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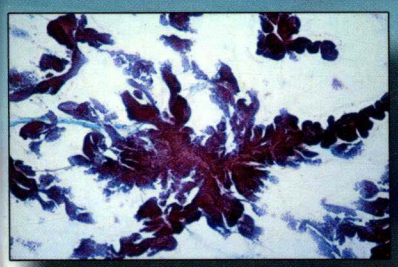
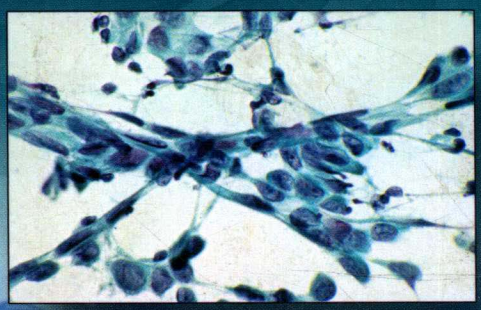
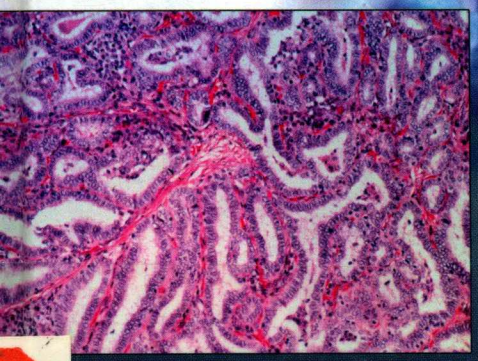
Thyroid Cytopathology

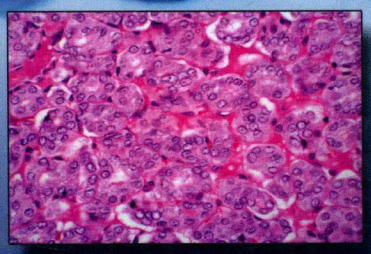
SECOND EDITION

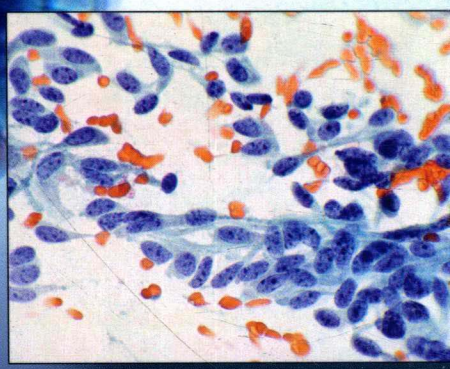
An Atlas and Text

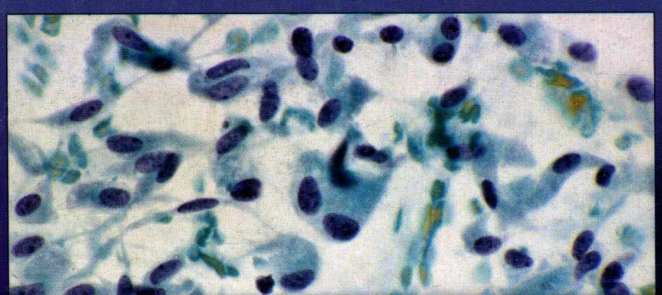












SUDHA R. KINI

Wolters Kluwer

Thyroid Cytopathology

SECOND EDITION

Sudha R. Kini, MD

Formerly Division Head (retired),
Cytopathology
Department of Pathology
Henry Ford Hospital
Detroit, Michigan

Wolters Kluwer

Philadelphia • Baltimore • New York • London
Buenos Aires • Hong Kong • Sydney • Tokyo

Acquisition Editor: Ryan Shaw
Product Development Editor: Kate Marshall
Production Project Manager: David Saltzberg
Design Coordinator: Stephen Druding
Manufacturing Coordinator: Beth Welsh
Prepress Vendor: S4Carlisle Publishing Services

Second edition

9 8 7 6 5 4 3 2 1

Printed in China

Library of Congress Cataloging-in-Publication Data
Available upon request
ISBN 978-1-4511-9389-3

LWW.com

DEDICATED TO

Late Dr. John K. Frost, whose *Basic Concepts to General Cytopathology* served as a foundation for my cytopathology learning process and practice

AND

Late Dr. J. Martin Miller, for his deep concerns for the patients, his enthusiasm in launching the thyroid fine needle biopsy project in 1976, for his excitement with the success of and strong faith in the utility of thyroid needle biopsies, both fine and large, in reducing unnecessary thyroid surgeries

AND

As always, to the loving memories of my late husband, Dr. Ratnakar Kini

PREFACE

The landmark event in the field of Thyroid Cytopathology was the State of the Science consensus meeting sponsored by the National Cancer Institute (NCI), Bethesda, Maryland, in 2007. The intention was to bring uniformity and consistency to the diagnostic terminologies for reporting the cytopathologic findings of thyroid aspirates and management strategies across the medical community. The proceedings of this meeting were referred to as Bethesda System for Reporting Thyroid Cytopathology (BSRTC). At the time the previous edition of this atlas went to press, in late 2007, the proceedings of the consensus meeting were unavailable for publication. One of the main reasons for this edition is to present BSRTC, since, it is widely accepted, utilized, and popular among all the disciplines dealing with thyroid diseases in the United States. The reasons are several.

The six-tiered BSRTC system has amply simplified the reporting of the cytopathologic findings of thyroid aspirates. BSRTC has ended the dilemma many cytopathologists/pathologists faced in interpreting minimal or borderline changes, or separating nonneoplastic from neoplastic follicular/Hürthle cell lesions. Category 3 of BSRTC includes aspirates with any degree of atypia, something cytopathologists have had a hard time categorizing and communicating their findings/concerns to the clinicians. By recommending the terms "Follicular Lesions of Undetermined Significance (FLUS)" or "Suspicious for Follicular/Hürthle cell lesion" in Category 4, BSRTC has eliminated the frustrations trying to separate nonneoplastic and neoplastic follicular and Hürthle cell lesions; or benign from malignant follicular/Hürthle cell tumors. BSRTC has also provided the risk for malignancy in each category, so that management strategies have been easier and consistent. Now most everyone speaks the same language when it concerns thyroid cytopathology.

In this atlas, however, I have chosen to retain the reporting scheme for thyroid aspirates that was used at Henry Ford Hospital, Detroit. This reporting system was developed over the last several years with the blessings of endocrinologists and endocrine surgeons. The reporting categories were based on the fact that follicular and Hürthle cell neoplasms could be recognized cytologically (contrary to the general belief) and could be separated, in most instances, from nonneoplastic lesions. This practice of cytopathology of thyroid was followed ever since the thyroid FNA biopsies were launched in 1976–1977 to this date, with a primary goal of reducing unnecessary thyroid surgeries. Replacing the existing reporting system totally with the BSRTC would mean negating all the criteria and description of cytologic features of these lesions presented in this atlas.

The clinicians at the author's institution were comfortable with the existing reporting system. But in order to be in "synch" with the rest of the Cytology world, both systems have now been integrated. Chapter 4 describes both reporting systems in detail. I sincerely thank Dr. Dina Mody for presenting the BSRTC succinctly and clearly.

What else is new and/or current in the field of Thyroid Cytopathology? I have noted that the liquid-based cytologic preparations of thyroid aspirates are fast becoming very popular owing to the simplicity of specimen collection, with no dependence on assistance for making thin smears, no worries about prompt fixation and air-drying, less manual labor for cytopreparation, and only one slide to examine per case. The previous edition of this atlas included an Appendix for liquid-based technology. In this edition, I have included it (liquid-based technology) along with traditional methods and integrated the images from liquid-based preparations with the wet-fixed Papanicolaou-stained and air-dried Romanowski-stained preparations. I personally prefer spray-fixed material stained by the Papanicolaou method. Readers can appreciate this fact while reviewing images of lesions prepared and stained by different techniques. The cytologic criteria described and illustrated in this atlas are entirely based on spray-fixed material stained by the Papanicolaou method. I firmly believe that the interpretation of a cytologic specimen not only requires appreciation of the pattern but, most importantly, the nuclear details such as those presented in the Papanicolaou-stained wet-fixed, direct smears.

The diagnostic problems in follicular/Hürthle cell lesions of the thyroid gland as well as prognostication of papillary thyroid carcinomas continue to serve as an impetus for developing special markers either at the tissue level or at the molecular level. This field has exploded with newer diagnostic techniques in the hope of finding a magic tumor marker that would solve all the controversies and differentiate the various follicular/Hürthle cell lesions. Research in molecular techniques has made great strides. I am indeed very grateful to Dr. Dhananjay Chitale for his contribution to Molecular Techniques for thyroid cancers in Chapter 22.

FNA biopsy is an indispensable, widely used diagnostic technique. The biopsy is performed frequently with the aid of an ultrasound machine, by both endocrinologists and radiologists. Therefore, I have both radiologists and the endocrinologist contribute to the Chapter 2 on Biopsy Techniques. I thank wholeheartedly my endocrinology colleagues Drs. Arti Bhan and Max Wisgerhof as well as staff radiologists Drs. Julie Ruma and Shadi Azar from the University of Michigan, Ann Arbor, Michigan, for their contribution. I am also indebted to Drs. Arti Bhan, Max Wisgerhof, and Vinod Narra for Chapter 23 on Management of Thyroid Nodules based on biopsy results. I also want to express my sincere thanks to Drs. Inamdar and Mennon for updating Chapter 14 on Malignant Lymphomas of the Thyroid.

I could not have completed this atlas without the assistance of my past fellow and currently a staff pathologist at VA System in Ann Arbor, Michigan, Dr. Shilpa Rungta. Dr. Rungta provided hundreds of images on liquid-based preparations for the atlas and also contributed to Chapter 3 on Cytopreparatory Techniques, for which I am very grateful.

Over the years, the cytologic criteria described for thyroid lesions have not changed. The illustrations used in the previous publication are still applicable. They are all retained. The newer ones represent liquid-based preparations. Most of the images were photographed by Mrs. M. Jane Purslow, CT (ASCP, MIAC), and are of unsurpassed quality. I am forever indebted to Jane for the same. As in the past, I have heavily relied on Mrs. Linda Brandt for her secretarial assistance. I am forever grateful for her patience, diligence, and accurate and timely work.

Finally, I must acknowledge the efforts of Ms. Reva Sayegh-McCullen of the Department of Media Resources at Henry Ford Hospital, Detroit, Michigan, for preparing the image files and color balancing.

Sudha R. Kini, MD

PREFACE
TO THE FIRST EDITION

This *Atlas and Text on Cytopathology of the Thyroid Gland* is essentially the third edition of *Thyroid–Guides to Clinical Aspiration Cytology*. It comes 12 years after the second edition, in a new format and all in color.

The atlas has retained the organization of the second edition and also most of the text, modified whenever necessary with additional information. Several hundred images have been added to illustrate the wide spectrum of cytologic features for each disease entity. I have attempted to include the usual and unusual patterns of disease entities in each chapter, as well as their diagnostic pitfalls. A few images have been repeated just to emphasize the characteristics. Familiarity with the histopathologic features of various thyroid lesions is extremely important. I have therefore included more images in this atlas than in the second edition. The urge to illustrate more examples was irresistible, and I thank the publishers for allowing me to do so.

The contributions made by the late Dr. Martin Miller (Chapters 1, 2) in the two editions of the *Thyroid—Guides to Clinical Aspiration Cytology* are retained in this atlas for several reasons. First of all, the credit for the success of fine needle aspiration biopsy of thyroid in the United States goes to a large extent to the efforts of Dr. Miller.[1] He strongly believed that too many thyroid glands with benign disease were being removed and was willing to explore ways to differentiate benign from malignant nodules. Dr. Miller's expertise in thyroidology, his deep concern for patients, his enthusiasm and persistence in carrying through the biopsy project since it was launched are all testimony to the success of fine needle biopsy. I am indeed privileged to have had a long association with him. Dr. Miller's observations and approach are still applicable, and in my opinion worth retaining.

Writing this atlas was not as easy a task as I had thought it would be. The target audience now is more sophisticated (and opinionated), experienced, and knowledgeable in thyroid cytopathology. This is in sharp contrast to the time, some three decades ago, when most cytopathologists were inexperienced in thyroid cytology, especially the author, who had to struggle her way through. As aspiration biopsy of thyroid nodules has become a standard of practice, the literature has been inundated with case reports, review articles, differential diagnosis and ancillary diagnostic tests, chapters, and textbooks. I have made every attempt to review most of the publications and incorporate the important information.

The diagnostic criteria for various thyroid lesions described in previous editions have not changed but are expanded in this atlas. The criteria are still valid, applicable, and reproducible (if tried on Papanicolaou-stained preparations). The old statistical data are also retained, as they have been a very important part of my learning experience. The importance of cytohistocorrelations of misinterpreted cases cannot be overemphasized.

One of the main reasons for the wide variations in interpretations in thyroid cytology is the inconsistency and lack of standardization in cytopreparations. Fixation of the cellular material, cytopreparatory techniques, and type of staining vary considerably from laboratory to laboratory. Cytopathologic criteria based on one type of preparation may not be applicable to the specimen processed by other techniques and stains. The cytologic criteria described and illustrated in this atlas are entirely based on spray-fixed material stained by the Papanicolaou method. I firmly believe that the interpretation of a cytologic specimen requires not only appreciation of the pattern but, most importantly, the nuclear details such as those presented in the Papanicolaou-stained preparations. I am also not convinced that the liquid-based cytology is a good alternative. This may be due to my lack of experience with the preparations for nongynecologic cytology, specifically for thyroid aspirates. But I make no apologies. Something that has worked wonderfully for the last 30 years need not be changed unless there are striking advantages in terms of diagnostic yield, accuracy, and cost containment. I see none with liquid-based cytologic preparations. However, I have included images of the Romanowsky-stained preparations and have added a section on liquid-based cytology for the benefit of a wider audience.

I still believe that follicular and Hürthle cell neoplasms can be cytologically differentiated from nonneoplastic lesions in a high proportion of cases, especially with the Papanicolaou- stained preparations. Diagnostic accuracy of follicular and Hürthle cell lesions cannot be judged fairly against the gold standard of surgical pathology when there is no consistency in surgical pathology diagnoses of these neoplasms. It is always taken for granted that the histologic diagnosis is accurate when cytologic and histologic diagnoses in any given case are discordant. The fact that histologic diagnoses could be in error is usually not taken into consideration when accuracy of cytologic diagnosis is measured. I have personally reviewed several discordant cases where the diagnoses rendered by pathologists were inaccurate (in my opinion). I have illustrated some examples in the chapter on Papillary Carcinoma.

The diagnostic problems in follicular/Hürthle cell lesions of the thyroid gland have served as an impetus for developing special markers either at the tissue level or at the molecular level. This field has exploded with newer diagnostic techniques in the hope of finding a magic tumor marker that would solve all the controversies and differentiate the various follicular/Hürthle cell lesions. The chapter on ancillary diagnostic techniques barely touches this subject.

I am extremely grateful to so many individuals for their participation. I sincerely appreciate the contributions by my professional colleagues Max Wisgerhof, MD, Vinod Narra, MD, Osama Alassi, MD, and Melina Cancovic, PhD. I am very thankful to Clair Michael, MD for contributing the section on liquid-based cytology for thyroid aspirates.

The images are an essential part of any atlas, and its success depends on the quality of the images. I cannot thank enough our past supervisor of the Cytopathology Laboratory,

Mrs. M. Jane Purslow, CT (ASCP, MIAC), for taking thousands of images of a wide variety of thyroid lesions during her years at Henry Ford Hospital, Detroit, Michigan. The quality of those images has always been superb. I am indebted to my past fellows Osama Alassi, MD, Songling Liang, MD, and Dongping Shi, MD, who were always willing to photograph any new cases that I needed for this atlas. I had requested several of my professional colleagues from the United States and abroad for examples of interesting and rare lesions. I sincerely appreciate their generosity and prompt response. In particular, I would like to thank Mariza dePeralta, MD, and Mithra Baliga, MD, for several cases, especially of Romanowsky-stained preparations.

I am very grateful to Mrs. Linda Brandt for her secretarial assistance. Ms. Laure Porzondek's help in retrieving the voluminous literature necessary to compile this text is gratefully acknowledged. I would like to express my appreciation to Mrs. Toni Klimowicz, our Cytopathology Laboratory supervisor, for providing the archival data and to Ms. Dawn M. Webb for her input in cytopreparatory techniques.

Finally, I must acknowledge the efforts of the members of the Department of Media Resources at Henry Ford Hospital, Detroit, Michigan. Scanning hundreds of kodachromes, merging the files with digital images, color balancing, and keeping all in order (1,800 of them, to be exact) had been a laborious process. I am grateful to Ms. Patricia Muldoon, Ms. Reva Sayegh, Mr. John Grybas, Mr. Jeff Boni, and Mr. Ray Manning for their diligence and prompt work.

Sudha R. Kini, MD

Reference

1. Gharib H. Changing trends in thyroid practice: understanding nodular thyroid disease. *Endocrin Pract*. 2004;10:31–39.

ACKNOWLEDGMENTS

Permission to reproduce the following is gratefully acknowledged:

From Miller JM, Kini SR, Hamburger JI. *Needle Biopsy of the Thyroid*. New York, NY: Praeger Publishers; 1983 for Figure 2.3.

From Kini SR, Miller JM, Hamburger JI, et al. Cytopathology of follicular lesions of the thyroid gland. *Diagn Cytopathol.* 1985;1:123–132, published by Igaku-Shoin: New York for Figures 5.21 and 5.25.

From Cervino JM, Paseyro P, Grosso O, et al. La exploration citologic de la glandula tirodes y sus correlaciones anatomo-clinicas. *An Facultad Med.* 1962;47:128–143, for Figure 7.48.

From Crissman JD, Druzdowicz S, Johnson C, et al. Fine needle aspiration diagnosis of hyperplastic and neoplastic follicular nodules of the thyroid: a morphometric study. *Anal Quant Cytol Histol.* 1991;13(5) for Tables 7.10–7.13.

From Lippincott Williams & Wilkins. Kini SR. *Color Atlas of Differential Diagnosis in Exfoliative and Aspiration Cytopathology*. 1999; for Figure 5.18.

The permission to photograph cases or reproduce the images is gratefully acknowledged from: Marizza de Peralta-Venturina, MD, Cedar Sinai Hospital, Los Angeles, California, for Figures 6.22A; 6.30A, B; 6.40; 6.45; 7.20A–E; 7.42A–D; 7.54A–D; 8.21A, B; 9.14G; 9.17E; 9.18D; 9.19; 9.36B; 9.58I–K; 12.33C; 12.55F–J; 17.11A–C; 18.12; 18.31C; 19.52; 21.17A–G.

Mithra Baliga, MD, University of Mississippi, Jackson, Mississippi, for Figures 7.13A, B; 7.56A–C; 8.14A–D; 8.20A–F; 10.19A, B; 11.27A–F; 12.49A, B; 16.14A, B.

David B. Kaminsky, MD, Palm Springs Pathology Associates, Palm Springs, California, for Figures 19.9 and 19.19A, B.

Sedigheh-Keyhani, MD, FIAC, Professor of Clinical Pathology, Ohio State University Hospital, Columbus, Ohio, for Figure 13.3.

John F. Goellner, MD, formerly of Department of Pathology, Mayo Clinic Rochester, Minnesota, for Figures 12.54 and 19.20.

W. K. Ng, MBBS, Department of Pathology, University of Hong Kong, Queen Mary Hospital, Hong Kong, for Figure 19.46.

Renĕ Gerhard, MD, Department of Pathology, Hospital das Clinicas, University of Sao Paulo, SP, Brazil, for Figure 19.47A–D.

Edward Bernecki, MD, William Beaumont Hospital, Royal Oak, Michigan, for Figures 19.48A–C.

Claire W. Michael, MD, Case Western University, Cleveland, Ohio, for Figures 6.22B; 6.23C, D; 7.9D–F; 7.13D, E; 8.12C, D; 8.21F; 9.15H, J; 9.16I; 9.18F; 9.21F–H; 9.24G; 11.19B; 12.49E, F; 13.23D; 19.48D–F.

Chris Jenson, MD, University of Iowa Hospitals, Iowa City, Iowa, for Figure 19.49.

Ricardo Gonzalez-Campora, MD, FIAC, Department of Pathology, Faculty of Medicine, University of Seville, Seville, Spain, for Figure 19.51.

A. Vodovnik, MD, Calderdale Royal Hospital, HX3 OPW Halifax, England, for Figure 12.69A, B; 19.53A–C.

Fadi Abdul-Karim, MD, Institute of Pathology, University Hospitals of Cleveland, Cleveland, Ohio, for Figures 19.54A, B.

Ms. I. Kikuchi, CT (IAC), Department of Pathology, Central Clinical Laboratory, Iwate Medical University, Morioka, Japan, for Figures 19.56A–F.

A. Watts, MD, Cedar Sinai Hospital, Los Angeles, California, for Figure 13.2B.

Yun Gong, MD, University of Texas M.D. Anderson Cancer Center, Houston, Texas, for Figure 16.19.

Ami J. Walloch, MD and Rashead Hammadeh, MD, Christ Hospital, Oaklawn, Illinois, for Figure 15.21.

D.V. Trivedi, MD, Methodist Hospital, Peoria, Illinois, for Figures 13.51A–C.

Michael Glant, MD, Formerly Director, Diagnostic Cytology Clinic, Indianapolis, Indiana, for Figures 21.4A–D.

Zhang Ziying, MD, Department of Pathology, Henry Ford Hospital, Detroit, Michigan, for Figures 8.9C, D; 9:15I; 9.16F–H; 9.18E; 13.22E; 19.54C–K; 21.16A–H.

Shilpa Rungta, MD, Veterans Affairs Ann Arbor Health System, Ann Arbor, Michigan, for Figures 6.22C, D; 6.23E; 6.24B; 6.27B; 6.37B; 6.48B, C; 6.51B, C; 7.10C–E; 7.11C; 7.26F–O; 7.36G–I; 8.9B; 8.21C–E; 8.44C, D; 9.13G; 9.14H–K; 9.15F, G; 9.16E; 9.24F; 9.25B; 9.28B–D; 9.35B–D; 9.37B; 9.45B–E; 11.13A–C; 12.33D; 12.61C; 12.66C; 13.22D; 13.24D, E; 13.27E; 13.29C; 13.39C, D; 13.41C; 13.45C, D; 17.8C; 17.13C; 17.15F, G; 17.27A–C; 18.13C; 18.28B, C; 18.31A, B; 18.32.

Janine Benoit, MD, Saskatoon Hospital, Saskatoon, Canada, for Figure 8.12E.

Late Ajay Shah, MD, of Fine Needle Aspiration Clinic, Toledo, Ohio, for Figures 12.69C–G; 19.53D–I.

Paul Wakely, MD, Ohio State University, Columbus, Ohio, for Figures 7.13D, E; 8.12D.

Michael Henry, MD, Mayo Clinic, Rochester, Minnesota, for Figure 9.24G.

ABBREVIATIONS

AT	Autoimmune thyroiditis
ATC	Anaplastic thyroid carcinoma
AUS	Atypia of undetermined significance
BSRTC	Bethesda System for Reporting Thyroid Cytopathology
C-Cells	Calcitonin producing cells
CE	Capillary electrophoresis
CEA	Carcinoembryonic antigen
CGH	Comparative genomic hybridization
CISH	Chromogenic in-situ hybridization
CK	Cytokeratin
CS	Conventional smear
DLBCL	Diffuse large B-cell lymphoma
EM	Electron microscopy
EMA	Epithelial membrane antigen
ENMZL	Extranodal marginal zone lymphoma
FA	Follicular adenoma
FC	Follicular carcinoma
FISH	Florescent in-situ hybridization
FLUS	Follicular lesion of undetermined significance
FN	Follicular neoplasm
FNA	Fine needle aspiration
FVPC	Follicular variant of papillary carcinoma
GEC	Gene expression classifier
GTP	Guanosine-5′-triphosphate
H&E	Hematoxylin and eosin
HT	Hashimoto's thyroiditis
LBP	Liquid-based preparation
LNB	Large needle biopsy
LT	Lymphocytic thyroiditis
MALT	Mucosa associated lymphoid tissue
MEN	Multiple endocrine neoplasia
ML	Malignant lymphoma
MNG	Multinodular goiter
MRI	Magnetic resonance imaging
MTC	Medullary thyroid carcinoma
N/C	Nuclear/cytoplasmic
NCI	National Cancer Institute, Bethesda, Maryland
NG	Nodular goiter
NGS	Next generation sequencing
NHL	Non-Hodgkin lymphoma
NSE	Neuron specific enolase
PAP	Papanicolaou
PAS	Periodic acid-Schiff
PCR	Polymerase chain reaction
PET	Positron emission tomography
PTC	Papillary thyroid carcinoma
PTH	Parathyroid hormone
RT-PCR	Reverse transcriptase PCR
SAT	Subacute thyroiditis
SISH	Silver in-situ hybridization
SP	SurePath
TP	ThinPrep
TTF-1	Thyroid transcription factor-1
UD	Undifferentiated
US	Unsatisfactory
WHO	World Health Organization

CONTRIBUTORS

Shadi Azar, MBBS, MD
Staff Radiologist
Veterans Affairs Ann Arbor Health System
Clinical Lecturer
Department of Radiology
University of Michigan Hospitals & Health System
Ann Arbor, Michigan

Arti Bhan, MD
Senior Staff Endocrinologist
Department of Internal Medicine
Henry Ford Hospital
Detroit, Michigan

Dhananjay Chitale, MD
Senior Staff Pathologist
Division Head, Molecular Pathology and Genomic Medicine
Director, Biorepository
Assistant Clinical Professor, Wayne State University School of Medicine
Henry Ford Hospital
Detroit, Michigan

Kedar Inamdar, MD, PhD
Division Head, Hematopathology
Department of Pathology
Henry Ford Hospital
Clinical Assistant Professor
Wayne State University School of Medicine
Associate Program Director
Pathology Residency Program
Henry Ford Hospital/WSU
Detroit, Michigan

Sudha R. Kini, MD
Formerly Division Head (retired) Cytopathology
Department of Pathology
Henry Ford Hospital
Detroit, Michigan

Madhu P. Menon, MD, PhD
Senior Staff Pathologist
Division of Hematopathology
Department of Pathology
Henry Ford Hospital
Detroit, Michigan

J. Martin Miller, MD*
Emeritus Consultant
Division of Endocrinology
Department of Internal Medicine
Henry Ford Hospital
Endocrinologist
Associated Endocrinologists
Southfield, Michigan
Emeritus Clinical Associate Professor
University of Michigan
Ann Arbor, Michigan

Dina Mody, MD
Medical Director of Cytology
Cytopathology Fellowship Program Director
Department of Pathology and Genomic Medicine
The Methodist Hospital
Houston, Texas

Vinod Narra, MD
Attending Surgeon
Beverly Hospital
Beverly, Massachusetts

Julie Ruma, MD
Staff Radiologist
Veterans Affairs Ann Arbor Health System
Clinical Lecturer
Department of Radiology
University of Michigan Hospitals & Health System
Ann Arbor, Michigan

Shilpa Rungta, MD
Attending Pathologist
Department of Pathology
Veterans Affairs Ann Arbor Health System
Clinical Lecturer
Department of Pathology
University of Michigan Health System
Ann Arbor, Michigan

Max Wisgerhof, MD
Endocrinology
Department of Internal Medicine
Henry Ford Hospital
Detroit, Michigan

*Deceased

To the readers,

Stains
Most of the thyroid aspirates were examined by making direct smears, wet-fixed, using spray fixatives and stained by the Papanicolaou method. Any other type of preparation or stain used is so specified.

Magnifications
Unless otherwise specified, the photomicrographs are taken at 40× (or high power). All other magnifications are noted in the legends (low power at 4× and medium power at 10×). All electron micrographs are taken on uranyl acetate and lead citrate preparations.

TABLE OF CONTENTS

*Deceased

1 Introduction

J. Martin Miller* | Max Wisgerhof

The approach to thyroid nodularity, as recounted in late Dr. Miller's introduction to the second edition of *Thyroid: Guides to Clinical Aspiration Biopsy*, has not been eclipsed. Instead, the attempt at a cytologic diagnosis of thyroid nodularity by fine-needle aspiration has become the standard of care. The clinical purpose of *Thyroid Cytopathology: An Atlas and Text* remains the same as that stated by the late Dr. Miller in *Thyroid: Guides to Clinical Aspiration Biopsy*.

—Max Wisgerhof, MD

Shortly after World War II, articles appeared in the medical literature stating that the incidence of thyroid cancer in surgically removed thyroid nodules was 20% to 30%. These articles also suggested that these findings were representative of the entire nodular goiter population. Opponents of this point of view cited the low incidence of thyroid cancer as a cause of death in autopsy material, and a controversy was born regarding the true risk of a thyroid nodule. By the 1950s, it was generally agreed that the morbidity and mortality associated with thyroid cancer did not justify removal of all thyroid nodules; today the controversy focuses on the means of selection of patient nodules for surgical biopsy—that is, the method of determining the risk of a given thyroid nodule.

During the 1960s and 1970s, it became evident to physicians in the United States that radionuclide or ultrasound images of the thyroid were successful in eliminating consideration of thyroid surgery for no more than 10% to 20% of thyroid nodules. However, as early as 1950 in the Scandinavian countries, attention was focused on the use of a fine needle to aspirate a cytologic sample from thyroid nodules and thus determine the probable pathologic diagnosis. For 25 years, such reports evoked little interest in North America. The reasons for this are speculative and include dissatisfaction with the variably reported sensitivity of the European studies, failure of authors to provide direction for use of biopsy data in avoiding thyroid surgery, and the "certain knowledge" that cytology would not provide a diagnosis of a lesion, often requiring many histologic sections for identification. Overreaction to one reported case of subcutaneous tumor implant by needle biopsy was also a factor, as was the use of Giemsa stain by the Europeans, a cytologic stain not popular among American cytopathologists accustomed to Papanicolaou staining techniques.

By the late 1970s, the Canadians had reported experience with fine-needle biopsy, and groups in Cleveland and Boston had evaluated large-needle biopsy. The first American study combining both was reported in 1979 by our group. Since that time, numerous reports have appeared in the English-language literature on the diagnosis of thyroid nodules by needle biopsy, mostly by the cytologic specimens obtained by fine-needle aspiration. In spite of limited but definite advantages to the combined use of large- and fine-needle biopsy in a biopsy program, the universal application, simplicity, safety, ease of performance, and patient acceptance of fine-needle biopsy account for its exclusive use in most reported studies.

Our experience with over 4,500 satisfactory biopsies spans the 10 years from 1975 to 1985 and has provided us with over 1,100 correlations with surgical specimens. Our purpose has been twofold: (i) to provide diagnostic information for the management of our patients and those of our referring doctors and (ii) to record our experience in obtaining and diagnosing thyroid needle biopsy specimens in such a way that others might profit from our trials and errors. This book is our third attempt to make available to our colleagues our total needle biopsy experience. Unlike the first two attempts, we have limited this work to fine-needle biopsy. Its purpose is to assist the cytopathologist in the proper interpretation of cytologic samples from the thyroid gland. Therefore, most of the text is concerned with our experience in obtaining these samples by the fine needle and interpreting them. If cytologic diagnosis was an exact science, and if there was a predictable correlation between a particular diagnosis and tumor behavior, this information would suffice. Such is not the case, and certain ancillary information is of value to the interpreter of thyroid cytopathology. This includes the gross and histologic anatomy of the lesion subjected to biopsy, the life history of benign and malignant thyroid nodules, and the management of thyroid nodules with and without biopsy.

IMPORTANCE OF NEEDLE BIOPSY

The morbidity and mortality associated with thyroid cancer do not qualify it as an important public health problem. The number of noninvasive diagnostic tests and surgical lobectomies done to establish or exclude its presence, however, makes it a disease of economic importance. Living in a society concerned with containment of medical costs, we should carefully select the most cost-effective diagnostic tests. The experience of our group is that needle biopsy is far more accurate for the selection of patients with nodules for diagnostic lobectomy and is much cheaper than any combination of noninvasive tests. Its use has

*Deceased.

halved the number of operations prescribed and has doubled the number of cancers identified per 100 surgical removals. Cutting surgical and hospital bills for nodule management in half is a worthwhile achievement. Our figures also suggest that we are now identifying cancers that were initially diagnosed as benign nodules, or we are making the diagnosis of cancer at an earlier stage. Determining whether this too is advantageous, and will favorably influence the morbidity and mortality associated with thyroid cancer, will require many years of study.

In summary, most physicians agree that neither removing all thyroid nodules nor removing no thyroid nodules is a sensible management approach. Therefore, they employ some process of selection in prescribing surgical lobectomy. The most cost-effective method of selection is needle biopsy.

SUGGESTED READINGS

Ashcraft MW, Van Herle AJ. Management of thyroid nodules, II: scanning techniques, thyroid suppression therapy and fine needle aspiration. *Head Neck Surg.* 1981;3:297.

Cerise EJ, Randall S, Ochsner A. Carcinoma of the thyroid and nontoxic nodular goiter. *Surgery.* 1952;31:552.

Cole WH, Majarakis JO, Slaughter OP. Incidence of carcinoma of the thyroid in nodular goiter. *J Clin Endocrinol Metab.* 1949;9:1007.

Crile G Jr, Hawk WA Jr. Aspiration biopsy of thyroid nodules. *Surg Gynecol Obstet.* 1973;136:241–245.

Crockford PM, Bain GO. Fine-needle aspiration biopsy of the thyroid. *Can Med Assoc J.* 1974;110:1029–1032.

Hamburger JI, Miller JM, Kini SR. Clinical-pathological evaluation of thyroid nodules. In: *Handbook & Atlas, Part I.* Southfield, MI: Private Publication; 1979:15.

Miller JM. Carcinoma and thyroid nodules: problem in endemic goiter. *N Engl J Med.* 1955;252:247–251.

Miller JM, Hamburger JI, Kini SR. Diagnosis of thyroid nodules by fine needle aspiration and needle biopsy. *JAMA.* 1979;241:481–486.

Miller JM, Hamburger JI, Kini SR. Fine needle aspiration cytology, cutting biopsy or both in the evaluation of thyroid nodules? In: Thompson NW, Vinik AI, eds. *Endocrine Surgery Update.* New York, NY: Grune & Stratton; 1983:23.

Miller JM, Hamburger JI, Kini SR. The impact of needle biopsy on the preoperative diagnosis of thyroid nodules. *Henry Ford Hosp Med J.* 1980;28:145.

Miller JM, Kini SR, Hamburger JI. *Needle Biopsy of Thyroid.* New York, NY: Praeger; 1983.

Rogers WF, Asper SP, Williams RH. Clinical significance of malignant neoplasms of the thyroid gland. *N Engl J Med.* 1947;237:569.

Söderström N. Puncture of goiters for aspiration biopsy: a preliminary report. *Acta Med Scand.* 1952;144:235–244.

Wang C, Vickery AL Jr, Maloof F. Needle biopsy of the thyroid. *Surg Gynecol Obstet.* 1976;143:365–368.

2 Techniques of Fine-Needle Aspiration Biopsy

Arti Bhan | Max Wisgerhof | J. Martin Miller*

It is axiomatic that a pathologist must have an adequate biopsy specimen to make a satisfactory interpretation. Obtaining an adequate cellular sample requires enough capillary blood or tissue fluid to serve as a vehicle, but not so much as to cause a problem by dilution. The sample must then be fixed and stained in such a way as to permit the most accurate interpretation possible. Obtaining an adequate cytologic sample from the thyroid is a simple procedure. However, the number of failures by physicians with little experience suggests that matters of technique, although simple, are indeed essential.

In the past, fine-needle aspiration (FNA) of thyroid nodules was based on palpation. With the advent of bedside thyroid ultrasound, the vast majority of aspirations are image guided. This requires the operator to be well versed with the use of thyroid ultrasound. Several studies have shown that ultrasound guidance can serve as a valuable aid in improving the diagnostic yield of the FNA.

PATIENT PREPARATION

Proper mental preparation is the first step in the performance of a thyroid biopsy. Most of the pain experienced by patients is minor discomfort magnified by anxiety. The patient should be reassured about the simplicity, painlessness, and brevity of the procedure. It should be explained to the patient that he or she should expect a prick from the anesthetic needle, followed by a sting from the local anesthetic. The patient should be asked to not swallow while the needle is in the nodule, and should be assured that this represents a small fraction of the total time involved in doing a biopsy—that is, swallowing is minimally restricted. Most operators prefer to perform the biopsy when the patient is in a supine position, with the head and neck extended over a pillow. In case the patient is not able to lie down, the procedure can be performed in a sitting position as well. The site of the needle puncture is cleaned by firm application of an alcohol swab.

ANESTHETIC

Although some operators prefer not to use local anesthetic, we have always chosen to do so in order to minimize patient discomfort.

We use 1 to 2 mL of 1% lidocaine for the skin and subcutaneous tissues. Care is exercised not to infiltrate the nodule, which might cause a "lidocaine aspirate."

*Deceased.

SYRINGE

A 10-mL syringe provides ample negative pressure for obtaining cytologic specimens.

NEEDLES

The larger the needle, the larger the tissue sample is, and the greater the possibility of an unwanted volume of blood. We have found the 25-gauge, 1.5-inch needle to be suitable for the majority of nodules. With less vascular nodules, a 22- or even a 20-gauge needle gives better results. For nodules with thick inspissated colloid, using a 22-gauge needle is recommended.

NEEDLE PLACEMENT

With the advent of thyroid ultrasound, most biopsies are now performed with image guidance. The nodule is localized first by placing the ultrasound probe over the thyroid. The operator then places the needle in the periphery of the nodule. Larger nodules tend to have central degeneration, and needle placement in the periphery yields cells that are intact.

SUCTION: TO USE OR NOT TO USE?

Suction is applied once, repetitively, or during maneuvers designed to further disrupt the follicular epithelium. The total procedure should be sufficient to make aspirate appear in the hub of the needle, but not in the barrel of the syringe.

The use of an additional mechanical device for producing suction has also been advocated (Fig. 2.1). We have not used such devices in our practice.

Some operators prefer not to use suction. Here the needle is inserted into the nodule, without an attached syringe. The operator holds the needle hub and rapidly moves the needle vertically until material appears in the hub by capillary action. Alternatively, the needle is rotated while in the nodule, to achieve a cutting action, which dislodges material from the nodule. The advantage of using this technique is that there is minimal amount of obscuring blood.

ULTRASOUND-GUIDED FNA

Real-time ultrasound guidance has technically refined the FNA technique by decreasing the number of inadequate biopsy specimens. Many investigators have shown that combining ultrasonography and FNA into a single procedure decreases the

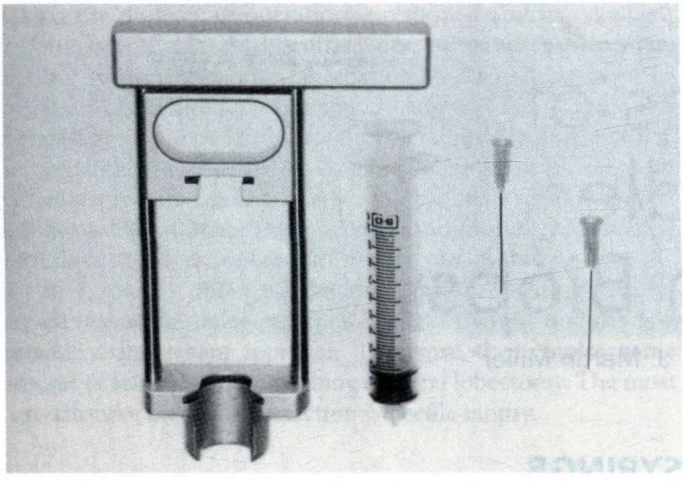


FIGURE 2.1. Mechanical syringe holder; 10-mL plastic BD syringe; 22-gauge, 1.5-inch needle; and 25-gauge, 1.5-inch needle.

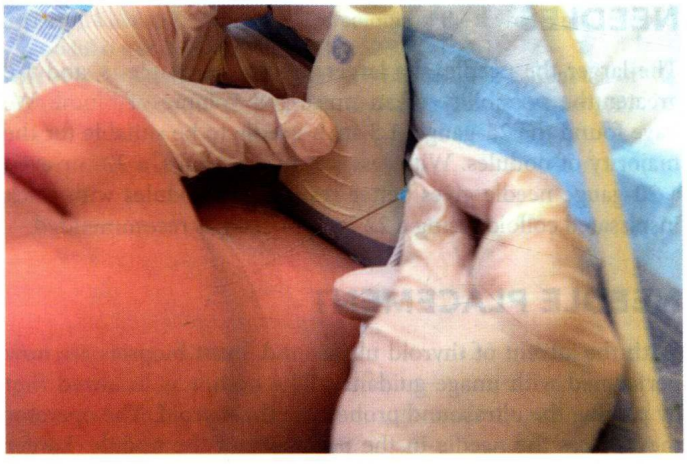


FIGURE 2.2. Technique of ultrasound-guided FNA.

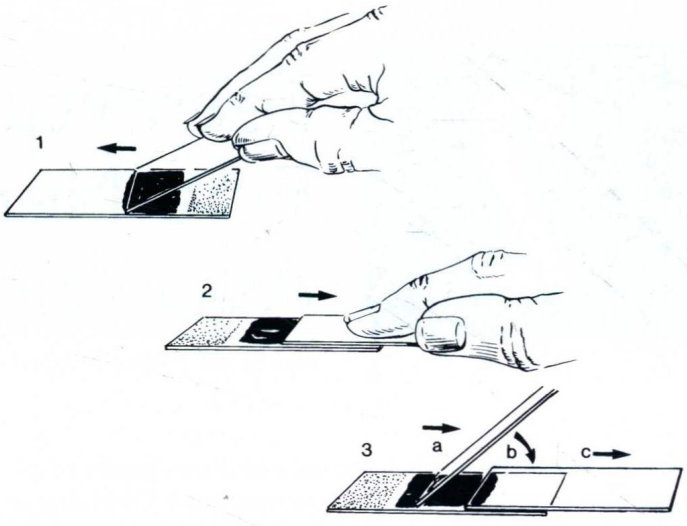


FIGURE 2.3. Three methods of smearing the fine-needle aspirate. See text for details. (From Miller JM, Kini SR, Hamburger JI. *Needle Biopsy of the Thyroid*. New York, NY: Praeger Publishers; 1983, with permission.)

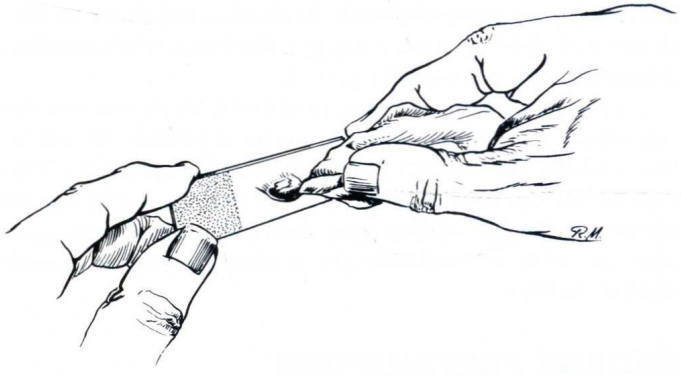


FIGURE 2.4. To remove excess blood or fluid, the slide is tilted and the free end of the drop is touched with a tongue or absorbing tissue.

frequency of inadequate specimens from approximately 15% to 3%. The performance of a bedside ultrasound allows an evaluation of the entire thyroid anatomy. Several ultrasound features that suggest a higher risk of malignancy in a nodule have been validated. In the presence of several nodules, the clinician can preferentially aspirate nodules with ultrasound features suggesting malignancy.

The operator usually stands at the head of the table (Fig. 2.2). With one hand, the ultrasound probe is placed on the neck and a small amount of sterile gel is applied to the probe. This facilitates the transmission of ultrasound waves to the thyroid. The other hand guides the insertion of the needle. The bevel of the needle is turned toward the transducer and the needle is advanced until the bevel is seen within the nodule. The operator watches the ultrasound screen while guiding the tip of the needle into the nodule. The vertical and rotational movements of the needle tip can be visualized on the screen. When material appears in the hub of the needle, it is withdrawn. If the nodule is too fibrotic or cystic, a syringe is attached to the needle.

SMEARS

After suction, the needle is removed and the plunger is withdrawn a couple of milliliters. The needle is reaffixed, and the specimen is expressed on the slide. This procedure is the same with or without the use of a mechanical suction device. At this point, an estimate is made as to whether the volume of the aspirate is suitable for smearing on the slide. If it is not excessive, it may be either smeared with the edge of another slide, as is usual with a blood smear (Fig. 2.3, method 1), or, if particulate matter or colloid is visibly present, compressed between two slides and smeared (Fig. 2.3, method 2). If the volume of the specimen seems too great for the slide, tilt it and remove the blood that flows to the lower side by using an absorbent tissue (see Fig. 2.4). Smearing is then done as described earlier. Another recommended technique for concentrating cellular material is shown in Figure 2.3, method 3. The slide with the specimen may be tilted, frosted end down, to enlist the aid of gravity while the edge of the smearing slide is drawn up. After the blood has been separated, the smearing slide is flattened and the smear is completed.

FIXATION

Fixation must be matched to the staining technique employed. We use a modified Papanicolaou staining technique and therefore fix immediately with alcohol as part of a spray.