicular cells showing enlargement and atypia, distortion and disruption of the capsule, all of which give a false picture of capsular invasion during interpretation of follicular neoplasm. Occasionally, squamous cell metaplasia and spindle cell nodules are seen in the needle tract several weeks and months after

FNAC. Tumour infarction is common after FNAC, especially in the case of Hürthle-cell neoplasms.

The histopathology of papillary, follicular and Hürthle-cell carcinoma is well presented in terms of their pathogenesis, gross features, microscopic appearance, histological types and prognosis. However, I would like to highlight the following points:

A. *Papillary carcinoma*

- An increased incidence is also seen in Hashimoto thyroiditis.
- An occult presentation is common, with the patient presenting with only cervical lymphadenopathy without a clinically detectable lesion/enlargement of the thyroid gland.
- In the follicular variant of PTC, follicles are irregular, often tubular and branching, with an abortive attempt to form papillae.
- Psamomma bodies give a clue to the diagnosis.
- Immunohistochemically, these tumour cells are reactive to thyroglobulin, TTF-1, CK 7+/CK 20, CK 19, high molecular-weight keratin, HBME–1 and RET protein. RT-PCR can be used to detect gene rearrangement in specific RET/PTC.

B. *Follicular carcinoma*

- This is never occult.
- Skeletal metastasis is multicentric.
- Immunohistochemically the tumour cells are reactive to thyroglobulin, TTF–1, low molecular-weight keratin and epithelial membrane antigen, similar to follicular adenoma. However, widespread, strong positivity of galectin-3 supports the diagnosis of follicular carcinoma.

C. *Hürthle-cell carcinoma*

- CK 14 is emerging as a selective marker for these tumour cells.
- Tumours with a Ki–67 index of >5% show aggressive behaviour.

Regarding comments on the Indian situation, in a study performed at our department, entitled *Cancer profile in Department of Pathology of Sri Devaraj Urs Medical College, Kolar: A 10-year study* between January 1997 and December 2006, thyroid cancer constituted ~3.43% (94 cases) of the total cancers, of which 18 were in males and 76 in females. The majority were papillary carcinomas of the classical type, followed by the follicular variant of PTC, follicular carcinoma and medullary carcinoma. Thyroid cancers are among the top 10 cancers, according to various studies from different parts of India, such as Bangalore, districts of South Karnataka, Hyderabad, Thriruvanthapuram, Dehradun and eastern Rajasthan. This can be attributed to the use of borewell water, which contains a high content of fluorine/iodine, ionizing radiation, and intake of cruciferous and goitrogenic vegetables. It is reported that too much iodine causes papillary carcinoma and iodine deficiency causes follicular carcinoma.