Management of Differentiated Thyroid Cancer

Anne T. Mancino
Lawrence T. Kim
Editors

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Editors
Anne T. Mancino
General Surgery
Central Arkansas Veterans Healthcare System, University of Arkansas
Little Rock, Arkansas
USA

Lawrence T. Kim
Division of Surgical Oncology
University of North Carolina
Chapel Hill, North Carolina
USA

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Foreword

I am deeply honored to write the Foreword for Dr. Larry Kim and Dr. Anne Mancino's book on thyroid cancer. They have recruited 22 expert endocrine thyroidologists and co-authors who have contributed up-to-date and clearly written chapters regarding thyroid cancer. The book's well-organized chapters include considerably new information regarding epidemiology, molecular biology, pathology, and the reasons for different thyroid operations and lymph node dissection as well as a nonoperative treatment with a close observation of small papillary thyroid cancers. The authors clearly describe current prognostic and risk assessment guidelines as well as new information regarding the quality of life of patients with thyroid cancer. The authors also note that what was formerly considered to be encapsulated follicular variant of papillary thyroid cancer is now considered to be a benign thyroid tumor rather than a thyroid cancer. Several chapters address the use of ultrasound, CT, MRI, and PET scans as well as the use of thyroglobulin and calcitonin as tumor markers with more selective use of radioactive iodine. *Differentiated Thyroid Cancer* provides an essential resource for endocrinologists, endocrine and head and neck surgeons, as well as surgical residents and surgical fellows and students.

San Francisco, CA, USA — Orlo H. Clark

Preface

Thyroid cancer is an endlessly fascinating disease. Patients generally do well which is pleasant and rewarding. However the unpredictability of the disease can be striking, as some individuals, for reasons that are still essentially completely unknown, have disease that rapidly progresses to death. Over the past several years, our understanding of thyroid cancer has grown dramatically. We have a fairly clear picture of the high prevalence of asymptomatic and clinically innocuous thyroid cancer and a better understanding of the driver mutations responsible for the transformation of follicular epithelium. The previous rush toward ever more aggressive treatment has reversed toward the recognition that less treatment is adequate in most cases. This has even extended to the point where observation alone can be considered for some thyroid cancers. Yet important questions remain. As of today we are unable to reliably correlate aggressive clinical behavior with specific genetic changes. This will be key if we are to customize treatment for individual patients and develop more effective targeted therapy.

This book is intended for all practitioners interested in thyroid cancer. It is intended to provide a foundation for understanding treatment options and treatment guidelines, even as they change in the future. The editors hope that it can contribute to more informed, rational, and appropriate treatment for individual patients.

The creation of this book has been a challenging and rewarding effort for the editors. We would like to thank all of the authors who have written truly outstanding original material. Their work, dedication, and talent cannot be over-recognized. We would also like to thank our patients who have taught us humility. In some cases this humility is required because of our complications or because the disease defies all our best predictions. And in a few cases, we are humbled by our patients' courage as they face an inevitable and unbeatable disease. We would also like to thank our colleagues, residents, and students who challenge and educate us on a daily basis. And finally we would like to thank our families for their tolerance and love.

Little Rock, Arkansas, USA — Anne T. Mancino
Chapel Hill, North Carolina, USA — Lawrence T. Kim

Contents

Contributors

Jonathan Black Department of Surgery, University of North Carolina, Chapel Hill, NC, USA

Naifa Lamki Busaidy Department of Endocrine Neoplasia and Hormonal Disorders, The University of Texas MD Anderson Cancer Center, Houston, TX, USA

Louise Davies White River Junction Department of Veterans Affairs Hospital, White River Junction, VT, USA

Geisel School of Medicine at Dartmouth, Hanover, NH, USA

The Dartmouth Institute for Health Policy and Clinical Practice, VA Outcomes Group—111B, White River Junction, VT, USA

Leslie G. Dodd Department of Pathology, University of North Carolina, Chapel Hill, NC, USA

Dina Elaraj, M.D. Department of Surgery, Section of Endocrine Surgery, Northwestern University Feinberg School of Medicine, Chicago, IL, USA

Trevan Fischer, M.D. Department of Surgical Oncology, John Wayne Cancer Institute at Providence Saint John's Health Center, Santa Monica, CA, USA

Paul G. Gauger, M.D. Division of Endocrine Surgery, Department of Surgery, University of Michigan, University of Michigan Hospitals and Health Centers, Ann Arbor, MI, USA

Benjamin Gigliotti, M.D. Division of Endocrinology, Department of Medicine, Massachusetts General Hospital, Boston, MA, USA

Melanie Goldfarb, M.D., M.Sc., F.A.C.S., F.A.C.E. Department of Surgical Oncology, John Wayne Cancer Institute at Providence Saint John's Health Center, Santa Monica, CA, USA

Ian D. Hay, B.Sc., M.B. Ch.B., Ph.D, F.A.C.E., F.A.C.P., F.R.C.P. Division of Endocrinology and Internal Medicine, Mayo Clinic and College of Medicine, Rochester, MN, USA

Jenny Hoang Diagnostic Radiology, Duke University Medical Center, Durham, NC, USA

Shelby Holt Departments of Surgery and Pathology, University of Texas Southwestern Medical Center, Dallas, TX, USA

David T. Hughes, M.D. Division of Endocrine Surgery, Department of Surgery, University of Michigan, University of Michigan Hospitals and Health Centers, Ann Arbor, MI, USA

Nicole M. Iniguez-Ariza, M.D. Division of Endocrinology and Internal Medicine, Mayo Clinic and College of Medicine, Rochester, MN, USA

Yasuhiro Ito Department of Surgery, Kuma Hospital, Kobe, Japan

Tania Jaber Department of Endocrine Neoplasia and Hormonal Disorders, The University of Texas MD Anderson Cancer Center, Houston, TX, USA

Xiaoyin Sara Jiang Department of Pathology, Duke University, Durham, NC, USA

Suneetha Kaggal, B.S. Division of Biostatistics, Mayo Clinic and College of Medicine, Rochester, MN, USA

Saad Khan Departments of Surgery and Pathology, University of Texas Southwestern Medical Center, Dallas, TX, USA

Lawrence Kim Division of Surgical Oncology and Endocrine Surgery, Department of Surgery, University of North Carolina, Chapel Hill, NC, USA

Deepa Kirk, M.D. Division of Endocrinology, Department of Medicine, University of North Carolina School of Medicine, Chapel Hill, NC, USA

Kristin L. Long, M.D. Department of Surgery, Section of Endocrine Surgery, University of Wisconsin School of Medicine and Public Health, Madison, WI, USA

Susan Maygarden Department of Pathology, University of North Carolina, Chapel Hill, NC, USA

Akira Miyauchi Department of Surgery, Kuma Hospital, Kobe, Japan

Jeff Moley Section of Endocrine and Oncologic Surgery, Department of Surgery, Washington University School of Medicine, St. Louis, MO, USA

Iain J. Nixon, Ph.D. Edinburgh University, Edinburgh, UK

Fiemu Nwariaku Departments of Surgery and Pathology, University of Texas Southwestern Medical Center, Dallas, TX, USA

Hitomi Oda Department of Surgery, Kuma Hospital, Kobe, Japan

Jorge Daniel Oldan Diagnostic Radiology, University of North Carolina-Chapel Hill Hospitals, Chapel Hill, NC, USA

Vardan Papoian Department of Surgery, MedStar Washington Hospital Center, Washington, DC, USA

Sareh Parangi, M.D. Division of Endocrine Surgery, Department of General and Gastrointestinal Surgery, Massachusetts General Hospital, Harvard Medical School, Boston, MA, USA

Jennifer M. Perkins, M.D., M.B.A. Duke University Health System, Durham, NC, USA

Nancy D. Perrier, M.D., F.A.C.S. Department of Surgical Oncology, MD Anderson Cancer Center, Houston, TX, USA

Laura N. Purcell, M.D. Department of Surgery, University of North Carolina, Chapel Hill, NC, USA

Reese W. Randle, M.D. Section of Endocrine Surgery, Department of Surgery, University of Wisconsin, Madison, WI, USA

Jennifer Rosen Department of Surgery, MedStar Washington Hospital Center, Washington, DC, USA

Benjamin Schmidt Division of Surgical Oncology and Endocrine Surgery, Department of Surgery, University of North Carolina Lineberger Comprehensive Cancer Center, Chapel Hill, NC, USA

Ashok R. Shaha, M.D. Department of Surgery, Memorial Sloan Kettering Cancer Center, New York, NY, USA

Rebecca S. Sippel, M.D. Section of Endocrine Surgery, Department of Surgery, University of Wisconsin, Madison, WI, USA

Paula D. Strassle, M.S.P.H. Department of Epidemiology, University of North Carolina, Chapel Hill, NC, USA

Cord Sturgeon, M.D., M.S. Department of Surgery, Section of Endocrine Surgery, Northwestern University Feinberg School of Medicine, Chicago, IL, USA

Mark Sywak, M.B.B.S., F.R.A.C.S., MMed Sci University of Sydney Endocrine Surgery Unit, Sydney, NSW, Australia

Terry Zekon Wong Diagnostic Radiology, University of North Carolina-Chapel Hill Hospitals, Chapel Hill, NC, USA

Shirley Yan Departments of Surgery and Pathology, University of Texas Southwestern Medical Center, Dallas, TX, USA

Anthony Yang, M.D. Department of Surgery, Section of Endocrine Surgery, Northwestern University Feinberg School of Medicine, Chicago, IL, USA

Jen Jen Yeh, M.D. Division of Surgical Oncology and Endocrine Surgery, Department of Surgery, University of North Carolina, Chapel Hill, NC, USA

Nicole Zern, M.D. Department of Surgery, University of Washington, Seattle, WA, USA

1 The Rising Incidence of Thyroid Cancer: Contributions from Healthcare Practice and Biologic Risk Factors

Benjamin Schmidt and Louise Davies

Abbreviations

Gy	Gray unit of ionizing radiation
HR	Hazard ratio
Sv	Sievert unit of ionizing radiation
TSH	Thyroid-stimulating hormone

B. Schmidt (✉)
Division of Surgical Oncology and Endocrine Surgery, Department of Surgery, University of North Carolina Lineberger Comprehensive Cancer Center, Campus Box 7213, 170 Manning Drive, 1150 POB, Chapel Hill, NC 27599-7213, USA
e-mail: Benjamin.schmidt@unchealth.unc.edu

L. Davies
White River Junction Department of Veterans Affairs Hospital, White River Junction, VT, USA

Geisel School of Medicine at Dartmouth, Hanover, NH, USA

The Dartmouth Institute for Health Policy and Clinical Practice, VA Outcomes Group—111B, 215 North Main Street, White River Junction, VT 05009, USA
e-mail: Louise.Davies@dartmouth.edu

Introduction

The epidemiology of thyroid cancer has followed a peculiar pattern over the past several decades. The reporting of new cases of thyroid cancer has increased dramatically, whereas mortality from thyroid cancer has changed little. Examination of this pattern reveals a heavy influence of nonbiologic factors in the reporting of thyroid cancer, namely, increased healthcare utilization, imaging, and aggressive management of thyroid nodules. Much of our knowledge of this issue and a great portion of this chapter rely on investigations by a task force organized through the American Association of Clinical Endocrinologists and the American College of Endocrinology [1]. The term "cancer" covers a broad spectrum of disease from rapidly fatal or malignant processes to tumors that may never threaten life despite neoplastic features. Measures of disease incidence are often deeply influenced by nonbiologic factors, particularly for low-mortality cancers [2–4]. In this chapter we review how changes in healthcare practice are largely responsible for change in reported incidence of thyroid cancer, and we discuss a number of investigations into underlying biologic risk factors for thyroid cancer. Underlying biologic processes potentially contributing to thyroid cancer often require dramatic exposures, and their clinical significance is otherwise uncertain. The lack of dramatic changes in these biologic factors over the past several decades is consistent

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with the relatively stable mortality rate of thyroid cancer. Exposure to ionizing radiation, particularly at a young age, remains a well-established risk factor for the development of thyroid cancer. This has largely been established through study of nuclear disasters and children undergoing radiation therapy. The risk of other exposures to radiation including background environmental radiation, occupational exposure, and medical imaging is exceedingly small, and their clinical importance in regard to thyroid cancer is minimal. Thyroid-stimulating hormone (TSH) is known to play a role in the progression and behavior of thyroid cancer, particularly the differentiated subtypes [5]. A number of behavioral and environmental factors are thought to influence TSH levels, particularly obesity, the metabolic syndrome, a few specific micronutrients, and smoking. These factors have been proposed and investigated as contributors to the incidence of thyroid cancer. It is unclear if the risks associated with these factors can be established beyond the multiple confounders associated with healthcare practice. The relevance of diet, obesity, and smoking to the incidence of thyroid cancer in terms of intervention and mortality requires additional study.

Incidence of Thyroid Cancer

In 2014, over 60,000 cases of thyroid cancer were estimated to occur, while fewer than 2,000 individuals died of this disease [1]. The increasing incidence of thyroid cancer has attracted much academic discussion [6–8]. Thyroid cancer incidence has tripled over the past three decades, specifically within the differentiated subtypes of thyroid cancer (papillary and follicular) (Fig. 1.1) [1]. Differences in incidence rates by size suggest that healthcare practices play a large role in this increase. Thyroid cancers of all sizes are increasingly reported, but the greatest increase in both relative and absolute numbers have come from tumors less than 2 cm, which have increased nearly fourfold (Fig. 1.2). The increase in incidence has predominantly been reported in individuals over the age of 20, with parallel increases between adult age groups (Fig 1.3).

Mortality from thyroid cancer is stable, hovering around 0.5 per 100,000 people (Fig. 1.1). It does fluctuate: between 1975 and 2010, the highest was recorded in 1977 at 0.57 per 100,000 people (approximately 1,710 deaths per year nationwide), and the lowest was recorded in 1994 at 0.42 per 100,000 people (approximately 1,260 deaths per year nationwide). The annual rate of

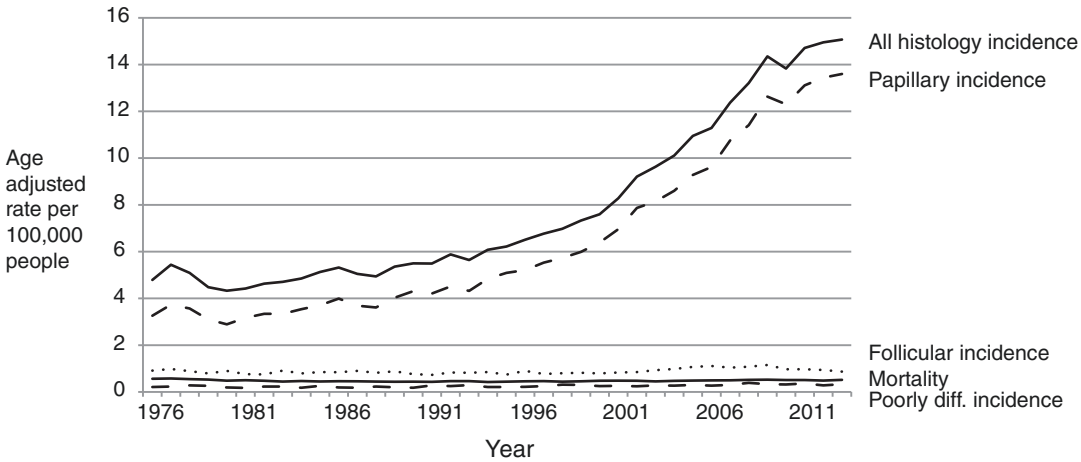

Fig. 1.1 Incidence by histology of thyroid cancer and mortality of thyroid cancer, 1975–2011. Data are from the Surveillance, Epidemiology, and End Results (SEER) program (www.seer.cancer.gov) SEER*Stat Database: Incidence—SEER 9 Regs Research Data, Nov 2012 Sub (1973–2011) ⟨Katrina/Rita Population Adjustment⟩—Linked To County Attributes—Total US, 1969–2011 Counties, National Cancer Institute, DCCPS, Surveillance Research Program, Surveillance Systems Branch, released April 2014, based on the November 2013 submission. Underlying mortality data for 1975–2010 are provided by NCHS (www.cdc.gov/nchs)

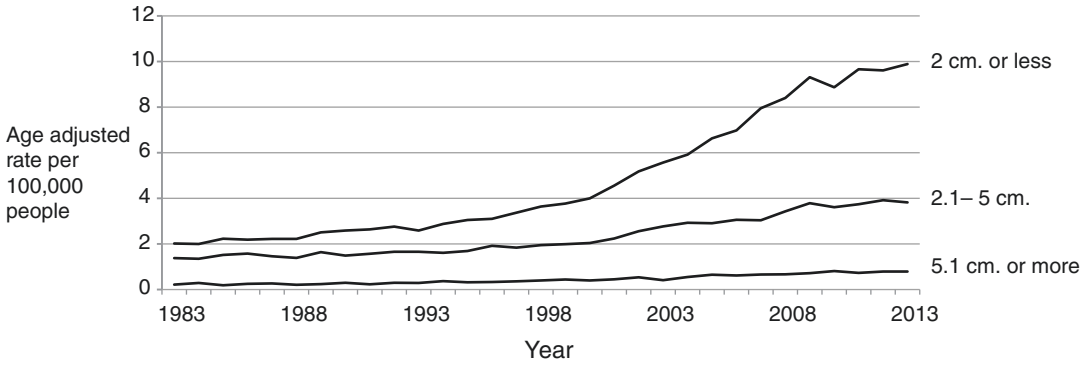

Fig. 1.2 Differentiated thyroid cancer incidence trends by size, 1983–2011. Data are from the Surveillance, Epidemiology, and End Results (SEER) program (www.seer.cancer.gov) SEER*Stat Database: Incidence—SEER 9 Regs Research Data, Nov 2012 Sub (1973–2011) ⟨Katrina/Rita Population Adjustment⟩—Linked To County Attributes—Total US, 1969–2011 Counties, National Cancer Institute, DCCPS, Surveillance Research Program, Surveillance Systems Branch, released April 2014, based on the November 2013 submission

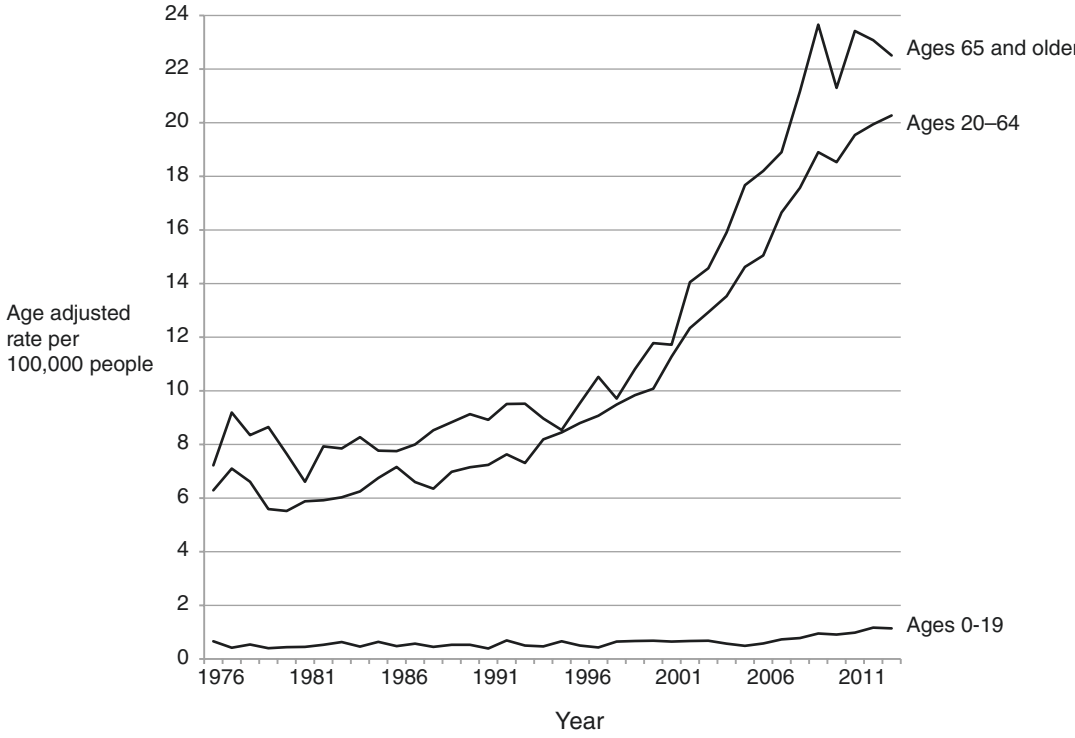

Fig. 1.3 Thyroid cancer incidence trends by age group, 1975–2011. Data are from the Surveillance, Epidemiology, and End Results (SEER) program (www.seer.cancer.gov) SEER*Stat Database: Incidence—SEER 9 Regs Research Data, Nov 2012 Sub (1973–2011) ⟨Katrina/Rita Population Adjustment⟩—Linked To County Attributes—Total US, 1969–2011 Counties, National Cancer Institute, DCCPS, Surveillance Research Program, Surveillance Systems Branch, released April 2014, based on the November 2013 submission

thyroid cancer mortality in the USA has not varied outside the range observed for the past 30 years. Recently, statistical tests have shown a very small 0.9% increase in the most recent years of data, but the clinical relevance of this increase is not yet clear and is under investigation.

Increased Detection of Subclinical Disease

A great proportion of the dramatic increase in the incidence of thyroid cancer over the past two decades may be due to detection of tumors that are subclinical. There is a large reservoir of thyroid cancer for which the value of treatment is uncertain, since papillary thyroid cancer is commonly found at autopsy in people who died of other causes [9–12]. These tumors are referred to as subclinical disease, and this phenomenon is termed "overdiagnosis" in cancer epidemiology. Overall a number of changes in healthcare practice have led to the increased detection of thyroid cancer through increased imaging, more frequent biopsy and surgery, and more thorough analysis of tissue by pathologists. These healthcare practices are reviewed in Table 1.1.

One key piece of evidence for overdiagnosis is that the majority of increasingly detected thyroid cancers are small tumors. Small cancers are typically asymptomatic at discovery and are detected within the size range commonly found in the autopsy studies described above. The detection of early stage thyroid cancer has rapidly outpaced the detection of late stage disease for the past three decades in the SEER database [13]. Larger and more advanced (node-positive) tumors have also increased in incidence [7, 14, 15]. This may also be due to changes in healthcare practice as even 40% of tumors larger than 4 cm may be discovered incidentally on imaging. Improvements in technology also frequently upstage disease by detecting what would be previously occult lymph nodes [16, 17]. A meta-analysis of 35 separate autopsy studies since 1949 has shown that differentiated thyroid cancer is common and has been identified at a steady rate of around 11% when whole specimens are evaluated, with no time trend observed [18]. This strongly suggests that the increasing incidence of thyroid cancer is due to diagnostic detection and does not reflect population-level increases in tumorigenesis.

Table 1.1 Potential healthcare practices contributing to the increasing incidence of thyroid cancer

Contributor	References
Healthcare system access	[20–23]
Increased use of imaging tests	[16, 17, 19, 24, 26]
Changing thresholds to work up thyroid nodules	[29–30]
Increase in number and extent of surgery	[30–33]
Increased scrutiny of pathology specimens	[34–39]

Subclinical disease may be more frequently detected as imaging technology is more frequently utilized. High-resolution ultrasound has become commonplace in the evaluation of thyroid nodules and detects five times the number of lesions detected by palpation [19]. Access to healthcare services correlates with thyroid cancer incidence rates [20–22] as access makes it more likely that a subclinical cancer is found. Private funding of healthcare is also significantly associated with thyroid cancer incidence [23]. Even when patients with a history of disease are followed longitudinally, the SEER database has shown that increases in ultrasound and PET scans increase the likelihood of undergoing additional therapy with no effect on mortality [24]. Iodine 131 is associated with improved disease-specific survival in this study, probably because it is used to detect advanced disease amenable to radioactive iodine therapy.

One particularly studied example of the interplay between healthcare delivery systems, advanced imaging, economic incentives, and thyroid cancer is South Korea. Between 1996 and 2010, the age-adjusted incidence of thyroid cancer in some South Korean provinces increased dramatically, with a notable tenfold increase from 10.6 to 111.3 per 100,000 women. During this time, thyroid cancer mortality remained unchanged, while asymptomatic cancers increased from less than 5% to more than 50% of all cancers [25]. This coincided with a rapid increase in ultrasound screening for thyroid nodules. A 2009 survey showed 13% of South Korean adults had undergone a screening thyroid ultrasound, with the highest rate among middle-aged women [26]. At this time a number of hospitals and providers were offering ultrasound screening as a $30–50 "add-on" to a nationally

approved, government-subsidized screening program for other cancers. Previous public health campaigns for early detection of cancer in South Korea had been vigorous, and later media attention to the "overdiagnosis" of thyroid cancer caused national controversy [27]. Since intense media coverage of this issue in 2014, there has been a 30% decrease in the incidence of thyroid cancer based on insurance data and a 35% reduction in the number of thyroid operations in South Korea [28].

Subclinical disease may also be increasingly reported due to an increase in diagnosis from sampled tissues. Among thyroid specimens removed for benign disease, up to 50% harbor small, incidental papillary thyroid cancers [29]. Over the past several decades, guidelines have shifted toward recommending biopsy for smaller nodules [30]. This trend has only recently reversed as investigations have shown that lesions less than 1 cm are low risk and should not be routinely biopsied [30]. Similarly, recommendations for thyroid surgery for small papillary cancers historically trended toward performing total thyroidectomy instead of lobectomy. Hemithyroidectomy has recently returned to consideration in the American Thyroid Association guidelines for tumors up to 4 cm [30, 31]. More frequent biopsies and larger specimens provide more opportunities for pathologists to find cancer, thus it is likely that these two phenomena are contributing to the increasing incidence of thyroid cancer. Thyroidectomy volumes have increased in parallel with increases in imaging rates and physician behavior. A study using the population-based Nationwide Inpatient Sample and National Survey of Ambulatory Surgery databases estimated that annual thyroid surgery volumes increased 39% over 10 years, from 66,864 in 1996 to 92,931 in 2006 [32]. Resident case logs show similar results, even doubling for otolaryngology trainees over a few decades [33]. The evaluation of greater volumes of tissue through both biopsy and surgery contributes to increased diagnosis of thyroid cancer.

Evaluation of thyroid specimens by pathologists has also changed with time. Suggested descriptive areas have increased from 5 in 1982 to a minimum of 14 in 2012, suggesting that each thyroid specimen is examined much more closely compared to the past [34, 35]. Individual institutions have also reported increased scrutiny of specimens over time [36]. An increase in the total diagnosis of cancer has also occurred as a shift toward labeling cases "follicular variant of papillary carcinoma" rather than follicular adenoma [37, 38]. This phenomenon has been investigated, and the very low risk of adverse outcomes associated with this diagnosis has led to a reclassification of this variant to "noninvasive follicular thyroid neoplasm with papillary-like nuclear features" and thus not a true invasive cancer [39]. The phenomena described in this section clearly compound on each other. Over the past several decades, thyroid lesions are increasingly more likely to be identified by imaging; identified lesions are more likely to undergo biopsy or surgical removal, and specimens are more thoroughly evaluated for cancer.

Biologic Risk Factors for Thyroid Cancer

The biologic development of thyroid cancer is still incompletely understood, and the strong effects of healthcare system practices on detection of thyroid cancer complicate epidemiologic investigations. It is commonly thought that cancer develops as a result of genetic mutation. Thyroid cancer has one of the lowest rates of underlying mutations [40]. Recent genetic characterization of papillary thyroid cancer has now identified driver mutations for over 96% of cases [41]. Ionizing radiation causes DNA double-strand breaks that often lead to somatic mutations that drive the development of thyroid cancer [42, 43]. Given the indolent course of differentiated thyroid cancer, it is expected that exposure to radiation is most important in early childhood and epidemiologic studies substantiate this expectation. As most thyroid cancers remain small, even until the point of death by other causes, additional risk factors may play a role in the progression of thyroid tumors to clinical significance. Thyroid-stimulating hormone is

Table 1.2 Potential biologic factors that may cause thyroid cancer and potentially contribute to the increasing incidence of thyroid cancer

Contributor	References
Radiation exposure	[42–61]
Obesity and diabetes	[62–85]
Estrogen	[86–92]
Iodine insufficiency or excess	[93–100]
Dietary nitrates	[101–104]
Autoimmune thyroid disease	[105–109]
Smoking	[110–115]

well known to stimulate the growth of thyroid cancer, and suppression of TSH is an established practice in thyroid cancer patients [44]. A number of proposed risk factors for thyroid cancer include obesity, nutrition, underlying endocrine disease, and smoking. All may theoretically influence the hormonal milieu that enables thyroid cancer to progress. These studies are typically observational and highly complicated by difficulty controlling for the influence of healthcare practices described above. Biologic contributors to the incidence of thyroid cancer are summarized in Table 1.2.

Ionizing Radiation as a Risk Factor for Thyroid Cancer

Exposure to ionizing radiation is the most extensively studied and clearly defined risk factor for thyroid cancer. Radiation exposure mainly increases the risk of thyroid cancer for exposures during childhood, especially for those younger than 5 years old [45]. Much of the understanding of these exposures comes from studies of survivors of catastrophic nuclear events [46–49]. In a cohort of just over 45 thousand survivors of Hiroshima and Nagasaki under the age of 20 at the time of the bombings, 191 cases of thyroid cancer have been reported, compared to 154 expected by population-matched controls (HR 1.28 per Gy of radiation exposure). Most of these cases however occurred once survivors were over the age of 40. Adults at the time of the atomic bombings have statistically similar rates of thyroid cancer to unexposed individuals [48]. The radiation effect is clearly a biologically established effect as thyroid cancer is also increasingly identified at autopsy in nuclear bomb survivors [50]. The effects of radiation influence the entire continuum of thyroid neoplasms with a dose-response effect established for benign thyroid nodules and cysts as well as malignant disease [51].

The carcinogenic effects of the Chernobyl power plant disaster have also been well studied. A large increase in the incidence of thyroid cancer was observed for two decades following the disaster, with a number of characteristic mutations attributed to radiation identified [52]. Longitudinal studies of Eastern Europeans exposed to the Chernobyl nuclear accident suggest an additional 4/100,000 male cases and 16/100,000 female cases of thyroid cancer in exposed individuals [53]. Age at exposure to the power plant catastrophe is the most notable modifier of thyroid cancer risk, similar to the Japanese bombings. A slight increase risk for adults exposed to radiation has been reported, but this may also be confounded by aggressive postexposure screening.

Patients undergoing radiation treatment also present the opportunity to understand the effects of radiation dose and age at exposure on the development of thyroid cancer. Pooled analysis of pediatric patients undergoing radiation therapy suggests a linear relationship between the risk of thyroid cancer and radiation dose up to 10 Gy with this effect plateauing from 20 to 30 Gy [54]. This dose-effect curve is also related to age at exposure with the steepest relationship between dose and relative risk in the youngest patients ($\beta = 9.17$ for patients <1 year old vs. $\beta = 1.51$ for patients 15–19 years old). Lower dose radiation below 1 Gy is less certain to have any effect on thyroid cancer. In a Swedish cancer registry including patients undergoing radiation for benign spinal conditions, sub-gray doses of radiation were only associated with increased thyroid cancer when delivered directly to the cervical region [55]. This represented about eight additional cases in an exposed population of 8000, and most cases were diagnosed >15 years after exposure.

Changes in exposure to ionizing radiation are responsible for a small proportional increase in the overall thyroid cancer incidence at most. Annual radiation exposure for people who do not experience the exceedingly rare events of a nuclear disaster or radiation treatment for cancer has increased from 3.6 to 6.2 mSv since the 1980s. This dose is roughly equivalent to the same values in mGy, 1000 to 10,000 fold less than the exposures described in the previous paragraph. This increase is nearly entirely attributable to medical imaging, predominantly due to the use of CT scanning [56]. In the USA, the number of CT scans performed annually has increased over tenfold in the past several decades [57], but most CT scans are performed in patients over 55 years of age [45]. Multiplying CT utilization numbers [58] by mean excess lifetime thyroid cancer risk per scan [45] suggests that 150–350 additional thyroid cancers annually are attributable to pediatric CT scans in the USA. Adult exposure to ionizing radiation through background or occupational exposure remains uncertain, with a few studies reporting an association [59–62]. These studies typically do not control for healthcare utilization or report highly attenuated results when doing so.

Obesity, Estrogen, and the Metabolic Syndrome

Obesity has rapidly increased during this same period of rising thyroid cancer, and the metabolic syndrome has had a pervasive effect on innumerable aspects of healthcare [63]. Data are conflicting over the relationship between diabetes, obesity, and thyroid cancer [64]. Numerous studies have demonstrated a correlation between body mass index (BMI)-defined obesity and thyroid cancer with a hazard ratio ranging from 1.09 to 1.5 depending on the BMI cutoff value [65, 66]. Proposed mechanisms include exposure to adipokines such as leptin and adiponectin or thyroid-stimulating hormone and estrogens, insulin resistance and the insulin-IGF-1 axis, increased aromatase activity, chronic inflammation, and oxidative stress [67]. Leptin, a neuroendocrine regulator, stimulates thyroid cancer cell line proliferation through phosphatidylinositol 3-kinase/Akt signaling [68, 69]. A number of small cohort studies have suggested increased levels of leptin [70, 71] and decreased levels of adiponectin [72] in patients with thyroid cancer. Excess weight and BMI has been associated with larger and more aggressive thyroid tumors [73, 74]. However a causal relationship between obesity and thyroid cancer has not been proven. There may even be a common factor between genetically determined body size and thyroid cancer risk as adult thyroid cancer risk was associated with both childhood BMI and height in a large Danish population study [75]. A study of obesity-related genetic polymorphisms did not demonstrate an association with thyroid cancer risk [76]. The association between obesity and thyroid cancer may also be due to increased medical attention given to obese populations and thus a higher rate of detection [77]. More prospective studies and studies designed to assess causality would be needed to establish a relationship between the risk of thyroid cancer and obesity-related markers of thyroid function.

A slight positive correlation exists between type 2 diabetes and thyroid cancer [64, 78]. Beyond the mechanisms described previously for BMI, elevated insulin, long-term exposure to high levels of glucose or triglycerides, and use of antidiabetic medications have been proposed [79]. Insulin is homologous in structure to insulin-like growth factor-1 (IGF-1), which drives follicular cell proliferation in some animal studies [80]. Overall cancer mortality in diabetics using insulin is twice that of diabetics using metformin, but this has not been specifically studied in thyroid cancer [81]. Hyperglycemia has been associated with increased incidence and mortality of numerous malignancies including thyroid cancer in a large European population study [82]. Associations between diabetes and thyroid cancer may also be due to screening bias rather than a true biologic cause, as there is a positive association between diabetes and the likelihood of undergoing thyroid ultrasound and thyroid fine-needle aspiration [83]. As with obesity, more

work is necessary to establish any direct causal mechanism between diabetes and thyroid cancer.

Estrogen has historically been proposed as a mechanistic cause of thyroid cancer, given the higher prevalence of thyroid cancer among women. It is interesting that a number of the previously described studies of obesity have shown a stronger association between obesity and thyroid cancer in men [65, 66, 81, 84] noting that abdominal fat causes excess estrogen through the aromatization of androgens [85]. Research supporting a direct hormonal cause of thyroid cancer is predominantly limited to cell line studies. Laboratory studies using thyroid cancer cell lines show cancer cell proliferation is enhanced by estrogen stimulation through various mechanisms including modulation of ER-α, ER-β, cyclin D1, GPR30 activity, and MAPK activity [86–89]. Clinical studies linking estrogen to thyroid cancer are less compelling. One case control study showed higher estrogen-DNA adducts in the urine of women with thyroid cancer [90]. Another study showed thyroid cancers with ER-α-positive, ER-β-negative, and positive androgen receptor expression were associated with a more aggressive disease course [91]. In one meta-analysis, factors related to endogenous estrogen exposure including parity, breastfeeding, and age at menopause moderately correlate with thyroid cancer risk, but exogenous exposures such as oral contraceptive use and estrogen replacement therapy do not [92]. More clinical and epidemiologic work is necessary to support estrogen as a cause of the increasing incidence of thyroid cancer.

Other Proposed Modulators of Thyroid-Stimulating Hormone and Thyroid Cancer Risk

Iodine deficiency and excess is known to affect the proportions of thyroid cancer histologies [93, 94]. Animal studies support iodine deficiency as a risk factor for thyroid cancer [95], but data in humans are lacking. Two epidemiologic studies comparing iodine-sufficient and iodine-insufficient areas have shown opposite effects of iodine intake on thyroid cancer rates [93, 96]. Iodine supplementation is difficult to study as this typically coincides with modernization and expansion of healthcare with greater use of imaging technology and detection [97–99]. Nitrates compete with the uptake of iodine by the thyroid, impairing thyroid hormone synthesis and thereby driving chronic elevation of thyroid-stimulating hormone. Dietary nitrate is a contaminant of drinking water in agricultural areas and is found at high levels in some vegetables such as beets. Epidemiologic studies linking dietary nitrate to thyroid cancer risk show mixed results, failing to establish a dose-dependent response, and can also be confounded by associated changes in screening [100–103]. A recent systemic review and meta-analysis has concluded that no association between dietary nitrate exposure, thyroid hormone function, and thyroid cancer exists [104]. Overall, a clinically relevant and directly causal relationship between diet and thyroid cancer remains to be proven.

Autoimmune thyroid disease has been proposed as a cause of thyroid cancer. Elevated levels of TSH are found in hypothyroid patients with autoimmune thyroid disease and may stimulate follicular epithelial proliferation, promoting the development of papillary carcinoma. Studies examining FNA biopsy for patients with autoimmune thyroid disease have not shown a statistically significant correlation between Hashimoto's thyroiditis and papillary thyroid cancer [105, 106]. Retrospective studies of patients with autoimmune thyroid disease undergoing thyroidectomy typically report a statistically significant positive correlation [107–109]. This study design is highly flawed and confounded by indication as patients with autoimmune thyroiditis who have features worrisome for malignancy are highly more likely to elect thyroidectomy. More prospective studies with longer follow-up would be needed to test the relationship between autoimmune thyroid disease and thyroid cancer.

Cigarette smoking, despite its strong causal association with many highly lethal cancers, may be protective against thyroid cancer. Pooled analysis of several US studies has shown a reduced risk (HR = 0.68) for thyroid cancer in smokers

[110]. The proposed mechanism is similar to other factors in this section as smoking reduces levels of TSH in circulation [110, 111]. Smoking is also associated with increased risk of Graves' hyperthyroidism and decreased risk of Hashimoto's autoimmune hypothyroidism [112–114]. Recent worldwide decreases in cigarette consumption [115] have been suggested to contribute to the increased incidence of thyroid cancer [116] but without more well-designed studies, this remains speculative. In particular, smoking is highly associated with socioeconomic status and thus likely to correlate with healthcare access and utilization. The above studies have not been able to rigorously control for likely differences in healthcare utilization. In one study, the association between smoking and thyroid cancer becomes nonsignificant in subpopulations with less healthcare utilization, such as men, individuals without a high school education, and regular alcohol consumers [110].

Conclusion

The incidence of thyroid cancer has dramatically increased over the past several decades, while mortality from thyroid cancer remains low. This has attracted academic scrutiny and significant debate among clinicians about the influence of medical practice and a need for change in these practices. The simplest explanation for this change is an increase in detection, pathologic reporting, and physician management of identified thyroid nodules. A number of biologic mechanisms have been proposed, but any significant impact on global disease remains speculative and unlikely to account for the dramatic upward trend in incidence over such a short time. Radiation exposure at a young age is an established cause of thyroid cancer, but this typically requires doses equivalent to nuclear catastrophe or radiation cancer treatment and thus is unlikely to have a significant global impact on the increasing incidence despite some increases in radiation exposure due to increased medical imaging. Similarly a number of behavioral and environmental factors influence TSH levels and other proposed hormonal drivers of thyroid cancer cell proliferation. Of these, an increase in obesity and a decrease in smoking could plausibly contribute to a small increase in thyroid cancer, but this would require significantly larger and more rigorous studies to formally establish.

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Molecular Genetics of Thyroid Cancer

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Laura N. Purcell and Jen Jen Yeh

Papillary Thyroid Cancer

Papillary thyroid cancer (PTC) is the most common differentiated thyroid carcinoma, making up 80% of these cancers. The gold standard diagnosis for PTC is based on histological architecture and nuclear characteristics. In PTC, normal follicular cells are replaced with papillae, which are layers of neoplastic thyroid epithelial cells. The characteristic nuclear alterations for PTC are nuclear membrane grooves, pseudomembrane inclusions, and optical clearing [1]. Mutations in PTC can be subdivided into BRAF- or RAS-like, which have fundamentally different biologies [2, 3].

Driver mutations are thought to be responsible for the survival advantage and clonal expansion of tumor cells. In differentiated thyroid cancers, these mutations are mutually exclusive, meaning very few tumors harbor more than one of these mutations [2]. Mutations identified in papillary thyroid cancer (PTC) include *BRAF*, *RET/PTC*, *RAS*, *TRK*, *TERT,* and *EIF1AX*. The leading genetic alterations in follicular thyroid carcinoma (FTC) are *RAS*, *PAX8/PPARG*, *PTEN*, *PI3K/AKT* pathway, and *IDH1*. Mutations are summarized in Table 2.1. Overall, the mutation density of thyroid cancers is very low as compared to other malignancies [2]. Age, which is an important clinical prognostic factor for thyroid cancer, also increases mutational density. A clear correlation between aggressive clinical behavior and specific genetic mutation(s) is not yet established and remains one of the most important questions to be answered in thyroid cancer.

Table 2.1 Common genetic mutations and rearrangements associated with differentiated thyroid carcinomas

Tumor	Genes	Frequency	Citations
PTC	*BRAF*	40–50%	[2, 4–8]
	RET/PTC	10–20%	[2, 9, 10]
	RAS	10–20%	[11–15]
	TRK	5–13%	[16]
	TERT	9%	[2]
	EIF1AX	2%	[2]
FTC	*RAS*	20–50%	[13, 15, 17, 18]
	PAX8/PPARG	30–40%	[19]
	P13K/AKT	6%	[20, 21]
	PTEN	7%	[20]
	IDH1	5%	[22]
	TERT	17.1%	[23, 24]

L.N. Purcell, M.D. (✉)
Department of Surgery, University of North Carolina, 4001 Burnett-Womack Building, CB #7050, Chapel Hill, NC 27599-7050, USA
e-mail: laura.purcell@unchealth.unc.edu

J.J. Yeh, M.D.
Division of Surgical Oncology and Endocrine Surgery, Department of Surgery, University of North Carolina, CB7213, 170 Manning Drive, 1150 POB, Chapel Hill, NC 27599-7213, USA
e-mail: jjyeh@med.unc.edu

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BRAF

Genetics

BRAF mutations are found in a wide variety of tumors including 40–70% of melanomas, 10% of colorectal tumors, as well as ovarian, breast, and lung tumors [25, 26]. *BRAF* germline mutations have been identified in Leopard syndrome, a developmental disorder with multiple granular cell tumors, pulmonary stenosis, deafness, and cardiac conduction abnormalities [27, 28]. In thyroid cancer, *BRAF* mutations are limited to papillary, poorly differentiated, and anaplastic carcinomas. There is no evidence of involvement of *BRAF* in follicular thyroid carcinoma (FTC) or benign thyroid nodules [29].

The members of the RAF family proteins are cytoplasmic serine/threonine protein kinases in the mitogen-activated protein kinase (MAPK) signaling cascade. The cascade begins with RAS, a small membrane-bound G protein, activating RAF to the plasma membrane. The activated RAF phosphorylates MAP-ERK kinase (MEK), which in turn phosphorylates and activates extracellular signal regulated kinases (ERK). ERK has over 150 nuclear and cytosolic targets, which include transcription factors that regulate cellular differentiation, proliferation, senescence, and survival [30]. There are three isoforms of *RAF*: *ARAF*, *BRAF*, and *CRAF* (*RAF-1*). *BRAF*, v-raf murine sarcoma viral oncogene homolog BI, is the most frequently mutated in the kinase superfamily and is the strongest MAPK activator [28, 31–33]. The majority of *BRAF* mutations in thyroid carcinomas are at V600E (95%) [34]. Wild-type BRAF has a hydrophobic interaction with residues G465 to V472 located in the ATP-binding site, which keeps the kinase activity inactivated until appropriately signaled by RAS. *BRAF* ^{V600E} is created by an oncogenic T to A transversion at nucleotide 1799, which changes glutamate to valine at codon 600 of the kinase activation segment [26, 35, 36]. This mutation causes the BRAF kinase to fold into the catalytically active formation, which increases its activity almost 500-fold [37]. Other rare BRAF activating mutations associated with differentiated thyroid carcinomas includes small in-frame insertions and deletions that make up a small minority of the BRAF mutations (1–2%) [38]. Point mutations around codon 600 include a K601E mutation found primarily in the follicular variant of PTC (FVPTC) [39, 40]. *AKAP9-BRAF* is a paracentrically inverted oncogenic rearrangement found on chromosome 7, which is associated with PTCs arising in the setting of radiation exposure [41].

Clinical and Pathology Characteristics

BRAF is the predominant genetic mutation in adult sporadic PTC, making up 29–69% of cases. The majority of studies from the United States report the frequency of *BRAF* mutations in PTCs between 40 and 50% [4–8]. *BRAF* mutant tumors have well developed nuclear features typically associated with PTC. BRAF mutant tumors have a high degree of lymphocytic infiltration and are less frequently associated with psammoma bodies (20%) than tumors with *RET/PTC* rearrangements [42]. Tumors with *BRAF* mutations are associated with aggressive histologic features such as tall cell variant, older patient age, lymph node metastasis, and extrathyroidal extension [2, 43, 44]. Tall cell variant PTC, an aggressive subset of PTC, has been found to have a higher frequency of *BRAF* mutations (70–80%) [45–47]. In a study of 190 fine needle aspiration specimens, 73 of which were positive for *BRAF* mutations, Xing et al. reported *BRAF* mutations predicted extrathyroidal extension (23%, $n = 17$) versus wild type (11%, $n = 13$), thyroid capsular invasion (29%, $n = 21$ vs. 16%, $n = 19$), and persistence or recurrence of disease (36%, $n = 19$ vs. 12%, $n = 9$) [48]. In a recent landmark integrated genomic study of 496 PTCs from The Cancer Genome Atlas (TCGA), two major subgroups of PTCs were identified, one of which is driven by BRAF and associated with tall cell variant tumors [2]. However, it is important to note that *BRAF* mutant tumors are complex and not a homogenous group. Thus additional alterations occurring within the context of *BRAF* mutations will need to be considered for tumor behavior and prognosis [2].

BRAF mutant tumors are also associated with I^{131} resistance [49]. This resistance is likely due

to silencing of thyroid-specific iodine expressing genes, such as sodium iodine symporter, apical iodide transporter, thyroperoxidase, and thyroglobulin [50, 51]. In elegant preclinical studies, inhibition of *BRAF* and the downstream signaling cascade resulted in cells regaining their sensitivity to I^{131} [52, 53]. I^{131} response was further enhanced by dual inhibition of the pathway using a BRAF and MEK inhibitor [51]. Further clinical studies will be needed to determine if this dual inhibitor approach may improve sensitivity to I^{131} in patients as monotherapy did not have a significant effect on patient outcome [52, 53].

RET/PTC

Genetics

The *RET* (*re*arranged during *t*ransfection) proto-oncogene is a single-pass transmembrane tyrosine kinase located on chromosome 10q11.2 [54, 55]. Activation of RET is highly regulated by ligand-binding dimerization with glial-derived neurotrophic factor family ligands [56]. This proto-oncogene is integral in regulating cell growth and survival [55]. It is essential in the development of the sympathetic, parasympathetic, and enteric nervous systems, the gastrointestinal lymphoid system, as well as the kidneys and testis. Germline loss of function *RET* mutations result in impaired formation of the enteric nervous system and congenital agangliosis of the colon (Hirschsprung's disease) [57]. Wild-type *RET* is necessary for the development of neuroectodermal cells that become thyroid C cells [58].

RET is activated when its 3′ tyrosine kinase intracellular domain fuses with the 5′ end of an alternate gene with a coiled-coil domain. This fusion creates ligand-independent dimerization. The new chimera does not contain the intracellular juxtamembrane domain, which is an important component of the auto-inhibited RET dimer interface [59, 60]. The *RET/PTC* rearrangement contains intrinsic and constitutive tyrosine kinase activity, which results in subcellular relocalization where cell growth and survival are constitutively activated [61–63].

There are at least 15 *RET/PTC* rearrangements identified in PTC [56, 64]. *RET/PTC1* rearrangements are the most common (60–70%), followed by *RET/PTC3* (20–30%), while the remaining rearrangements make up less than 5% of all *RET/PTC* rearrangements [65]. The tumorigenicity of the *RET/PTC* rearrangements may be attributed to the *RET* fusion partners, such as *PRKAR1A*. *PRKAR1A* is a cyclic AMP-dependent protein kinase type I regulatory subunit, a tumor suppressor gene mutated in Carney complex and *CCDC6* (coiled-coil domain-containing protein 6) [66, 67]. *RET/PTC1* is a balanced intrachromosomal inversion with *CCDC6*, formally known as H4/D10S170, on chromosome 10 [61, 65, 68, 69]. Loss of an allele of *CCDC6* as a result of this rearrangement is believed to promote transcription and thyroid hyperplasia [70]. *RET/PTC2* is the result of an interchromosomal translocation with *PRKAR1A* [71]. *RET/PTC3* is an intrachromosomal inversion with nuclear receptor coactivator gene-4 (*NCOA4*), formally known as ELE1/ARA70/RFG, a transcriptional coactivator on chromosome 10 [10, 64]. *RET/PTC2* and less frequent *RET* rearrangements are interchromosomal translocations [72]. *RET/PTC* rearrangements can be clonal rearrangements, affecting all cells of a tumor or non-clonal, that is specific to a single or small fraction of cells within a tumor.

Clinical and Pathology Characteristics

Overall, *RET/PTC* rearrangements are more likely associated with classic papillary thyroid architecture and microadenomas [42]. Psammoma bodies, lamellated calcified collections of necrotic papillae, have been noted in 100% of *RET/PTC* rearrangement associated PTC compared to only 20% of *BRAF* mutant PTC [42, 73]. *RET/PTC1* rearrangements are more common in papillary microcarcinomas seen in younger patients with PTC and when present are associated with a higher frequency of lymph node metastasis and classic histology. The *RET/PTC3* rearrangement is most commonly seen in solid variant PTC [74–76]. Increased incidence of *RET/PTC* rearrangements (50–80%), especially *RET/PTC3*, are seen in patients with a previous history of radiation [9, 71, 77–81]. *RET,*

CCDC6, NCOA4 genes are all adjacent on chromosome 10. Ionizing radiation promotes double-strand DNA breaks, catalyzing a nonhomologous recombination between these juxtaposed genes [82, 83]. These findings have been corroborated in patients after exposure to the nuclear accident at Chernobyl, atomic bombings at Hiroshima and Nagasaki, Semipalatinsk nuclear testing site, and children who have been irradiated for benign conditions [84]. The incidence of *RET/PTC* rearrangements is especially increased in children, likely due to rapid thyroid cell proliferation.

RAS

Genetics

Members of the rat sarcoma viral oncogene homologue (RAS*)* superfamily of GTP-binding proteins include three genes: *HRAS* (chromosome 11p15.5), *KRAS* (chromosome 1p13.2), and *NRAS* (chromosome 12p12.1) [85]. These genes, which are nearly ubiquitously expressed and conserved across species, encode membrane-associated guanine nucleotide-binding proteins (p21ras). *RAS*, an oncogene, encodes a small GTPase that cycles between an active (GTP-bound) and inactive (GDP-bound) state. Activated RAS then stimulates a diverse cascade of downstream effectors and signaling networks [86]. These proteins regulate extracellular receptor signals to influence downstream intracellular pathways, including RAF/MAPK, PI3K/AKT, and others. RAS is integral in the modulation of cellular differentiation, survival adhesion, migration, apoptosis, and senescence [36, 87, 88].

RAS mutations are the second to *BRAF* for the most common genetic mutation in thyroid cancers. *RAS* mutations have been credited with the dramatic increase in thyroid carcinomas over the last 40 years [89]. Mutations in *RAS* associated with differentiated thyroid carcinoma most commonly occur in codons 12, 13, and 61 (99%). Rarely, other mutations such as amplifications and polymorphisms may occur [90]. Codons 12 and 13 code for the GTP-binding domains, and codon 61 encodes the GTPase domain; therefore, mutations in these codons dampen the GTPase activity. As a result, these mutations disrupt the RAS and guanine nucleotide interaction which results in constitutively active *RAS* [91]. *KRAS* mutations are most commonly found in codon 12 (65%) and 95% of *NRAS* mutations are in codon 61. Codon 61 mutations in *NRAS* (chromosome 1p13) and *HRAS* (chromosome 11p11), which inactivate the autocatalytic GTPase, are the most common in thyroid cancers [38]. This inactivation results in constitutive RAS activation and chronic stimulation of MAPK, PI3K/AKT, and other downstream signaling pathways. *NRAS* (8.5%) is the predominant mutation in PTCs, with *HRAS* (3.5%) and *KRAS* (1%) composing a smaller proportion of these tumors [2].

Clinical and Pathology Characteristics

RAS mutations are seen in 10–20% of PTCs [11–15]. The recent Cancer Genome Atlas analysis divided PTCs into BRAF-like, discussed previously, and RAS-like subgroups. As expected, RAS-like tumors were significantly associated with *RAS* mutations but more importantly showed concurrent activation of PI3K/AKT and MAPK signaling. RAS-like tumors were associated with follicular variant (FV) PTC and lower risk of recurrence [2, 92, 93]. Psammoma bodies, extrathyroidal extension, and lymph node metastasis are rarely seen with *RAS* mutations. *RAS* mutant PTCs are more frequently encapsulated, with a female preponderance and tendency toward increased size [42]. *RAS* mutations make up 20–50% of conventional-type FTCs and 20–40% of conventional-type follicular adenomas, which will be discussed in more depth later in this chapter [94–96]. Even though FVPTCs are genotypically and histologically more similar to FTCs rather than classic PTC, they are currently still classified with PTCs [97, 98]. Multiple studies have correlated *RAS* mutations with increased bone metastasis, aggressiveness, and mortality [15, 99, 100]. However, *RAS* mutations are seen in a significant number of benign follicular adenomas and low risk FVPTC [91, 101–103]. The impact on clinical prognosis and pathological classification of thyroid cancers with a *RAS* mutation continues to be uncertain, and further evaluation into this molecular subgroup is warranted.

TRK

Genetics

Neutrotrophic receptor-tyrosine kinase 1 (*NRTK1*, *TrkA*) is a proto-oncogene located on chromosome 1q21–22. This gene encodes for a transmembrane tyrosine kinase receptor with high affinity for nerve growth factor (NGF). Its wild type expression is important for development of the central and peripheral nervous system, especially for the neurons of sensory spinal and cranial ganglia of neural crest origin [104, 105]. In addition, it promotes proliferation of lymphocytes, keratinocytes, prostate cells, and others cell types [106–108].

Binding of the TRTK1 receptor by NGF results in dimerization and autophosphorylation of five tyrosine residues. Autophosphorylation results in elevated NTRK1 activity and activation of downstream signaling cascades, including RAS, PI3K, phospholipase C-gamma, and MAPK [109]. Rearrangements of *NRTK1* result in a fusion of the tyrosine kinase domain to the amino terminus of different activating genes which results in aberrant expression of chimeric oncogenes. The tyrosine kinase domain becomes constitutively active, leading to deregulation of cell proliferation and oncogenic transformation [110]. The most common fusion partner forming chimeric oncogenes with *NRTK* is *TPM3* (isoform of non-muscle tropomyosin) on chromosome 1q31 creating the *TRK* (thyroid oncogene receptor kinase) oncogene [110–112]. Less frequently involved is *TPR* (translated promotor region), which encodes a large protein of a nuclear pore complex involved in mRNA export on chromosome 1q25. When mutated, the *TPR* gene product forms the oncogene *TRK-T1* and *TRK-T2*. Lastly fusion products involving *TFG* (*TRK*-fused gene) on chromosome 3q12 forms the *TRK-T3* oncogene [113–119]. These fusion interactions result in proteins folded into alpha helices, which are further wound into a super helix that promote protein dimerization and constitutive activation [120]. No cytogenetic studies have been performed on *NTRK1* rearrangements in PTC [120]. However, mutations are likely to be due to intrachromosomal inversion, preferentially with chromosome 1 in *NTRK1* [121].

Clinical and Pathology Features

NRTK1 rearrangements are found in 5–13% of sporadic PTCs and only 3% of post-Chernobyl childhood PTCs, suggesting that there is no association with radiation exposure [16]. *NRTK2* is also associated with a younger age at presentation and worse prognosis compared to other PTCs [65, 122].

TERT

Genetics

Telomerase activation is a hallmark of cancer in up to 80% of malignant tumors [123–125]. Telomerase, a RNA-dependent DNA polymerase, contributes to cell immortality by lengthening the telomeres at the ends of chromosomes and decreasing apoptosis by protecting important chromosomal DNA [23]. Telomerase reverse transcriptase (*TERT*) is the rate-limiting step in transcriptional regulation of the telomerase complex. Oncogenic transformation in cells with abnormal telomerase results most often from deregulation of *TERT* transcription, resulting in *TERT* overexpression [126]. Mutations in the promotor region enhance TERT activity [124, 125]. Frequent mutations have been found in *TERT* promoter regions in melanomas, gliomas, bladder, and thyroid cancers [127–129]. Normal thyroid tissue and benign lesions do not express telomerase, and reactivation of this gene may play an important role in thyroid carcinoma [24, 127, 130, 131]. This mutation is reported to be present in 7.5–12% PTC and 17.1% FTCs [23, 24].

Two focuses for mutations have been identified at 124 and 146 base pairs upstream from the ATG start codon, named C228 and C250, respectively. C228T, the most common mutation (87%), represents a C to T nucleotide change [23]. Less commonly identified are C228A (C to A conversion) and C250T (C to T conversion) substitutions [2]. These point mutations create a consensus binding motifs site for E-twenty-six (ETS)/ternary complex transcription factors, which can also be upregulated by the MAPK pathway [23].

Clinical and Pathology Characteristics

Tumors with *TERT* promoter mutations are associated with an increase in aggressiveness of the tumor and are seen in conjunction with a high frequency of *BRAF* and *RAS* mutations up to 60% [24, 127, 130, 131]. There is an observed association with older patient age, larger tumor size, more distant metastasis, and higher stage. Although *TERT* promoter mutations were found in less-differentiated PTCs, there has been no identified correlation between *TERT* mutations and vascular invasion, extrathyroidal extension, or lymph node metastasis [2]. The presence of this mutation did have an increase in disease-specific mortality [24]. At follow up, Melo et al. showed *TERT* promoter mutations to be more likely to have persistent disease, as well as correlate with male gender and lymph node metastasis [24].

Other Significantly Mutated Genes

Recent whole exome sequencing of 402 tumor and normal pairs of PTC samples has provided unprecedented insight into the landscape of PTCs and the opportunity to evaluate less common somatic mutations [2]. Eukaryotic translation initiation factor 1A, X-linked (*EIF1AX*), was found to be mutated in six PTC tumors that lacked other known drivers, suggesting that *EIF1AX* may be a novel cancer gene in PTC [2]. Additionally genes involved in DNA repair, including *PPM1D* (protein phosphatase, Mg2+/Mn2+ dependent 1D) and *CHEK2* (checkpoint kinase 2), were associated with higher mutation density unadjusted for age and high-risk patients [2]. Findings of additional DNA repair-associated genes may suggest that defects in DNA repair may be associated with more aggressive PTCs.

Follicular Thyroid Carcinoma

Follicular thyroid carcinoma (FTC) makes up 20% of differentiated thyroid cancers. The leading genetic alterations in FTC are *RAS, PAX8/PPARG, IDH1,* and the PTEN/PI3K/AKT pathway.

RAS

Genetics

The predominant mutation in the majority of reports of *RAS* mutations in FTC are *NRAS*, with lesser contributions from *HRAS* and *KRAS* [11, 18, 103, 132]. The most common *NRAS* point mutation includes a mutation changing glutamine to arginine (CAA → CGA; Q61R), followed by a mutation converting glutamine to lysine (CAA → AAA; Q61K) [91, 92, 133]. As mentioned above, *RAS* mutations are present in 20–40% follicular adenomas and 30–45% of FVPTC cases. In addition, 20–40% of poorly differentiated carcinomas and 20–30% of anaplastic carcinomas harbor *RAS* mutations [17, 134]. Explanations for *RAS* mutations throughout every stage of thyroid nodule include *RAS* as a de-differentiation factor from well-differentiated thyroid carcinomas versus *RAS*-positive follicular adenomas being precursor lesions to thyroid carcinoma [100, 135, 136].

PAX8/PPARγ

Genetics

PAX8/PPARγ is the result of a translocation between chromosome 2 and 3, resulting in t(2;3)(q13;p25). This translocation results in an in-frame fusion of a thyroid-specific paired box domain transcription factor (2q13) and PPARγ's translated reading frame, which leads to the overexpression of fusion proteins [137, 138]. Expression of the PAX8/PPARγ fusion protein (PPFP) is controlled by PAX8's upstream fusion protein. Expression of PPFP correlates with the tumor differentiation, high expression in well-differentiated tumors, and low expression in poorly differentiated tumors [137]. *PAX8*, paired box 8 gene, is integral to thyrocyte development. PAX8 controls expression of the sodium iodide symporter, thyroglobulin, and the TSH receptor. Therefore, PAX8 is an important regulator of thyroid differentiation, development, and growth [139, 140]. During human development, PAX8 is expressed in thyroid, kidney, and neural tissues; but in adulthood, expression is limited to thyroid tissue [141, 142].

PPAR (peroxisome proliferator-activated receptor) is a subfamily of the steroid/thyroid hormone nuclear receptor superfamily. Its role is to regulate adipogenesis and insulin sensitization via multiple cell signaling pathways [143, 144]. PPARγ is one of four subtypes of PPAR, the others include α, β, and δ. PPARγ modulates transcription by recruiting coactivators to DNA binding sites to increase transcription and interacts with corepressors to result in gene silencing. PPARγ is activated by thiazolidinediones, a class of medications used to treat diabetes [145]. Another *PPARγ* translocation associated with differentiated thyroid carcinoma is *CREB3L2-PPARγ*, resulting from a t(3;7)(p25;q34) chromosomal rearrangement of the transactivation domain of the CREB3L2 gene and PPARγ [146]. Multiple other genes have been identified that translocate with PPARγ at chromosome 3p25 [147].

Clinical and Pathology Characteristics

PAX8/PPARγ gene rearrangements comprise 30–40% of conventional-type FTCs. This translocation has been detected in follicular adenomas, which decreases the utility for using this rearrangement to diagnose FTC [19]. FTCs with *PAX8/PPARγ* tend to present at a younger age with smaller tumors, solid or nested growth pattern, and frequent vascular invasion [19, 40, 101, 148].

PI3K/AKT

Genetics

The PI3K/AKT cellular pathway is involved in regulation of glucose uptake, metabolism, growth, cellular motility, and crucial cellular functions. Phosphoinositide-3 (OH) kinase (PI3K) phosphorylates the beta-hydroxyl group of phosphatidylinositol inositides generating phosphatidylinositol-3, 4, 5-trisphosphate (PIP3). When activated by PIP3, phosphoinositide-dependent kinase 1 (PDK1) phosphorylates and activates AKT, a serine/threonine protein kinase also known as protein kinase B (PKB), mobilizing PDK1 to the cell membrane [149, 150]. Activated AKT then phosphorylates downstream effectors to promote cell proliferation and survival [20]. Phosphate and tensin homologue (PTEN) protein terminates this signaling cascade by degrading PIP3 via dephosphorylation [151].

PI3K is composed of a regulatory subunit (p85α, p85β, and p55γ) and a p110 catalytic subunit (α, β, γ, and δ). Thus far, only carcinoma-producing mutations have been identified in the p110α catalytic subunit [149]. *PIK3CA* mutations in FTC are relatively infrequent, occurring in only 6% of FTCs [20, 21]. The identified mutations (E542K, E545K, and H1047R) are in the helical (exon 9) and kinase (exon 20) domains [20, 152]. More commonly in FTC, *PIK3CA* and *PIK3CB* are amplified rather than mutated [21]. Approximately 25–45% of FTCs contain these amplifications as defined by a copy number gain of four or more [20, 21]. This amplification is due to duplication of the gene or chromosome 3 region, rather than aneuploidy. *PIK3CA* and *PIK3CB* result in an increase of AKT phosphorylation [152]. These findings are also prevalent in anaplastic thyroid carcinoma [20, 21].

PTEN

PTEN is a dual specificity phosphatase and tumor suppressor gene that negatively regulates the PI3K/AKT signaling pathway via dephosphorylation of the three positions on phosphoinositides [149]. Germline mutations of *PTEN* on chromosome 10q-22q24 result in Cowden's syndrome, an autosomal dominant disorder. Mucocutaneous manifestations of Cowden's syndrome include multiple hamartomas, specifically trichilemmomas, mucocutaneous papillomatous papules, as well as acral and palmoplantar keratosis. At least 66% of those affected with the disorder have breast or thyroid cancers, specifically FTCs [153]. Sporadic *PTEN* mutations occur at approximately 7% of FTCs [20]. More commonly found is methylation of the *PTEN* promoter that results in silencing of the gene [149]. In addition, loss of heterozygosity has been identified in up to 26% of FTCs, with homozygous deletions being rare [154–156]. *PTEN* silencing results in constitutive activation of the PI3K/AKT pathway.

IDH1

Isocitrate dehydrogenase 1 (IDH1) is a key enzyme in the tricarbocyclic acid cycle (TCA or Krebs cycle), which catalyzes the oxidative decarboxylation of isocitrate to produce alpha-ketoglutarate [157]. IDH1 is found within the cytoplasm, whereas IDH2 is located in the mitochondria [36]. *IDH1* mutations associated with FTC occur in highly conserved residues and include G70D, I130M, H133Q, V178I, and V71I [22, 158]. G70D, I130M, and H133Q are located near the substrate-binding site, R132. The wild type codon R132 contains a highly conserved arginine integral to the catalytic activity of IDH1. The R132 residue is the location where the isocitrate's α- and β-carboxylate binds in order to produce α-ketoglutarate. Mutations in this region likely result in decreased catalytic activity of the enzyme. The significance of the V178I mutation is still unclear [158]. There have been no associations found between the presence of *IDH1* mutations and clinical features such as age, gender, tumor size, extrathyroidal invasion, and presence of metastases [158]. *IDH1* mutations have been identified in a small number of papillary and follicular-type PTCs, as well as anaplastic and Hürthle cell carcinomas [36].

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Evaluation of a Thyroid Nodule

3

Jennifer Rosen and Vardan Papoian

Introduction

Thyroid nodules are a common finding in the general population. The reported prevalence of nodules varies based on the epidemiologic methods for evaluation. In a population with no known thyroid disease, ultrasound can detect nodules in up to 17% of the study group [1]. In autopsy studies of a population with no known thyroid disease, the prevalence of nodules greater than 1 cm has been reported to be 8% [2]. In more prudent autopsy studies, much higher rates are reported [3]. The ranges for the prevalence are reported to be 2–6% with palpation, 19–35% with ultrasound, and 8–65% in autopsy data [4].

Although there is no known environmental risk factor for the development of thyroid nodules, there has been a notable increase in the incidence of thyroid nodules and thyroid cancer in the United States over the previous three decades. This incidence has increased from 3.6 per 100,000 in 1973 to 8.7 per 100,000 in 2002 [5]. Interestingly, the increase in incidence is predominately due to the increase in the incidence of papillary thyroid cancer.

J. Rosen M.D., F.A.C.S. (✉) • V. Papoian M.D., M.P.H.
Department of Surgery, MedStar Washington Hospital Center, Physicians Office Building Suite 124, South Tower 106 Irving St. NW, Washington, DC 20010, USA
e-mail: Jennifer.E.Rosen@medstar.net

This observation is explained by two known processes. First, the incidence of nodules increases with age. Second, the median age of the population in the United States has been increasing over the previous decades. Additionally, nodules are being identified more commonly on imaging studies performed for other reasons, as the sensitivity of computed tomography (CT), magnetic resonance imaging (MRI), and positron emission tomography (PET) has increased and their use has increased with more accessibility in developed countries. In patients undergoing PET scan for non-thyroid diseases, 3–4% of the scans will show abnormal thyroid activity with half showing focal uptake [6, 7].

Once a nodule has been identified, a proper evaluation is necessary as the primary concern is the presence of thyroid malignancy. The initial evaluation is usually performed by a primary care physician or endocrinologist. A stepwise, evidence-based practice is necessary to avoid unnecessary testing, procedures, surgeries, and stress on the patient. The fundamental goal of the evaluation is to assess the presence of thyroid malignancy and need for intervention. Important factors that will be discussed include the concept that not all nodules need to be biopsied, as delay in surgical intervention in small nodules, even if harboring a malignancy, has not shown to affect the long-term survival of the patient.

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Clinical Evaluation

Thyroid nodules are heterogeneous in size, characteristics, and pathology. Identification of a nodule prompts an evaluation consisting initially of a complete history and physical exam.

Pertinent information to obtain will include the past medical history and treatments that the patient has undergone, family history, and social history. There are a number of risk factors that the clinician must account for during the evaluation as it increases the risk for the development of thyroid malignancies.

A history of previous malignancy, specifically in childhood, which required radiation therapy to the head and neck or to the entire body places the patient at a higher risk for the development of thyroid malignancy [8–10]. Exposure to radioactive fallout also places a patient at higher risk of thyroid malignancy [11]. Although exposure to radiation during adulthood does increases the risk for thyroid malignancy, the increased risk is dramatically less in comparison to patients with radiation exposure during childhood.

A more challenging risk factor to assess is the presence of genetic susceptibility to thyroid cancer. A number of disorders, such as multiple endocrine neoplasia type 2 (MEN2), Cowden's disease, familial adenomatous polyposis (FAP), Carney complex, and Werner syndrome/progeria, have been associated with thyroid cancer. A family history with multiple cancers should make the clinician suspicious of genetic susceptibility to thyroid malignancy even in the absence of thyroid malignancy in the given family history, as most of these genetic-based diseases can present with many types of cancer [12].

A complete physical exam will yield valuable clues to the nature of the nodule as sign of hyperthyroidism or hypothyroidism can be an initial step in determining the likelihood of malignancy. Subtle clues can increase the suspicion for a malignancy, such as nodule size, vocal cord paralysis, fixation of nodule to surrounding structures, or presence of cervical lymphadenopathy.

After proper assessment for the risk of malignancy, a serum thyrotropin (TSH) is the initial test of choice. Evidence has shown an association with increasing TSH levels with malignant findings on pathology [13, 14]. Levels above 5 mIU/L have shown to be at much higher risk than subnormal values. The TSH serum level, even if it is within normal range, has a direct association with the risk for presence of malignancy. This should not be understood as a global exclusion of malignancy in hyperthyroid or euthyroid states, rather as one piece of evidence in the evaluation of a nodule. For these reasons, an elevated level of TSH in the setting of a thyroid nodule should raise concern for harboring a malignancy, and a low level of TSH should alleviate but not exclude the likelihood of a malignancy.

If the TSH is below normal or normal, implying hyperthyroidism, a radionuclide scan with iodine-123-, iodine-131-, or technetium-99m-labeled pertechnetate is the primary imaging test that is recommended. This allows for the evaluation for the source of the overproduction of thyroid hormone [12]. If a nodule is found to be hyperfunctioning, the probability of malignancy is relatively small; thus, a biopsy is not recommended. In a study by Boelaert et al., when the TSH was less than 0.4, then the rate of malignancy was shown to be 2.8% [13, 15].

Other laboratory tests which have been considered in the evaluation algorithm include serum thyroglobulin (Tg) levels and serum calcitonin levels. It is the recommendation by the American Thyroid Association that routing testing for Tg is unnecessary as the value is usually elevated in thyroid disease and is not specific to cancer, thus giving incomplete information about the pathology of the thyroid nodule. Calcitonin may have a more diagnostic role, as there may be an association between calcitonin levels and presence of malignancy. Unfortunately, the studies which evaluated the role of calcitonin in the diagnostic algorithm had limitations in their design, thus making it difficult to generalize the role that this serum marker may play [16, 17]. Although routine calcitonin is not a recommendation at this time, it does have a place in the evaluation for patients who are at higher risk for medullary thyroid cancer. Thus, measuring calcitonin in patients with known or suspected fam-

ily history of MEN2 can be justified to prompt the clinician to make a diagnosis earlier [16].

Imaging Evaluation

Several imaging modalities are used for evaluation of thyroid nodules (Table 3.1). The most information-yielding study for a thyroid nodule is an ultrasound. The key information that must be evaluated for in the study includes correlation of palpable findings with sonographic findings, size of nodule, and characteristics which increase suspicion of malignancy.

In terms of correlation between physical exam findings and ultrasound findings, a number of studies have shown a weak correlation. In a sample of 2441 patients, physical exam was able to palpate nodules in 169 patients, while ultrasounds located nodules in 249 patients. Of the nodules located on ultrasonography, only 21% were palpable, and of those 169 palpable nodules, 115 were not confirmed by ultrasound. It was notable that only 6.4% of nodules less than 0.5 cm were identified by physical exam, while only about half (48%) of nodules larger than 2 cm were identified with palpation [18]. Additionally, inter-physician variability for palpation of thyroid nodules has been shown to be relatively high [19]. Thus, ultrasound is the preferred and reliable method for evaluation of nodules as palpation can be elusive and provide inaccurate information. This does not imply that a physical exam is not necessary, but rather that findings need to be confirmed by further testing.

Characterization of the nodule is important as there are features that increase the suspicion for malignancy and help the clinician assess for the need for a fine needle aspiration (FNA). Features to account for during imaging include the structural makeup of the nodule (solid vs. cystic vs. spongiform), presence of calcifications (none vs. micro vs. macro), invasion into surrounding structures, vascularity, lymphadenopathy, and location of nodule [20, 21]. In a study at the Mayo Clinic, 360 consecutively surgically removed thyroids showed that the majority (88%) were solid with only 9% having up to 50% cystic component and 3% having more than 50% cystic component [22].

In a case control study, the three characteristics most associated with presence of cancer were microcalcifications, size greater than 2 cm, and an entirely solid composition. The suggestion was made to only perform biopsies if at least two of those characteristics were met to decrease the number of unnecessary biopsies and false-positive results. Biopsy criteria based on only one characteristic would have a low positive predictive value, and those based on all three characteristics would miss diagnosis of nodules which justifiably should be biopsied [20].

One of the most important features to assess is the size of the nodule. Although size of the thyroid nodule has not been shown to be associated with the presence of malignancy in a thyroid nodule in numerous studies, it is still a major criterion for determination for the need of an FNA [23]. The rationale for the use of nodule size during the evaluation is centered around the concept of prognosis and overall survival. Nodules of small size have a low rate of metastasis and overall mortality, even when containing cancer [12]. It has been shown that the probability of distant metastasis does not seem to be significant until tumor size is >20 mm, although spread to lymph nodes and extrathyroidal growth do occur with smaller nodules of PTC [24]. This rationale is supported by findings on autopsies of patients with no previously known thyroid disease in which small thyroid nodules with malignancy were found. In the United States, over half a million thyroid ultrasounds are performed annually. If every nodule, regardless of size or characteristics, was biopsied, the number of unnecessary procedures and false-positive results would lead to a great number of unnecessary surgeries.

A more recent emerging evaluation technique is ultrasound elastography. The evaluation is

Table 3.1 Sensitivity and specificity of imaging modalities of the thyroid

	Sensitivity	Specificity
Ultrasound [29]	63–87	80–94%
Elastography [30, 31]	92%	90%
MRI [27]	90%	95%
CT/PET [28, 32]	88–92%	64–87%

performed by using the B-mode of the ultrasound to evaluate changes in the nodule with applied pressure. Nodules with partial or no elasticity are associated with higher levels of malignancy [25].

CT has a limited role in the workup of thyroid nodules. The main limitation is the inability to help distinguish benign from malignant nodules, as well as the associated cost increase. The main utility is for evaluation of nodules that are substernal and inaccessible to ultrasound evaluation [26].

MRI is not a commonly used modality for evaluation of a thyroid nodule, but studies have shown that it can be used to help differentiate a malignant nodule from a benign nodule fairly accurately [27].

PET/CT has been shown to have a high level of sensitivity when evaluating thyroid nodules. In a small study, it has been shown to be efficient in cases where the FNA has shown FLUS or AUS [28]. While theoretically it might add diagnostic information, insufficient sensitivity and specificity have limited its routine use. In the majority of cases, thyroid nodule is noted on PET/CT incidentally while evaluating a different malignancy. At the current time, a major limitation to a PET/CT is the high cost and difficulty of access [28].

Lymph Node Evaluation

Patients with known or suspected thyroid nodule should undergo evaluation of cervical lymph nodes via sonography [12]. Characteristics of lymph nodes which should be evaluated include size, shape, vascularity, presence of an echogenic hilus, hypoechoic cortex, cystic changes, and calcification [33]. Metastasis of thyroid carcinoma to lymph nodes is usually in the peripheral aspect of the lymph node; thus, many of the changes seen initially with lymph node invasion are changes in the peripheral aspect of the nodes [33]. Lymph nodes concerning for harboring malignancy need a biopsy performed for proper evaluation and surgical planning.

Indication for Biopsy

Fine needle aspiration (FNA) with ultrasound guidance is the preferred method for a biopsy of a thyroid nodule. It is performed by inserting a 25- or 27-gauge needle attached to 10 cc syringe through the nodule with aspiration of nodular cells. Standard of care includes ultrasound guidance for FNA; blind biopsy is no longer warranted. The process is repeated approximately with five passes for conventional cytopathologic evaluation. More passes may be necessary if genetic testing is considered as fresh tissue cells are required. If tissue for genetic testing is not obtained initially, it would require the patient to undergo repeat FNA [34]. Common misconception is that genomic and genetic testing is a blood test, which it is not; it is a test requiring tissue specimen.

The criteria used to assess for an FNA take into account the size of the nodule, the patient's risk for a thyroid malignancy, and characteristics noted on ultrasound. The most widely followed recommendations are by the American Thyroid Association (ATA) and the National Comprehensive Cancer Network (NCCN).

Based on the American Thyroid Association guidelines, in patients who are considered at high risk of malignancy, nodules 5 mm or greater in size are recommended for a biopsy. For patients without abnormal lymph nodes or microcalcifications or high-risk history, the ATA guidelines then divide the thyroid nodules into categories on the basis of the nodule composition. Nodules are characterized as entirely solid, mixed cystic-solid, spongiform, or purely cystic. Biopsy is recommended for all solid hypoechoic nodules that exceed 1 cm in diameter. Isoechoic or hyperechoic nodules exceeding 1–1.5 cm should undergo biopsy. Biopsy is recommended for mixed cystic-solid nodules that exceed 1.5–2 cm, if they have irregular margins, microcalcifications, or infiltration of the surrounding tissue. The recommendation for mixed cystic-solid nodules without suspicious ultrasonographic features is for biopsy of nodules larger than 2 cm. Those nodules exhibiting a spongiform echotexture should undergo biopsy only if

they are larger than 2 cm in diameter. Finally, purely cystic nodules do not require biopsy under the ATA guidelines [12].

Based on these guidelines, a biopsy is indicated in a solid nodule greater than 1 cm with suspicious features and 1.5 cm without suspicious features. Biopsy for mixed cystic-solid nodules is indicated for nodules over 1.5–2 cm with suspicious features and 2 cm without suspicious features. Spongiform nodules may be biopsied if greater than 2 cm in size [35].

The American Association of Clinical Endocrinologists (AACE) is also a major clinical organization with a different recommendation. AACE recommends that nodules 1 cm or greater in size showed be biopsied. Additionally, in patients at high risk for developing thyroid malignancy, nodules of any size should be biopsied [36].

In a subset of patients with multinodular disease, the recommendations are similar. It has been shown that the presence of multinodularity does not significantly affect the risk of cancer. Any given nodule has a lower probability of being cancerous, but the presence of numerous nodules makes the overall risk of harboring a malignancy similar to the risk carried by patients harboring a single nodule [37]. The recommendation is to evaluate the nodules individually and determine which nodules meet the criteria for biopsy.

Pathology Reporting

Although this topic will be captured in full detail elsewhere, we present an overview in this chapter.

In an effort to facilitate communication among cytopathologists, endocrinologists, and surgeons, a reporting system has been proposed to standardize findings into a predefined category. The Bethesda system was developed by a panel hosted by the National Cancer Institute. Findings are classified into one of six categories. The first category is that of nondiagnostic or unsatisfactory specimens.

If the initial biopsy is shown to be nondiagnostic, the recommendation is to repeat the biopsy. Reviews of biopsy results show that up to 13% may be nondiagnostic. A second biopsy may be appropriate, as it has been shown to provide a diagnosis in up to 63% of cases. Those that had a nondiagnostic biopsy were patients with a higher proportion of cystic content of the nodule [38]. In cases with multiple biopsies that are nondiagnostic, the decision to pursue diagnostic thyroidectomy is determined by the level of concern for the presence of a malignancy.

The remaining categories for describing findings are (1) benign, (2) atypia of undetermined significance (AUS) or follicular lesion of undetermined significance (FLUS), (3) follicular neoplasm or suspicious for a follicular neoplasm, (4) suspicious for malignancy, and (5) malignant [39]. The treatment for these nodules will be discussed in appropriate chapters.

The more challenging finding to manage is nodules in the category of AUS/FLUS. The presence of a malignancy has been shown to be as high as 30% in this category; thus, continued evaluation for this category of uncertain nodules is recommended. Further evaluation is performed by one of three methods. The first is to repeat the FNA. The second is to perform a lobectomy or thyroidectomy for diagnostic and therapeutic purposes. The final is to perform genetic testing on the aspirate. Currently the most commonly used genetic test is the Afirma gene panel. The role proposed by Veracyte (the manufacturers for test) is to rule out malignant nodules, as the negative predicative value has been shown to be 95%, thus helping to prevent unnecessary surgical interventions [40]. The role of genetic testing is not widely accepted in clinical practice at this time in the evaluation algorithm.

Conclusion

Thyroid nodule is a common finding in the general population and is increasing in incidence. Although the majority of nodules are benign, a proper evaluation is necessary to identify those that harbor malignancy. Evaluating for risk factors or concerning signs of malignancy on physical exam or imaging will allow the clinician to further evaluate the need for invasive procedures. Given the large number of

nodules that is evaluated by clinicians, having a logical, evidence-based approach is key to optimizing patient care and safety.

The proper evaluation of a thyroid is a multidisciplinary process in which primary care physicians, endocrinologists, pathologists, and surgeons all work together for the accurate diagnosis and treatment of a nodule.

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Pathologic Diagnosis of Thyroid Cancer

4

Xiaoyin Sara Jiang, Susan Maygarden, and Leslie G. Dodd

Introduction

Pathologic examination of the thyroid gland consists of two distinctly different types of procedures. The purpose of the first, biopsy, is for diagnosis of a nodule or mass in effort to determine the nature of the process. Although open biopsy (with or without intraoperative consultation (frozen section)) followed by excision may be used, a more common approach is a fine-needle aspiration (FNA) procedure. The latter will be discussed in depth in this chapter.

The first part of this chapter will discuss some of the technical issues of tissue acquisition, primarily with respect to cytologic analysis of biopsies. This chapter will also discuss in depth the current "Bethesda classification" system of reporting needle biopsies with an emphasis on the cytologic features that distinguish one particular "class" of specimen from the other. The final portion of this chapter will feature a pictorial and narrative review of the most common forms of differentiated thyroid neoplasia.

Specimen Acquisition and Slide Preparation

Fine-needle aspiration (FNA) biopsy is the most widely accepted method of sampling of thyroid nodules. Specimens from the thyroid are obtained by a percutaneous sampling of the lesion of interest with a small or "fine" needle, usually of a 25 or 27 gauge. A gentle negative pressure or suction is often used during the procedure to maximize the amount of tissue obtained with each needle puncture or "pass." This is most commonly facilitated by pulling back the plunger mechanism on the attached syringe. There are also a number of handheld assist devices for syringes that allow the aspirator to maneuver the needle and syringe with one hand. Some practitioners prefer to avoid negative pressure and allow capillary action to draw cells into the needle as it moves through the tissue.

Once the needle is removed from the patient, a cytologic specimen should be prepared as quickly as possible. Any delay in expelling the sample from the needle, attached tubing or syringe results in clotting which may render the cytologic sample uninterpretable for the cytopathologist.

X.S. Jiang
Department of Pathology, Duke University, Box 3712, Durham, NC 27710, USA
e-mail: jiang009@mc.duke.edu

S. Maygarden • L.G. Dodd (✉)
Department of Pathology, University of North Carolina, Chapel Hill, NC 27514, USA
e-mail: Susan.Maygarden@unchealth.unc.edu; Leslie.Dodd@unchealth.unc.edu

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Samples are most commonly pushed or "blown" onto glass slides, often with force applied by a syringe plunger. If specimens are clotted, the needle contents may be difficult to near impossible to express. In this instance, there are several options for specimen salvage:

- The syringe may be removed and refilled with enough air to attempt a second, more forceful push of the needle contents onto the slide.
- The needle containing the clotted specimen can be removed, turned over, and "tapped" forcefully onto a glass slide in an effort to remove the sample through the opposite end of the needle (Fig. 4.1). This often results in a clotted specimen which needs to be "smeared" (discussion below) with more pressure than a more liquid sample.
- Another alternative, although less desirable, is to rinse the entire contents of the specimen into a liquid-based medium, either commercially prepared or normal saline. The lab can then process the sample for cytologic analysis. In this instance, the direct smears of the aspirated material cannot be prepared, and the cytopathologist may be at a disadvantage in interpreting the results [1, 2].

Once a small amount of aspirated material is placed on a glass slide, smear preparations need to be made very quickly. Although there are some variations on the exact technique, making direct smears is a simple and straightforward process. One glass slide (face up) containing an aliquot of specimen is pressed against another glass slide (face down), and slight pressure is placed on the "glass sandwich" to spread the material across the surface area of both glass slides (Fig. 4.2). At this point, the slides are slid across each other, and the specimen is ideally "smeared" evenly across both slide surfaces. In this manner, two slides are obtained per aliquot of specimen. In most instances, one slide will be left to "air-dry," and the remaining slide will be placed in an alcohol-based fixative.

Most cytopathologists have been trained to evaluate both types of "direct smear" specimens. The air-dried slide is usually stained with a Giemsa-based stain. The advantages of this type of preparation are visualization of extracellular colloid, a feature which is extremely important for evaluation of the presence or absence of neoplasia. The second type of preparation, prepared from the alcohol-fixed slide, allows for better interpretation of individual cell nuclear detail. These two types of slide preparation emphasize different features of the cytologic sample and provide complementary information for cytologic evaluation.

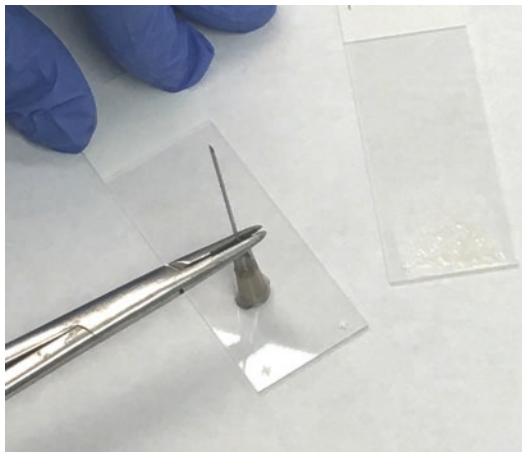

Fig. 4.1 Overturning the aspiration needle and tapping the material on the slide can often facilitate removal of partially clotted specimen in the needle hub

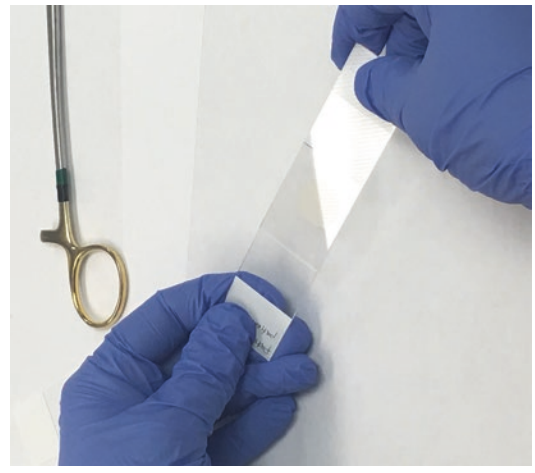

Fig. 4.2 Aspirated specimen is "smeared" over two glass slides by applying gentle pressure while sliding slides away from each other

There are no recommendations on the number of needle "passes" that are required to obtain a diagnostic specimen. Specimen "adequacy" is a function of several factors including the nature of the thyroid lesion to be sampled and operator expertise. Any additional material remaining after preparation of "direct smears" may be submitted to the laboratory as a "rinse" of the needle contents. The rinses are often prepared as additional components of the patients' case materials. The latter may include a "cell block" which often contains microscopic fragments of intact tissue. Alternatively, the needle may be "rinsed" into a liquid-based medium for further preparation. Of note, liquid-based media slides (without direct smears) perform poorly vs. conventional preparations [1–3].

Rapid on-site evaluation (ROSE) of aspirated material involves interpretation of a portion of the specimen during the procedure. This usually involves a cytotechnologist or cytopathologist be present at the time of the procedure with appropriate resources (microscope, stains, slides, etc.) to render an immediate interpretation. With thyroid FNAs, this is usually performed to assess the sample for adequacy. Studies have shown that the addition of ROSE to FNA of the thyroid is likely to reduce the rate of inadequate specimens [4, 5]. This results in increased efficiency and cost savings for the patient. Unfortunately, the performance of ROSE involves a substantial input of resources, both time and effort, upon the part of the laboratory. Each practice should evaluate the pros and cons of utilizing ROSE.

Terminology for Reporting Thyroid Fine-Needle Aspiration

Fine-needle aspiration of the thyroid has become a mainstay in screening and triaging individuals with thyroid nodules. Some estimates show that less than 5% of all nodules are malignant, and FNA has led to a significant decrease in the number of operations performed for benign thyroid nodules [6, 7].

Prior to widespread cytologic screening, less than 15% of surgically resected nodules were malignant [7]. Since implementation of a widespread screening program, the percentage of malignancy in resected nodules is now estimated at 50% [8]. It is clear that FNA plays an important role in management of thyroid nodules and has led to extensive cost savings and a reduction in unnecessary overtreatment.

The current system for reporting FNA of the thyroid, *The Bethesda System* (*TBS*) *for Reporting Thyroid Cytopathology*, came from a 2007 consensus conference of expert pathologists, radiologists, surgeons, and endocrinologists. The goal of the group was to provide a system for reporting thyroid cytopathology results that was clear, concise, and unambiguous [9]. An additional goal was to promote uniformity in practice and reporting of thyroid FNAs. There were also efforts to link each individual category with defined risks of malignancy and to propose guidelines for further management.

TBS has since been implemented and widely adopted in the USA. The current iteration of TBS includes six discreet diagnostic categories. The categories include a "nondiagnostic" or unsatisfactory for diagnosis (Class I) as well as an additional five categories associated with variable levels of concern and implied risk of malignancy for any given thyroid sample. While "risk" of malignancy is estimated for each category, it is important to know that true sensitivity, specificity, and positive and negative predictable values are difficult to determine as only a subset of thyroid nodules will be removed for histologic examination, currently considered the "gold standard" for cytologic accuracy. These features are summarized in Table 4.1. Characteristics of each individual class are discussed in more detail in the following descriptions.

Class I: *Nondiagnostic or Unsatisfactory*

First and foremost, specimens need to contain a minimum number of cells in order to be deemed "satisfactory" for evaluation. Under the current Bethesda guidelines, the cellularity requirement is at least six groups of ten cells. A specimen may also be deemed unsatisfactory if there is excessive air-drying artifact, if the cells are largely obscured with blood, or if the smears are

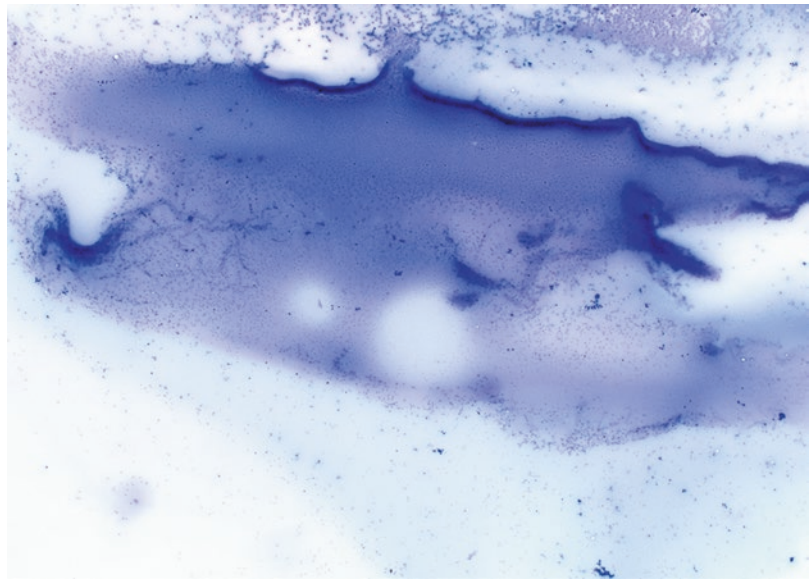

Fig. 4.3 Colloid is best visualized on air-dried Giemsa-based preparations. It can be variably thick or "watery" but appears as a thin film in the background of fine-needle aspirate smears (Diff-Quick, mag × 10)

overly thick. Exceptions to the numerical requirement include a number of different scenarios:

- A specimen with abundant colloid can be presumed to be benign despite the cell requirement. In this instance, the presumed diagnosis is a colloid nodule.
- When a specific diagnosis can be rendered, such as lymphocytic thyroiditis, the specimen is by definition adequate, even if the number of identifiable follicular cells is less than the adequacy threshold.
- If there is any significant cytologic atypia in an otherwise hypocellular aspirate, a Class III or higher diagnosis may be rendered.
- In some instances, cytopathologists are comfortable interpreting a specimen consisting entirely of macrophages (cyst contents) as benign. This practice is not uniformly accepted by all laboratories.

The recommended management of a nondiagnostic specimen is repeat aspiration. Repeat aspiration should be performed with ultrasound guidance for nodules that are small and/or difficult to detect by palpation alone. The percentage of cases that are deemed unsatisfactory will depend on numerous factors including operator expertise, utilization of ROSE, specimen preparation, and individual cytopathologists' comfort with low cellularity samples. The benchmark for percentage of unsatisfactory specimens is below 10% of all thyroid samples [10].

Class II: *Benign*

The majority of thyroid nodules (70%) are reported as benign [10]. These lesions characteristically have abundant colloid and small, normally sized groups of thyroid follicular epithelium (Fig. 4.3). The histologic correlate to these findings is usually a benign follicular nodule or a hyperplastic nodule, often in a background of multinodular goiter. The false-negative rate associated with a benign diagnosis very low, estimated at 1–3% [11]. Clinical follow-up of the patient is recommended for patients with a Class II diagnosis.

Class III: *Atypia of Undetermined Significance or Follicular Lesion of Undetermined Significance*

This particular diagnosis is often frustrating for both the patient and clinician because of the use

of the vague word "atypia" without any further clarification. There is also an implied "low" but nevertheless present risk of malignancy. There are many different strategies for follow-up of a Class III diagnosis ranging from repeat FNA to surgical excision. Reasons for an "atypical" diagnosis often include one or more of the following factors:

- There is a prominent population of thyroid follicular epithelium in an otherwise sparsely cellular aspirate.
- There is a predominance of Hürthle cells in a sparse aspirate with scant colloid (without other features to suggest lymphocytic (Hashimoto) thyroiditis).
- There are numerous Hürthle cells in the aspirate yet the clinical or imaging features suggest a benign thyroid nodule.
- There are focal features of atypia (nuclear grooves or enlarged overlapping cells) in aspirate in patients with known or suspected Hashimoto thyroiditis.
- Focal cytologic atypia is identified in association with cyst lining cells.

When the Bethesda system of reporting approved the inclusion of the category of atypia of undetermined significance/follicular lesion of undetermined significance (AUS/FLUS), they legitimize the presence of an equivocal diagnostic category for cytopathologists to utilize to communicate their uncertainty about the potential for malignancy. As suspected, the overall number of cases (previously termed "atypical") increased from an estimated 3% of total diagnoses to approximately 7% in a single institution study [12]. The 7% threshold has become the accepted benchmark for percentage of specimens reported under TBS; however, there is significant variation among different laboratories and individual cytopathologists [13–15]. In an effort to contain potential overutilization of the AUS/FLUS category, there have been attempts to develop performance measures (specifically ratios of AS/FLUS rates to "malignant" rates) as guidelines or benchmarks for individual laboratories [16]. This type of ratio guideline is currently well accepted and utilized as a performance measure for cervical cancer screening reporting [17].

Current estimates of a true malignancy associated with a Class III AUS/FLUS diagnosis are relatively low (5–15%) but nevertheless real [18–20]. The NCI consensus treatment algorithm for these patients is repeat FNA after an appropriate interval [8, 20]. A significant number of these patients will receive a subsequent diagnosis of a Class III or higher diagnosis on repeat aspiration. At this point, appropriate approaches include biopsy with molecular testing (see Chap. 5) or more aggressive management strategies. Despite the recommended guidelines, many patients with an AUS/FLUS diagnosis will proceed directly to surgery. While there may be numerous extenuating factors to justify this strategy (patient desire, worrisome imaging features, etc.), this approach has been deemed less cost-effective than recommended strategies for overall patient management [21].

Class IV: *Follicular Neoplasm or Suspicious for Follicular Neoplasm*

This reporting category is largely confined to aspirates comprised of either follicular epithelium arranged in "microfollicles" or with an abundance of Hürthle cells. The latter is a morphologically distinctive cell type and should be reported as such (Fig. 4.4). When a microfollicular arrangement of slightly enlarged but otherwise normal-appearing epithelial cells is present, the lesion is most likely to correspond to one of the following: an adenomatoid nodule, follicular adenoma, or carcinoma. Likewise, a hypercellular aspirate comprised of Hürthle cells can correspond to a hyperplastic proliferations within a background benign disease (Hashimoto thyroiditis or multinodular goiter), Hürthle cell adenoma, and carcinoma.

While some have opined that this category overlaps substantially with the previous category of "FLUS" and is thus redundant, there are numerous reasons for separating this lesion from the former. Firstly, the specific nomenclature ("lesion" vs. "neoplasm") is meant to convey a higher diag-

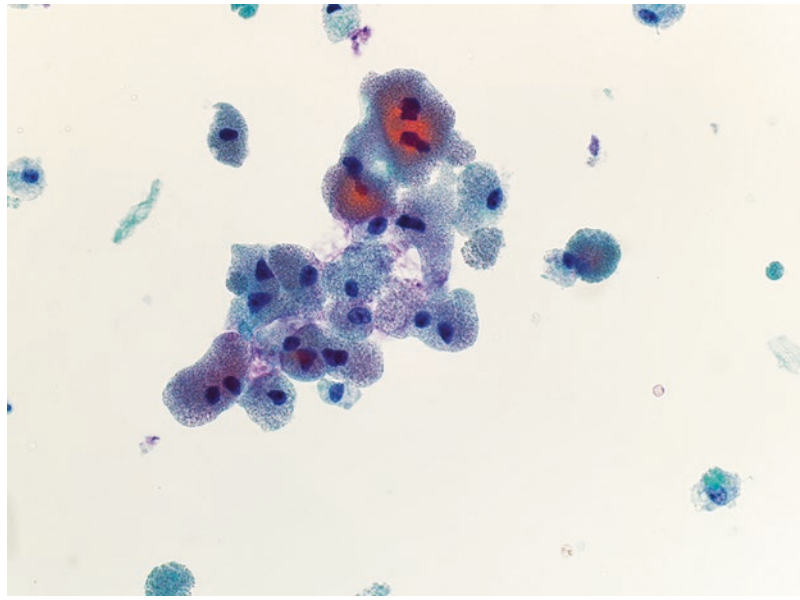

Fig. 4.4 Hürthle cells can appear in a variety of circumstances. They appear as epithelioid or polygonal cells with abundant granular cytoplasm (Pap stain, mag × 200)

nostic concern for possible malignancy. Secondly, "follicular neoplasms" include both the benign adenoma and the malignant counterpart, follicular carcinoma. In aspirates, these two lesions are cytologically indistinguishable; the only way to separate one from another is complete removal of the nodule with careful examination of the capsule of the lesion. Lastly, the terms "lesion" linked to category III and "neoplasm" linked to category IV have been linked to "low-risk" and "high-risk" nodules from a clinical standpoint [22].

Class IV diagnoses (follicular neoplasm (FN) and suspicious for follicular neoplasm (SFN)) are more likely to correspond to significant thyroid pathology than any of the previously three categories. In this instance, up to 35% will correspond to benign lesions, an estimated 15–30% corresponds to true malignancies (carcinoma), and the remainder likely represents adenomas [19, 23–25]. The corresponding management recommendation for a Class IV diagnosis is either molecular testing or surgical lobectomy.

Class V: *Suspicious for Malignancy*

Class V specimens generally display some but not all features of cytologic malignancy. For papillary carcinoma these include cellular enlargement and overlapping, arrangement in irregular papillary-like groups, and nuclear groves or pseudoinclusions. "Suspicious" samples often contain less colloid than benign aspirates. The term suspicious for malignancy will also include samples suspected to be from medullary carcinoma, anaplastic carcinoma, metastases, and lymphoma. Cytopathologists are strongly encouraged to report which particular subtype of malignancy is suspected.

One of the most common reasons for a "suspicious" diagnosis (vs. malignant) is aspirations of either a very small or largely cystic papillary carcinoma. The latter is particularly difficult to diagnose with confidence as the aspirates display lower cellularity and usually have a secondary population of cyst lining cells. Cyst lining cells may predominate to an extent that the neoplastic cells are a small minority of the aspirated sample. In addition, hyalinizing trabecular adenoma (HTA) will often show numerous cytologic features that overlap substantially with papillary carcinoma. An aspirate of HTA can be misread as either a Class IV or V papillary carcinoma and represents a well-known pitfall in thyroid cytopathology diagnosis [26, 27].

Malignancy rates associated with a Class V diagnosis are reported to range from 60 to 75% [9]. The most commonly associated malignancies include papillary carcinoma, the follicular variant of papillary carcinoma, and follicular neoplasms.

Class IV: *Malignant*

This category is used when unequivocal features of malignancy are identified. The most commonly diagnosed malignancy in this category is papillary carcinoma. Other types of cancers identifiable in aspirates include medullary and anaplastic carcinomas, as well as metastases and lymphomas. The positive predictive value for this category is 97–99%. The recommended treatment is thyroidectomy (for primary malignancies).

Core-Needle Biopsy

Core-needle biopsy (CNB) of the thyroid has evolved as an alternative to fine-needle aspiration (FNA) for sampling thyroid lesions. Studies comparing CNB and FNA have largely shown that sensitivity and specificity are similar for both techniques; however, CNB is less likely to yield a nondiagnostic or inadequate sample [28–30]. The one exception to this trend was in a cohort of pediatric patients, for whom the nondiagnostic rate was higher than comparable values for FNA (in adult patients) [31]. For the present, CNB is being used largely as an alternative to repeat FNA (rFNA) in patients with an initial indeterminate diagnosis (atypia of uncertain significance (AUS) or follicular lesion of undetermined significance (FLUS)). Several studies have noted that a combination of FNA and CNB (performed simultaneously) increases both sensitivity and specificity over either technique used alone [30, 32, 33]. In this setting, CNB appears to be useful and can be helpful in discriminating patients who should be referred to surgery versus those that should be managed more conservatively [32, 34–37].

CNB of the thyroid has some definite advantages over FNA in selected cases. In primary thyroid lymphoma, CNB appears to be more efficacious in establishing a definitive diagnosis than FNA [38–40]. The superiority of CNB in the diagnosis of lymphoma may be related to the need for additional material for ancillary studies: particularly flow cytometry and/or immunohistochemistry. In contrast, CNB does not perform well in the "follicular neoplasm" category [41, 42]. Because both FNA and CNB cannot adequately assess the completeness and integrity of the capsule of these lesions, neither of these modalities is useful for discriminating the benign follicular adenoma from a follicular carcinoma.

The Role of Frozen Section Examination in Thyroid Disease

The role of frozen section in the management of thyroid disease has changed since the fine-needle aspiration cytology has become widely used. Before preoperative FNAs became common, frozen section was often used to guide operative management of patients with thyroid nodules. All patients with "cold" nodules on scintigraphy were referred for surgery, and intraoperative frozen section was performed to determine the necessary extent of surgery (benign lesions underwent a lobectomy, malignant lesions underwent total thyroidectomy). Now, FNA is the preferred triage test, and the role of frozen section is much more limited, although it continues to be requested in some settings. The primary reason for obtaining a frozen section is to allow a total thyroidectomy as the initial procedure and avoid a second (completion) procedure.

Overall, frozen section of the thyroid is reported to be highly specific (approximately 95%) but relatively insensitive (approximately 66%), with a positive predictive value of approximately 95%. Fine-needle aspiration has similar specificity, sensitivity, and positive predictive value [43]. However, sensitivity and specificity of both fine-needle aspiration and frozen section vary dramatically depending on the type of lesion sampled (follicular vs. non-follicular), and unfortunately most of the lesions which are problematic by fine-needle aspiration are also problematic

by frozen section [44]. Neither test has 100% positive predictive value. However, there are some situations where frozen section may add additional information to a preoperative FNA that may help guide surgical management.

Given the accuracy of the diagnosis of "positive for malignancy" (Bethesda category 6) and "negative for malignancy" (Bethesda category 2), several studies have concluded that frozen section does not significantly add useful information that would aid in planning the scope of surgery for patients with these FNA diagnoses, although this is not uniformly accepted [45, 46]. An FNA categorized as positive for malignancy has a specificity rate above 90%, so those that do not support frozen section in this situation argue that even if a frozen section was benign, it would likely be considered a false negative [45, 46]. In a study of cases with a benign preoperative FNA, 16% of these were shown to be malignant on final diagnosis, but only 29% of these were detected by frozen section. Overall, in cases with a benign preoperative FNA diagnosis, frozen section rarely provided a definitive diagnosis of malignancy that converted a planned surgical procedure to a total thyroidectomy [46].

There does appear to be a role for frozen sections with preoperative FNA diagnoses of "suspicious for malignancy" (Bethesda category 5), particular for those interpreted as suspicious for papillary thyroid carcinoma. This category has a risk of malignancy of 60–75% [9]. In many cases, frozen section provides a definitive cancer diagnosis to allow a total thyroidectomy as an initial procedure [45–47]. If the frozen section is benign or deferred, the procedure might be limited to a lobectomy. In the minority of cases with benign or deferred frozen sections and permanent pathology showing a malignancy (sometimes related to sampling error of the frozen section, sometimes for subtle malignancies such as follicular variant of papillary carcinoma which can be challenging on frozen section), then the patient might need a completion procedure, but the number of these can be minimized by frozen section. The goal of frozen section in this category is to allow as many as cases as possible to undergo an initial total thyroidectomy, if necessary, without overtreating a benign nodule.

As the treatment paradigm has shifted toward more liberal use of lobectomy as definitive treatment of differentiated cancers, an important consideration in the use of frozen section is whether or not the result will change management. If lobectomy will be considered adequate for the tumor in question, then clearly the addition of frozen section will not be useful. Some features of the tumor that might indicate the need for more aggressive treatment, such as microscopic extrathyroidal invasion or vascular invasion, would not be expected to be reliably detected on frozen section.

The most problematic management areas are cases with preoperative FNAs of atypia of undetermined significance/follicular lesion of undetermined significance (AUS/FLUS, Bethesda category 3) and follicular neoplasm/suspicious for follicular neoplasm (FN/SFN, Bethesda category 4). These will be considered separately. AUS/FLUS is estimated to have a malignancy rate of 5–15%, though this rate varies by institution [9], and the recommended management is to repeat the FNA in 3–6 months. Molecular testing is also an option for lesions with this diagnosis. However, some patients and surgeons choose surgical management for nodules which show AUS/FLUS on FNA (particular for repeated AUS/FLUS results), and in these patients, frozen section may be a useful adjunct to clinical findings in choosing appropriate surgery. Some have advocated incorporating ultrasound findings in choosing which patients for which to request frozen sections (with nodules >1 cm, increased vascularity, calcifications, irregular cystic areas, and irregular borders being indications for frozen section) [48].

Follicular neoplasm/suspicious for follicular neoplasm is a particularly difficult area for both cytology and frozen sections. As described previously, this category is used for lesions composed of microfollicles, which may be seen in both benign follicular adenomas and malignant follicular carcinomas, and the distinction between the two is made by identifying capsular and/or vascular invasion. Invasive properties of the capsule cannot be identified by cytology, and thus the diagnosis of malignancy in a follicular neoplasm by FNA is essentially impos-

sible. Capsular or vascular invasion may be very focal, making sampling by frozen section problematic. A meta-analysis comparing fine-needle aspirations and frozen sections of thyroid nodules found that for follicular neoplasms, frozen section had a 21% sensitivity but a 99% specificity for the diagnosis of malignancy in a total of 23 studies covering 2531 cases [43]. Whether this low rate of definitive diagnosis is worth the cost of the frozen section remains a topic of intense debate. Additionally, surgeons need to understand that a follicular neoplasm with a negative or deferred frozen section may be shown to be a follicular carcinoma with complete submission of the capsule for histologic evaluation, something that is not possible at frozen section [47].

In summary, there appears to be little to no role of frozen section in cases that have cytologic diagnoses of benign and malignant. Frozen sections may be useful in cases with cytologic diagnoses of AUS/FLUS (particular persistent AUS/FLUS and/or those with suspicious ultrasound findings). The consensus of the literature is that the category suspicious for malignancy can benefit from a frozen section (particularly in cases with a preoperative diagnosis of suspicious for papillary carcinoma). Frozen section for follicular neoplasms can, in rare instances, add additional information to the preoperative cytologic diagnosis.

Surgical Pathology of Differentiated Thyroid Cancers

Differentiated thyroid tumors arise from thyroid follicular cell origin and fall generally into two broad categories, papillary carcinoma and follicular carcinoma, with some morphologic areas of overlap between the two entities [49–51].

Papillary Thyroid Carcinoma

Papillary thyroid carcinoma (PTC) is the most common thyroid malignancy and presents in a wide range of sizes, from nodules appreciated on physical examination to so-called microcarcinomas that are often found incidentally in thyroids removed for benign disease. In its classical form, PTC is characterized by papillary architecture and distinct nuclear features that may appreciated on fine-needle aspiration (FNA) cytology [9, 50] Table 4.1.

Table 4.1 Pathologic hallmarks of PTC

Nuclear features	Architectural features
Nuclear grooves "coffee bean," "crushed ping-pong ball"	Papillae
Intranuclear cytoplasmic inclusions (INCIs) or pseudoinclusions	Psammoma bodies
Elongated nuclei, powdery chromatin	Nuclear crowding
"Orphan Annie eyes"—only seen on surgical pathology specimens	May be encapsulated or infiltrative—this cannot be assessed on cytology

FNA

PTC is characterized by nuclear contour irregularities, which manifest on cytology as nuclear grooves and pseudoinclusions. The "pseudo" in pseudoinclusions, or intranuclear cytoplasmic inclusions (INCIs), refers to the fact that these are not truly inclusions within the nuclei, but rather are pockets formed by the irregular nuclear membrane surrounding cytoplasm which remains contiguous with the rest of the cell's cytoplasm. Other nuclear features include powdery chromatin and nuclear elongation [9, 10, 52].

Architectural features may include papillary structures or sheets and nuclear crowding (Fig. 4.5). Psammoma bodies, concentric calcified structures, are not always present in PTC, but are highly suggestive of PTC as they are only rarely seen in benign entities. These psammoma bodies may correspond to the microcalcifications seen on ultrasound [53].

Regarding FNA of PTC, the diagnostic nuclear features are best appreciated on alcohol-fixed material, which better preserves nuclear detail (Fig. 4.6). While a well-preserved and adequately cellular FNA sample of a classical PTC allows for ready diagnosis, conversely, a sample with

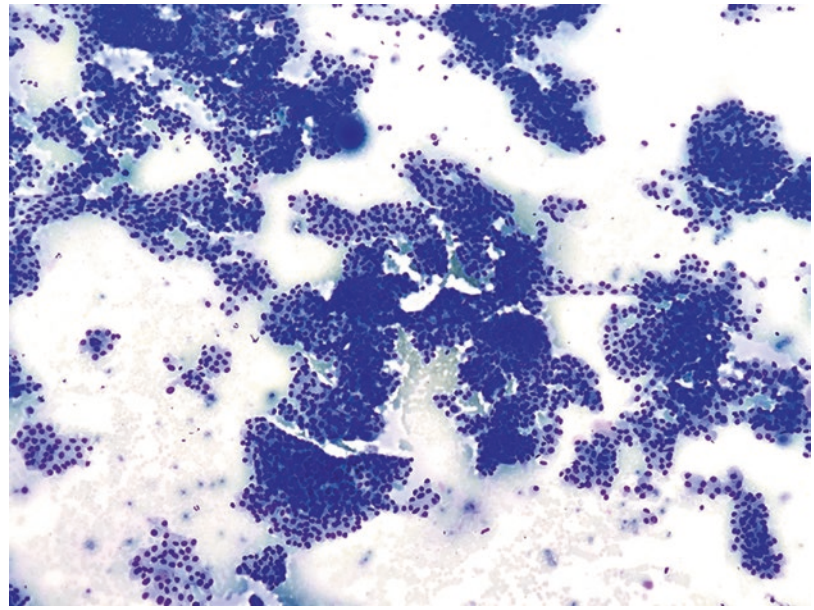

Fig. 4.5 Papillary thyroid carcinoma, fine-needle aspiration cytology, Diff-Quik, 4×: cellular sample with scant colloid, papillary architecture, and overlapping nuclei

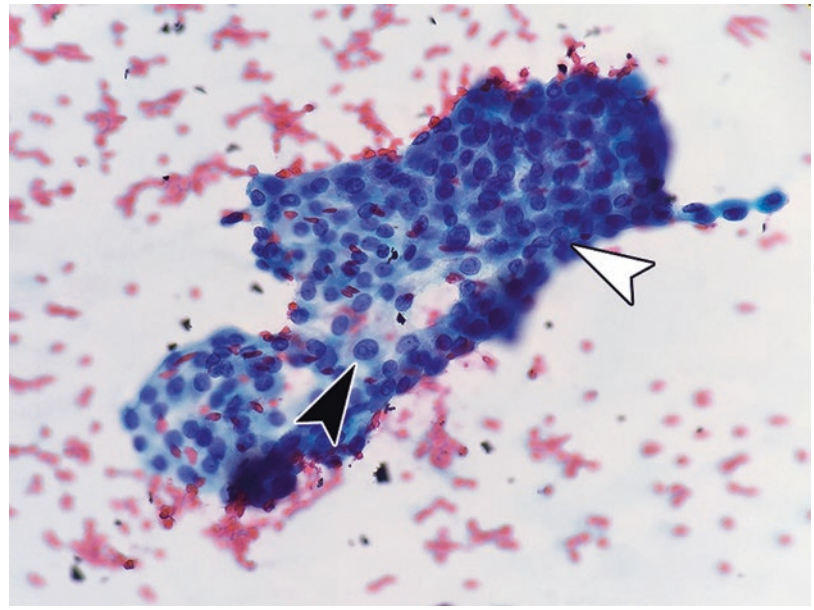

Fig. 4.6 Papillary thyroid carcinoma, fine-needle aspiration cytology, alcohol-fixed Papanicolaou stain, 40×: nuclei demonstrating classic features of pseudoinclusions (*arrowhead*), elongation, and grooves (*open arrow*) [note to publisher: this figure will need to be large]

scant cellularity, lack of alcohol-fixed material, or obscuring factors may limit the ability of the cytopathologist to render a definitive diagnosis of malignancy.

Gross Examination

At the time of gross examination, papillary thyroid carcinomas are variable in their appearance and may be firm and white in color (Fig. 4.7), in contrast to the gelatinous consistency and red color of normal thyroid. Depending on the subtype, they may be infiltrative or encapsulated.

Microscopic Features

The features seen on cytology are mirrored in the papillary architecture and nuclear features seen

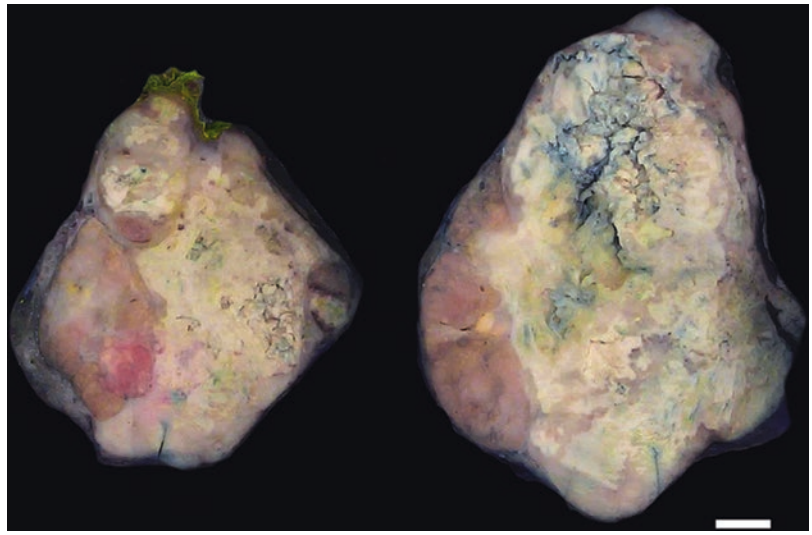

Fig. 4.7 Gross photograph of thyroid carcinoma: a heterogenous pale process effaces normal thyroid parenchyma. Necrosis is grossly evident. On microscopic examination, this lesion was an oncocytic carcinoma with areas of anaplastic carcinoma corresponding to the areas with necrosis

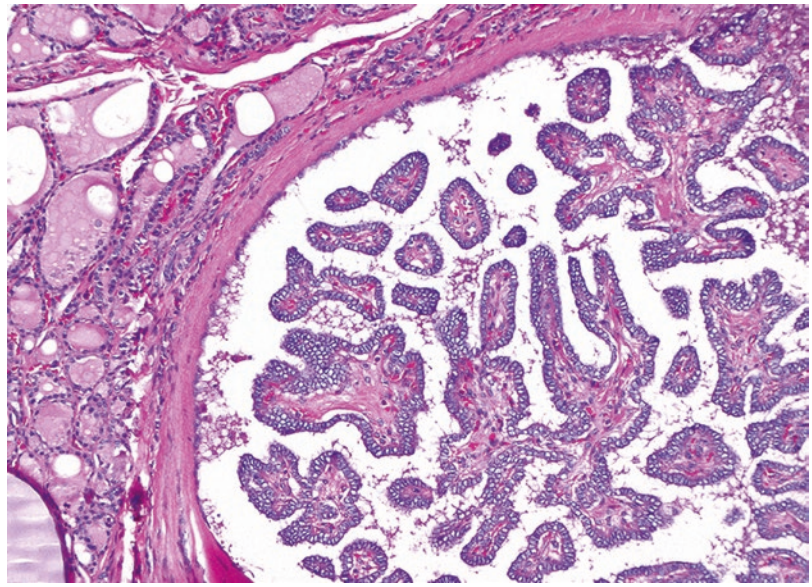

Fig. 4.8 Papillary thyroid carcinoma, H&E, 10×. Well-demarcated tumor demonstrating papillary architecture and nuclear clearing (compare to normal thyroid on left of image)

on H&E stained sections (Figs. 4.8, 4.9, and 4.10). In addition, nuclei may demonstrate chromatin clearing (an artifact of formalin fixation) resulting in an "Orphan Annie eye" appearance after the comic of yesteryear. While the classical type of PTC is the most common, comprising approximately 40% of PTC, there are a number of additional subtypes. These subtypes are not only important in that they can pose diagnostic challenges for the surgical pathologist but also in that certain ones may carry prognostic significance [49, 51, 54].

PTC Variants

Papillary microcarcinoma is defined as a carcinoma that is 1 cm in size or less and is found incidentally [49] (Fig. 4.11). These tumors are common and may be found in thyroids removed for benign reasons such as compressive symptoms [55]. The majority of these small tumors have indolent clinical behavior, but a small proportion of these tumors will still have worrisome characteristics such as extrathyroidal extension, lymph node metastases, and recurrence [56–58].

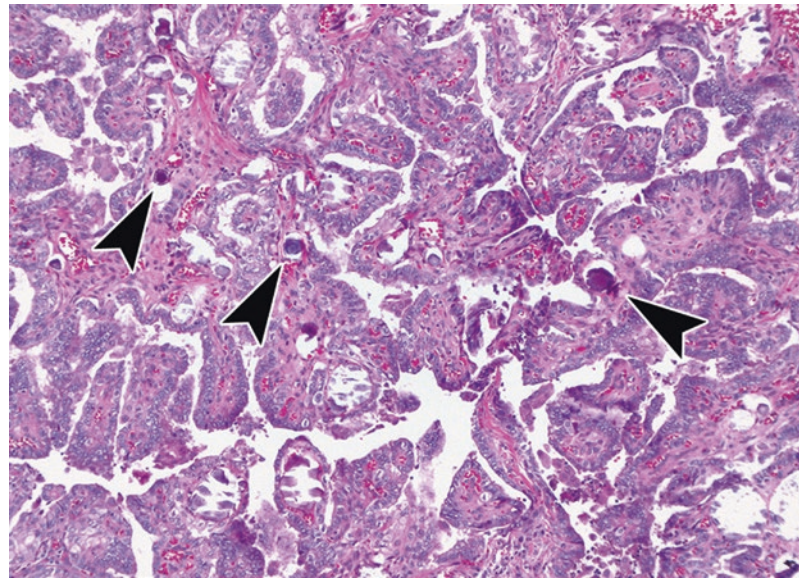

Fig. 4.9 Papillary thyroid carcinoma, H&E, 10×. Papillary architecture with numerous psammoma bodies, concentrically laminated basophilic structures (*arrowheads*). These may correspond to the "microcalcifications" classically seen on ultrasound

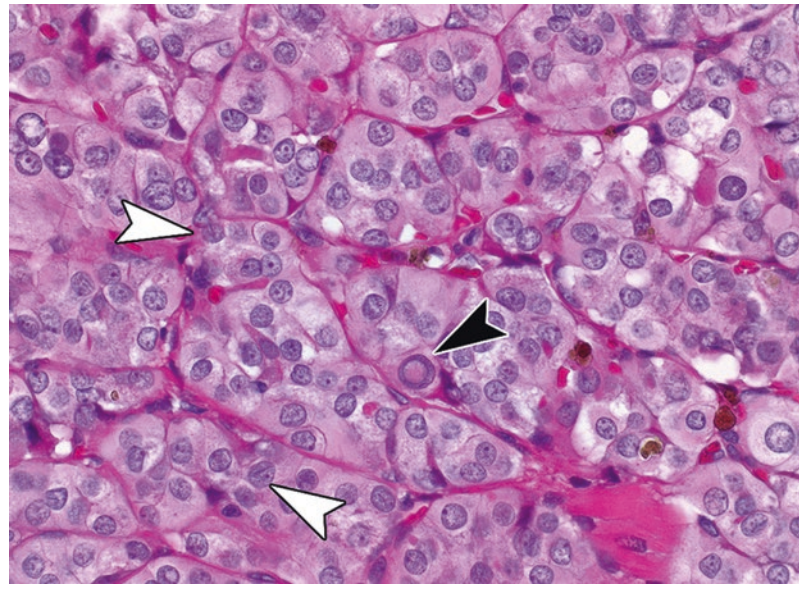

Fig. 4.10 Papillary thyroid carcinoma, 40×. A prominent nuclear pseudoinclusion is seen (*arrowhead*) as well as nuclear elongation and grooves (*open arrows*)

Follicular variant of PTC (FVPTC) is the second most common variant of PTC characterized by a predominant follicular pattern, lack of papillae, and the presence of nuclear features of PTC (Fig. 4.12). This variant poses challenges diagnostically, as it is a heterogenous and controversial group of tumors that shares features with PTC, follicular carcinomas, and follicular adenoma [59–61]. There is considerable interobserver variability in the diagnosis of these tumors, which may be due to attempting to impose a binary diagnostic classification (cancer/not cancer) upon a biological continuum of mutation accumulation leading from benign follicular adenoma to malignant follicular lesion [23, 24, 47, 51, 60, 62–65]. Due to the follicular architecture and generally less well-developed nuclear features of PTC, these tumors are often not able to be definitively diagnosed on FNA, rather yielding FNA diagnoses of AUS/FLUS,

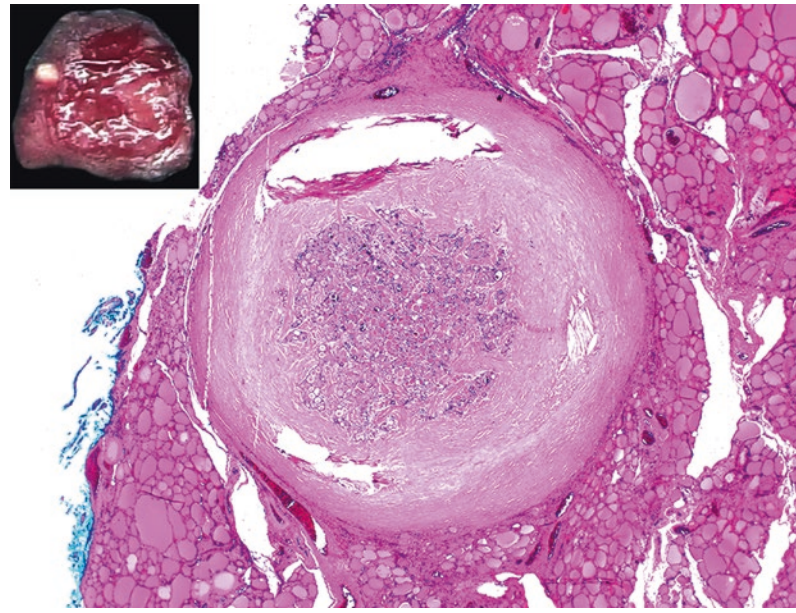

Fig. 4.11 Papillary microcarcinoma, H&E, 2×. A well-circumscribed nodule with a thick fibrous capsule. *Inset*: Gross photo of this papillary microcarcinoma: a well-demarcated white fibrotic nodule is seen

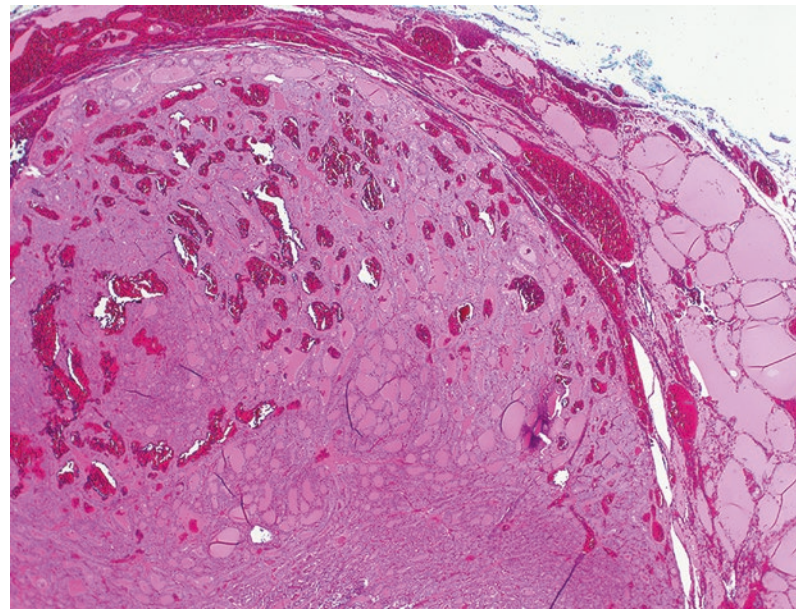

Fig. 4.12 Follicular variant of papillary thyroid carcinoma, H&E, 2×. A well-circumscribed tumor with follicular architecture

SFN, FN, or suspicious for malignancy [65, 66]. Genetically, these tumors tend to be characterized by mutations (RAS, BRAF K601E, Pax8/PParyɣ) which are more similar to those seen in follicular tumors than in classical PTC [67–71].

The encapsulated follicular variant of PTC is a subgroup characterized by clearly encapsulated tumors with follicular architecture and often does not show evidence of invasion into adjacent structures or vessels. These noninvasive encapsulated FVPTCs have recently been characterized by an effort of a consortium of endocrine pathologists as having indolent behavior, and it has been suggested that these represent a separate entity to be termed *noninvasive follicular thyroid neoplasm with papillary-like nuclear*

features rather than true malignancies [72]. As all of these tumors were in the past treated as PTC, time and additional follow-up data will be needed to determine whether these truly represent a benign entity; however, the initial reports are promising [73, 74].

In contrast to the above variants, *tall cell variant* is a variant which carries potentially a worse prognosis than classical PTC. In order to qualify as tall cell variant, >50% of the tumor cells must show tall cell morphology, where the tumor cell height is at least 3× width [49]. These tumors often present in older patients and at a higher tumor stage based on extrathyroidal extension and metastases [75]. Perhaps due to these findings, these tumors are associated with a worse 5-year survival than classical PTC [76]. In addition, these tumors are often found as a differentiated component in anaplastic and poorly differentiated thyroid carcinomas, suggesting they are more likely to undergo dedifferentiation [77]. It has been suggested that even a minor tall-cell component less than 50% may also carry worse prognosis, though further study is required to determine whether this is truly the case [78, 79].

There are numerous other rare variants including columnar cell, solid, Warthin-like, clear cell (Fig. 4.13), cribriform-morular, oxyphilic (Hürthle cell), diffuse sclerosing, and variants with hobnail features or fasciitis-like stroma. The prognostic significance of these other variants is generally less well established, likely due to their rarity.

Follicular Thyroid Carcinoma

Follicular thyroid carcinoma (FTC) is the second most common thyroid carcinoma, after PTC. These tumors are characterized by a follicular pattern and lack of nuclear features of PTC and are defined by evidence of capsular or vascular invasion. Capsular and lymphovascular invasion are architectural features that require histologic examination and cannot be assessed on cytology. For this reason, FNA as a modality cannot reliably make the distinction between follicular adenoma and follicular carcinoma [25]. The FNA findings for both follicular adenomas and carcinomas are generally in the spectrum of FLUS/SFN/follicular neoplasm [12, 14, 19, 24, 64, 65] (Fig. 4.14).

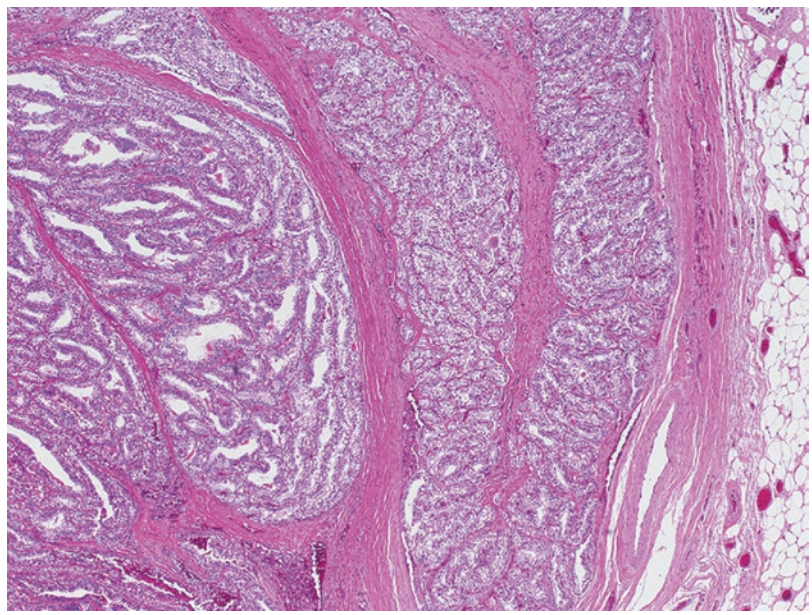

Fig. 4.13 Clear cell variant of PTC, H&E, 4×. Thyroid tumor with diffuse cytoplasmic clearing

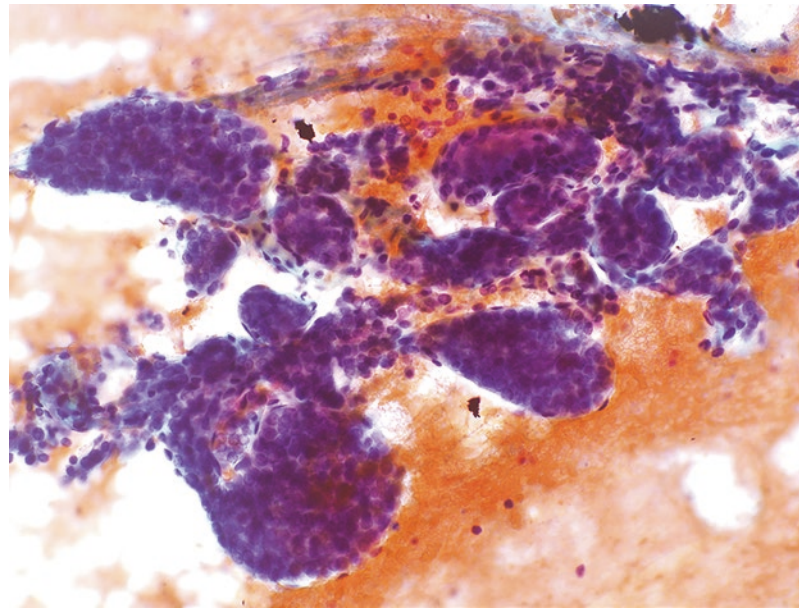

Fig. 4.14 Follicular lesion, fine-needle aspiration cytology, alcohol-fixed Papanicolaou stain, 20×. A cellular sample with follicular architecture. This lesion, on excision, was a follicular carcinoma. The distinction between follicular adenoma and carcinoma cannot be made on cytology

Gross Examination

Follicular carcinomas often have a thick capsule which may be visible grossly. These nodules may be solitary. The cut surface is solid and fleshy, and areas of capsular invasion may or may not be visible at the time of prosection. In cases where there is widespread invasion, the tumor may grossly appear as an infiltrative process, with no residual capsule visible.

Microscopic Features

Follicular carcinomas, microscopically, are composed of a follicular proliferation which may have a well-formed, thick capsule. The follicular architecture is microfollicular in the majority of cases, with little colloid, though some follicular carcinomas have macrofollicular architecture and/or colloid. The cells lining the follicles may show nucleoli or occasional nuclear irregularity but lack the diagnostic features of PTC previously described. The defining histologic characteristic distinguishing FTC from follicular adenoma is invasion, either of vessels or the tumor capsule [49, 63, 80, 81] (Figs. 4.15 and 4.16). Both the diagnosis of vascular invasion and that of capsular invasion, when minimal, may be difficult and subjective [65, 81–87]. Particularly in the case of capsular invasion, technical factors such as disruption of the capsule due to prior FNA or at the time of surgery may render true assessment of invasion difficult [88–90].

FTC Subtyping

The extent of invasiveness has been used to risk-stratify FTC. The term "minimally invasive" has been used to describe encapsulated tumors with foci of vascular or capsular invasion only identified by microscopic examination. Widely invasive tumors are tumors with grossly evident invasion and may involve structures outside the thyroid. As would be expected, tumors that are minimally invasive have a better prognosis than widely invasive tumors [63, 91–95].

The *oncocytic (Hürthle cell) variant of FTC* shows follicular tumor cells with oncocytic morphology; that is, they have abundant granular cytoplasm, eccentrically placed nuclei, and prominent nucleoli. The architecture of the proliferation remains generally follicular, and as in other forms of FTC, nuclear features diagnostic of PTC are absent (Figs. 4.17 and 4.18). This variant is relatively common. As with other forms of FTC, the distinction between a benign oncocytic adenoma and an oncocytic carcinoma rests

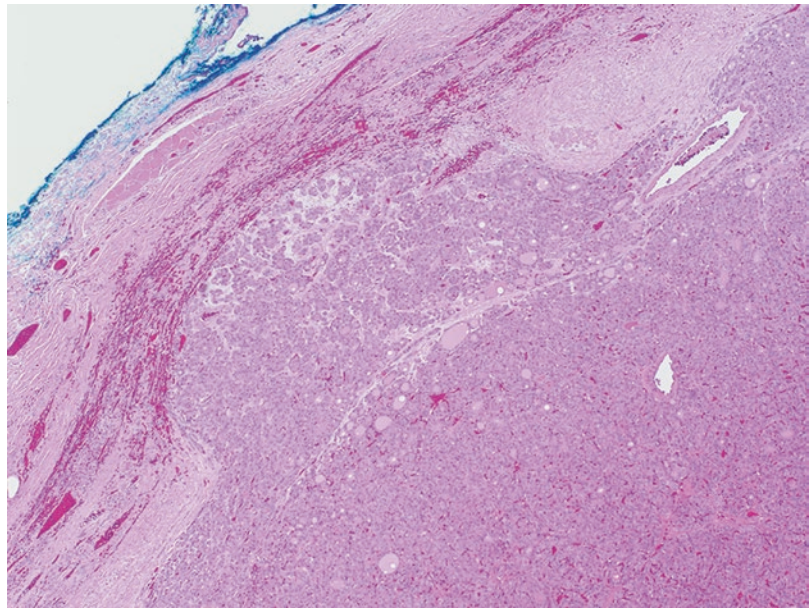

Fig. 4.15 Follicular carcinoma, H&E, 4×. A focus of capsular invasion in a follicular-patterned tumor, diagnostic of carcinoma

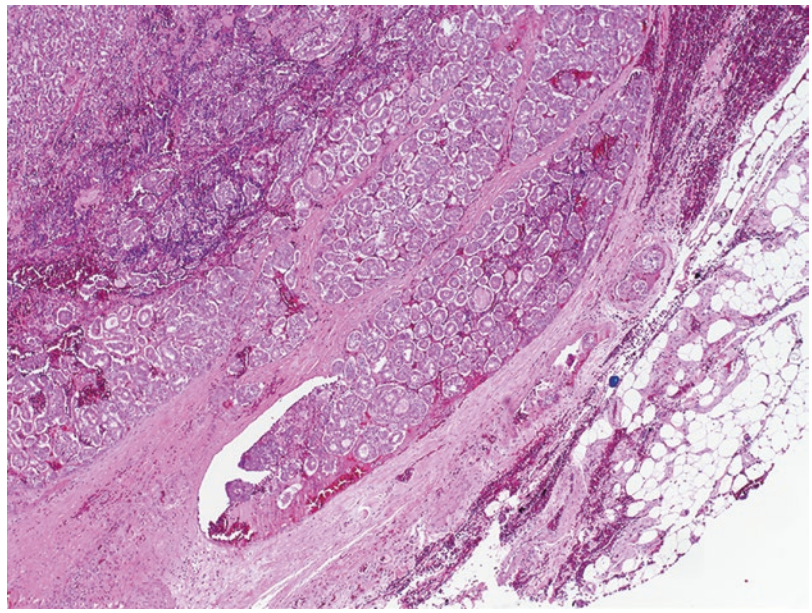

Fig. 4.16 Follicular carcinoma, H&E, 4×, vascular invasion: tumor with direct extension into a blood vessel

on the identification of capsular or vascular invasion [49]. In the past, there was an argument made that all oncocytic neoplasms of the thyroid represented malignancies. While this is no longer considered to be the case, there is evidence that oncocytic carcinomas harbor distinct genetic alterations from other follicular carcinomas and may have more aggressive behavior in the form of increased recurrence rate, rate of spread to lymph nodes, and increased mortality [96–99]. In addition, oncocytic carcinomas may often be seen as a differentiated component in anaplastic carcinomas [100, 101] (Fig. 4.19).

Other variants of FTC are rare and include clear cell [102], mucinous [103], and signet-ring cell variants.

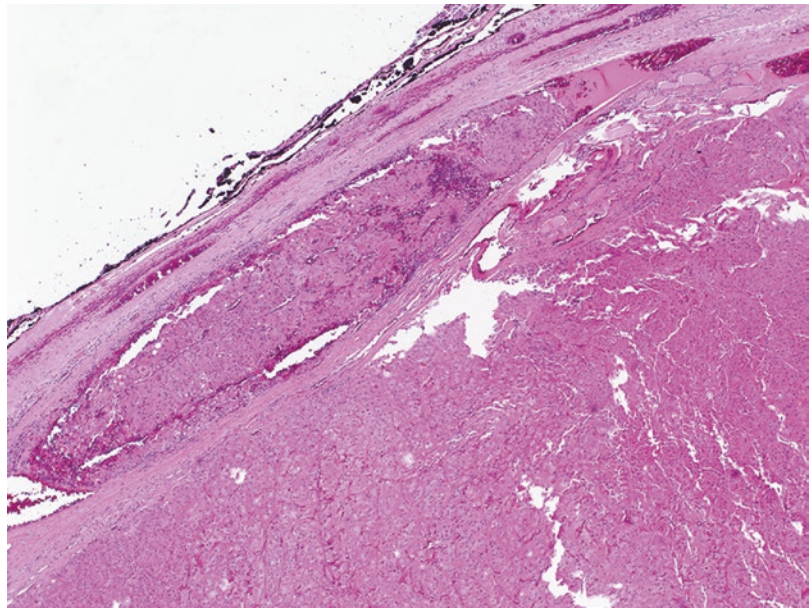

Fig. 4.17 Oncocytic (Hürthle cell) variant of FTC, H&E, 4×. Oncocytic tumor cells with vascular invasion into a capsular vessel. Elsewhere this tumor demonstrated anaplastic transformation (Fig. 4.19)

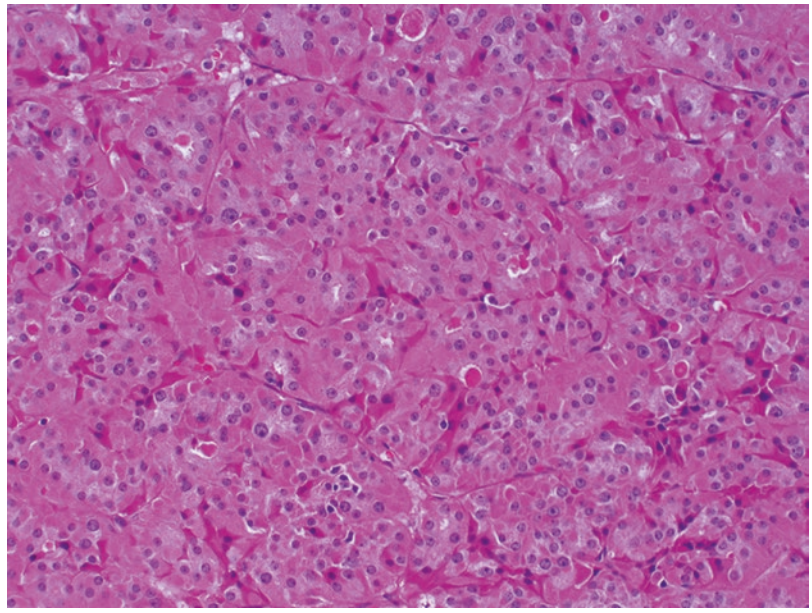

Fig. 4.18 Oncocytic (Hürthle cell) variant of FTC, H&E, 20×. Higher-power view of oncocytes from case seen in Fig. 4.17. Tumor cells with abundant granular, eosinophilic cytoplasm and eccentrically placed nuclei. Nucleoli are readily apparent. Nuclear features of papillary thyroid carcinoma are absent

Pitfalls

The thyroid is an endocrine organ and as such is prone to a variety of inflammatory and proliferative changes that pose diagnostic challenges for the pathologist, endocrinologist, and surgeon.

Limitations of FNA

While fine-needle aspiration biopsy remains the standard of care and an appropriate, minimally invasive first step toward diagnosis of thyroid nodules, the sampling modality is subject to limitations. The interpretation of the FNA sample is

very much dependent on optimal technique, previously covered in this chapter, and adequate sampling of the intended target lesion. In addition, the small sample size and lack of ability to assess certain architectural features, such as invasion, are inherent limitations to the technique. Inflammatory changes and "endocrine atypia" may lead to changes on cytology which may be difficult or impossible to distinguish from neoplasms [9, 15, 52, 89]. Various molecular studies have been developed to aid in refining diagnosis and prognosis of thyroid nodules on cytology, which will be covered in a separate chapter. However, given that many molecular alterations can been seen in both benign and malignant proliferations of the thyroid, results of molecular testing must be interpreted in the context of clinical and cytologic findings [18, 62, 104–107].

Hyalinizing Trabecular Tumor

Hyalinizing trabecular tumor (HTT) is a rare tumor composed of a well-circumscribed proliferation of follicular epithelial cells with a trabecular or nested architecture and hyaline material between the cell nests [26, 108–111]. The tumor is well circumscribed and in some cases may have a capsule. The nuclear features of this tumor have significant overlap with those of PTC, including nuclear grooves, elongation, and prominent pseudoinclusions [26, 27, 112]. Due to these features, these tumors are often diagnosed on FNA cytology as papillary thyroid carcinomas [113] (Figs. 4.20, 4.21, and 4.22). Features unique to HTT are refractile cytoplasmic yellow bodies and hyaline extracellular material, which, if present on FNA, may allow for accurate characterization as HTT [112]. Initially, this tumor was termed hyalinizing trabecular adenoma, but since then, there has been one report describing lymph node metastasis [110], and one report of pulmonary metastasis [109], out of hundreds of patients with HTT. While the vast majority of these tumors behave in an indolent fashion, these reports have led to the preferred use of the "tumor" or "neoplasm" for this lesion [26, 109].

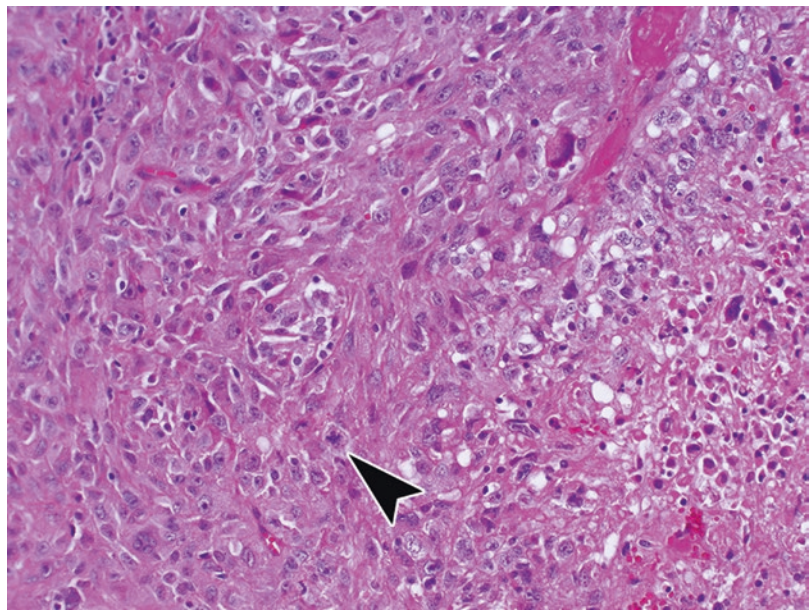

Fig. 4.19 Anaplastic transformation, H&E, 20×. Abnormal mitotic figure (*arrowhead*) and marked nuclear anaplasia. Necrosis is present at the right of the image. This field is from an area of anaplastic transformation in the oncocytic carcinoma pictured in Figs. 4.17 and 4.18

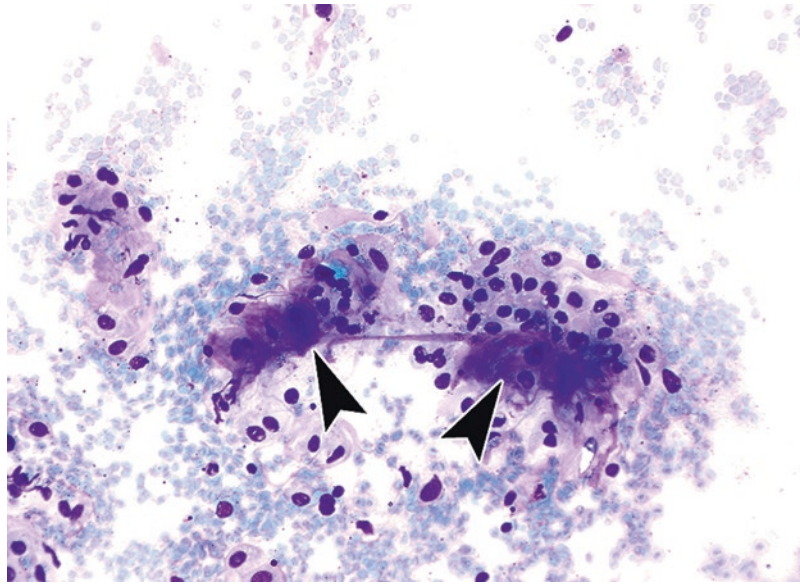

Fig. 4.20 Hyalinizing trabecular tumor, fine-needle aspiration cytology, Diff-Quik, 20×. Amorphous hyaline material is present (*arrowheads*), a clue to the diagnosis. Nuclei show elongation

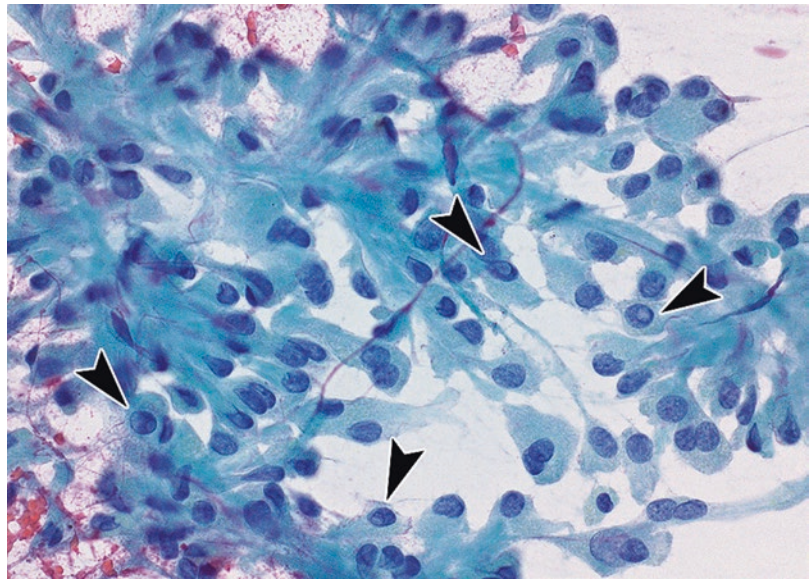

Fig. 4.21 Hyalinizing trabecular tumor, fine-needle aspiration cytology, alcohol-fixed Papanicolaou stain, 40×. Nuclei are elongated, with abundant pseudoinclusions (*arrowhead*) and grooves. The presence of these pseudoinclusions may lead to a misdiagnosis of papillary thyroid carcinoma on cytology

Thyroiditis

Chronic lymphocytic thyroiditis (Hashimoto thyroiditis) is commonly encountered in clinical practice and may lead to nodular change in the thyroid. The histologic findings in chronic lymphocytic thyroiditis are lymphoid infiltrates and oncocytic (Hürthle cell) change (Fig. 4.23). When both components are sampled on FNA, the diagnosis of chronic lymphocytic thyroiditis is easily made [9, 10, 52]. However, a sample

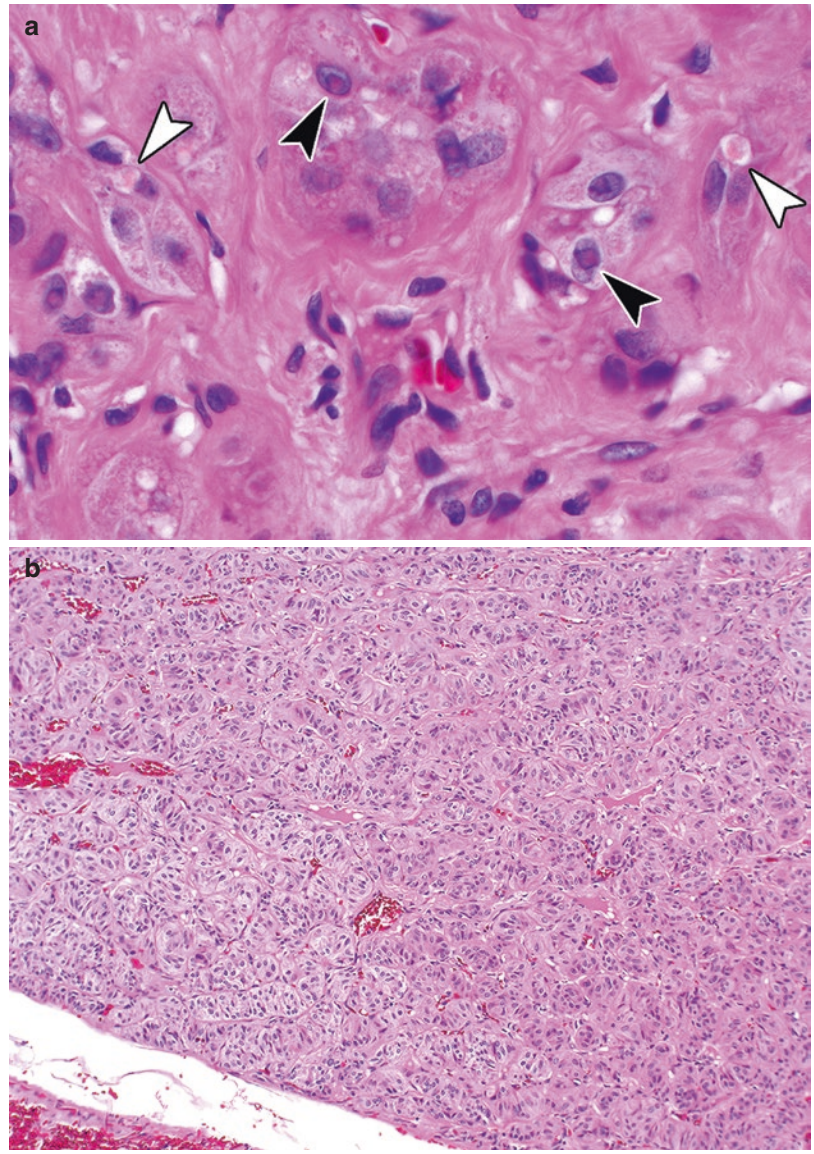

Fig. 4.22 Hyalinizing trabecular tumor, H&E. (**a**) High-power view (40×) of nuclear pseudoinclusions (*arrowheads*) and cytoplasmic yellow bodies (*open arrow*). (**b**) Lower-power view (10×) of a nested proliferation of tumor cells

composed of only the oncocytic component on FNA, in the context of a worrisome nodule on ultrasonography, may lead to a cytologic diagnosis of oncocytic neoplasm or suspicious for oncocytic neoplasm. Conversely, a cytologic sample of only the lymphocytic component, in the same context, may raise the possibility of intrathyroidal lymph node or even lymphoma.

So-called "parasitic" nodules that arise in Hashimoto thyroiditis may lead to diagnostic difficulties as well. Nodules of thyroid tissue involved by thyroiditis may not be connected to the main thyroid gland (Fig. 4.24). These nodules may present on ultrasound as suspicious masses adjacent to the thyroid or be clinically suspicious for abnormal lymph nodes. Biopsy of these "abnormal lymph nodes" may result in a cytology sample comprised of lymphocytes and follicular epithelium with atypia, presenting the differential diagnosis of parasitic nodule in thyroiditis or lymph node with atypical follicular epithelium present, suspicious for metastasis.

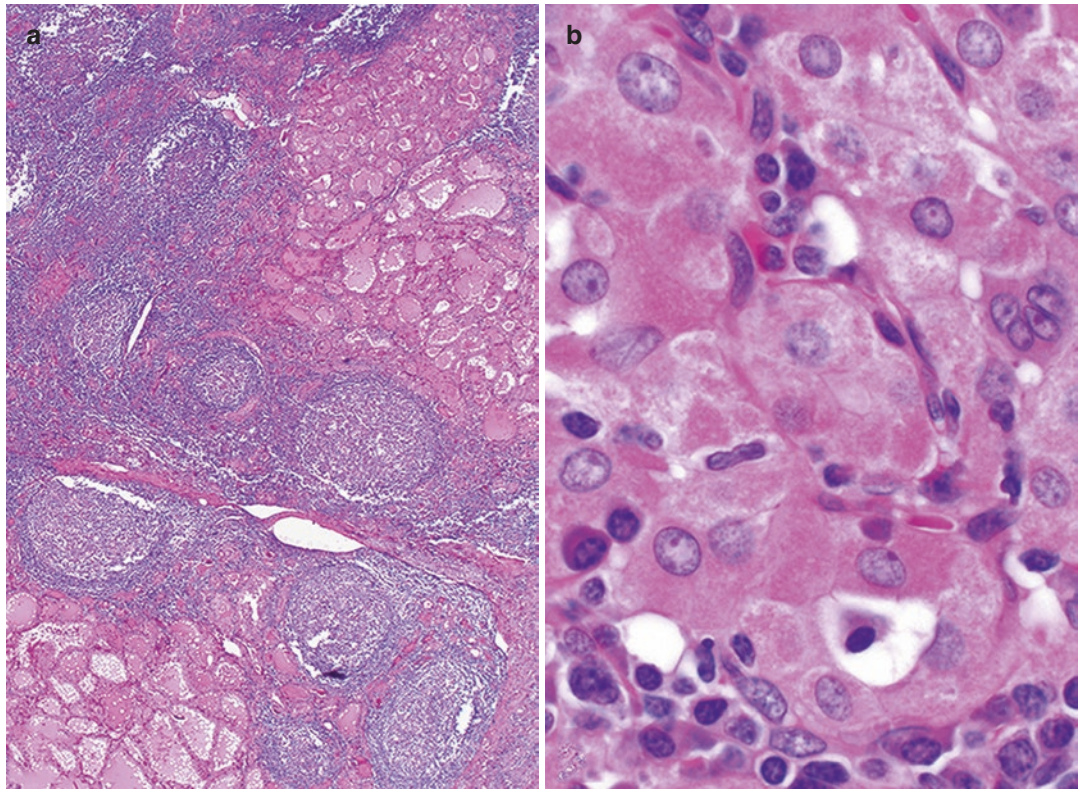

Fig. 4.23 Chronic lymphocytic thyroiditis (Hashimoto thyroiditis), H&E. (**a**) Low-power view (2×) of florid lymphocytic infiltrate with germinal center formation and oncocytic change in follicular epithelium. (**b**) 40×: High-power view of oncocytic (Hürthle cell) change and atypia in follicular epithelium

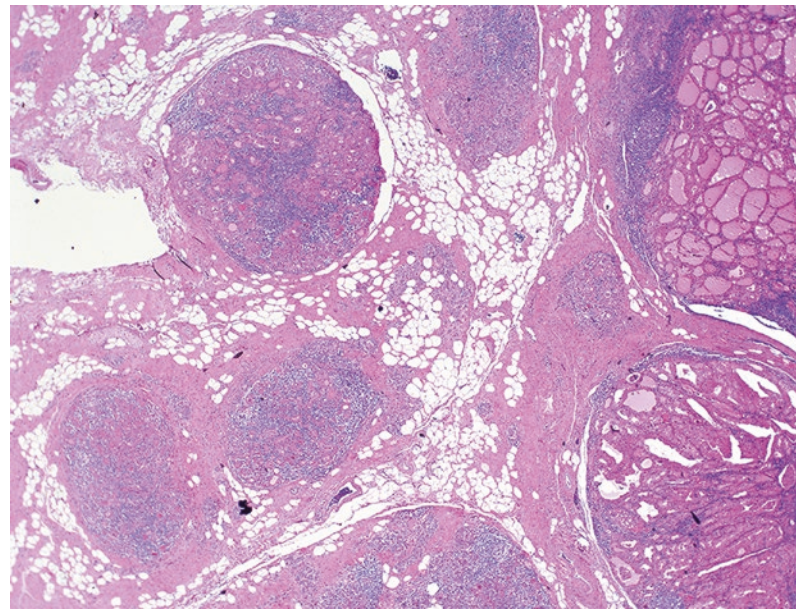

Fig. 4.24 Chronic lymphocytic thyroiditis (Hashimoto thyroiditis), H&E, 2×. Multiple nodules of follicular epithelium with inflammation are present within perithyroidal soft tissue. These nodules may present as potential "suspicious lymph nodes" on ultrasonography

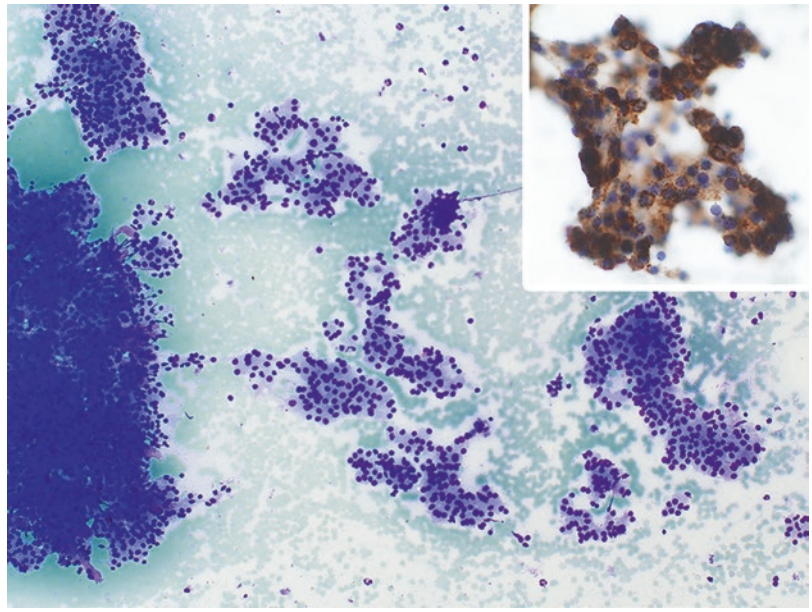

Fig. 4.25 Intrathyroidal parathyroid adenoma, fine-needle aspiration cytology, Diff-Quik, 10×. Cellular sample with abundant bland cells arranged in pseudo-follicular pattern. *Inset*: Immunohistochemical stain for parathyroid hormone on cytologic smear, 40×

The clinical information of a history of Hashimoto thyroiditis and lack of known thyroid malignancy can appropriately guide clinical treatment in these scenarios [114, 115].

Intrathyroidal Parathyroid

Rarely, an intrathyroidal parathyroid may present as a solitary thyroid nodule. In the absence of hyperparathyroidism or suspicion for ectopic parathyroid tissue, FNA may be the first step taken for evaluation of these nodules. The FNA of parathyroid tissue is cellular and has a microfollicular architecture that morphologically may be indistinguishable from a follicular proliferation of the thyroid (Fig. 4.25). Without additional clinical information, the FNA diagnosis of these lesions may be rendered as "follicular neoplasm" or "suspicious for follicular neoplasm" [113, 116]. With the appropriate clinical suspicion, however, additional material may be obtained for a fluid parathyroid hormone level, or immunohistochemical stain for PTH, which will be positive, confirming the diagnosis of intrathyroidal parathyroid tissue/adenoma [117].

Endocrine Atypia

The thyroid is an endocrine organ and as such is prone to a variety of inflammatory changes caused by autoimmune disease, mechanical issues such as follicle rupture, and degenerative change that can lead to cytologic changes that are worrisome for malignancy [9, 15, 52, 89]. Even benign hyperplastic nodules and follicular adenomas may harbor focal areas of nuclear irregularities. Autoimmune diseases such as Graves can lead to papillary hyperplasia of follicular epithelium as well as nuclear irregularities. All of these changes, when sampled on FNA, have the potential to create cytologic changes that may be concerning for potential malignancy and lead to an indeterminate FNA diagnosis.

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Molecular Diagnostic Approaches and Their Clinical Utility

5

Laura N. Purcell, Paula D. Strassle, and Jen Jen Yeh

Introduction

In the Bethesda System for Reporting Thyroid Cytopathology (TBSRTC), which is widely used to classify thyroid fine needle aspirations (FNAs), the most complicated area for management is the indeterminate nodule, which represents up to 25% of all samples [1]. These indeterminate classifications are usually explained by minimal cellular or nuclear changes, but pathologists are unable to determine if there is cancer due to an inability to detect capsular and vascular invasion [2–4]. Within the indeterminate nodule criteria, there are three categories as listed in Table 5.1.

The majority of these indeterminate nodules will undergo a repeat FNA and/or diagnostic lobectomy due to inability to rule out carcinoma from a FNA sample. Operations for indeterminate nodules that are benign may in retrospect be unnecessary. Indeterminate nodules that are benign may occur in up to 70–75% of patients undergoing diagnostic lobectomies [2]. As a result, researchers have been looking for methods to improve molecular testing to improve indeterminate thyroid nodule management.

Table 5.1 Indeterminate categories in the Bethesda system for reporting thyroid cytopathology (TBSRTC) [1]

	Implied risk of malignancy according to TBSRTC (%) [1]	Estimated risk based on reported studies (%) [5]
Atypia of unknown significance/follicular lesion of unknown significance (AUS/FLUS)	5–15%	6–48%
Follicular neoplasm/ suspicious for follicular neoplasm (FN/SFN)	15–30%	14–34%
Suspicious for malignant cells (SMC)	60–75%	53–87%

Afirma Gene Expression Classifier (GEC)

The Afirma GEC is considered a thyroid cancer "rule out" test developed by Veracyte, Inc. (South San Francisco, CA). It was created by screening 240,000 genes and exon transcripts in 178 benign

L.N. Purcell, M.D. (✉)
Department of Surgery, University of North Carolina, 4001 Burnett-Womack Building, CB #7050, Chapel Hill, NC 27599-7050, USA
e-mail: laura.purcell@unchealth.unc.edu

P.D. Strassle, M.S.P.H.
Department of Epidemiology, University of North Carolina, 4001 Burnett-Womack Building, CB #7050, Chapel Hill, NC 27599-7050, USA
e-mail: pstrass@live.unc.edu

J.J. Yeh, M.D.
Division of Surgical Oncology and Endocrine Surgery, Department of Surgery, University of North Carolina, CB7213, 170 Manning Drive, 1150 POB, Chapel Hill, NC 27599-7213, USA
e-mail: jjyeh@med.unc.edu

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thyroid samples. After examining these samples, the 142 gene cDNA Affymetrix cassette was derived using a linear support vector machine model utilizing a recursive learning process from 167 mRNA expression patterns found in nodules with known benign histology [6, 7].

Test Characteristics

To perform the GEC test, a clinician obtains three designated FNA passes. One is designated for routine FNA cytomorphology, while two are stored in a RNA preservative for the multidimensional proprietary algorithm. The test has the ability to tolerate variations in RNA amount (4–25 ng) [8, 9]. The FNA sample first undergoes cytology testing at the centralized cytopathology lab, Thyroid Cytopathology Partners (Austin, TX). Samples classified as benign, malignant, or suspicious for malignancy do not undergo further testing, and the results are returned to the ordering physician. Indeterminate samples, according to TBSRTC described above (AUS/FLUS, FN/SFN), proceed to GEC testing [8].

During the first step of GEC testing, the sample is tested against a panel of 25 genes on six cassettes. This testing identifies thyroid nodules with expression profiles consistent with subtypes of follicular thyroid carcinoma (FTC) and non-follicular cell-derived thyroid tumors such as medullary thyroid carcinoma (MTC), oncocytic follicular (Hürthle cell) lesions, parathyroid tissue, as well as breast, renal cell, and melanoma metastasis. Afirma MTC evaluates expression of calcitonin-related polypeptide alpha (CALCA), carcinoembryonic antigen-related cell adhesion molecule 5 (CEACAM5), secretogranin III (SCG3), sodium channel voltage-gated type IX alpha subunit (SCN9A), and synaptotagmin IV (SYT4), which are all genes specific to MTC. If the expression of these genes is positive, GEC reports a positive "Afirma MTC" test in this first round of GEC reporting. If expression panels in one of the other five screening cassettes in the first round of GEC testing are positive, the nodule is reported as "suspicious" and does not undergo further testing. All other indeterminate samples proceed to the second round of GEC testing, which uses a support vector machine to classify the samples as benign or suspicious. The thyroid FNA sample is classified as "suspicious" if it has >50% risk of malignancy and "benign" if the negative predictive value is greater than 95% for AUS/FLUS or greater than 94% for FN. SMC nodules have a high pretest probability for malignancy, which results in a suboptimal NPV, and are not included in GEC testing [8–10].

Analytical validity of the Afirma GEC was studied by Walsh et al. and was found to meet the Evaluation of Genomic Applications in Practice and Prevention (EGAPP) level 1 analytic validity criteria [11]. The nucleic acids extracted were found to be stable, and the testing proved reproducible findings. To determine how much sample RNA would be required, samples were mixed with blood nucleic acid. GEC proved to hold up to dilution by maintaining the correct classification for up to 83% blood RNA. Limitations of GEC testing include the need for multiple needle passes [11].

Clinical Validity

Sensitivity, the probability of a positive test among persons with the disease, and specificity, the probability of a negative test among those disease-free, are both inherent qualities of all diagnostic tests and assumed to be independent of disease prevalence. However, the positive predictive value (PPV), the probability a patient who tested positive has the disease, and negative predictive value (NPV), the probability a patient who tested negative is disease-free, are dependent on the sensitivity, specificity, and disease prevalence in the patient population. For example, when the cancer prevalence is 80%, the PPV and NPV for the Afirma GEC test are 88.2% and 56.5%, respectively; however, when the prevalence decreases to 20%, the PPV decreases to only 31.9%, and the NPV increases 95.4% (Fig. 5.1). As the prevalence of malignant thyroid nodules may be significantly variable between populations and institutions studied, the utility of diagnostic tests must be carefully considered in the context of the population that is being applied [12].

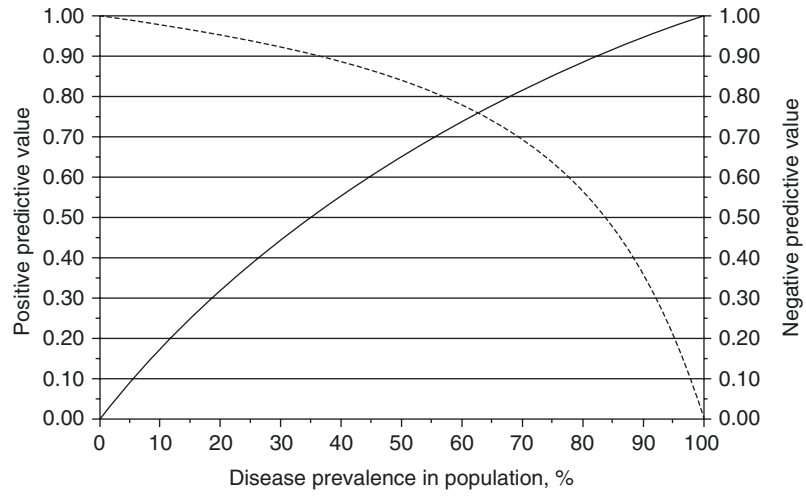

Fig. 5.1 The positive predictive value (*solid line*) and negative predictive value (*dashed line*) of the Afirma GEC test across disease prevalence, assuming a sensitivity and specificity of 90% and 52%, respectively [1]

In the first published study on Afirma GEC by the test creators, Chudova et al. described GEC AUS/FLUS and FN/Hürthle cell neoplasm (HCN) nodules to have a 5–6% posttest probability of malignancy for a "benign" result and 37–38% for a "suspicious" result [10]. These findings are more often described as a negative predictive value (NPV) of 94–95% and a positive predictive value (PPV) of 37–38% [10]. The 5–6% posttest probability risk of a GEC benign with cytological AUS/FLUS or FN/HCN is a risk deemed acceptable by the National Comprehensive Cancer Network to consider "observation in lieu of surgery" [13].

Afirma GEC was first clinically validated by Alexander et al. in a prospective, multicenter study examining 210 indeterminate nodules (AUS/FLUS and FN/SFN) [14]. In histopathology, 51 of the 210 thyroid samples were classified as malignant resulting in an overall 24% incidence of malignancy. The GEC evaluation correctly diagnosed 46 of the 51 malignant samples. The majority of false negatives were attributed to be suboptimal samples. Classification of the false negatives were as follows: three PTCs (size range, 0.6–1.2 cm), one follicular variant PTCs (size range, 1–3 cm), and one 3.5 cm Hürthle cell carcinoma [14].

For AUS/FLUS nodules, Alexander et al. showed GEC had a sensitivity of 90% (53% specificity) and NPV of 95% (38% PPV) in a population with a malignancy prevalence of 24%. Similar findings were seen in FN/SFN lesions, with a sensitivity of 90% (49% specificity) and NPV of 94% (37% PPV), with a malignancy prevalence of 25%. However in SMC nodules, there was a higher prevalence of malignancy (62%), which reduced the NPV to 85%. AS, the lower NPV in these nodules makes the findings unreliable, and GEC should not be used for indeterminate SMC lesions [14].

Clinical validity has been further studied in several subsequent studies. The study performed by Harrell et al. was limited by its small sample size of 36 suspicious GECs from Nova Southeastern University [15]. However, important results to note from this study were a disproportionate distribution of oncocytic lesions in the GEC suspicious category. Further evaluation proved that most of the oncocytic lesions were benign on the final pathologic evaluation. This study had a 51% malignancy prevalence and a NPV of 80%. This was the first study to highlight the significant decrease in NPV and thus limited utility when the GEC is used in a population with greater than 25% malignancy prevalence [15].

Marti et al. studied Afirma GEC at two tertiary care centers, Memorial Sloan Kettering (MSK) Cancer Center, a tertiary cancer referral center with a high prevalence of thyroid malignancy (55%), and the Mount Sinai Beth Israel, which has a low prevalence (10%). Since samples from MSK had a higher probability of malignancy, it resulted in a lower NPV (86–92%) and the

Table 5.2 Afirma GEC studies and result for indeterminate nodules (AUS/FLUS and FN/SFN)

Study	Chudova 2012 [10]	Alexander 2012 [14]	Alexander 2014 [16]	Harrell 2014 [15]	McIver 2014 [9]	Lastra 2014 [17]	Marti [12] MSK	Marti [12] Mount Sinai Beth Israel
N	24	210	309	56	36	132	94	71
Prevalence (%)	29	24	39	51	17	44	55	12
Sensitivity (%)	100	90	98	94	83	100	100	100
Specificity (%)	76	52	12	24	10	7	10	22
PPV (%)	63	37	42	57	16	46	57	14
NPV (%)	100	94	90	80	75	100	86–92	95–98

inability of the GEC to sufficiently rule out cancer. In fact, to obtain a NPV >94% for the Afirma GEC, Marti et al. found that the pretest cancer risk (i.e., cancer prevalence) needs to be between 15% and 21% [12, 14]. This study reinforced that the NPV and PPV of a test are not uniformly applicable and vary widely across patient populations with different disease prevalence (Table 5.2).

As highlighted by McIver et al. and Lastra et al., the majority of subsequent GEC studies have lacked surgical pathology correlation for a preponderance of benign GEC nodules [9, 17]. This means that due to the inability to identify true positives and false negatives, the sensitivity, specificity, PPV, and NPV could not be calculated [9, 17]. For example, while McIver et al. also found a significantly lower PPV of 16% with 80% of suspicious nodules found to be benign after surgery, it is unclear if this is due to a lower pretest probability, diminished sensitivity, and/or diminished specificity.

Clinical Applicability

Indications for the biopsy of thyroid nodules should continue to be determined according to the 2015 American Thyroid Association (ATA) guidelines [5]. GEC testing should be used when results of the test will influence management decisions, especially for nodules with indeterminate Bethesda criteria (AUS/FLUS and FN/SFN) in populations where the malignancy prevalence is ≤25%. For example, GEC testing would be especially useful for FN/SFN lesions when deciding between surgery and watchful waiting.

For AUS/FLUS and FN/SFN nodules that are GEC suspicious (Fig. 5.2), the 2015 ATA guidelines recommend at least a diagnostic thyroid lobectomy. If the nodule is GEC benign, active surveillance is advised, but diagnostic lobectomy may be appropriate for selected patients. Routine GEC testing is not recommended for SMC nodules [5]. Due to a lack of long-term follow-up on benign GEC results, both the ATA and the American Association of Clinical Endocrinologists continue to recommend long-term clinical and ultrasound follow-up [18].

Patients who should *not* undergo the Afirma GEC include those who have thyroid nodules that are greater than 4–5 cm due to increased sampling error and patients less than 21 years of age due to lack of clinical validation studies. For patients which, regardless of GEC results, surgery is indicated, GEC testing should not be performed. For example, patients with local or compressive symptoms, strong clinical or ultrasound findings consistent with malignancy, or in patients who desire surgery regardless of further testing [19].

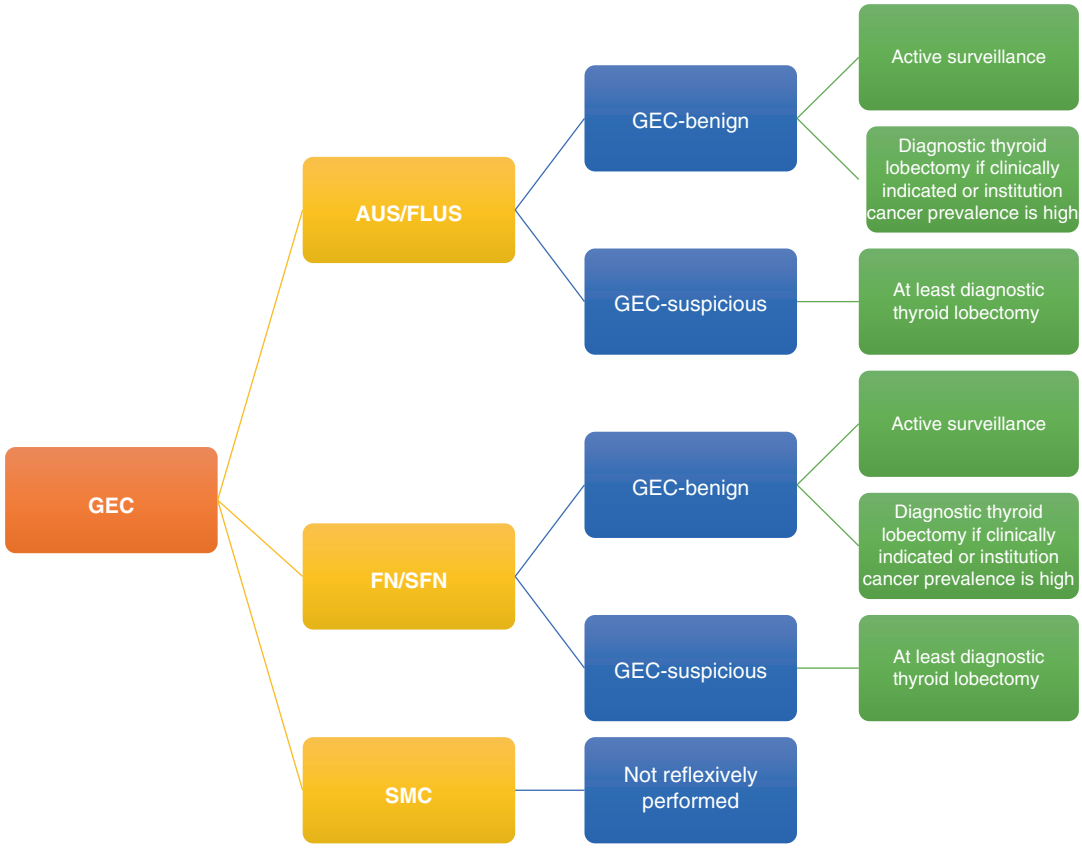

Fig. 5.2 Clinical application of Afirma GEC results as recommended by the ATA 2015 guidelines [5]

Studies have reported mixed results whether GEC utilization has decreased the number of surgeries performed. Singer et al., Alexander et al., and Duick et al. showed significant decreases in surgery after GEC testing. Duick et al., a study funded by Veracyte, showed that the use of GEC testing decreased thyroidectomies (hemithyroidectomy and total thyroidectomies) from 74% for cytologically indeterminate nodules to 7.6% [20]. However, the lower rate of GEC benign nodules found in McIver et al. challenges Afirma GEC's healthcare cost reduction by reducing one in four surgeries (16 of 48 nodules were benign) compared to the previously reported one in two surgeries seen in Alexander et al. [9, 14, 20]. Marti et al. also showed no significant difference in number of surgeries due to the high thyroid carcinoma prevalence at MSK and resulting low NPV [12, 16, 20, 21]. Given that healthcare costs have the opportunity to be reduced by $2600 per patient tested, using the 2010 Medicare estimates for thyroidectomy with complications ($12,000) and the predicted Medicare reimbursement for Afirma GEC ($3200), further exploration into the utility of Afirma GEC is needed [18, 20].

Future Direction

Afirma BRAF has been developed to supplement the Afirma GEC. *BRAF* mutations have nearly 100% specificity for thyroid malignancy and are present in approximately 45% of thyroid carcinomas. In addition, *BRAF* mutations have been associated with more aggressive behavior [22–24]. Thus, *BRAF* mutation testing has the potential to improve the diagnostic and clinical decision-making value of GEC [25].

Gene Mutation Panels

Genetic mutations are associated with 70–80% of malignant thyroid cancers. The 7-gene mutation panel evaluates thyroid FNA samples for *BRAF*, *NRAS*, *HRAS*, and *KRAS* mutations as well as translocations of the *RET/PTC1*, *RET/PTC3*, and *PAX8/PPAR* gamma genes [26]. The presence of *BRAF* mutation has a PPV of 99.3% for PTC, and the presence of *RAS* mutations has a 74–87% PPV for thyroid carcinoma [13, 26–28].

Test Characteristics

Currently there are multiple commercially available 7-gene mutation panels. Interpace Diagnostics' ThyGenX (Parsippany, NJ), previously known as the miR*Inform* test, requires one FNA sample with a minimum of 50 ng of cellular material to run multiplex polymerase cycling assembly (PCA) to detect mutations and rearrangements using sequence-specific probes. If ThyGenX is positive, the sample has the opportunity to undergo reflex ThyraMIR testing (Interpace Diagnostics, Parsippany, NJ) determined by provider preference in order to evaluate microRNA expression. ThyraMIR will be discussed in more detail later in the chapter [8]. Quest Diagnostics (Madison, NJ) performs a 7-gene mutation panel using DNA from formalin-fixed paraffin-embedded (FFPE) tissue blocks or four FNA samples. Real-time PCR and post-PCR melting curve analysis are used to detect mutations and rearrangements. PCR-based DNA Sanger sequencing is then performed to confirm genetic alterations. *RET/PTC* alterations are detected using fluorescence in situ hybridization (FISH) when FFPE samples are provided [29].

Clinical Validity

The original study testing the thyroid cancer gene mutation panel was performed by Nikiforov et al. This study used DNA from samples to test for *BRAF* V600E and K601E; point mutations in *NRAS* codon 61, *HRAS* codon 61, and *KRAS* codons 12 and 13; and RNA from samples to test for *RET/PTC1*, *RET/PTC3*, and *PAX8/PPAR* rearrangements using real-time PCR. For indeterminate FNA samples, the 7-gene panel showed a specificity of 100% and a PPV of 100% in 52 samples (prevalence 40%). Nodules with indeterminate cytology and lacking mutations had a 16% risk of malignancy when confirmed with surgical histology. Based on these findings, the researchers concluded there would be a 30% reduction in second surgeries for completion total thyroidectomies and no inappropriate total thyroidectomies would be performed. However, a major limitation to this study was the lack of blinding of the cytopathologist to the molecular mutation results [26].

Subsequently Nikiforov et al. evaluated the 7-gene panel with a larger sample size. Similar to the initial study, there was still no blinding of the cytopathologist. Lack of blinding promotes biased results if there is a tendency to look more closely or call borderline cases of cancer if there was evidence of mutation(s) [13]. All false positives (eight) in this study were attributed to *RAS* mutations in follicular adenomas without definitive features of malignancy based on histology. In an unrelated validation study performed by Cantara et al. in 2010 with 41 thyroid samples, the presence of any mutation resulted in a 91.1% PPV, and the false-positive results were follicular adenomas [30]. Mutations found in follicular adenomas were all attributed to *RAS* mutations and made up of 26% of all *RAS* mutations identified [18]. Some have hypothesized that *RAS* mutation-positive follicular adenomas may be precursor lesions to invasive lesions given the role of RAS in promoting malignant transformation and differentiation [13, 31, 32].

Studies performed by Eszlinger et al. showed that air-dried FNA samples were comparable to fresh FNA samples that had been previously studied for use in the 7-gene mutation panels. These studies were performed to evaluate the 7-gene mutation panel in a more routine daily lab practice setting. The initial retrospective study performed by Eszlinger et al. in 2014 showed a specificity of 86% and PPV of 19% with a 16% prevalence, which was significantly worse compared to prior

Table 5.3 7-gene mutation panel studies and result for indeterminate nodules

Study	Nikiforov 2009 [26]	Cantara 2010 [30]	Nikiforov 2011 [13]	Beaudenon-Huibregtse 2014 [36]	Eszlinger 2014 [33]	Eszlinger 2015 [34]
Design	Prospective, two centers	Prospective, single center	Prospective, single center	Prospective, multicenter	Retrospective, single center	Prospective, single center
n	52	41	513	55	141	163
Prevalence (%)	40	17	24	49	16	28
Sensitivity (%)	71	86	61	48	18	49
Specificity (%)	100	97	98	89	86	92
PPV (%)	100	86	89	81	85	71
NPV (%)	84	97	89	64	85	82

reported gene mutation panel studies. In the follow-up prospective study performed by Eszlinger et al., the specificity improved to 92% and PPV to 71% (prevalence 28%) (Table 5.3).

There were several differences in Eszlinger et al.'s study compared to previous studies performed, which complicate the comparison of results. These differences include using samples from air-dried FNA smears for cytological analysis and FNA sample classification based on the Società Italiana di Anatomia Patologica e Citologia Diagnostica (SIAPEC) in conjunction with the British Thyroid Association guidelines instead of TBSRTC. The initial 2014 study included a subset with a higher number of follicular thyroid carcinomas (FTCs) in order to evaluate the true sensitivity of the test. The authors explained the low sensitivity in this test was due to the finding that only 8 of 32 of the FTCs contained a mutation, while 18 of the 156 follicular adenomas harbored a mutation which resulted in a higher false-positive rate. In combination with the high proportion of FTC compared to PTC, these results were significantly different than previous reported studies [33, 34]. Finally, the follow-up study performed by Eszlinger et al. had a cytopathologist review histology after molecular results. The pathologist reclassified three of the ten *RAS*-positive follicular adenomas to microinvasive FTC, while none of the *RAS*-negative follicular adenomas were reclassified. In this study, the authors concluded that *RAS*-positive follicular adenomas may be underdiagnosed due to limitations with histologic thyroid nodule evaluation which is known to have a high sampling bias as described in Ciabas et al. [35].

Clinical Utility

The major strength of the 7-gene mutation panel is its "rule in" ability. Specifically, if a patient has an indeterminate FNA thyroid nodule which is positive for a mutation or translocation, patients can be directed immediately to an initial total thyroidectomy. Yip et al. observed, with the utilization of molecular testing, a 30% increase in optimal initial total thyroidectomy for significant thyroid cancer and a 33% increase of appropriate use of initial lobectomy nodules in cases which were not thyroid carcinoma [37]. These findings indicate that both healthcare costs and repeat surgeries may be reduced with the utilization of the mutation panel by performing the appropriate first surgeries.

One major limitation for the 7-gene mutation panel is the dependency on the pretest probability of malignancy, otherwise known as disease prevalence. For example, if the pretest probability of malignancy is between 14 and 17%, then a negative test result indicates a malignancy risk of less than 6% (NPV >94%), which has been deemed a risk acceptable by the National Comprehensive Cancer Network (NCCN) for clinical observation. However, significant variation in pretest probability of cancer is present across institutions. If an institution has a differentiated thyroid cancer prevalence ≥20%, the NPV of the test will be too low to not perform a diagnostic lobectomy (Fig. 5.3) [8, 13, 30]. There also continues to be ambiguity with *RAS* mutations and *PAX8-PPAR* translocations—PPVs for identifying both of these have a highly

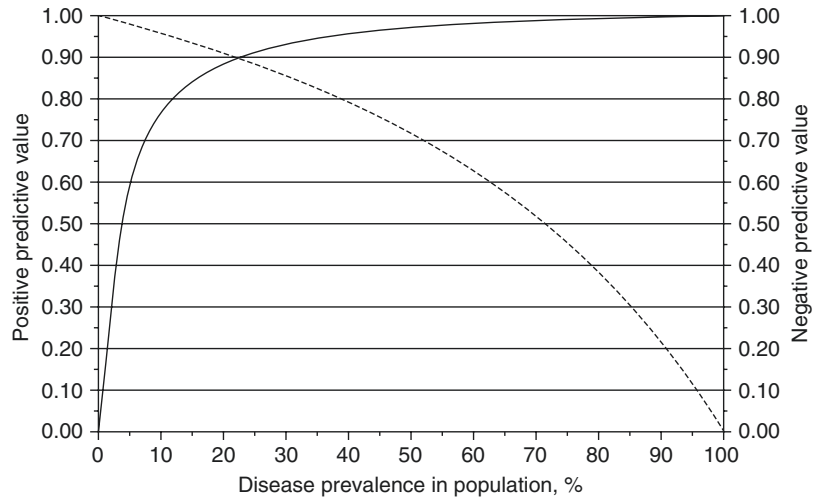

Fig. 5.3 The positive predictive value (*solid line*) and negative predictive value (*dashed line*) of the 7-gene mutation panel across disease prevalence, assuming a sensitivity and specificity of 61% and 98%, respectively

variable range due to adenomas harboring a significant proportion of mutations identified, 12–26% and 8%, respectively [38–40].

Clinical Applicability

Patients who have benign or malignant FNA results, concerning clinical findings, such as positive cervical lymph nodes or evidence of metastasis, or those who have a strong desire for or against surgery should not undergo 7-gene mutation testing [7]. The 2015 ATA recommends 7-gene mutational panel testing if nodules are indeterminate according to TBSRTC and if there is not already an indication for total thyroidectomy. If a mutation is identified, the ATA recommends an initial oncologic thyroidectomy (Fig. 5.4). Of note, according to 2015 ATA guidelines, an oncologic thyroidectomy may be a complete lobectomy for low-risk lesions [41]. Further nuances as to whether specific mutations such as *BRAF* may be associated with prognostic implications that may be high risk and thus requiring total thyroidectomy need to be studied [22–24]. If no mutations are found in AUS/FLUS lesions, then observation or diagnostic lobectomy may be considered. If no mutations are found in FN or SMC lesions, then a diagnostic thyroid lobectomy should be performed [5].

Future Horizons

MicroRNAs are small noncoding RNA that regulates cellular processes by upregulating or silencing target genes, which then become oncogenes or tumor suppressors. A wide variety have been studied, including miR-222, miR-21, miR-181a, and miR-146b. In a sample set, these four microRNAs had a sensitivity of 100% and specificity of 86% [42].

ThyraMIR combines the 7-gene mutational panel in combination with a gene expression classifier evaluating ten microRNAs, miR-29-b-1-5p, miR-31-5p, miR-138-1-3p, miR-139-5p, miR-146b-5p, miR-155, miR-204-5p, miR-222-3p, miR-375, and miR-551b-3p. Test validation by Labourier et al. shows a sensitivity of 89%, specificity of 85%, NPV of 94%, and PPV of 74% when the disease prevalence is 32% [43]. Currently this test is being used as a reflex test if the 7-gene mutation panel, ThyGenX, performed by Interpace Diagnostics is positive to further elucidate gene expression (Parsippany, NJ).

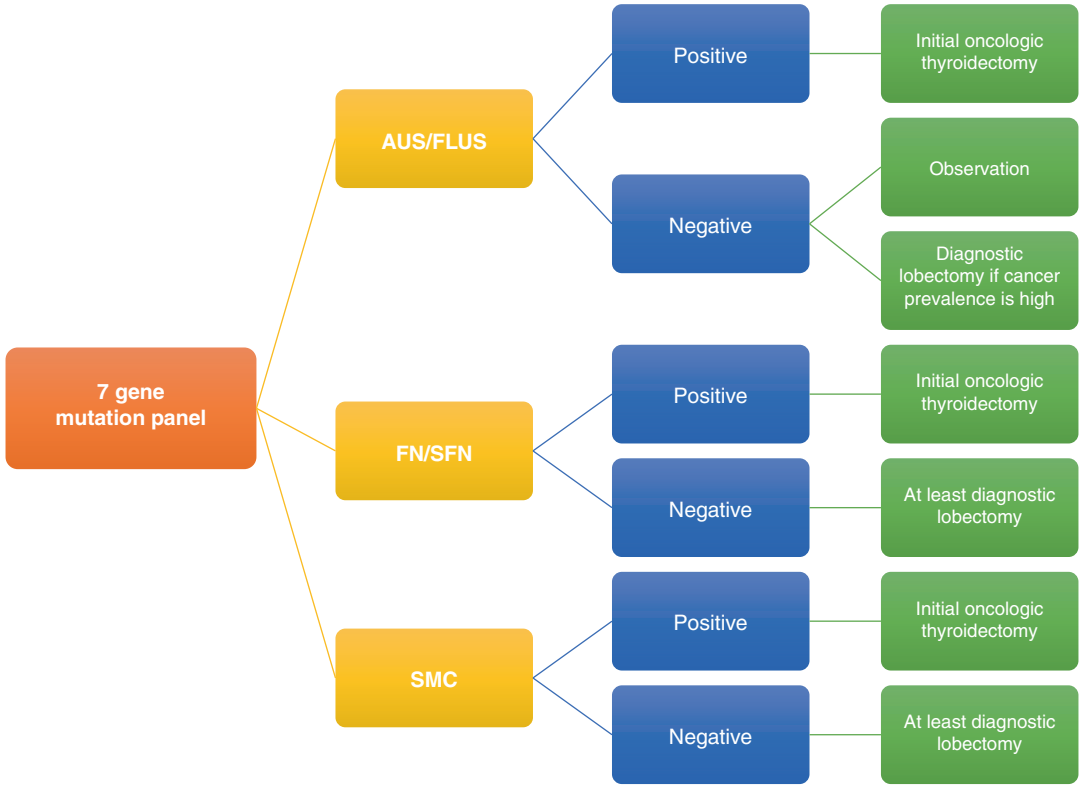

Fig. 5.4 Clinical application of 7-gene mutation panel as recommended by the ATA 2015 guidelines [5]. Oncologic thyroidectomy may include complete lobectomies for low-risk lesions

Next-Generation Sequence Panel

In an effort to optimize diagnostic tests with both high sensitivity and specificity and thus significant "rule in" and "rule out" ability, researchers at the University of Pittsburgh have supplemented the 7-gene mutation panel with other molecular markers.

Test Characteristics

Designed by the University of Pittsburgh, ThyroSeq v2 evaluates 60 genes using next-generation sequencing to evaluate 90% of known thyroid mutations. The test is commercially available through CBL Pathology (Rye Brook, NY), but performed and interpreted by the University of Pittsburgh Medical Center [8]. The test requires 10 ng of DNA from the initial FNA thyroid nodule sample. The test includes a panel of 14 genes: v-akt murine thymoma viral oncogene homolog 1 (*AKT1*), *BRAF*, *NRAS*, *HRAS*, *KRAS*, phosphatase and tensin homolog (*PTEN*), tumor protein 53 (*TP53*), thyroid-stimulating hormone receptor (*TSHR*), *GNAS* complex locus, which are associated with benign conditions, catenin, *CTNNB1*, *RET*, and *PIK3CA* at the codons 228 and 250 (C228T and C250T, respectively), as well as hotspots of the telomerase reverse transcriptase (*TERT*) gene promoter. In addition, there are 42 gene rearrangements which include *RET* fusion genes; *BRAF* proto-oncogenes; neurotrophic tyrosine kinase receptor, types 1 and 3 (*NTRK1*, *NTRK3*); *PPARγ*; and

thyroid adenoma-associated protein (*THADA*). Eight genes are used to evaluate the quantity and type of cells in a given sample, including phosphoglycerate kinase 1 (*PGK1*), *TG*, *TTF1*, *NIS*, and *KRT7* for thyroid follicular cells and calcitonin-related polypeptide alpha (*CALCA*) for C cells and parathyroid tissues [44, 45].

Clinical Validity

The initial study of ThyroSeq v2 was performed by Nikiforov et al. In a study which only included FN/SFN thyroid nodules, they evaluated a set of samples both retrospectively and prospectively. Cytopathologists were not blinded to the results of the 7-gene mutation panel in the retrospective cohort and to ThyroSeq v1 in the prospective cohort. The prevalence of thyroid cancer ranged from 14 to 34%, resulting in a test NPV of 95–98% and a PPV of 68–87% (Table 5.4). Four cancers were missed in this cohort—all nonaggressive subtypes (two follicular variant PTCs, one classic PTC, and one minimally invasive oncocytic variant FTC). The authors hypothesized that this was due to inclusion of the *TERT* promoter mutation in ThyroSeqv2, as this mutation has been correlated with increase in aggressiveness of tumors [45–48]. In 2015, Nikiforov et al. evaluated ThyroSeqv2 using only AUS/FLUS samples. Again, cytopathologists were not blinded to the results of the molecular testing. ThyroSeq v2 proved in this study to have both high sensitivity (91%) and specificity (92%) while maintaining reasonable PPV (42–91%) and NPV (92–99%) and with a disease prevalence of 6–48% [49].

Table 5.4 Next-generation panel studies and results for indeterminate nodules

	Nikiforov 2014 [45]	Nikiforov 2015 [49]
N	143[a]	98
Histology	FN/SFN	AUS/FLUS
Prevalence (%)	27	22
Sensitivity (%)	90	91
Specificity (%)	93	92
PPV (%)	83	77
NPV (%)	96	97

[a]91 samples tested retrospectively and 52 tested prospectively

Clinical Utility

The clinical utility of the ThyroSeq v2 seems promising, but validation studies are needed to confirm the benefit in both ruling in and ruling out thyroid carcinoma. To date, no study has evaluated the exact gene composition seen in ThyroSeq v2. While a study performed by Le Mercier et al. in Belgium is the most similar and evaluates many of the same genes, differences in the mutation screened for make comparison difficult [50].

Future Directions

Other promising biomarkers include those that are expressed during the normal thyrocyte cell cycle and during abnormal growth, which have been found to have high sensitivity and specificity for thyroid carcinoma. Galectin-3 (*GAL3*) is a carbohydrate-binding lectin involved in cell adhesion, cell cycle, apoptosis, and tumorigenesis. *GAL3*, with the highest sensitivity and specificity of the immunohistochemical markers, has shown to have a 78% sensitivity and 93% specificity [51]. Other biomarkers include hector battifora mesothelial-1 (*HBME-1*) and cytokeratin-19 (*CK-19*), as well as *CD-117* and *c-kit*, a type III tyrosine kinase receptor. Both *CD-117* and *c-kit* are thought to be important in maintaining the homeostasis of follicular epithelium and, when lost, may promote malignant transformation [52–54].

Conclusions

The search for an indeterminate nodule thyroid test that is both highly sensitive and specific is ongoing. Many researchers have proposed combining the sensitive GEC and specific 7-gene mutation panel to find the perfect balance, in addition to including ultrasound characteristics and other genomic alterations [55,

56]. Unfortunately, no combination has proven to be ideal [57]. It is likely that predictive modeling incorporating patient, imaging, and molecular characteristics will be needed to best tailor treatment planning for indeterminate FNAs.

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6 Clinical Presentation and Diagnosis of Papillary Thyroid Cancer

Cord Sturgeon, Dina Elaraj, and Anthony Yang

Introduction

Over the past half century, the primary treatment for biopsy-proven papillary thyroid cancer (PTC) has been surgical, and in the United States (US), it has been almost always treated with a total thyroidectomy [1]. Recent reports on the outcomes of hemithyroidectomy for PTC [2, 3] and observation of small, low-risk cases of PTC [4] have renewed the controversy over extent of surgery and have even suggested that some patients with quiescent disease can be placed into active surveillance protocols. In addition, there have been several recent high-profile publications indicating that there is an epidemic of unnecessary overdiagnosis of thyroid cancer [5, 6]. Due to these factors, the clinical decision-making process for patients with PTC is more complex than ever. There must be a rational approach to the workup of thyroid nodules and the management of thyroid cancers in order to avoid placing undue burden on patients and the healthcare system. Herein, we discuss the clinical presentation of PTC and outline the steps for the evaluation of the patient with thyroid nodules or newly diagnosed PTC.

C. Sturgeon, M.D., M.S. (✉)
D. Elaraj, M.D. • A. Yang, M.D.
Department of Surgery, Section of Endocrine Surgery, Northwestern University Feinberg School of Medicine, 676 North Saint Clair Street, Suite 650, Chicago, IL 60611, USA
e-mail: Cord.Sturgeon@NM.org

The Incidence of Thyroid Cancer Is Rising

Thyroid cancer is the fifth most common cancer in women in the United States, and over 62,000 new cases occurred in both men and women in 2015 [7]. Although the most common presenting symptom of thyroid cancer is a neck mass, most thyroid nodules and in turn, thyroid cancers, are diagnosed when asymptomatic nodules are evaluated. Thyroid cancer is steadily, and some would say explosively, increasing in incidence in the United States. The incidence of thyroid cancer in 1973 was 3.6 cases per 100,000 people. The incidence of thyroid cancer as of 2009 has increased almost fourfold to 14.3 cases per 100,000. This dramatic increase is virtually completely attributable to an increase in the incidence of PTC, with the incidence increasing from 2.7 cases per 100,000 people in 1973 to 12.5 per 100,000 in 2009 [8, 9].

One explanation for this phenomenon is that there has been some change in the risk of thyroid cancer in the general population in the United States. The most well-established risk factor for the development of thyroid cancer is a history of exposure to ionizing radiation, particularly during childhood. There is evidence to support

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that the general population has had increasing exposure to ionizing radiation over time, particularly from medical sources; however, there is insufficient evidence to attribute any significant proportion of the increase in thyroid cancer incidence to increasing radiation exposure [10]. In contrast to other malignancies, cigarette smoking has been shown to have a protective effect on the risk of thyroid cancer [11], and smoking has decreased in the United States along with the increased incidence of thyroid cancer. However it is difficult, and dangerous, to attribute a large part of the rise in incidence in thyroid cancer to a decrease in smoking rates. Other risk factors for thyroid cancer that have been described include obesity [12], taller height [13], and changes in dietary iodine fortification [14].

An alternate explanation for the apparent increase in the incidence of thyroid cancer is the substantial evidence that increased detection, or overdiagnosis, has played an important role over time [8, 9, 14]. A study recently published by the International Agency for Research on Cancer suggests that the rising incidence of thyroid cancer in multiple countries across the globe can be attributed to overdiagnosis [5]. In industrialized countries, the introduction of widely available ultrasound machines and population screening appear to be the key factors associated with overdiagnosis. Increases in the incidence of thyroid cancer have also been attributed to the incidental detection of asymptomatic thyroid nodules on computed tomography (CT), magnetic resonance imaging (MRI), and positron-emission tomography (PET) scans. As a result, more small nodules harboring early stage thyroid cancers are being detected and treated.

It is well known that there are a substantial proportion of patients that have subclinical thyroid cancer. This subpopulation of patients, if never diagnosed with thyroid cancer, will die of other causes, and the untreated thyroid cancer will not contribute in a negative way to their health or longevity. The idea of a "substantial reservoir" [9] of patients with subclinical thyroid cancer is supported by multiple autopsy studies, most notably that of Harach et al. [15], which demonstrated that 36% of people not known to have thyroid cancer during their lifetime had one or more foci of thyroid cancer at the time of autopsy. The mean diameter of incidentally discovered thyroid cancers in one multicenter study was 1.1 cm [16]. Well-differentiated thyroid cancers less than 1 cm in diameter ("microcarcinomas") have an exceedingly low rate of distant metastatic disease and mortality rates near zero [17]. Those who believe that overdiagnosis is the driver of increasing thyroid cancer incidence point to the evidence that the overall mortality rate for thyroid cancer has remained relatively stable over the same time period (0.5 deaths per 100,000 people) [5, 9]. Critics of the overdiagnosis theory cite the evidence that thyroid cancer mortality has increased in the United States in recent years, with an annual percent change of 0.8% per year from 1992 to 2012 [14]. In the end, it is likely that both a change in the risk profile of the US population and overdiagnosis have contributed to the increase in incidence of thyroid cancer.

What Are the Risk Factors for Developing PTC?

Demographics and Epidemiology of Thyroid Cancer

The probability of malignancy in a thyroid nodule is affected by the patient's age, sex, race, and ethnicity [18, 19]. New nodules identified in patients under 30 years of age or older than 60 have a higher risk of malignancy compared with those arising in the fourth or fifth decade [20]. Approximately 75% of all patients with PTC are women, but a new thyroid nodule found in a male has a higher likelihood of being malignant [19]. Non-Hispanic whites have the highest risk of thyroid cancer by ethnicity, followed by Asian/Pacific Islanders, Hispanics, and non-Hispanic blacks [14].

Thyroid cancers of follicular cell origin comprise the vast majority of thyroid cancers; 85% of cases are PTC, 12% of cases are follicular or Hurthle cell carcinomas, and <3% of cases are poorly differentiated carcinomas [21]. Variants of

PTC exist, including the follicular variant of PTC (FVPTC), and more aggressive variants such as the tall cell variant, columnar variant, insular variant, solid/trabecular variant, and diffuse sclerosing variant. FVPTC and follicular and Hurthle cell carcinomas have been demonstrated to have similar prognoses as classic PTC [22, 23]. Recently, the encapsulated noninvasive variant of FVPTC has been reclassified as noninvasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP) rather than a carcinoma due to its indolent course [24].

Family History

A family history of thyroid cancer or a syndrome associated with the development of thyroid cancer should be specifically sought. Approximately 3–9% of cases of follicular cell-derived thyroid cancers are familial and are inherited in an autosomal dominant pattern. The majority of these are PTCs that are inherited in a non-syndromic fashion. These non-syndromic familial thyroid cancers are referred to as familial non-medullary thyroid cancer (FNMTC). Recent studies from the NIH have identified a putative susceptibility gene (HABP2) [25]; however, at this time there are no clinical genetic tests available. The definition of FNMTC is satisfied when two or more first-degree relatives are found to be affected with the same follicular cell-derived thyroid cancer [26]. There is controversy regarding this definition because the specificity is low. In families with only two relatives with thyroid cancer, there is still a 60% chance that the cancer is sporadic [27]. A stricter definition of FNMTC requiring three or more affected family members yields a higher probability of genetic linkage. For larger kindreds it should be possible to adequately evaluate this risk factor by taking a history, whereas those smaller kindreds with less than two siblings may be impossible to detect. Follicular cell-derived thyroid cancers are also a recognized component of several familial cancer syndromes including familial adenomatous polyposis, Gardner syndrome, Cowden syndrome (PTEN hamartoma tumor syndrome), Carney complex type 1, Werner syndrome (adult progeria), and the DICER1 syndrome.

Radiation History

Radiation exposure in childhood, either from external sources or when ingested, is a risk factor for the development of thyroid cancer. The experience of using radiation for benign conditions in infants and children led to the discovery that a significant exposure to ionizing radiation in childhood, particularly to the head and neck area, is a risk factor for the development of thyroid pathology [28]. In the first half of the twentieth century, many benign childhood conditions were treated with external beam radiation including acne, tinea capitis, ringworm, tonsillitis, and enlarged thymus. Specifically, it was found that there was a higher risk of both benign and malignant thyroid disease in those who received radiation treatments in childhood [29]. The lag phase for the development of thyroid cancer appears to be approximately three decades following the exposure of low-dose external radiation to the head and neck [30]. In one study of over 12,000 survivors of childhood cancer, the risk of developing thyroid cancer was related to the dose of radiation received up to 20 Gy and peaked at 14.6-fold [31]. The risk of cancer appears to be dose dependent, have a linear dose-response curve, and also is dependent upon age of exposure [32]. The greatest risk appears to be for those who were aged 5 or younger at the time of radiation exposure [32–34]. It was later recognized that external beam radiation in childhood is also a risk factor for the development of hyperparathyroidism, salivary tumors, acoustic neuromas, and other neural tumors [35, 36]. Mantle field radiation used for the treatment of Hodgkin's lymphoma and total body irradiation for bone marrow transplantation are also risk factors for the development of thyroid cancer [31, 37]. Several studies have also indicated that patients who received radioactive iodine ablation for hyperthyroidism also have an increased risk of thyroid cancer [38–40]. Following the meltdown at the Chernobyl nuclear reactor in Ukraine in April of 1986, radioactive fallout of iodine (I-131)

led to contamination of the local environment. The incidence of thyroid cancer rose sharply in the following decades, primarily for those individuals who were children living in Belarus, western Russia, and Ukraine at the time of the meltdown [41–44]. The risk of developing thyroid cancer was increased for individuals exposed to nuclear fallout from the Chernobyl meltdown, atmospheric nuclear tests in Nevada in the 1950s, the Marshall Islands nuclear bomb testing, and Hiroshima and Nagasaki atomic bomb survivors [41, 44–47].

Nodular Goiter

The presence of a nodular thyroid has been associated with increased risk of thyroid cancer [16]. The overall rate of incidental thyroid cancer in surgical specimens of patients treated for benign thyroid conditions is 15.6%. Most notably, 17.5% of patients with multinodular goiter harbor incidental thyroid cancer, mostly papillary thyroid carcinoma. Toxic nodular goiter, historically described as having low rates of malignancy, has been more recently described to harbor thyroid cancer in 18.3% of surgical specimens in which malignancy was not suspected [48]. The lowest rate of incidental thyroid cancer (6.1%) is found in patients with nodular Graves' disease [16, 48]. In populations with iodine deficiency, there is a higher risk of endemic goiter and a higher risk of thyroid cancer. Specifically, there are more follicular and anaplastic carcinomas in iodine-deficient populations, whereas there appears to be a higher rate of PTC in populations with high iodine intake [49]. Meta-analysis has also shown PTC to be associated with Hashimoto thyroiditis [50].

Evaluation of Patients with a Thyroid Nodule

History and Physical Examination

The evaluation of a patient with a thyroid nodule should begin with a history and physical examination. A history of significant radiation exposure or a family history of thyroid cancer both increases the risk of thyroid cancer as well as influences the decision regarding the extent of surgery because in either case the entire gland is at risk for the development of cancer. A history of symptoms of possible local invasion including voice hoarseness, progressive dysphagia, dyspnea, or hemoptysis should be sought.

Physical examination has notoriously poor sensitivity and specificity for the detection of thyroid cancer [51]. In addition, many patients with thyroid cancer have no signs or symptoms. Consequently, PTC is often incidentally discovered. The physical examination of a patient with a thyroid nodule should pay particular attention to thyroid gland size, mobility, presence of tracheal deviation, substernal extension, and cervical or supraclavicular lymphadenopathy. Physical exam findings that are worrisome for thyroid cancer include fixation of a thyroid nodule, cervical lymphadenopathy (especially ipsilateral to a thyroid nodule), and vocal cord paralysis (also, particularly when ipsilateral to a thyroid nodule). Approximately 10% of patients with differentiated thyroid cancer present with invasion of local structures, and these patients are at a twofold higher risk of recurrence and have increased mortality rates [22, 52]. Although palpation of the neck nodal basins is routine, physical examination is often unreliable for the detection of abnormal neck lymph nodes. In studies evaluating patients with differentiated thyroid cancer with nonpalpable lymph nodes on physical examination, neck ultrasound detected abnormal lymph nodes in 16–34% of patients [53, 54].

The quality of the speaking voice should be documented in the physical exam. A paralyzed or paretic vocal fold will often manifest as dysphonia; however, a normal voice is no guarantee that vocal fold motion is normal [55]. Up to 8% of patients with thyroid cancer present with a vocal fold paralysis. The majority of these patients will be symptomatic with breathy dysphonia and/or aspiration; however, up to one-third of patients may be completely asymptomatic. Preoperative laryngeal exam is indicated for patients with voice abnormalities, a history of neck or chest surgery during which the recurrent laryngeal or

vagus nerves are at risk for injury, or thyroid cancers with posterior extrathyroidal extension or extensive paratracheal lymph node metastases [21]. Some experts recommend routine laryngeal exam for all patients [56]. The finding of preoperative laryngeal paralysis influences extent of surgery and has medicolegal implications.

Role of Ultrasonography in the Evaluation of Thyroid Nodules

Due to the poor sensitivity and specificity of physical exam for thyroid cancer, ultrasound has become an extension of the physical exam. High-resolution ultrasound is the optimal imaging study for the characterization of the primary thyroid tumor and the status of the regional nodal basins [21]. Ultrasound can detect lesions as small as 1–2 mm within the thyroid and can be used to distinguish cystic from solid, determine blood flow characteristics through Doppler, accurately measure size of lesions, and give information that increase or decrease suspicions for malignancy in a thyroid nodule or cervical lymph node. Recently, ultrasound of the larynx has been found to be an accurate and reproducible method to screen for vocal fold motion abnormalities [57].

Advantages to ultrasound over other imaging modalities include low cost, portability, speed, lack of exposure to radiation, and accessibility to those outside of a radiology department. It is highly operator dependent, however. Compared to cross-sectional imaging modalities (e.g., CT and MRI), ultrasound has a higher sensitivity and specificity and does not require exposure to radiation or placement within uncomfortable confined spaces.

Several sonographic features of thyroid nodules that have a high specificity for PTC have been recognized. PTC usually manifests as a solid nodule, but also is rarely found within the mural component of a predominantly cystic nodule. PTC is usually sonographically hypoechoic, but can also appear isoechoic or hyperechoic. Microcalcifications, or small bright reflectors without reverberation artifact or posterior acoustic shadowing, are commonly seen in both PTC and medullary thyroid cancer. There is considerable interobserver variability in the differentiation of true microcalcifications from other more benign findings of cystic interface or inspissated colloid. The simultaneous detection of a hypoechoic solid nodule with microcalcifications has a high positive predictive value for thyroid cancer [58]. A meta-analysis of 52 observational studies found that the features with the highest specificity for malignancy were nodules taller than wide in axial imaging (i.e., the anteroposterior measurement is greater than the transverse measurement), microcalcifications, or an irregular margin [59].

Fine Needle Aspiration Biopsy

Fine needle aspiration (FNA) biopsy is the first test of choice for thyroid nodules that meet specific size or imaging criteria [21]. FNA biopsy for cytology is highly accurate for the detection of PTC [60, 61]. In 2007 a State of the Science Conference was held at the National Institutes of Health in Bethesda, Maryland, in order to develop consensus guidelines on how to classify cytologic specimens from thyroid FNA biopsies [62]. Briefly, there is a six-tiered scheme for categorizing thyroid FNA results with defined criteria and an associated specific risk of cancer for each category. Expert guidelines detail recommendations for the interpretation and management of cytology results based on these Bethesda categories [21]. A detailed description of the Bethesda categories can be found elsewhere in this text. Furthermore, gene expression classifiers and gene panel tests designed to detect specific DNA mutations and RNA rearrangements in FNA aspirates are commercially available and are also described elsewhere.

Evaluation of Patients with Biopsy-Proven PTC

Laboratory Tests

Measuring thyrotropin (TSH) is useful in the preoperative evaluation of a patient with biopsy-proven PTC. Several studies have demonstrated

that an elevated TSH is an independent risk factor for the development of thyroid cancer [19, 63–66]. Perhaps one of the most interesting findings from these studies is that the risk of thyroid cancer was higher than expected for patients with a TSH at the upper end of the normal range [65, 66]. The lowest risk of thyroid cancer appears to be for patients with a low TSH. Conversely, there is a stepwise linear increase in the risk of thyroid cancer within the population as the TSH rises. TSH levels were found to be significantly higher in patients with stage III and IV thyroid cancer compared to those with stage I and II thyroid cancer in one study [66] and are also associated with the presence of gross extrathyroidal extension and lymph node metastases [67]. It is hypothesized that higher TSH levels affect signaling pathways associated with more aggressive thyroid cancer behavior [67]. Detecting elevated TSH before surgery also impacts the risk of hypothyroidism following lobectomy and also may be an indication for total thyroidectomy. A preoperative diagnosis of hyperthyroidism or hypothyroidism might also influence the timing of surgery because either condition should be managed prior to a general anesthetic.

Expert guidelines clearly state that assessment of serum thyroglobulin (TG) and antithyroglobulin (anti-TG) levels are indicated only in the surveillance of patients with differentiated thyroid cancer and are not sensitive or specific for the diagnosis of thyroid cancer, or the prediction of the stage of disease [21]. TG is a protein made by both thyroid follicular cells and differentiated cancers that arise from follicular cells. The amount of TG circulating in the bloodstream is proportional to the number of benign and well-differentiated malignant follicular thyroid cells present and the status of the TSH receptor on the surfaces of those cells. TG is not specific for thyroid cancer; many benign conditions are associated with an elevation in TG including goiter, thyroiditis, and autoimmune thyroid disease. Approximately 10% of the population has detectable anti-TG antibodies, whereas approximately 20% of patients with PTC have anti-TG antibodies [68, 69]. The presence of anti-TG interferes with the immunometric assay for TG and prevents an accurate measurement of TG [69]. In patients in surveillance for thyroid cancer, the anti-TG titer may be used as a surrogate marker of the amount of TG present, but it may not reliably estimate the true volume of disease [69, 70]. TG is not elaborated by medullary thyroid cancers (MTC) or anaplastic thyroid cancers (ATC) and, therefore, is not useful for monitoring those cancers.

Other laboratory tests have been employed in an attempt to influence the surgical or postoperative management of a patient with PTC, but data supporting their use have been mixed. Some authors have proposed testing for BRAF-V600E mutation status and using this information to decide when to perform prophylactic central neck lymph node dissection, as some studies have shown an association between this mutation and the presence of lymph node metastases [71, 72]. Other studies, however, have not found this association [73, 74], and the most recent version of the American Thyroid Association (ATA) guidelines state that BRAF-V600E mutation status should *not* be used to influence the decision to perform prophylactic central compartment nodal dissection [21].

Screening for hyperparathyroidism is recommended for all patients before thyroidectomy for any indication, since hyperparathyroidism can be addressed at the time of thyroidectomy and may necessitate a bilateral exploration [75].

Imaging Studies in the Patient Diagnosed with PTC: Ultrasound

Because PTC first metastasizes to the cervical lymph nodes, the initial imaging test recommended in the preoperative evaluation of a patient with PTC is cervical ultrasound, which should include the thyroid and both the central and lateral compartments of the neck [21]. Ultrasound can characterize the number, size, location, and appearance of cervical lymph nodes. Under normal circumstances the nodal basins of the lateral neck should appear symmetric. Normal cervical

lymph nodes are usually flattened and elongated, are never cystic, and are usually homogenous. The lymphovascular pedicle can be demonstrated sonographically in most benign lymph nodes and appears as a hyperechoic "fatty" hilum. The following sonographic features of lymph nodes are concerning for metastatic disease: enlarged or rounded shape, loss of the fatty hilum, calcifications, cystic changes, or peripheral vascularity [76–78]. Ultrasound has higher sensitivity for the identification of lateral compartment nodal metastases compared to central compartment nodal metastases. The sensitivity of ultrasound in the central neck is limited by the overlying thyroid gland, the tracheal air shadow, the clavicle, and the sternum [79, 80].

Abnormal lymph nodes should undergo ultrasound-guided FNA biopsy. An adjunct to the cytologic evaluation of an abnormal lymph node is the measurement of lymph node aspirate TG, particularly in cases when the FNA yields an inadequate number of cells for cytologic evaluation or when a sonographically suspicious lymph node has benign cytology [81, 82]. Measurement of TG in a lymph node aspirate can increase the accuracy of cytology (sensitivity of 95% and specificity of 94.5%) and is recommended in expert guidelines, but is not mandatory [60]. Limitations in the use of TG "washouts" include that there is no standardization of this procedure, false positives may occur in patients in whom the thyroid gland is still in place, and circulating anti-TG antibodies can theoretically interfere with the measurement of TG [83].

Additional Imaging Studies in the Patient Diagnosed with PTC: Cross-Sectional Imaging

Cross-sectional imaging tests (e.g., CT, MRI) may also be indicated in the preoperative evaluation of a patient with PTC, particularly when there is a fixed thyroid mass, concern for substernal extension, aerodigestive tract invasion, or bulky lymphadenopathy [21]. CT or MRI generates high-resolution images that can be reconstructed in multiple planes [84, 85] and can therefore display the full extent of the primary tumor and its effect on adjacent structures, including the presence of aerodigestive tract invasion or invasion or encasement of the internal jugular vein or carotid artery. Cross-sectional imaging can also detect lymph node metastases in areas that are poorly assessed by ultrasound (i.e., the retropharyngeal or retrotracheal space and the inferior central neck/superior mediastinum) [85]. Furthermore, technical limitations such as kyphosis, obesity, and other neck pathology may limit the ability of ultrasound to characterize the entire thyroid and cervical nodal basins. CT is the primary modality for the evaluation of lung parenchymal metastases and mediastinal lymphadenopathy. However, these events are sufficiently rare enough that it is not necessary to routinely obtain a CT of the chest for staging thyroid cancer, unless indicated by symptoms or physical exam findings. The main limitation of CT is that the iodine load associated with the intravenous contrast may affect the timing of postoperative radioactive iodine treatment [86, 87]. The main limitation of MRI is that respiratory motion artifact can affect the clarity of the structures in the paratracheal and retrosternal spaces [88].

Additional Imaging Studies in the Patient Diagnosed with PTC: Nuclear Medicine Studies

Approximately 35% of nodules with focal 18-fluorodeoxyglucose (18-FDG) uptake on PET scans are malignant [89]. Despite this fact, 18-FDG PET has not been found to be expedient for the detection of thyroid cancer because many well-differentiated PTCs are not FDG avid. 18-FDG PET is useful in the evaluation of poorly differentiated, recurrent, or radioiodine-negative thyroid cancer. However, its utility in the initial detection of PTC or the preoperative staging of PTC is limited by false positives and decreased specificity [90].

Treatment of PTC: Implications of Tumor Size, Multifocality, and Metastatic Disease

Some patients with small-volume, low-risk cancers are being actively observed as part of research protocols [4]. In addition, some patients with low-volume disease have been treated with forms of lesion-directed therapy such as ethanol ablation, radiofrequency ablation [91], or percutaneous laser ablation [92]. A discussion of protocols used at some institutions for lesion-directed therapy or active observation is outside of the scope of this chapter, and the remainder of this chapter will instead focus on the factors that impact decisions about surgery in patients with biopsy-proven PTC.

Hemithyroidectomy is the preferred extent of surgery for well-differentiated papillary cancer less than 1 cm in diameter that is confined to the thyroid parenchyma in one lobe without overt evidence of metastatic disease [21]. The incidental finding of such a lesion in a hemithyroidectomy specimen, therefore, is usually not an indication for completion thyroidectomy.

Hemithyroidectomy and total thyroidectomy are acceptable surgical procedures for patients with PTC between 1 and 4 cm (T1 or T2 primary tumors) limited to one thyroid lobe, without overt evidence of metastatic disease [21]. This is a change from the previous version of the ATA guidelines, which recommended total thyroidectomy for nearly all PTCs > 1 cm without evidence of lymph node or distant metastases [93]. However, one issue that is not specifically addressed by both the most recent ATA guidelines recommendation and the AJCC staging system for PTC is that of multifocality. PTC is frequently multifocal, occurring in 18–87% of cases, and is usually characterized by a dominant tumor measuring >1 cm, with most of the remaining foci measuring <1 cm [94]. Multifocality has been found to be associated with a higher risk of lymph node metastases and regional recurrence compared to patients with unifocal disease [95–97]. Because contralateral foci of PTC in multifocal PTC are usually <1 cm, they are often an incidental pathologic finding in patients who underwent total thyroidectomy and are usually not identified at the time of initial diagnosis. Nevertheless, hemithyroidectomy is proposed to be adequate treatment for multifocal PTC with a dominant T1–T2 primary tumor, as rates of completion thyroidectomy have been reported to be <10% and recurrences do not appear to impact survival [98–100]. More investigation may be required to clarify the implications of multifocality and to guide clinical care when it is discovered.

Total thyroidectomy is the preferred approach for larger, more aggressive tumors, or tumors with nodal or distant metastases. According to expert guidelines, total thyroidectomy is the recommended approach for patients with primary tumors larger than 4 cm, overt bilobar disease, or clinically evident nodal metastases [21]. Total thyroidectomy may also be the more prudent approach for patients with coexistent thyroid disease such as multinodular goiter or lymphocytic thyroiditis. Patient preference must always be taken into consideration, and a strong preference for total thyroidectomy is recognized as a legitimate indication for bilobar resection. Advanced-stage primary tumors with extrathyroidal extension (clinical T3) or invasion into adjacent structures (clinical T4) should be treated with a planned total thyroidectomy when they are recognized preoperatively. Tumors that extensively invade into the larynx, trachea, esophagus, prevertebral space, or carotid artery require individualized planning and possibly multimodality treatment if the tumor is thought to be resectable [101].

The extent of lymph node dissection for patients with PTC has been debated over the last several decades. Patients with clinically positive lymph nodes in the central or lateral compartment should be treated with a planned total thyroidectomy with appropriate nodal basin clearance (therapeutic central ± lateral neck dissection). The role of prophylactic lymph node dissection, particularly of the central neck, is debated because while studies of routine, prophylactic central and lateral compartment lymph node dissection report high rates of microscopic lymph node metastases (33–63% in the central

neck and 57–64% in the lateral neck), the clinical significance of these subclinical lymph node metastases is controversial [102–105]. Some studies have shown that lymph node metastases are associated with higher rates of disease recurrence and patients who develop disease recurrence have higher rates of cancer-specific mortality, while other studies have demonstrated no impact of regional lymph node metastases on overall survival [106–110]. The most recent version of the ATA guidelines recommends consideration of prophylactic central compartment neck dissection in patients with T3 or T4 primary tumors or clinically involved lateral neck nodes, or if the information would be used to plan postoperative therapy [21].

Conclusion

A strong family history of thyroid cancer; a family or personal history of a syndrome associated with thyroid cancer; a history of significant exposure to radiation, especially in childhood; and a history of an elevated TSH are all well-established risk factors for PTC. When evaluating a patient with a thyroid nodule or newly diagnosed thyroid cancer, risk factors, patient symptoms, physical exam findings, laboratory results, and imaging features must be incorporated into the assessment. Each has implications on the indications for or interpretation of a biopsy, the index of suspicion for thyroid cancer, and the extent of surgery. The optimal endpoint of this practice is a shared decision-making process that incorporates these factors and the patient's desires and leads to the optimal treatment as defined by the patient.

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7 Clinical Presentation and Diagnosis of Follicular Thyroid Cancer

Reese W. Randle and Rebecca S. Sippel

Abbreviations

ATA	American Thyroid Association
BMI	Body mass index
CT	Computed tomography
FTC	Follicular thyroid cancer
PET	Positron emission tomography
SEER	Surveillance, Epidemiology, and End Results
TSH	Thyroid-stimulating hormone

Epidemiology

Overall, thyroid cancer is increasing in incidence at a steady rate [1, 2]. In 2016, an estimated 64,300 new cases of thyroid cancer will be diagnosed in the United States alone and result in about 1980 deaths [3]. While papillary thyroid cancer remains the most common type of thyroid cancer, FTC is estimated to account for 5–15% of well-differentiated thyroid cancers but can be higher in iodine-deficient areas [4, 5]. Most of the observed increase in thyroid cancer incidence is due to papillary thyroid cancer, but the incidence of FTC is also increasing albeit slightly, now occurring in just over 1 in 100,000 population [1]. Increased detection alone cannot explain this increase as primary tumors of all sizes seem to be increasing [6, 7]. Furthermore, at least in women, the incidence of regional disease is increasing at a greater rate than local disease [6].

R.W. Randle, M.D. • R.S. Sippel, M.D. (✉)
Section of Endocrine Surgery, Department of Surgery, University of Wisconsin, 600 Highland Avenue/K3/704 CSC, Madison, WI 53792, USA
e-mail: sippel@surgery.wisc.edu

Risk Factors

Most cases of FTC arise sporadically without clear evidence of an inciting cause, but several risk factors have been identified. In general, risk factors for well-differentiated thyroid cancers include a history of ionizing radiation and a positive family history. Known risks for the development of FTC specifically include ionizing radiation [8–10], iodine deficiency [11], certain genetic disorders [12, 13], and obesity [14].

Ionizing Radiation

Ionizing radiation is a well-known risk factor for well-differentiated thyroid cancer, and FTC is no exception [8, 9]. Children living in Ukraine near the Chernobyl Nuclear Power Plant during the nuclear accident in 1986 were more likely to develop thyroid cancer than age-matched children in Italy and France. About 5% of the cancers in Ukrainian children were follicular [10]. Another

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study has shown that the latency period between radiation exposure and clinically evident tumors averaged about 20 years for FTCs. Interestingly, the same study showed a longer latency period of 36.5 years for follicular adenomas [8].

Iodine Deficiency

Iodine deficiency is another risk factor for FTC but not for other well-differentiated thyroid cancers. This finding is based upon both animal- and population-based studies. Rats fed with iodine-deficient diets developed thyroid tumors at rates ranging from 54 to 100%, and many of these tumors were follicular adenomas or follicular cancers [11]. One study in rats demonstrated that low-dose ionizing radiation did not lead to cancer development in rats with normal iodine intake, but the low-dose radiation was carcinogenic in rats fed with iodine-deficient diets [15]. According to population-based data, the ratio of papillary thyroid cancer to FTC increased when iodinated salt was introduced in Austria [16], Spain [17], Switzerland [18], and Argentina [19]. While these data might be explained by increasing incidence of papillary thyroid cancer, most suggest that the papillary-to-follicular ratios increased because FTC decreased in incidence.

Genetic Disorders

While most cases of FTC are sporadic, they can be associated with genetic syndromes. The two most common of these disorders are Carney complex and Cowden syndrome. Carney complex, often considered a multiple endocrine neoplasia syndrome, is an autosomal dominant syndrome characterized by spotty skin pigmentation, cardiac myxomas, and various endocrine tumors both benign and malignant [20]. Thyroid nodules occur in the majority of patients and can represent follicular or papillary thyroid cancers [12]. Cowden syndrome, also inherited in an autosomal dominant fashion, is often associated with a mutation in the tumor suppressor gene, PTEN [21]. Characteristics of Cowden syndrome include goiters, fibrocystic breast disease, gastrointestinal polyps, lipomas, and macrocephaly [22, 23]. Although thyroid cancer only actually develops in a minority of people with Cowden syndrome, the risk of developing a well-differentiated thyroid cancer is about 10% greater than the general population [13, 23]. Additionally, FTC is considered one of the major clinical criteria in the diagnosis of Cowden syndrome [13].

Obesity

Obesity is implicated in increasing the risk for many carcinomas. For the thyroid, obesity has been associated with an increased risk of papillary, anaplastic, and follicular cancers. In one study, patients with a body mass index (BMI) 30 or greater had 1.6 times the risk of developing FTC than patients with a normal BMI (18.5–24.9) [14].

Clinical Presentation

FTC affects patients of any age, but the median age at diagnosis is about 50 years of age, which is slightly older than the median age for papillary thyroid cancer (about 44 years) [24, 25]. Like papillary thyroid cancer, there is a female predominance although the ratio of females to males with disease ranges from 2.2 to 2.6, less than that of papillary thyroid cancer which is a little greater than 3 to 1 [6, 24]. Most patients are Caucasian (79%) with African Americans constituting only about 10% of cases (Table 7.1) [24].

Table 7.1 Characteristics of patients with follicular thyroid cancer [6, 24, 25]

Median age	~50 years
Female-to-male ratio	~2.2–2.6 to 1
Ethnicity	
Caucasian	79%
African American	10%
Other	11%
Risk factors	Ionizing radiation, iodine deficiency, Carney complex, Cowden syndrome, obesity

Clinical Symptoms

Most FTCs will present initially as thyroid nodules. While large nodules may be symptomatic, many are identified on routine physical exam or incidentally on imaging for other reasons. Larger lesions are more likely to be symptomatic and may cause symptoms of mass effect such as dysphagia, voice changes, globus sensation, or choking sensation. FTC may be more likely to cause many of these symptoms [25]. The reason for increased symptoms in FTC relative to similarly sized and placed benign nodules is not entirely clear, but cancers are likely to have a faster growth rate and be denser than benign nodules. Besides these contributing factors, extra-thyroidal extension can account for symptoms when the cancer invades the recurrent laryngeal nerve, esophagus, trachea, or surrounding musculature. Because of a propensity for hematogenous spread over lymphatic spread, patients will rarely present with bulky nodal disease. Some patients with FTC will present with distant metastases to the skeleton, lungs, brain, or liver [26, 27]. In these cases, symptoms at presentation are often dictated by the location of the metastases.

Incidental Presentation

Small FTCs confined to the thyroid are generally asymptomatic and only identified incidentally. Such cancers may be discovered incidentally on any imaging modality that includes the neck with the most common being ultrasound, computed tomography (CT), magnetic resonance imaging, and positron emission tomography (PET). While dedicated review of cross-sectional imaging indicates that up to 10% of patients have incidental thyroid nodules, most of these are not actually reported in the radiology report [28]. Less than half of reported nodules receive an actual workup [28, 29]. Most of those biopsied are benign, but about 7% of those reported end up being malignant [28]. Follicular lesions, including FTC, have also been incidentally identified on more specialized imaging including Ga-68 prostate-specific membrane antigen PET/CT scans, Tc-sestamibi scans, (111)ln-pentetreotide scans, and (99m) Tc-tetrofosmin cardiac scans [30–32].

Diagnosis

The diagnosis of FTC requires one of two pathologic findings: invasion of the tumor capsule or invasion of the tumor vasculature. Without identification of either of these two features, a cancer diagnosis cannot be made. For this reason, and unlike papillary thyroid cancer, cytology is insufficient to distinguish between benign and malignant follicular lesions. Cytology may simply demonstrate normal-appearing follicular cells. Therefore, most FTCs are initially classified as indeterminate. Molecular testing may play a role in further characterizing indeterminate thyroid nodules based on their risk of malignancy. The role of molecular testing for follicular neoplasms is the subject of a previous chapter. Ultimately, about a third of follicular neoplasms are actually a cancer [33].

Not all follicular-appearing thyroid cancers represent a true diagnosis of FTC (Table 7.2). Some papillary thyroid cancers, namely, follicular-variant papillary thyroid cancer, appear to have a follicular architecture but contain cells with nuclear features characteristic of classic papillary thyroid cancer [34]. Historically, this variant of papillary cancer was frequently misclassified as FTC. More appropriate classification of the follicular variant of papillary thyroid cancer as papillary cancer may partially contribute to the fact that the incidence of FTC is not increasing as rapidly as papillary thyroid cancer. Although their behavior is intermediate between that of papillary thyroid cancer and FTC, they behave more like conventional papillary thyroid cancer [24]. Dissimilar to FTC, capsular or vascular invasion is not required for a diagnosis, but now encapsulated follicular-variant papillary thyroid cancer is being reclassified because of its remarkably indolent nature. In fact, the nomenclature of this tumor is changing to avoid overtreatment, and encapsulated follicular variant of papillary thyroid cancer should now be called non-invasive follicular thyroid neoplasm with papillary-like nuclear features or "NIFTP" [35].

Table 7.2 Distinguishing characteristics of select follicular lesions

	Follicular thyroid cancer	Minimally invasive follicular thyroid cancer	Follicular-variant papillary thyroid cancer	Noninvasive follicular thyroid neoplasm with papillary-like nuclear features	Hürthle cell thyroid cancer
Alternate nomenclature	–	–	–	Encapsulated follicular-variant papillary thyroid cancer	Oncocytic or oxyphilic cell cancer
Histologic findings	Follicular tumor with invasion of the tumor capsule or tumor vasculature	Follicular tumor with only minimal invasion into but not through the tumor capsule	Follicular lesion containing cells with nuclear features similar to those of papillary thyroid cancer	Entirely encapsulated lesions with follicular architecture and nuclear features of papillary thyroid cancer	Variant of follicular lesion containing large cells with abundant acidophilic cytoplasm
Mode of dissemination	Primarily hematologic	Metastases are rare	Primarily lymphatic	Considered extremely low risk for spread	Primarily hematologic

Another important consideration in the diagnosis of FTC centers on the classification of Hürthle cell thyroid cancer. Much debate exists about how to classify Hürthle cell (or oncocytic or oxyphilic cell) tumors [36]. Although often considered a variant of FTC, Hürthle cell cancer has many unique features that separate them from the other well-differentiated thyroid cancers [5]. Hürthle cancer will be discussed in more detail in a later chapter.

Staging and Prognosis

Although the prognosis for both types of well-differentiated thyroid cancer is relatively favorable, patients with FTC experience slightly worse survival than patients with papillary thyroid cancer [24, 27, 37–42]. Despite this fact, many studies evaluating the prognosis of patients with well-differentiated thyroid cancers often group FTC together with papillary thyroid cancer. Since the prevalence of papillary cancer is much greater than FTC, these studies generally present results that are skewed toward outcomes of patients with papillary thyroid cancer. Overall, patients with FTC experience 5-year survival ranging from 71 to 94% and 10-year survival ranging from 43 to 95% [4, 24, 43–47].

The most commonly used staging system for FTC is the TNM staging system published by the American Joint Committee on Cancer, and staging for FTC in this schema is identical to that for papillary thyroid cancer (Table 7.3) [48]. One of the unique features of this TNM staging system is the inclusion of an age as a staging variable. For instance, patients under 45 years of age cannot be staged greater than stage II at diagnosis even with metastatic disease. Even though the inclusion of patient age into the staging system results primarily from outcomes in papillary thyroid cancer, younger age is associated with improved survival in FTC as well [39, 43–47, 49, 50].

Besides age, other prognostic factors for FTC include the size of the primary tumor [39, 47], the presence of any or marked vascular invasion [45, 46], the degree of invasion [44, 49, 51], the presence of metastatic disease [43, 46, 50], and incomplete resection [50]. Vascular invasion is considered one of the strongest prognostic factors for FTC. The 2015 American Thyroid Association (ATA) management guidelines for adults with differentiated thyroid cancer have modified the risk stratification of FTC within the context of other differentiated thyroid cancers [52, 53]. According to the new stratification system and reflecting the importance of vascular invasion in the prognosis of FTC, well-differentiated, intrathyroidal FTC is classified as either “low risk” or “high risk” based on the degree of vascular invasion with four foci of vascular invasion being the cutoff between the two [53]. Once FTCs contain

Table 7.3 TNM staging for follicular thyroid cancer

Primary tumor (*T*)—*Note:* All categories may be subdivided: (s) solitary tumor and (m) multifocal tumor (the largest determines the classification)			
TX	Primary tumor cannot be assessed		
T0	No evidence of primary tumor		
T1	Tumor 2 cm or less in greatest dimension limited to the thyroid		
T1a	Tumor 1 cm or less, limited to the thyroid		
T1b	Tumor more than 1 cm but not more than 2 cm in greatest dimension, limited to the thyroid		
T2	Tumor more than 2 cm but not more than 4 cm in greatest dimension limited to the thyroid		
T3	Tumor more than 4 cm in greatest dimension limited to the thyroid or any tumor with minimal extrathyroidal extension (e.g., extension to sternothyroid muscle or perithyroid soft tissues)		
T4a	Moderately advanced disease		
	Tumor of any size extending beyond the thyroid capsule to invade subcutaneous soft tissues, larynx, trachea, esophagus, or recurrent laryngeal nerve		
T4b	Very advanced disease		
	Tumor invades prevertebral fascia or encases carotid artery or mediastinal vessels		
Regional lymph nodes (*N*)—Regional lymph nodes are the central compartment, lateral cervical, and upper mediastinal lymph nodes			
NX	Regional lymph nodes cannot be assessed		
N0	No regional lymph node metastasis		
N1	Regional lymph node metastasis		
N1a	Metastasis to level VI (pretracheal, paratracheal, and prelaryngeal/Delphian lymph nodes)		
N1b	Metastasis to unilateral, bilateral, or contralateral cervical (levels I, II, III, IV, or V) or retropharyngeal or superior mediastinal lymph nodes (level VII)		
Distant metastasis (M)			
M0	No distant metastasis		
M1	Distant metastasis		
Under 45 years			
Stage I	Any T	Any N	M0
Stage II	Any T	Any N	M1
45 years and older			
Stage I	T1	N0	M0
Stage II	T2	N0	M0
Stage III	T3	N0	M0
	T1	N1a	M0
	T2	N1a	M0
	T3	N1a	M0
Stage IVA	T4a	N0	M0
	T4a	N1a	M0
	T1	N1b	M0
	T2	N1b	M0
	T3	N1b	M0
	T4a	N1b	M0
Stage IVB	T4b	Any N	M0
Stage IVC	Any T	Any N	M1

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more than four foci of vascular invasion or tumor extension beyond the capsule, patients begin to experience worse outcomes.[47, 54–58] Part of the rational for this distinction comes from the fact that FTCs with extensive vascular invasion are associated with distant metastatic disease in up to 55% of cases [55, 57–59].

Also according to the ATA risk stratification, the extent of regional nodal involvement separates well-differentiated cancers between the intermediate and high-risk categories. This classification is likely dominated by the inclusion of papillary thyroid cancers as nodal involvement is not necessarily a prognostic indicator in FTC [50]. Other ATA "high-risk" tumor characteristics include gross extrathyroidal extension, incomplete tumor resection, and evidence of distant metastatic disease. Tumors with minimal invasion into the surrounding soft tissues are considered intermediate risk [53].

Several other risk stratification systems can predict prognosis for patients with FTC [60–63]. These are discussed in detail in Chap. 16. Although each of these risk schemes includes prognostic indicators for FTC and can all predict disease specific survival for FTC, the AJCC TNM staging system is the best and most commonly used predictor of survival [50].

Minimally Invasive Follicular Thyroid Cancer

Minimally invasive FTC is defined as encapsulated FTC with only minimal capsular invasion. Some debate exists regarding whether or not encapsulated FTCs with less than four foci of vascular invasion should be considered minimally invasive FTCs [64]. Those with only minimal capsular invasion have a 7% or less chance of recurrence [54, 57, 65]. Even with a small number of vessels invaded within the capsule, a well-differentiated, encapsulated FTC has a recurrence rate of only up to about 5% [55, 56]. Furthermore, not all studies have correlated worse outcomes with tumor extension beyond the tumor capsule or with more than four foci of vascular invasion [50, 54]. Nevertheless, minimally invasive FTCs (assuming tumor size less than 4 cm) are considered low risk, and the ATA guidelines suggest that a thyroid lobectomy alone is sufficient for these cancers [53]. Despite the extremely favorable prognosis of minimally invasive FTCs, three out of four patients will receive a total thyroidectomy, and more than half will be treated with radioactive iodine [64].

Stage at Diagnosis

According to a population-based study using the Surveillance, Epidemiology, and End Results (SEER) registry from 1980 to 2009 [6], most FTCs are confined to the thyroid at diagnosis, and only a small proportion will present with distant metastatic disease. Overall, 52% of patients present with local disease, 38% with regional disease (including cervical nodal disease and extrathyroidal extension), and 7% with distant metastatic disease. Tumors greater than 4 cm constitute the greatest proportion of tumors (42%) at presentation. Follicular thyroid microcarcinomas (0–1 cm in diameter) make up less than 6% of tumors at diagnosis; tumors greater than 1 cm but no more than 2 cm constitute 17%, and those greater than 2 cm but no more than 4 cm constitute 36% [6].

Interestingly, a greater proportion of diagnoses are occurring with larger primary tumors now than they were in the 1980s [6]. These data coupled with the incredibly low incidence of tumors 1 cm or less suggest that the incidental discovery of microcarcinomas on final pathologic review accounts for very little if any of the observed increase in FTC incidence.

Another study using the SEER registry from 1988 to 2007 identified regional nodal metastases in only 2% of patients with tumors greater than 1 cm, further emphasizing the difference in the spread of FTC relative to papillary thyroid cancer [24]. Vascular invasion resulting in hematogenous spread likely explains how distant disease can be observed more often than regional nodal disease. The rate of distant disease in this particular study was 4%, twice that of regional disease [24].

Evaluation

Evaluation of the Primary Tumor

Once a thyroid nodule is diagnosed either clinically or incidentally, a dedicated ultrasound and a thyroid-stimulating hormone (TSH) level should be obtained. Hyper-functioning nodules, suspected based on a suppressed TSH and confirmed with a thyroid uptake scan, are rarely malignant. On dedicated ultrasound, characteristics of the nodule including size, shape, echogenicity, borders, calcifications, and vascularity should be noted (Fig. 7.1). Follicular lesions often appear hypervascular although ultrasound cannot distinguish between benign and malignant follicular lesions when lesions are contained within the thyroid. However, biopsy-proven follicular lesions with a hypervascular protrusion extending beyond the border of the thyroid are highly suggestive of FTC [66].

If the nodule meets the size threshold for biopsy, usually 1.5 cm for nodules without suspicious ultrasound findings or 1 cm for nodules with suspicious findings, a fine needle aspirate (FNA) should be obtained for cytologic examination [53]. This can categorize the nodule into several different categories according the Bethesda system [67]. With a good sample of cells, FTCs will give an indeterminate result, usually either

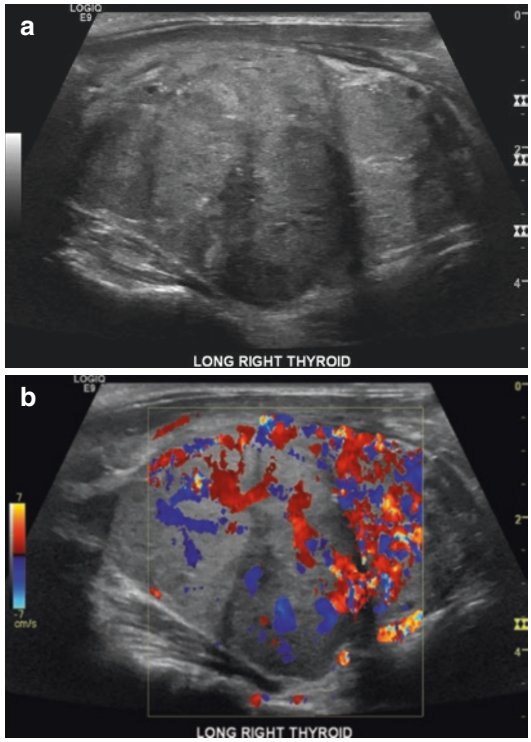

Fig. 7.1 Thyroid ultrasound showing follicular thyroid cancer. This figure demonstrates a large solid nodule with some microcalcifications and irregular borders (**a**) and increased internal vascularity (**b**). Cytology from fine needle aspiration was consistent with a follicular neoplasm. Ultimately, thyroidectomy revealed a 3.5 cm follicular thyroid cancer with three foci of vascular invasion

follicular lesion of undetermined significance or follicular neoplasms (Bethesda categories III and IV, respectively). Since follicular neoplasms are hypervascular and hypervascularity is a suspicious ultrasound finding, most follicular lesions meet the criteria for FNA biopsy at 1 cm.

Limitations of Biopsy

It is important to note that FNA biopsy cannot distinguish between benign and malignant follicular lesions since the diagnosis of cancer requires demonstrating invasion of the capsule or the vasculature. This limitation is unique to FTC relative to papillary thyroid cancer where the cells display enough characteristic nuclear findings to solidify a diagnosis. Due to the relatively small sample that results from a core needle biopsy, this technique generally offers no advantage over FNA and may be more painful and create more scar tissue. Another limitation of FNA biopsy for FTC results from their hypervascular nature. Occasionally, follicular neoplasms, including FTCs, will give non-diagnostic results when needle aspirates contain mostly blood. Non-diagnostic biopsies cannot be used to determine malignancy, so when they are obtained, re-biopsy or diagnostic lobectomy is required. If the FNA is non-diagnostic because there are too many blood cells within the specimen, repeat biopsy with the head elevated to decrease blood flow to the nodule may improve results. Alternatively, ultrasound guidance can also help to avoid biopsy of the more vascular areas within the nodule.

Evaluation of Regional Lymph Nodes

A thorough evaluation of the cervical lymph nodes should be a component of any evaluation of a thyroid nodule. Palpation can be helpful, but ultrasound is the main tool used to evaluate the lymph nodes. A dedicated examination of both the central and the ipsilateral lateral nodal compartments is an essential component of any neck ultrasound where a thyroid nodule is being characterized. Even though nodal disease is rare in FTC, many follicular lesions actually represent the follicular variant of papillary thyroid cancer where nodal involvement at presentation is common. Concerning lymph nodes may appear large, round, hypoechoic, or cystic and may have calcifications or lose their fatty hilum. Any concerning lymph nodes can be FNA biopsied once they hit a size threshold of about 7–8 mm. The presence of thyroid cells (even if benign appearing) or thyroglobulin on washout confirms a cancer diagnosis, but may not be able to distinguish the histologic type.

Evaluation of Metastatic Disease

Because the diagnosis of FTC is made only after surgery and final pathologic examination, a

metastatic workup preoperatively is impractical unless there is a very high suspicion of cancer. Preoperative thyroglobulin levels greater than 5000 ng/mL correlate with metastatic disease and might prompt chest imaging prior to thyroidectomy [68]. Postoperatively, thyroglobulin levels can be helpful in determining the presence of follicular cells if a total thyroidectomy was performed, although this lab value cannot distinguish between a benign remnant and residual disease. Thyroglobulin normally nadirs about 4–6 weeks following surgery; therefore, checking a level less than a month following surgery may be misleading. If the thyroglobulin is elevated, additional imaging of the neck with an ultrasound or CT scan may be indicated to localize disease that may be removed before pursuing radioactive iodine. Radioactive iodine uptake scans will allow the visualization of sites of distant metastases, but is only effective following a total thyroidectomy. Additionally, radioactive iodine is most useful in situations where all gross disease has been removed from the neck prior to its administration.

Treatment

Planning a treatment strategy preoperatively suffers the same practical difficulty as the preoperative evaluation given that a diagnosis can only be confirmed with a surgical specimen. Additionally, because risk stratification often requires identification of the amount of vascular invasion, risk categories are difficult to assign until the primary tumor has been removed.

Once a diagnosis is made, a treatment plan can be formulated. If the initial surgery was a diagnostic lobectomy, discussions ensue about the need to perform a completion thyroidectomy and then about whether radioactive iodine is needed. Currently, about half of the FTCs in the United States are treated with radioactive iodine [24]. Risk stratification can help guide these decisions, but the ultimate treatment course often depends on the patient's own values and anxiety. The derivation of FTC from thyroid follicular cells allows TSH suppression with thyroid hormone replacement to serve as an adjunctive therapy preventing undue stimulation of any remaining cancer cells to grow. The roles of surgery, radioactive iodine, and TSH suppression for differentiated thyroid cancer will be discussed in much greater detail in later chapters.

Even with successful treatment of FTC, surveillance for recurrence should continue for 3–5 years for low-risk lesions or indefinitely for high-risk lesions [5]. Thyroglobulin is helpful in this scenario especially following total thyroidectomy and remnant ablation with radioactive iodine. Cervical ultrasonography also plays a vital role in identifying recurrence and should be performed annually regardless of thyroglobulin levels. Surveillance following treatment for thyroid cancer will also be discussed in more detail in a later chapter.

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8 Clinical Presentation and Diagnosis of Hürthle Cell Thyroid Cancer

Benjamin Gigliotti and Sareh Parangi

Hürthle cell carcinoma (HCC) is a rare thyroid malignancy of follicular cell origin and represents approximately 3–5% of well-differentiated thyroid cancers [1, 2]. The classification, behavior, and prognosis of HCC have been widely debated over the last century owing to its variable presentation and natural history. The presence of Hürthle cells in many benign thyroid conditions and identification of both Hürthle cell adenomas and carcinomas have created unique challenges in histologic diagnosis. While some organizations classify HCC as an oxyphilic/oncocytic variant of follicular thyroid cancer (FTC), others have considered it as a unique subtype of differentiated thyroid cancer, especially with the advent of modern gene profiling methods [3, 4]. Historically, HCC has been described as a more aggressive variant due to its proclivity for metastasizing to regional lymph nodes and distant sites with low avidity for radioactive iodine, as well as higher associated mortality [5]. However, more recent population-based and single-institution studies using current standards of care have shown similar survival compared to FTC after adjusting for stage of disease [6, 7].

B. Gigliotti, M.D.
Division of Endocrinology, Department of Medicine, Massachusetts General Hospital,
55 Fruit Street, Boston, MA 02114, USA

S. Parangi, M.D. (✉)
Division of Endocrine Surgery, Department of General and Gastrointestinal Surgery, Massachusetts General Hospital, Harvard Medical School,
15 Parkman Street, Boston, MA 02114, USA
e-mail: sparangi@partners.org

Clinical Presentation

The most common presentation of HCC is a solitary painless thyroid nodule in a euthyroid patient. The average age at diagnosis is roughly 60 years, several years older than that of FTC and roughly a decade older than that of papillary thyroid carcinoma (PTC). Women outnumber men by 2–3 to 1, although some authors suggest that Hürthle cell neoplasms are more common in women, while HCC is more common in men [8, 9]. There is marked geographic variability in the relative frequency of differentiated thyroid cancer, and HCC is more common in areas of iodine sufficiency, similar to PTC and in contrast to FTC [10]. At diagnosis, the average tumor size of HCC is larger than that of PTC, and the majority of patients have pTNM stage II disease. Although the presentation as a solitary nodule is most common, HCC is more likely than FTC to be multifocal and up to 20% of patients have concomitant PTC. Approximately 5–15% of patients have regional nodal metastases, and 5–20% of patients have distant metastases (most commonly to the bone, liver, and lungs) at diagnosis owing to its proclivity for both lymphatic and hematogenous

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dissemination. While these figures are a representative average across several case series, it is important to note that there are wide ranges for each parameter, and more recent studies suggest that identification of multiple subtypes or mimics account for the wide variability [11–15].

Risk Factors

Risk factors for HCC are similar to other well-differentiated thyroid cancers and include a personal history of radiation exposure and family history of thyroid cancer. Iodine excess shifts the relative risk toward HCC rather than FTC. While the aforementioned risk factors are present for patients with both Hürthle cell neoplasms and HCC, tumor size is an independent predictor of carcinoma. In one study, tumors greater than 4 cm in size were associated with a 65% risk of malignancy, compared to a 17% risk of malignancy for tumors 1 cm or less [16]. Age has been variably associated with an increased risk of carcinoma compared to adenoma, with a suggestion that patients greater than 60 years of age have an increased risk of HCC [17]. An autosomal dominant syndrome due to a mutation in chromosome 19p13.2 has been described in a French family with oxyphilic thyroid tumors [18].

Pathology

Hürthle (or Askanazy) cells were originally described in 1898 by Max Askanazy, a German-Swiss pathologist who first noted their presence in Graves' disease [19]. Their discovery has been mistakenly attributed to Karl Hürthle who, in fact, described what we now consider to be parafollicular C cells [20]. Hürthle cells are large "swollen" follicular-origin epithelial cells characterized by their abundant, intensely eosinophilic, and granular cytoplasm; they typically contain a hyperchromatic nucleus with a very prominent nucleolus (Fig. 8.1) [21]. Electron microscopy has revealed that their granularity is due to abundant cytoplasmic mitochondria which often show inclusions and dense core granules,

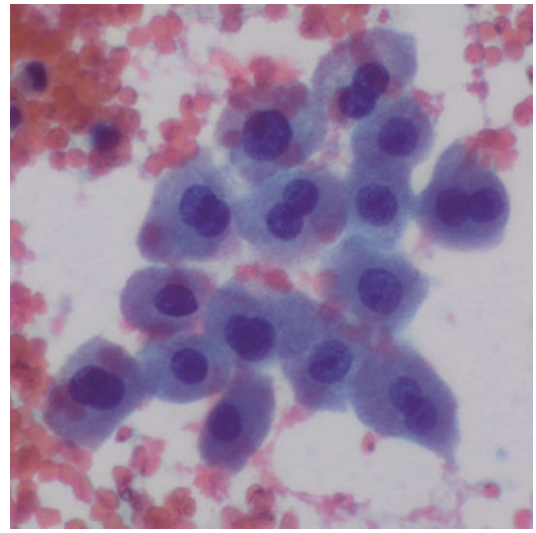

Fig. 8.1 High-power view of cytology obtained by ultrasound-guided fine needle aspiration biopsy of the thyroid, demonstrating characteristic Hürthle cells with markedly eosinophilic granular cytoplasm, and round hyperchromatic nuclei containing prominent nucleoli. Photomicrograph provided by Dr. Sheida Sharifi

which likely accumulate due to reduced mitochondrial activity from point mutations and deletions in mitochondrial DNA [22]. In the literature, many descriptive terms have been used for their morphology including "oncocytic" and "oxyphilic." Hürthle cells have been described in benign thyroid diseases including chronic lymphocytic (Hashimoto's) thyroiditis, Graves' disease, multinodular goiter, and in patients with prior neck radiation, chemotherapy, and/or advanced age. Their presence is nonspecific and must be interpreted in the context of their frequency, organization, and the presence of other cell types. While the presence of Hürthle cells in a background of lymphocytes and plasma cells is diagnostic of Hashimoto's thyroiditis, their presence in a fully encapsulated nodule with angioinvasion suggests malignancy.

Diagnosis

Hürthle cell neoplasms are microscopically defined by 75% or more of the cells having Hürthle cell morphology. Inspection of gross

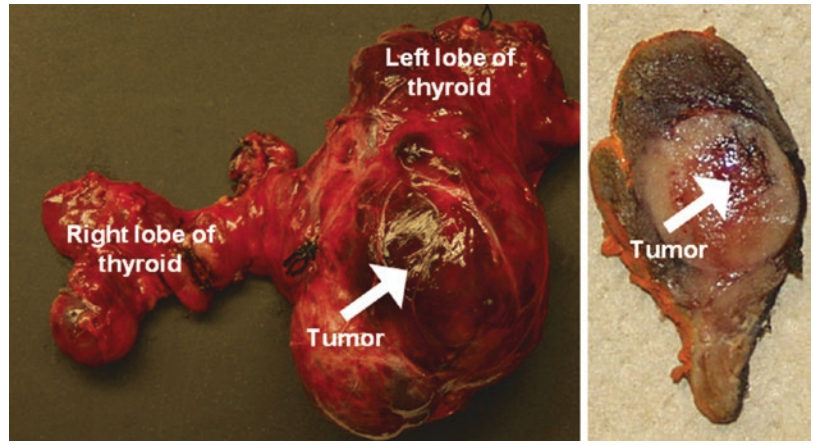

Fig. 8.2 Gross pathology specimen from a patient who underwent total thyroidectomy, showing a large Hürthle cell tumor in the left thyroid lobe with distinctive "mahogany" brown discoloration, hemorrhage, and necrosis. Photograph provided by Dr. Sheida Sharifi

surgical specimens reveals encapsulated nodules of varied size with a mahogany brown color due to plentiful cytochrome-containing mitochondria (Fig. 8.2). Hemorrhage is common, as is the identification of a central scar. Hürthle cell neoplasms may be benign or malignant, and the incidence of malignancy has been widely debated in the early thyroid literature. It is now clear that the significant heterogeneity in the behavior of various Hürthle cell neoplasms is due to the presence of distinct subtypes. The combination of molecular techniques and assessment for encapsulation and capsular/vascular/angioinvasion allows differentiation into specific entities including Hürthle cell adenoma, HCC, and oncocytic or "look-alike" (e.g., tall cell variant of PTC) variants of papillary and medullary carcinoma [21].

Malignant Hürthle cell tumors are characterized by the presence of capsular invasion, vascular invasion, or angioinvasion, which are absent in Hürthle cell adenoma (Fig. 8.3) [23, 24]. Consequently, fine needle aspiration biopsy of the thyroid is not able to differentiate benignity from malignancy. The presence of peri-thyroidal invasion or distant metastases also helps make this distinction. Atypical nuclei, necrosis, hemorrhage, and infarction may be seen in both benign and malignant lesions. Similar to FTC, HCC can be further subclassified as minimally or widely invasive. Specific definition of minimally invasive HCC has been controversial; a commonly accepted definition includes the presence of focal invasion into and/or through the capsule without vascular invasion and has been shown to predict less aggressive behavior (Fig. 8.4). The presence of four or more foci of vascular invasion, along with tumor size greater than 4 cm, the presence of mitosis, and a solid/trabecular growth pattern have all been shown to be predictive of reduced recurrence-free survival [25]. Widely invasive tumors have extensive capsular and vascular invasion, usually along with extra-thyroidal extension (Fig. 8.5).

Cytogenetics

Since the advent of modern cytogenetic testing methods, distinct molecular and genetic profiles have been identified in subtypes of well-differentiated thyroid cancer. Mutations and large deletions in mitochondrial DNA and/or in genes responsible for mitochondrial DNA maintenance (e.g., *ATPase6*) are significantly enriched in HCC compared to non-Hürthle cell neoplasms; this provides a potential explanation for the large numbers of mitochondria seen with ultrastructural analysis. Missense mutations in *GRIM19*, a negative regulator of cell growth and modulator of mitochondrial metabolism located at 19p13.2 (the same locus implicated in the genetic syndrome discussed above), are enriched in sporadic HCC [26]. Chromosomal gains in cyclin D1 and p53 gene loci identified with inter-phase florescence in situ hybridization are also more commonly seen in HCC [27, 28]. These techniques

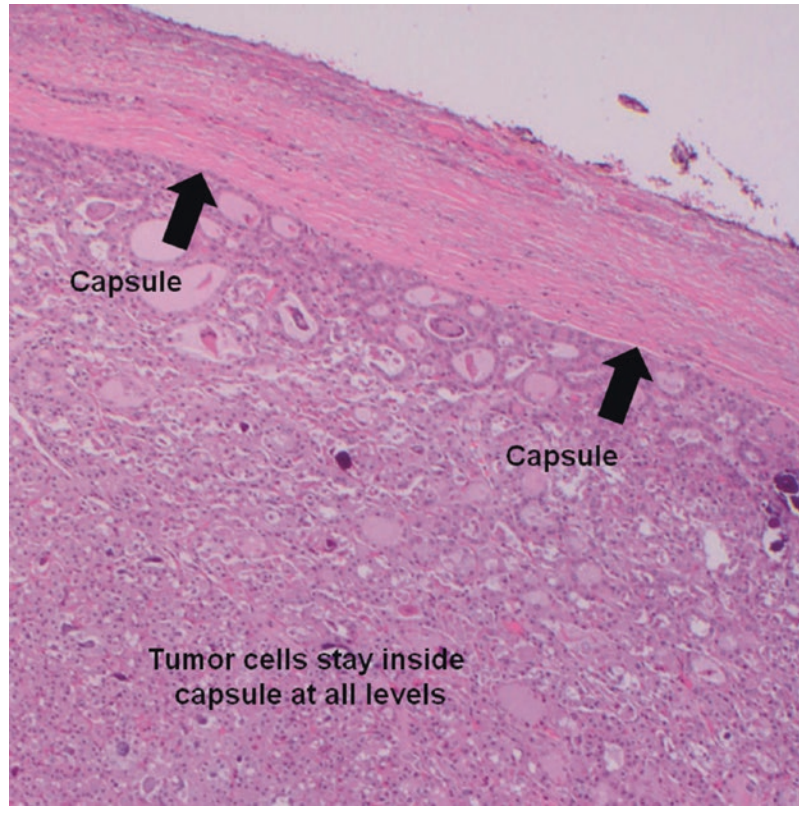

Fig. 8.3 Low-power view of thyroid surgical pathology specimen revealing abundant Hürthle cells with a fully intact fibrous capsule and no evidence of angio- or lymphovascular invasion, consistent with a Hürthle cell adenoma. Photomicrograph provided by Dr. Sheida Sharifi

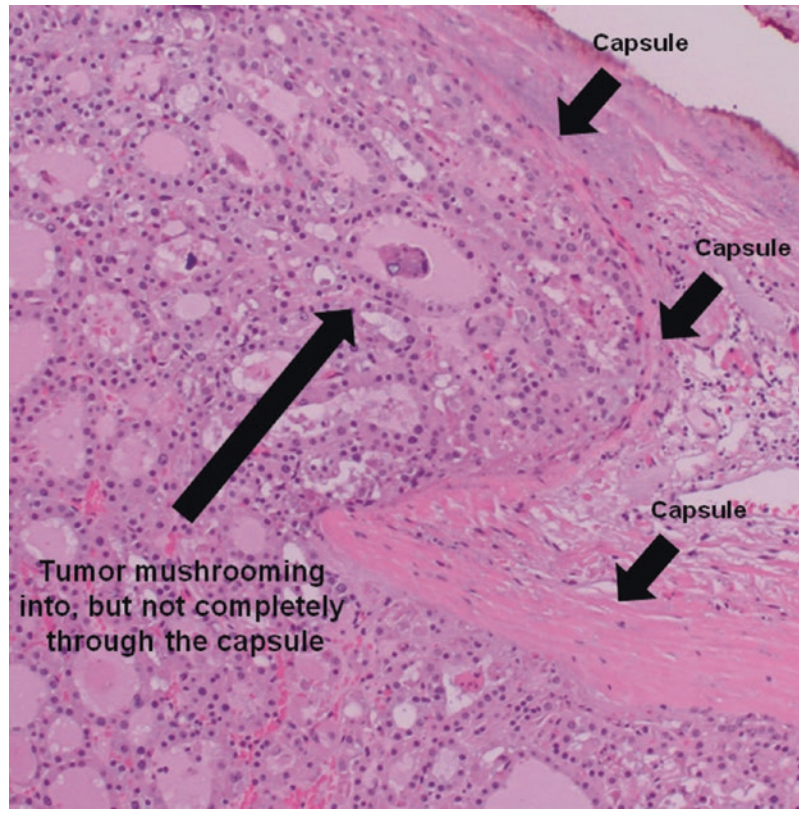

Fig. 8.4 Low-power view of thyroid surgical pathology specimen revealing abundant Hürthle cells extending into but not fully through the capsule with no foci of angio- or lymphovascular invasion, consistent with a minimally invasive Hürthle cell carcinoma. Photomicrograph provided by Dr. Sheida Sharifi

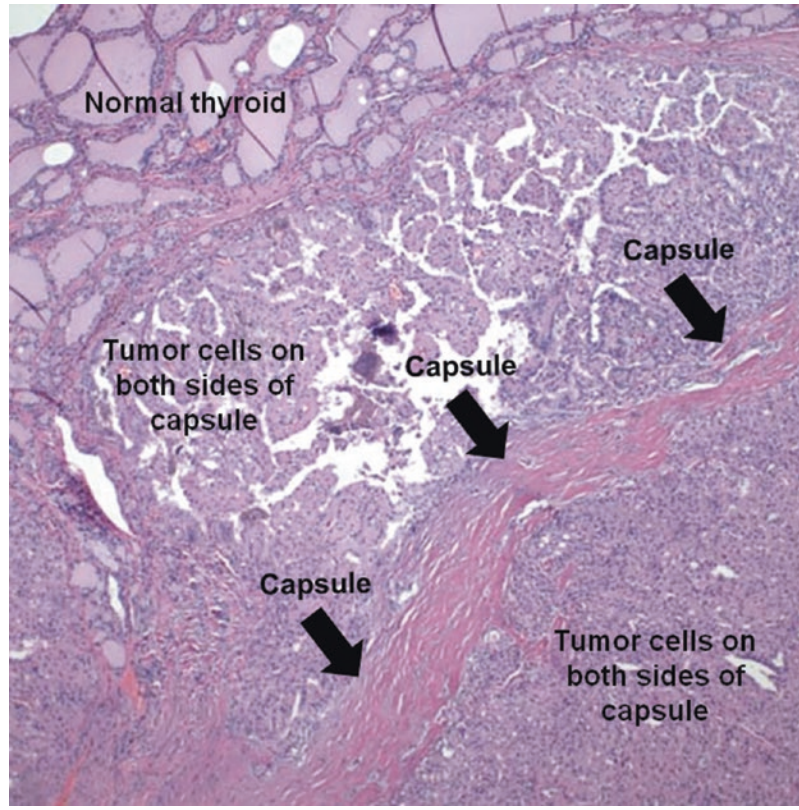

Fig. 8.5 Low-power view of thyroid surgical pathology specimen revealing abundant Hürthle cells extending outside of the capsule. High-power view (not shown) reveals extensive (greater than 4 foci) angioinvasion, consistent with a widely invasive Hürthle cell carcinoma. Photomicrograph provided by Dr. Sheida Sharifi.

have also led to the discrimination of HCC from oncocytic-appearing subtypes of PTC, thereby providing an explanation for the historical clinical heterogeneity of HCC. Use of atypical nuclear features in combination with *BRAF* or *RET/PTC* rearrangement testing differentiates oncocytic variant PTC from HCC; oncocytic variant PTC has a distinctly different clinical course that more closely resembles that of classical PTC [29, 30]. Further use of proliferation activity markers such as Ki-67 and PCNA appears to discriminate HCC variants with more aggressive behavior [31].

Recently, a large-scale integrated analysis of copy number alterations, gene expression, and mutations was performed on HCC specimens and revealed a unique profile in each parameter when compared to FTC and PTC. The pattern of chromosomal aberrations was very different between PTC, FTC, and HCC. PTC-associated mutations in *BRAF* and variants of *RET* hybrid oncogenes were not identified in HCC. Additionally, common mutations associated with FTC in *RAS*, *PIK3CA*, and *PPARγ* were less commonly or not seen in HCC. Within HCC subtypes, Hürthle cell adenoma, minimally invasive HCC, and widely invasive HCC also had unique molecular and genetic profiles; the highest activity in PIK3CA-Akt-mTOR and Wnt/β-catenin pathways was seen in widely invasive HCC [4]. There are conflicting reports of mutations in *TP53* and *PTEN* in the literature, some of which were confounded by previous treatment with radioactive iodine; this raises the important consideration that different exposures and risk factors may contribute to different models of pathogenesis [32].

The aforementioned observations have called into question the dogma of stepwise progression of genetic abnormalities in the carcinogenesis of thyroid cancer. Hürthle cell adenomas have been long-thought to progress to minimally invasive and subsequently widely invasive cancer. However, this model may yet hold true in the progression to poorly differentiated or undifferentiated thyroid cancers. Some HCC have been found to harbor trabecular/solid growth patterns typically seen in poorly differentiated carcinomas,

and reports exist of poorly differentiated thyroid carcinomas arising from pre-existing Hürthle cell carcinomas. Additionally, oncocytic cells have been identified alongside anaplastic cells in some anaplastic thyroid carcinomas [33, 34]. Hopefully, further study will define the critical events in malignant transformation. As additional genetic and molecular markers continue to be identified for each subtype, the hope is for the ability to better predict prognosis for individual patients and ideally, develop or co-opt previously developed targeted therapeutics.

Evaluation

Patients with HCC typically present with solitary or multiple palpable thyroid nodules identified by the patient, or on routine physical examination, or incidentally found on imaging for other indications. Careful history taking is important to assess for risk factors of thyroid carcinoma including a history of neck radiation, rapid growth of the nodule, and family history of thyroid cancer or tumor syndromes. Physical examination should also be performed to evaluate for the presence of neck masses, lymphadenopathy, or vocal cord paralysis. Serum TSH testing with a third-generation immunochemiluminometric assay should be performed since TSH concentrations are an independent predictor of malignancy, the risk of which rises with increases in TSH, peaking at 29.7% for TSH concentrations greater than 5.5 mIU/L [35]. Nodules harboring HCC or other forms of thyroid cancer are typically "cold" with poor uptake on thyroid scintigraphy. A diagnostic radioactive iodine uptake and scan should be performed for patients with subnormal TSH concentrations; less than 1% of "hot" nodules harbor malignancy. Dedicated thyroid ultrasonography should be performed if a nodule is suspected or identified by physical exam or other imaging. Compared to thyroid scintigraphy, computed tomography (CT), and especially physical exam, thyroid ultrasonography provides superior anatomic detail and enables the clinician to select nodules for biopsy. Although factors such as hypoechogenicity, central vascular flow, microcalcifications, irregular margins, and taller-than-wide geometry are associated with an increased risk of thyroid cancer, none of these findings are sensitive or specific for Hürthle cell adenoma or carcinoma [36]. There is weak evidence that multifocal and larger nodules have a higher risk of HCC. Identification of a "halo sign" or "eggshell-type calcifications" have been observed in many cases of HCC and appear to represent the sonographic equivalence of a tumor capsule on gross pathology [37, 38]. Although imaging studies have limited utility in making the diagnosis of HCC, the presence of high-risk sonographic features and/or pathologic lymph nodes (e.g., rounded shape, enlargement, loss of the fatty hilum, calcifications) on thyroid ultrasound raise the preoperative probability of malignancy and locoregional metastasis, respectively.

Ultrasound-guided fine needle aspiration biopsy (FNAB) is the diagnostic method of choice to evaluate thyroid nodules [39]. The Bethesda System for Reporting Thyroid Cytopathology was developed in 2008 at a conference hosted by the National Cancer Institute and is the most widely used system for diagnostic categorization of thyroid cytology [40]. There are six categories of thyroid FNAB cytology: (1) nondiagnostic/unsatisfactory, (2) benign, (3) atypia or follicular lesion of undetermined significance, (4) follicular neoplasm or suspicious for a follicular neoplasm, (5) suspicious for malignancy, or (6) malignant. Hürthle cells may be seen in many of these categories and HCC, like FTC, cannot be diagnosed by FNAB since this technique does not differentiate adenoma from carcinoma. The combination of four features including non-macrofollicular architecture, absence of colloid, absence of inflammatory cells, and presence of transgressing blood vessels has been found to be predictive of Hürthle cell neoplasia compared to non-neoplastic disorders such as Hashimoto's thyroiditis and Graves' disease [41]. Up to 45% of nodules with a category 4 cytopathology prove to be malignant [42, 43]. It is important to note that the presence of Hürthle cells alters the distribution of Bethesda system categories and has been described to enrich categories 3 and 4; of the patients who went to surgery with category 4 cytopathology, a significantly higher proportion of patients were diagnosed with a malignancy, roughly half of which were HCC [44].

Recently, molecular diagnostic testing of indeterminate cytology has become widely clinically available and aids in refining the preoperative risk of malignancy, supplementing clinical observation, sonographic assessment, and cytopathologic interpretation. These methods are an attractive option to help triage patients for surgery after testing tissue obtained by FNAB, given the molecular and genetic differences of HCC compared to PTC and FTC. Veracyte's Afirma gene expression classifier is an mRNA expression classifier using 167 genes and pattern recognition to yield a binary result of "benign" (<6% negative predictive value) or "suspicious" (35–40% positive predictive value) for category 3 cytopathology [45]. However, the original Afirma validation set included 21 Hürthle cell adenomas, 81% of which yielded a read of "suspicious." To date, five studies have examined the performance of Afirma on thyroid nodules with Hürthle cell features, the largest of which has shown a positive predictive value of only 19%. Other proprietary panels, including Asuragen's miRInform analysis panel and CBLPath's Thyroseq v.2 next-generation sequencing, test for mutations in common oncogenes, and to date their predictive performance on thyroid nodules with Hürthle cell features have not been specifically evaluated. Methods using the combination of mRNA expressing profiling and mutational analyses have been recently made available. Additionally, new molecular/genetic markers are being actively investigated; *PVALB* has been identified as one such genetic marker that appears specific to HCC [46].

Treatment

Ultimately, diagnosis of HCC requires surgical resection; all patients with FNAB results that are suspicious for Hürthle cell neoplasm should be offered surgery to establish a final diagnosis and to perform initial staging. Imaging studies are often helpful for preoperative planning. Thyroid ultrasound should be performed in all patients to assess for pathologic lymph nodes in the central and lateral neck compartments. Ultrasound-guided FNAB of sonographically suspicious lymph nodules should be performed if it would change management, and may be used to guide planning for a hemithyroidectomy versus total thyroidectomy. Patients with clinical suspicion for advanced disease (e.g., bulky disease on exam or ultrasound, prominent symptoms of local obstruction) should undergo CT and/or magnetic resonance imaging (MRI) with intravenous contrast to evaluate anatomic regions beyond those visible on ultrasound and assess for invasion of local structures. Preoperative 18F-fludeoxyglucose-positron emission tomography (18F-FDG-PET) imaging is not routinely recommended for differentiated thyroid cancer, although this test may be helpful to identify mediastinal involvement and distant metastases if suspicion is high [39]. In HCC specifically, the characteristically poor radioiodine avidity has led to evaluation of 18F-FDG-PET to visualize locoregional, metastatic, or recurrent disease. HCC tumors have been shown to have particularly intense 18F-FDG uptake; 18F-FDG-PET has been shown to have a diagnostic sensitivity and specificity of 92–96%. In patients who have had concurrent PET and CT imaging, PET reveals additional sites of disease in up to 50% of patients (Figs. 8.6 and 8.7). These findings have significant potential to impact patient management decisions and have been used to guide immediate postoperative risk

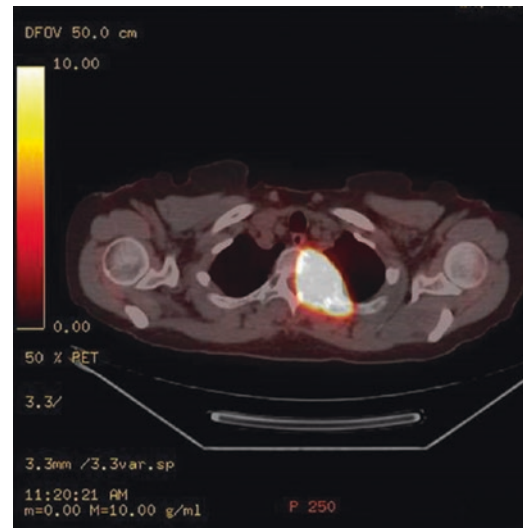

Fig. 8.6 Combined PET/CT image revealing thoracic vertebral and paraspinal muscle metastases in a patient with widely metastatic Hürthle cell carcinoma, represented by intense focal FDG uptake in T2, T3, and the surrounding soft tissue

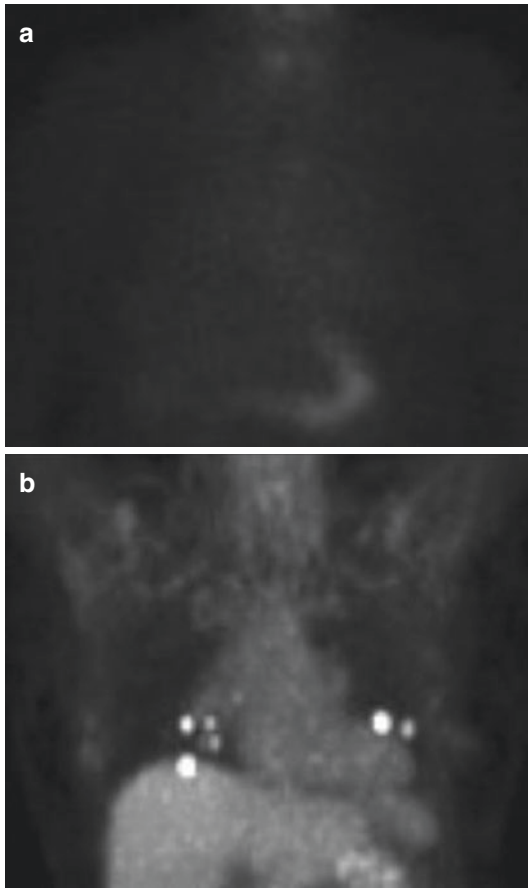

Fig. 8.7 Comparison of nuclear imaging in a patient with pulmonary metastases from widely metastatic Hürthle cell carcinoma. (**a**) Chest series from a I-131 posttreatment whole-body radioactive iodine uptake and scan without any obvious metastases. (**b**) Chest series from an 18F-FDG-PET obtained 3 months prior during initial staging, revealing multiple foci of FDG uptake in the bilateral middle and lower lobes

stratification as well as management of rising thyroglobulin levels in the setting of negative conventional imaging. Furthermore, intensity of 18F-FDG uptake has been demonstrated to aid in prognostication: maximum standardized uptake values (SUVmax) greater or less than ten units have been associated with 5-year survival rates of 64% and 92%, respectively, with a linear increase in mortality with increased SUVmax. Additional isotopes such as 124-iodine, 18F-DOPA, and 68GA-DOTA are under active investigation and development, with the goal of improving PET sensitivity and resolution [47–49].

In select patients who are high risk for contralateral lobe involvement at diagnosis (e.g., nodularity on ultrasound, prior radiation exposure) or high risk for complications from surgery or anesthesia, total thyroidectomy should be considered rather than hemithyroidectomy with completion thyroidectomy if needed. Regardless of the surgical approach chosen, patients with FNAB results of "suspicious for Hürthle cell neoplasm" should be counseled that there is an up to 65% chance that their lesion will be benign on final surgical pathology. This is reduced to 35–56% in patients with suspected tumors greater than 4 cm [16, 17]. Unfortunately, intraoperative frozen sections do not clearly and reliably show capsular or vascular invasion and therefore do not distinguish adenoma from carcinoma or enable real-time intraoperative planning [50, 51]. Prophylactic central neck lymph node dissection remains controversial, although tumors greater than 5 cm, especially in older male patients, have been associated with a 20% risk of lymph node metastasis [52].

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High-Risk and Poorly Differentiated Thyroid Cancer

9

Shirley Yan, Shelby Holt, Saad Khan, and Fiemu Nwariaku

Introduction

Follicular cell-derived thyroid carcinomas are classified based on their histology as, well differentiated (papillary carcinoma and follicular carcinoma), poorly differentiated, and undifferentiated thyroid carcinomas [1]. Although the vast majority of clinically diagnosed thyroid cancer today is of the well-differentiated variety arising from follicular thyroid cells, de-differentiation results in an aggressive phenotype which is responsible for an inordinate number of deaths from thyroid cancer.

The terms high-risk thyroid carcinoma and high-risk differentiated thyroid carcinoma have been used to describe follicular cell-derived differentiated thyroid carcinoma with aggressive behavior. High-risk differentiated thyroid cancer does not represent a distinct tumor entity but defines a group of thyroid carcinomas with varying histologies. Most well-differentiated thyroid carcinomas (WDTC) are low-risk thyroid carcinoma.

Classification of High-Risk Differentiated Thyroid Cancer

Current management approach of differentiated thyroid carcinoma of follicular cell origin is a risk-adapted approach by using American Thyroid Association (ATA) recurrence staging system. This system facilitates the identification of clinically significant residual or recurrent disease and can be used to more effectively treat thyroid cancer [2]. Tuttle et al. reviewed 588 adult follicular cell-derived thyroid cancer patients followed for a median of 7 years after total thyroidectomy and radioactive iodine remnant ablation. The data show that structurally identifiable persistent disease is present in 2%, 19%, and 67% in low-, intermediate-, and high-risk groups, respectively [3].

High-risk differentiated thyroid carcinoma is classified by the ATA risk stratification system (both 2009 and 2015) as having the following features: (1) the presence of macroscopic invasion of the tumor, (2) incomplete tumor resection, and (3) distant metastases including postoperative serum thyroglobulin suggestive of distant metastases [2, 4].

Histopathologic Stratification of High-Risk Thyroid Cancer

Histopathologic evaluation of thyroid carcinoma is one of the most important aspects of the initial assessment of individualized risk

S. Yan • S. Holt • S. Khan • F. Nwariaku (✉)
Departments of Surgery and Pathology, University of Texas Southwestern Medical Center,
5323 Harry Hines Boulevard, Dallas, TX 75390, USA
e-mail: fiemu@verizon.net

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classification. Pathology reports should follow an updated AJCC cancer staging method including status of resection margins, the presence of vascular invasion and the number of invaded vessels, the number of lymph nodes examined and involved with tumor, size of the largest metastatic focus in the lymph node, and the presence or absence of extranodal extension of the metastatic tumor.

Histologic variants of differentiated, follicular cell-derived thyroid carcinoma that are classified as unfavorable or aggressive histology include tall cell, columnar cell, hobnail, diffuse sclerosis, solid, and widely invasive follicular variants of papillary thyroid carcinoma (PTC) and poorly differentiated carcinoma [3]. Widely invasive follicular carcinoma is also classified into this category according to the American Thyroid Association (ATA) 2015 guideline [4]. The variants of columnar cell, hobnail cell, diffuse sclerosis in adults, and solid PTC are very rare.

The tall cell variant of PTC was first described by Hawk and Hazard in 1976 [5], which is defined as 50% or more of neoplastic cells having a height at least twice the cell width in an otherwise typical papillary carcinoma. The prevalence of tall cell variant PTC ranges from 3 to 19%, and these variants are more common in older patients [6–9]. The tumor is usually large, extends outside thyroid, and shows mitotic activity and vascular invasion more often than classical PTC. Tall cell variant of papillary thyroid microcarcinoma (1 cm or less) also shows more aggressive behavior, having 33% extrathyroidal extension and 15% lymphovascular invasion [5]. However, others have shown that the tall cell variant was not an independent variable for the prediction of a high risk of persistent/recurrent disease [10].

Poorly differentiated thyroid carcinoma (PDTC) is rare form of thyroid cancer that is associated with high risk of cancer recurrence, distant metastasis, and increased risk of death. Its incidence varies from less than 1% of thyroid cancers in Japan [9] and 2–3% of thyroid cancers in North America to 15% in Northern Italy [7]. The Mayo Clinic reported 56 cases of PDTC based on the Turin criteria counting 1.8% of thyroid cancers (56/3128 cases) between 1955 and 2000 [11]. PDTC designated as a separate entity was first proposed independently by Sakmoto et al. in 1983 [12]. Sakamoto and colleagues designated as poorly differentiated those thyroid tumors that demonstrated loss of glandular differentiation (follicular or papillary) and reduced survival. PDTC was first listed as a distinct tumor entity in the World Health Organization (WHO) Classification of Tumors in 2004 and defined as a "follicular-cell neoplasm that showed limited evidence of structural follicular cell differentiation and occupied both morphologically and behaviorally an intermediate position between differentiated (follicular and papillary carcinoma) and undifferentiated (anaplastic) carcinomas" [1]. The diagnosis of PDTC relies on the identification of three different histologic patterns (insular, trabecular, and solid) in the majority of the tumor together with an infiltrative pattern of growth, necrosis, and obvious vascular invasion. However, these diagnostic criteria are relatively subjective, and there is lack of consensus among pathologists and clinicians worldwide. The international conference of 2006 in Turin, Italy, reached a consensus to standardize the diagnosis of poorly differentiated thyroid carcinoma [13]. These include the (1) presence of a solid/trabecular/insular pattern of growth, (2) absence of the conventional nuclear features of papillary carcinoma, and (3) presence of at least one of the following features: convoluted nuclei, mitotic activity $\geq 3 \times 10$ HPF, and tumor necrosis.

PDTC is a clinically aggressive tumor. However, clinical studies on this entity have been limited due to its rare occurrence and heterogeneity of diagnostic criteria. The largest and most detailed study in the United States reported 91 cases of poorly differentiated thyroid carcinoma at Memorial Sloan Kettering Cancer Center from 1986 to 2009 [14, 15]. The tumors showed high primary tumor staging such as 50% pT3 and 30% pT4a, 16% pN1a and 24% pN1b, and 26% M1. There were 14 additional cases (15%) that developed distant metastasis during the follow-up. Patient outcomes were poor during a median follow-up of 50 months (range,

1–215 months). Specifically, 5-year overall survival and disease-specific survival were 62 and 66%, respectively.

Molecular Stratification of High-Risk Thyroid cancer

The molecular genetics of thyroid carcinoma can be translated into clinical practice as an ancillary tool for diagnosis and prognostication [16]. The most common genetic abnormalities in PTC are point mutations of BRAF and RAS genes as well as RET/PTC rearrangements [17]. Follicular carcinomas show RAS point mutations and PAX8/PPAR gamma rearrangement [18]. The BRAF mutation, V600E, is the most common mutation in PTC. The prevalence of BRAF mutation is approximately 45% (range 27–87%) [19–22]. BRAF mutation has been described in almost all variants of PTC but has a higher frequency in tall cell variant of PTC. The BRAF V600E mutation is caused by a c.1799 T>A transversion that results in constitutively mitogen-activated protein kinase (MAPK) pathway, leading to tumorigenesis and distinct biological consequences [16, 23].

Recent studies suggest that the BRAF V600E mutation is a marker of disease aggressiveness, disease recurrence, and poor prognosis [19, 24–28]. BRAF-mutant PTCs have changes in the expression of the sodium/iodide symporter [29, 30], the apical iodide transporter [30], and thyroid peroxidase [31] and reduced expression of key genes involved in iodine metabolism [32]. These effects may alter the effectiveness of diagnostic and/or therapeutic use of radioiodine in BRAF-mutant PTCs. However, the presence of a BRAF V600E mutation has a limited predictive value for recurrence. As such, many surgeons do not use the BRAF mutation status alone as a clinical decision-making tool for aggressive surgical therapy such as prophylactic central neck dissection [33, 34].

Detection of BRAF, TP53, and TERT mutation may provide more specific prediction of tumor recurrence and cancer-related mortality in well-differentiated thyroid cancers. Molecular tests that provide prognostic information or guide optimal initial/ongoing treatment decisions have the potential to significantly alter clinical management. In one study of 65 PDTCs, M. Volante et al. found RAS mutations in 23% and one BRAF mutation [35]. No KRAS, RET/PTC, and PAX/PPARγ were identified. All but one RAS mutations were in the *NRAS* gene. Asioli et al. also reported NRAS mutations in 6 of 32 cases (19%) of PDTC [11].

Clinical Risk Stratification for High-Risk Thyroid Cancer

While most patients with differentiated thyroid cancer (DTC) have an excellent prognosis, a small percentage of patients with DTC will die from their disease. Follicular cell-derived DTC with aggressive behavior and higher rates of disease-associated morbidity and mortality constitute high-risk DTC. Clinicians must identify patients with high-risk disease in order to maximize initial therapy and optimize surveillance. Current guidelines recommend risk-stratified disease management [3].

Patient demographics provide the first insight into potential disease behavior. Extremes of age (<10 and >60 years) and male gender are associated with more advanced disease at presentation, higher rates of recurrence, and reduced survival [36]. Additional variables important to risk stratification include tumor size (>4 cm), specific histologic variants (tall cell, columnar, insular, poorly differentiated) [6, 7], macroscopic extrathyroidal extension, vascular invasion, lymph node metastases, distant metastases, and completeness of resection [2]. These variables not only predict the risk of disease – specific mortality but also predict the risk of persistent disease (i.e., failure to respond to initial treatment) and recurrence [2].

According to the ATA 2009 risk stratification system, intermediate-risk group is classified as follows: (1) microscopic invasion into the perithyroidal soft tissue, (2) aggressive histology, and (3) vascular invasion. The ATA-2015-modified

criteria include (1) clinical N1 or >5 pathologic N1 with all involved lymph nodes <3 cm in largest dimension; (2) intrathyroid, papillary thyroid carcinoma, primary tumor 1–4 cm, V600E BRAF mutated (if known); and (3) multifocal papillary microcarcinoma with extrathyroidal extension and V600E BRAF mutated (if known) [4].

As was previously described, high-risk differentiated thyroid carcinoma is classified by ATA risk stratification system (both 2009 and 2015) as having the following features: (1) the presence of macroscopic invasion of the tumor, (2) incomplete tumor resection, and (3) distant metastases including postoperative serum thyroglobulin suggestive of distant metastases [2, 4].

Clinical Cases

The clinical presentation of patients with high-risk DTC ranges from incidental radiographic detection of an asymptomatic thyroid nodule to a locally invasive thyroid mass with aerodigestive compressive symptoms. The following clinical vignettes illustrate the clinical presentation of patients with high-risk DTC.

Case #1: 64-year-old female with multiple asymptomatic thyroid nodules detected on anatomic imaging of the cervical spine. She has no history of head and neck radiation exposure and no family history of thyroid cancer. There is left paratracheal fullness on physical exam. She is hypothyroid due to lymphocytic thyroiditis with a TSH of 6.6 and positive thyroid peroxidase antibodies. Ultrasonography shows multiple nodules with a dominant 2.0 cm solid left thyroid nodule and no suspicious lymphadenopathy. Fine needle aspiration cytology was suspicious for follicular neoplasm. During total thyroidectomy, she was found to have a firm left thyroid mass with obvious extrathyroidal extension. Complete macroscopic resection was performed. Histopathology revealed a 2.5 cm papillary thyroid cancer, tall cell variant, with extrathyroidal extension and focal lymphovascular invasion. Lab data 1 month after surgery included TSH 0.01 mcIU/mL, thyroglobulin 0.2 ng/mL, and thyroglobulin antibody 52 IU/mL. She underwent radioactive iodine ablation with 100 mCi. Post-iodine treatment scan showed neck uptake only. This patient is considered high risk due to age >60 years, tall cell histology, vascular invasion, and gross extrathyroidal extension [3].

Case #2: 55-year-old male found to have a right thyroid nodule and lateral lymphadenopathy on annual physician examination. He is asymptomatic and euthyroid. He has no history of head and neck radiation exposure and no family history of thyroid cancer. Ultrasonography shows a heterogeneous 4.5 cm right thyroid mass with microcalcifications and multiple abnormal central and right lateral lymph nodes (Figs. 9.1 and 9.2). Computed tomography was performed due to bulky disease, and no local invasion was identified (Figs. 9.3 and 9.4). Fine needle aspiration cytology showed papillary thyroid cancer in the thyroid mass and right level IV lymph node.

He underwent a total thyroidectomy, central neck dissection, and right modified radical neck dissection. Histopathology showed a 4.3 cm classical papillary thyroid cancer with minimal extrathyroidal extension, 23/50 positive lymph nodes with extranodal extension, and no vascular invasion. Lab data 2 weeks after surgery included

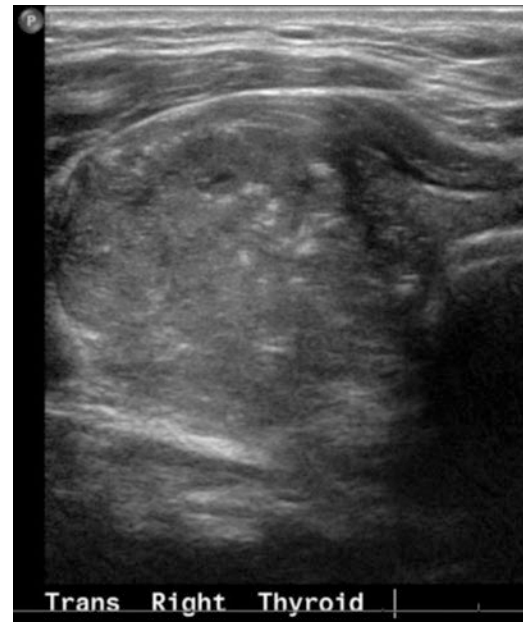

Fig. 9.1 Ultrasound, right transverse

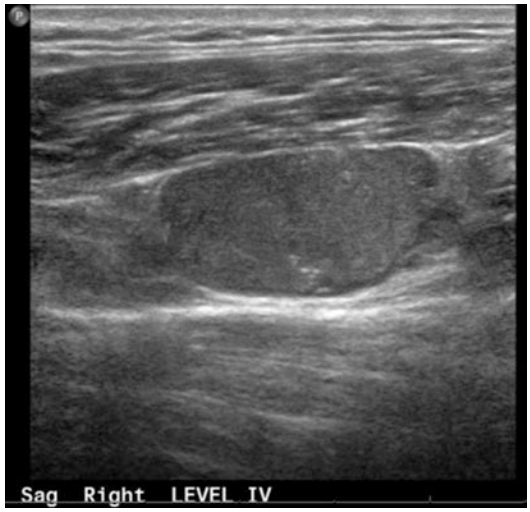

Fig. 9.2 Ultrasound, lymph node

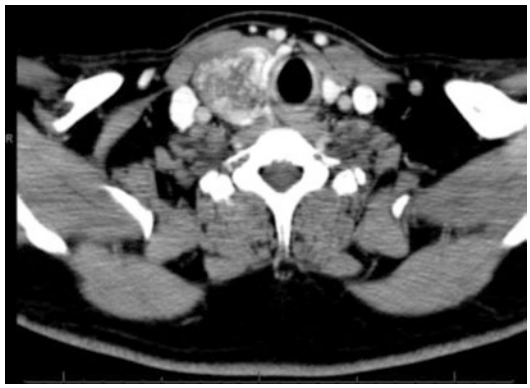

Fig. 9.3 CT showing right thyroid mass

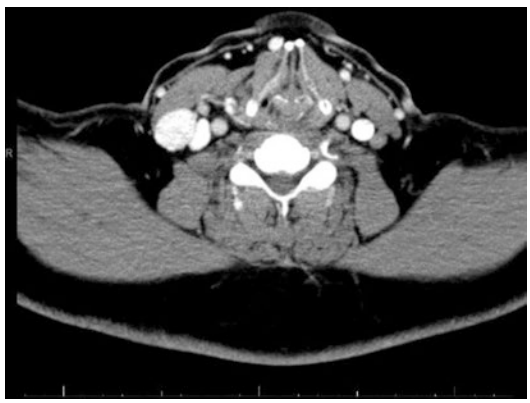

Fig. 9.4 CT

TSH 72.33 mcIU/mL, thyroglobulin 9.6 ng/mL, and thyroglobulin antibody <1.8 IU/mL. He underwent radioactive iodine ablation with 100 mCi. Post-iodine treatment scan showed neck uptake only. This patient is considered high risk due to male gender, tumor size >4 cm, and extensive bulky adenopathy with extranodal extension.

Case #3: 56-year-old female presents with a large compressive goiter. Past medical history is notable for radioactive iodine treatment for Graves' disease 10 years ago. Physical examination revealed stridor and an extensive firm immobile right neck mass. Flexible laryngoscopy confirmed right true vocal cord paralysis. Fine needle aspiration cytology showed papillary thyroid cancer. Computed tomography showed a locally invasive mass with erosion of the cricoid cartilage, tracheal invasion with intraluminal extension, and suspected esophageal invasion (Figs. 9.5 and 9.6). Due to extent of local invasion, the patient was started on systemic therapy with Lenvatinib. This patient is clearly high risk due to extensive local invasion.

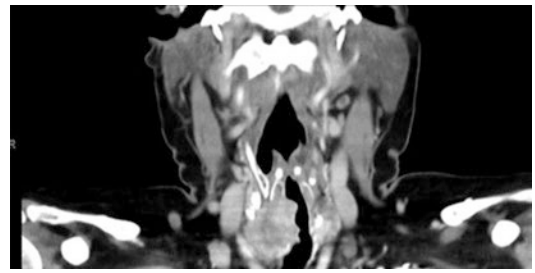

Fig. 9.5 CT showing intraluminal invasion, coronal

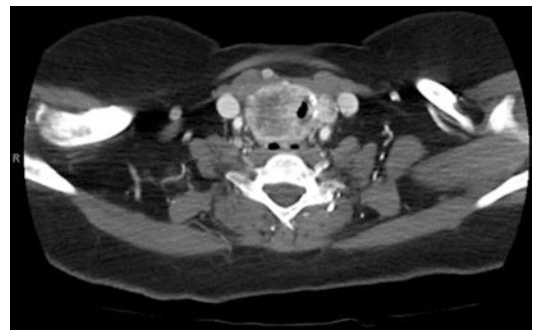

Fig. 9.6 CT showing intraluminal invasion

Systemic Therapy for High-Risk Poorly Differentiated Thyroid Cancer

Thyroid cancer is almost always treated successfully with a combination of surgery and radioactive iodine ablation. Poorly differentiated thyroid cancer has a high risk for recurrence despite of these treatments. For these patients, there is a definite role of systemic therapies in delaying progression. These drugs are associated with serious, potentially life-threatening toxicity and must be administered correctly to provide benefit to patients.

Overview of Agents, Specifically in Poorly Differentiated Thyroid Cancer

Recently approved systemic therapy options for poorly differentiated thyroid cancer include Sorafenib and Lenvatinib, both multikinase inhibitors. The phase 3 DECISION trial compared Sorafenib to placebo in RAI-refractory thyroid cancer [37]. It enrolled 38 patients with poorly differentiated thyroid cancer, and overall there was a benefit toward treatment with Sorafenib [37]. The phase 3 SELECT trial compared Lenvatinib to placebo in RAI-refractory thyroid cancer. It enrolled 47 patients with poorly differentiated thyroid cancer and found an improvement in progression-free survival for patients with poorly differentiated thyroid cancer compared to placebo (HR 0.21, 95% CI 0.08–0.56). Median PFS was 14.8 months compared to 18.3 months for the overall population. Though not directly comparable, lenvatinib was associated with greater response rates in the SELECT trial of approximately 50% compared to Sorafenib which had a response rate of 12% [38].

Timing of Initiation of Therapy

As with treatment of differentiated thyroid cancer, clear goals of therapy are necessary and should be discussed with the patient. With either of the approved drugs, there is no overall survival benefit seen to treatment compared to observation, possibly due to the crossover design of these trials [39–42]. The clinical trials also set stringent criteria for patient entry, and the patient groups were not identical. Patients should be considered for systemic therapy upon development of serious symptoms related to tumor growth, either due to anatomic growth or organ damage. Rapidity of tumor growth is also justification for the initiation of therapy, though that is often subjective and affected by many external factors. Asymptomatic progression often can be observed in differentiated thyroid cancer. In poorly differentiated thyroid cancer, tumors tend to grow more rapidly, and generally there is a lower threshold for starting systemic therapy. Most important is to tailor therapy not to histology but to actual malignant behavior in the patient.

Suitability of Patients

Multikinase inhibitors carry serious, sometimes fatal toxicities. Even with the close monitoring inherent to a clinical trial, there were six deaths in the SELECT trial that were attributable to Lenvatinib [38]. This class of drugs is associated with stroke, myocardial infarction, and pulmonary embolism. Drugs should not be administered to patients with unstable coronary artery disease, uncontrolled hypertension, or cardiovascular event within the last 6 months. However, both agents carry a similar toxicity profile.

Monitoring During Therapy

Two different approaches are often used with systemic therapy; patients may be started at the dose as indicated in the clinical trials and then reduced for toxicity, or they may start at a slightly lower dose and then escalate up to what is tolerated. This decision usually is personalized between the treating clinician and patient based on prior experience and tolerance for toxicity.

Toxicities of these drugs require close monitoring, as indicated in the package insert. Special attention is paid to blood pressure immediately after starting therapy, as well as changes in liver function tests. Though orally administered, patients should regularly be evaluated while on systemic therapy. Initially, this may be as frequent as weekly. Development of toxicity requires adjustment of medication dosage, since toxicity is generally dose-related. Though there are some similarities, there are subtle differences between the toxicity profile of both drugs that should be taken into account.

Assessment of Response

Poorly differentiated thyroid cancer often shows a rapid rate of tumor growth and dissemination. Upon initiation of systemic therapy, visible tumor growths such as those in the neck or skin may respond within weeks to Lenvatinib. Cutaneous or palpable tumors are often used to assess response to therapy, but clinical evaluation does not replace anatomic imaging. This is routinely done with CT scans every 2–3 months while on therapy. While noticeable tumor shrinkage is the desired outcome, it is not uncommon to see variations in tumor size between scans that do not represent true progression. With limited treatment options available, generally maintaining therapy until true progression is preferred. At the time of progression, another multikinase inhibitor may be administered.

Targeted Therapy and Investigational Approaches

Poorly differentiated thyroid cancer does not have the same durability of response as more differentiated thyroid cancer. Therefore, it is likely that patients may experience disease progression while on both multikinase therapies [43–48]. At that point agents not approved for use in poorly differentiated thyroid cancer such as Vandetanib and Cabozantinib may be attempted, though their utility is often limited [49–51]. Genomic analysis may sometimes demonstrate mutations with targeted therapy significance such as a BRAF V600E mutation. In that case BRAF inhibitors such a Vemurafenib may be attempted [52–54]. Other drugs that are in trials and have limited evidence of activity include MEK inhibitors and PI3 kinase inhibitors. In all cases of poorly differentiated thyroid cancers that are refractory to approved therapies, enrolment of the patient in a clinical trial should be the primary consideration.

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Pediatric Thyroid Cancer

10

Melanie Goldfarb and Trevan Fischer

Epidemiology

Differentiated thyroid cancer (DTC) in the pediatric population is rare. It comprises approximately 3% of all childhood cancers and 10% of all thyroid malignancies [1, 2]. Incidence rates are approximately 1.1 per million for children 0–14 years old and 15.1 per million for teenagers (ages of 15–19) and appear to be increasing [3]. Children <15 years with DTC had the highest annual percent change in incidence of any cancer (4%) from 2000 to 2011, and in young adults, the increase in DTC incidence accounted for nearly all of the increased overall cancer incidence in that age group [4]. In adolescents aged 15–19 specifically, DTC is now the second most common cancer (11%) [5]. Moreover, whereas in adults the greatest increase is in microcarcinomas <1 cm, in children the incidence of these small tumors is declining [6, 7].

"Pediatric" is defined by the American Thyroid Association (ATA) as ≤18 years of age, who have also advocated for subclassification in the future by pubertal status: prepubertal, pubertal, and postpubertal [8]. DTC in children has a different sex predilection than in adults, which changes with puberty. In adults, the female-to-male ratio is about 4:1, but in children less than 15 years of age, the ratio is only 1.5:1 [9, 10]. The highest incidence is in non-Hispanic Whites, followed by Hispanic Whites, Asian-American, and lastly Blacks [2, 5, 6].

Disease Presentation

Most thyroid cancer presents as an asymptomatic neck mass or thyroid nodule but can present as cervical lymphadenopathy or lung metastases [11]. Although thyroid nodules are relatively uncommon, in children they have a 25–50% of harboring malignancy compared to 5–10% of adult thyroid nodules [10, 12]. Other non-thyroidal diseases that can mimic thyroid nodules in children include abscesses, lymphatic and vascular malformations, ectopic thymus, thyroglossal duct cysts, and other tumors [13].

DTCs in childhood are usually well differentiated with papillary (PTC) histology or follicular variant of PTC (FVPTC) [9, 14]. Uncommon subtypes that are more common in children include the "solid" and "diffuse sclerosing" variants, which tend to be more aggressive [15–17]. Compared to adults, pediatric DTC typically presents with more advanced disease [18–20]. Extrathyroidal extension is present in 20–60% of patients, cervical node involvement in 40–80%, and lung metastases in 20% of cases [21–26].

M. Goldfarb, M.D., M.Sc., F.A.C.S., F.A.C.E. (✉)
T. Fischer, M.D.
Department of Surgical Oncology, John Wayne Cancer Institute at Providence Saint John's Health Center, Santa Monica, CA, USA
e-mail: melaniegoldfarbmd@gmail.com

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Children also have higher rates of local recurrence and subsequent development of distant metastases, which may be more pronounced in prepubertal children as opposed to older adolescents [21, 24, 27–29]. PTCs in younger patients have a higher prevalence of gene rearrangements and fusion oncogenes with less proto-oncogene point mutations [8, 30–38]. Similar to adults and in comparison to PTC, follicular thyroid carcinoma (FTC) is typically unifocal and more prone to hematogenous or bone spread, and FVPTC displays intermediate histologic features to PTC and FTC, but 5-, 10- and 15-year survival is similar [9, 39]. However, FTC in children is generally associated with less advanced disease and lower rates of recurrence.

Evaluation of Thyroid Nodules

Due to the high rate of malignancy, any thyroid nodule or palpable lymphadenopathy with diffuse thyroid enlargement identified in a child or adolescent should undergo further diagnostic testing and evoke a higher level of suspicion. Historically, this meant diagnostic surgical lobectomy for all young patients. Today, this consists of a thorough history and physical, thyroid function tests and a dedicated thyroid and lateral neck ultrasound by an experienced sonographer. Thyroid cancer is rare (but possible) in a hyperfunctioning nodule, so the majority of patients will have a normal (euthyroid) to high (hypothyroid) TSH level; however, an ultrasound should be performed regardless of the TSH level. Ionizing radiation, in a dose-dependent fashion, is the only known risk factor for thyroid cancer, especially if given before the age of 5 [40, 41]. Lastly, a detailed family history of familial nonmedullary thyroid cancer and familial syndromes associated with thyroid cancer (Box 10.1) should be discussed, and any history of radiation should be documented [8].

Thyroid ultrasound remains the most accurate, cost-effective, and least-invasive method for evaluating thyroid nodules. The same features that are suspicious for malignancy in adults, namely, microcalcifications, indistinct margins, a hypoechoic pattern, increased vascular flow, a taller greater than wider shape, and the presence of abnormal lymph nodes, are also suspicious for malignancy in children with combinations of features that have the most reliable predictive value [42–44]. Similarly, a nodule that has regular margins, mainly cystic content, an iso- or mixed echoic pattern, and peripheral-only blood flow pattern, is most likely benign [45]. A unique but important entity that can present in childhood (mainly prepubertal) is diffusely infiltrating disease which on ultrasound only appears as diffuse enlargement of the gland with microcalcifications. Abnormal features of lateral lymph nodes include round (vs elongated) shape, irregularity, loss of central hilum, cystic replacement, microcalcifications, and peripheral vascularity; two or more of these features raise a high suspicion for nodal metastases [46]. The addition of CT may be appropriate for patients that present with bulky metastatic disease or large, fixed masses to determine invasion of vascular or surrounding organs.

For any nodule >1 cm with suspicious features, ultrasound-guided fine-needle aspiration is recommended with the sensitivity and specificity of fine-needle aspiration biopsy in pediatric thyroid nodules on par with that of adults (94% and 81%, respectively) [47–50]. A size cutoff of "1 cm" is not as definitive in children; however, as their gland volume changes with maturity and in the prepubertal stage, a suspicious sub-cm nodule likely has clinical significance and should be further evaluated with biopsy. The same Bethesda classification system for reporting thyroid cytopathology applies for children. However, the rates of malignancy for both atypia of undetermined significance or follicular lesion of undetermined significance (AUS/FLUS) and suggestive of a follicular neoplasm (Bethesda categories III and IV) are much higher, and therefore surgery is generally appropriate for any child or adolescent with an indeterminate biopsy [8, 51–53]. Additionally, given the differences in molecular alterations in children compared to adults, the use of molecular testing for indeterminate nodules is debatable and little has been reported in this population [38, 54].

Initial Management of Differentiated Thyroid Cancer

The goals of therapy must be kept in mind during treatment planning for children. These are to (a) maintain the low disease-specific mortality currently experienced by children with DTC while (b) reducing potential complications from therapy that ensures a good quality of life during a very long survivorship. One way to ensure these goals are met is for thyroid surgery in children to be performed by a surgeon who performs least 30 or more cervical endocrine procedures annually, the majority of these being thyroid cancer surgeries, and for a multidisciplinary care team to include clinicians that regularly care for children and adolescents with DTC [8, 25, 55–57].

Extent of Surgery

For most children and adolescents with DTC, total thyroidectomy is recommended. Since many DTCs in children are bilateral and multifocal, total thyroidectomy improves local control and disease-free survival and decreases the need for reoperation [27, 58–61]. Additionally, removal of the entire gland optimizes the use of radioiodine (RAI) for imaging and treatment, as well as follow-up with serum thyroglobulin (Tg). However, total thyroidectomy also increases the frequency of complications, such as temporary or permanent hypoparathyroidism and recurrent laryngeal nerve injury even in experienced hands [55, 62, 63]. It may be reasonable to only do a thyroid lobectomy in very small lesions with no other pre- or intraoperative evidence of invasive, bilateral, multifocal, or locally spread disease. Additionally, for patients that initially had a diagnostic lobectomy for an indeterminate lesion, if the final pathology reveals an encapsulated FVPTC, minimally invasive FTC, or a small cancer without aggressive features, completion thyroidectomy is not necessary [64–66].

In patients with preoperative evidence of central or lateral neck nodal metastases, therapeutic central neck dissection (CND) should be performed. Similarly, if abnormal central nodes are encountered intraoperatively during surgery for a known cancer, frozen section analysis should be obtained followed by therapeutic CND if the pathology is positive. In these patients, performance of a CND is associated with decreased persistent and recurrent disease and may also increase the efficacy of subsequent RAI therapy [27, 61]. Prophylactic CND is controversial given the lack of impact on survival [67]. However, since it does appear to decreased recurrence and the extent of initial surgery has been shown to have the greatest impact on improving disease-free survival, consideration should be given to performing a CND at the time of initial surgery [8, 27, 68]. However, there are increased surgical complications from the added dissection even by experienced surgeons [57, 69, 70]. Lateral neck dissection should be performed when a preoperative biopsy of a suspicious lymph node confirms cancer or, in some instances, a very suspicious ultrasound may be sufficient to proceed with nodal dissection. When decision is made to perform a CND, only a compartmental (either unilateral or bilateral for CND and levels II/III/IV/anterior V for lateral) dissection should be done (i.e., no "berry picking" with removal of only the grossly abnormal nodes).

Radioiodine Therapy

Adjunctive or therapeutic RAI therapy historically was given to all pediatric DTC patients due to the increased radiosensitivity of the thyroid gland (especially prepubertal) during childhood. However, other organs in children also have increased sensitivity, and with increasing reporting of these side effects, a more tailored and individualized approach is warranted. Moreover, the true impact RAI has on nodal or local recurrence or long-term survival remains unknown because of the lack of randomized or large prospective studies [27, 61, 71]. Therapeutic RAI is definitely indicated in patients with persistent iodine-avid locoregional or nodal disease that cannot be resected as well as known or presumed iodine-avid distant metastases [8].

Issues specific to young patients include questions of later fertility, early menopause for

females, and secondary malignancies (see "Survivorship" section). Gonadal damage is a known potential consequence of therapy [72]. The testes are more sensitive to RAI than the ovaries, and doses >100 mCi can drop sperm counts in the long term [73–75]. Postpubertal testes are known to be more radiosensitive than prepubertal testes, and although no permanent sterility has been reported for doses <300–400 mCi, adolescent males receiving higher doses of RAI should be counseled and offered sperm banking. Similarly, no permanent sterility, birth defects, or increased rates of miscarriage has been reported after RAI doses <300 mCi in females, but early menopause is a known consequence with even more modest doses of therapy, up to 25% experience transient amenorrhea, and two recent large cohorts report a decreased incidence of pregnancy and successful delivery rate in the later birth years [76–80]. Postpubertal females requiring higher doses of therapy should also be counseled and offered egg preservation with referral to LIVESTRONG for financial assistance if needed and desired [81]. Additionally, attempts at conception should be avoided for at least 1 year after I131 administration.

Preparation for RAI is similar to adults, though children generally need to be off LT4 therapy for less time if withdrawal is the method of preparation. Only one study has specifically reported on the use of recombinant human thyrotropin (rHTSH) in children and adolescents [82]. They showed similar rates of remnant ablation and short-term recurrence compared to a matched group that underwent hormone withdrawal; long-term follow-up is still needed. A posttreatment scan is recommended for all children 4–7 days after therapy.

Thyroid Hormone Suppression

There are no data in children and adolescents comparing the outcomes and risks of different strategies of thyroid hormone suppression. A recent paper of over 100 pediatric survivors in the Netherlands did not show any relation of TSH level with recurrence [57]. Moreover, the impact of thyroid suppression for developing children and adolescents must be balanced with developmental stages. The recent ATA guidelines concluded that the degree of suppression should be tied to the risk stratification category: low risk 0.5–1.0 mIU/L, intermediate risk 0.1–0.5 mIU/L, and high risk <0.1 mIU/L [8].

Risk Stratification

No initial stratification system has been prospectively validated in a large number of pediatric patients. The TNM staging system seems to be the best for roughly describing the extent of disease, and the ATA pediatric risk stratification system further details this information and is similarly structured to the adult classification system [8, 83]. "Low risk" is a disease confined to the thyroid gland (including incidental microcarcinoma) and may include incidental or a small amount of microscopic metastases; "intermediate risk" includes extensive N1a or minimal N1b disease, and extrathyroidal extension may be reasonable to include in this category as well; "high risk" involves extensive lateral nodal disease, locally invasive (T4), or distant metastatic disease. This is much less expensive than the stratification system for adults due to a lack of data. However, these classifications can afford an individualized approach to initial post-op staging, subsequent therapy, and future surveillance. A notable difference involves the mention of a lack of CND in the low-risk category and how it may be reasonable to follow the patients with unknown nodal status more similar to the intermediate-risk group since they may be at risk for residual cervical nodal disease.

Post-surgery, for patients with a negative TgAb, a TSH-suppressed Tg is sufficient for low-risk patients, whereas intermediate- and high-risk patients should generally undergo a TSH-stimulated Tg and diagnostic whole-body scan (DxWBS) despite a lack of data in children. I123 is recommended due to the lower absorbed doses of radiation in tissue, and limiting the amount of exposure is beneficial in younger patients. SPECT/CT or PET may be useful adjuncts in patients with DxWBS to further characterize persistent disease [84].

The post-therapy ATA risk stratification system initially proposed by Tuttle that measures response

to therapy within the first 2 years was the best predictor (96.1% predictive ability) of long-term outcomes in 54 pediatric patients in Israel in comparison to both the ATA risk stratification system and their own proposed scoring system [8, 29, 85]. Their proposed scoring system has eight components, multifocality, bilaterality, extrathyroidal, extracapsular, and vascular invasion, nodal and distant metastases, and post-op TSH-stimulated Tg levels, and showed an improved predictive ability (86.3%) compared to the ATA risk classification system (80.4%). Currently, ATA re-stratification system should be used to assess patient's response to therapy and potentially reclassify their risk of subsequent recurrence.

Long-Term Survivorship and Surveillance, Including Psychosocial

Surveillance for Recurrence

Recurrence has been reported 30–40 years after childhood DTC, though more than half are reported within the first 5–7 years after completion of initial treatment [27, 28, 57]. No studies have incorporated serial Tg monitoring, Tg doubling time, or high-resolution ultrasound screening prospectively in children. Therefore, DTC survivors likely need to have lifelong follow-up that can decrease in intensity as they are disease-free further out from treatment. This includes annual TSH, Tg, and TgAb. The addition of cervical ultrasound, DxWBS, or other imaging should be individualized based on the patient's risk and time from therapy.

Secondary Malignancies

There has been a significant increase in secondary malignancies (SMN) after RAI that appears to follow the increased use of RAI in the late 1980s and 1990s [86–88]. The most common SMN is leukemia, with a reported relative risk of 2.5 times that of the normal population. Moreover, there is an association with an increased risk in mortality for these young DTC patients that get a secondary malignancy.

Survivorship

Much has been reported on the long-term psychosocial issues in other pediatric cancer survivors that may lead to a decreased quality of life (QOL). However, little research has been done specifically in pediatric thyroid cancer survivors as they are usually treated outside of oncology units and large cancer centers where this has been the focus. Similarly, improvements in psychosocial measures, medication, and treatment adherence have been observed for pediatric patients that participate in survivorship clinics which generally do not include thyroid cancer patients. In young adult DTC survivors (some of whom were <18 years at diagnosis), health-related QOL was lower in females than the normal age-matched population and measurable complaints of anxiety concentration, and neuromuscular issues had a negative impact [89]. It would likely benefit young DTC survivors if they could be incorporated in existing survivorship both to have access to resources as well as help facilitate appropriate transition of care upon reaching young adulthood.

Box 10.1: Familial Syndromes Associated with Pediatric Differentiated Thyroid Cancer

"More" common	"Rare"
APC-associated polyposis	Beckwith-Wiedemann
Carney complex	Familial paraganglioma
DICER1 syndrome	Li-Fraumeni
PTEN hamartoma	McCune-Albright
Werner	Peutz-Jeghers

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Active Surveillance as the Initial Course of Action in Low-Risk Papillary Microcarcinoma

11

Yasuhiro Ito, Akira Miyauchi, and Hitomi Oda

Background

Many autopsy studies have been performed regarding the incidence of latent papillary microcarcinoma (i.e., papillary thyroid carcinoma ≤10 mm or PMC) in individuals who died from non-thyroid diseases [1]. The incidence of PMCs measuring 3–10 mm (the size detectable by ultrasound examinations) ranged from 0.5 to 5.2% in these studies. A thyroid cancer study demonstrated that 3.5% of otherwise healthy Japanese women aged ≥30 years were diagnosed as having a small thyroid carcinoma by a mass screening using an ultrasound examination and an ultrasound-guided fine needle aspiration biopsy (FNAB), and 85% of these were ≤15 mm [2]. Curiously, the incidence of thyroid cancer revealed by that screening study was coincident with those of the autopsy studies. The incidence of PMC in the screening study was about 1000 times larger than the known prevalence of clinical thyroid carcinoma in Japanese women at that time. Taking these findings together, it has been hypothesized that most PMCs do not grow or grow very slowly, and the number of cases turning out to be clinically important is very limited.

In 1993 at a meeting of Kuma Hospital physicians, Akira Miyauchi proposed the active surveillance of PMCs without high-risk features or features of unsuitable conditions (details are provided below). His proposal was approved and the study was started the same year with his colleagues. The proposal was based on the hypothesis that most PMCs do not grow or grow very slowly and that it would not be too late for surgical treatment after the appearance of signs of progression such as size enlargement and novel node metastases detected by ultrasound. In 1995, the Cancer Institute Hospital in Tokyo initiated a similar observation study. Data from both institutions' studies were obtained and analyzed, and they support the validity of Dr. Miyauchi's hypothesis as described below.

Increase in the Incidence but Not Mortality of Thyroid Carcinoma in Recent Studies

Recent studies have provided data that strongly support Dr. Miyauchi's hypothesis. In the United States, the incidence of thyroid carcinoma increased by 2.4-fold between 1973 and 2002 and by 2.9-fold between 1975 and 2009 [3, 4]. In Korea, the incidence increased by 15-fold between 1993 and 2011 [5]. This phenomenon is mainly because of the increase in

Y. Ito (✉) • A. Miyauchi • H. Oda
Department of Surgery, Kuma Hospital, Kobe, Japan
e-mail: ito01@kuma-h.or.jp

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the detection of small papillary carcinomas, including PMCs, due to the development of imaging modalities. However, those studies also showed that the mortality rate from thyroid cancer was stable during the same periods. It has thus been suggested that many small, harmless carcinomas have been detected by screenings and that many patients have undergone possibly unnecessary surgeries and other treatments.

How the Active Surveillance of Low-Risk PMCs Is Performed

PMC patients with none of the exclusion criteria described above are regarded as having low-risk PMC and as being suitable for active surveillance. Their PMCs are followed up by ultrasound 6 months after the diagnosis and at least once per year thereafter to determine whether novel lymph node metastases or size enlargement is present. If suspicious nodes are detected (especially in the lateral compartment) in a PMC patient under active surveillance, we perform an FNAB and thyroglobulin measurement of the washout of the needles used for the FNAB [6] to diagnose whether the nodes are metastatic or reactive. A rescue surgery is performed when the tumor size has enlarged by ≥3 mm or lymph node metastases are diagnosed. Otherwise, the active surveillance is continued. For tumors with size enlargement only, a rescue surgery might be delayed until the tumor size has exceeded 13 mm or more.

Contraindications for the Active Surveillance of PMC

There are two types of contraindications for active surveillance, as shown in Table 11.1. Biologically aggressive cases should undergo an immediate surgical treatment [7]. Even if the size of main tumor is small at ≤10 mm, clinical node-positive (N+) and/or, although rare, distant metastasis-positive (M+) cases should be treated immediately. In cases in which the PMC is located at the course of the recurrent laryngeal nerve and the patient has suffered recurrent nerve paralysis, surgical treatment is mandatory. Needless to say, cases that are observed to be progressive during active surveillance should also be treated at that time.

Table 11.1 Contraindications for the active surveillance of PMC

Type	Contraindications
Clinically high-risk features	1. Presence of N or M (although very rare)
	2. Signs or symptoms of invasion to the recurrent laryngeal nerve or trachea
	3. High-grade malignancy on cytology (although very rare)
	4. Cases showing progression signs (size enlargement and novel appearance of lymph node metastasis) during observation
A feature unsuitable for observation unclear whether it is clinically high risk	1. Tumors located adjacent to the recurrent laryngeal nerve or trachea

Another issue is the location of the tumor. If the tumor is located at the course of the recurrent nerve (even if recurrent nerve paralysis has not yet occurred) or if there is a possibility that the tumor will invade the trachea, surgical treatment is recommended rather than active surveillance, although it remains unclear whether PMCs truly invade or will invade the trachea or recurrent nerve in the future. The question of how to evaluate an invasion of the trachea or recurrent nerve is addressed later in this text.

Multiplicity of tumors and positive family history for papillary thyroid cancer were not regarded as contraindications in our active surveillance study. We deemed that if these factors were included for the indications of immediate surgery, this might result in an increase in the incidence of surgical complications following total thyroidectomy, and that progression of the disease might not necessarily be associated with these factors.

Evaluation of the Relationships Between PMC and the Trachea and Recurrent Nerve

It is often difficult to judge whether carcinoma invades the trachea or recurrent nerve on imaging studies. Regarding the trachea, it would be best to evaluate the trachea by ultrasonography and CT scans based on the angles formed by the tracheal cartilage and the tumor's surface (Fig. 11.1). If the angle is acute, the tumor is regarded as providing a low risk of tracheal invasion; if the angle is unclear, the risk is considered intermediate; and if the angle is obtuse, the risk is regarded as high (Fig. 11.2a–c). A 2016 study showed that 19% of PMC patients at high risk for tracheal invasion required cartilage resection with or without resection of the tracheal mucosa, and the rest of these patients at high risk did not [8].

The risk of recurrent nerve invasion can also be evaluated by ultrasound and CT, and the risk can be graded based on whether the normal rim of the thyroid is clearly present in the direction of the recurrent nerve (low risk) or not (high risk) (Fig. 11.3a, b). Significant invasion requiring complete dissection with reconstruction or partial layer dissection of the recurrent nerve was seen in 7% of high-risk patients [8].

In this study, tumors <7 mm did not invade the trachea or recurrent nerve regardless of the risk grading, but it is unclear whether all microcarcinomas <7 mm do not invade the trachea or recurrent nerve [8].

Results of the Active Surveillance of Low-Risk PMCs

In 2003, the first report of our active surveillance of low-risk PMCs at Kuma Hospital was published [7]. In that study we enrolled 162 patients, and our findings demonstrated that the sizes of the tumors did not change or even decreased compared to the size at the initiation of active surveillance in 70% of the patients, at every examination point. The novel appearance of lymph node metastasis detectable by ultrasound during active surveillance was observed in only 1.2% of the patients.

In the second report from Kuma Hospital in 2010, the number of enrolled patients increased to 340, and the results showed that the proportion of PMCs showed enlargement by ≥3 mm and the rate of novel nodal metastasis were 6.4% and 1.4%, respectively, at the 5-year follow-up by the Kaplan-Meier method (average follow-up time 74 months) [9]. In the same year, Cancer Institute Hospital (Tokyo, Japan) demonstrated that 7% of 300 low-risk PMCs showed size enlargement and only 1% of 230 patients showed novel lymph node metastases during active surveillance, although that study did not adopt a time-sequence analysis [10]. In 2014, our report from Kuma

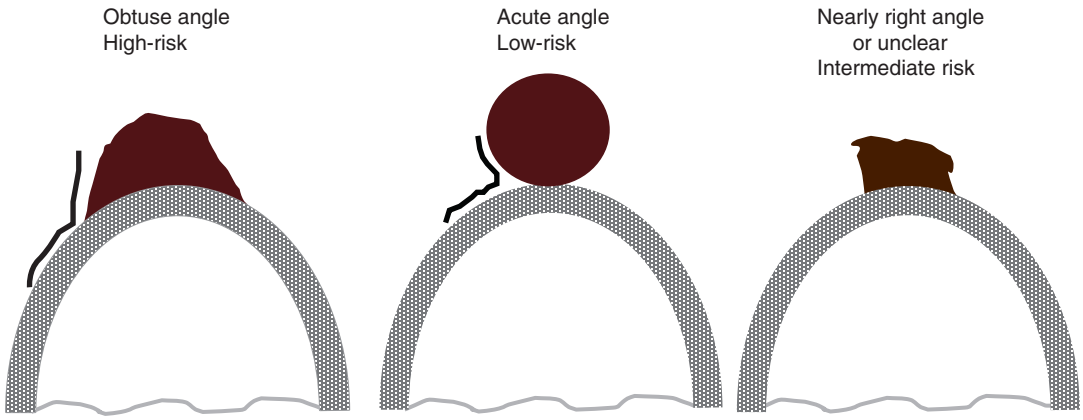

Fig. 11.1 Risk classification of tracheal invasion by PMCs

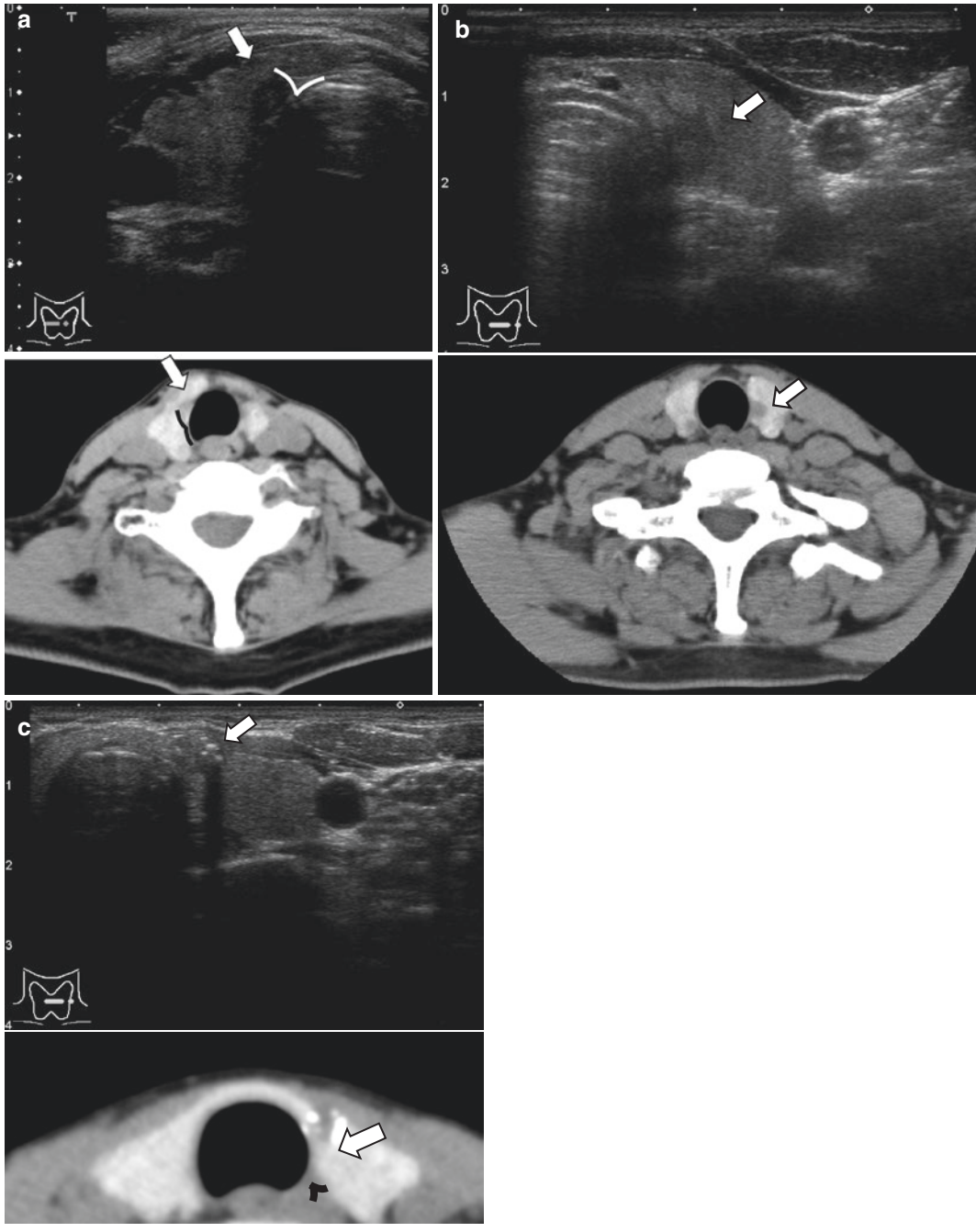

Fig. 11.2 (**a**) An example of a tumor at high risk for trachea invasion. This tumor required shaving of the trachea cartilage. (**b**) An example of a tumor at intermediate risk for trachea invasion. This tumor did not invade the trachea based on operative findings. (**c**) An example of a tumor at low risk for trachea invasion. This tumor did not invade the trachea

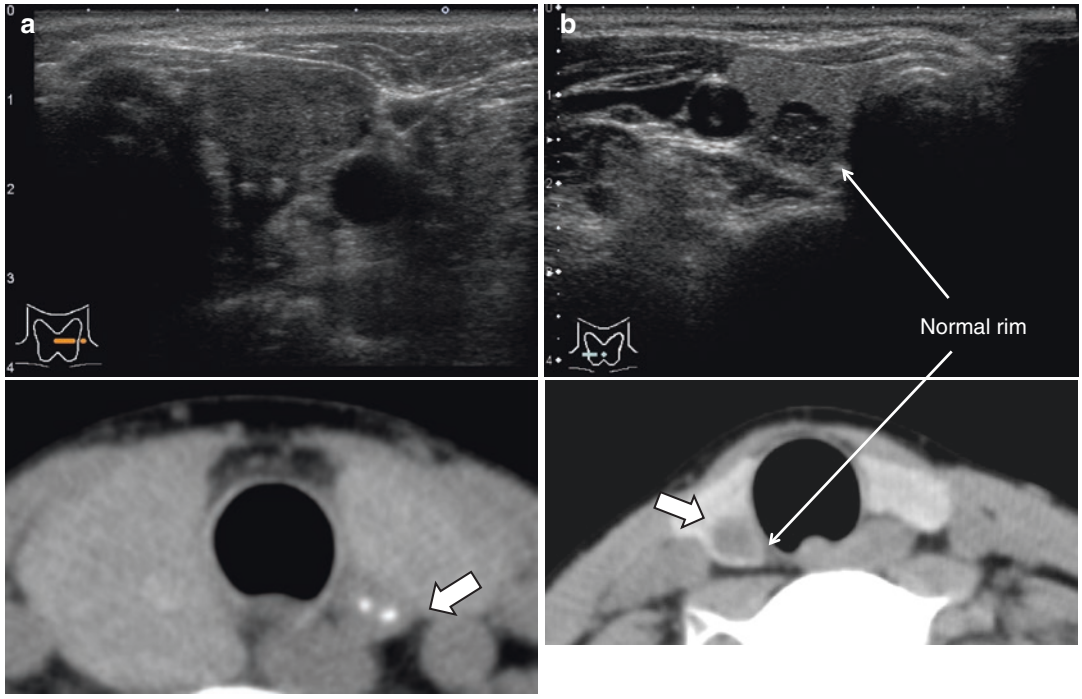

Fig. 11.3 (**a**) An example of a tumor at high risk for recurrent nerve invasion. Recurrent nerve shaving was required as part of the operation. (**b**) An example of a tumor at low risk for recurrent nerve invasion. The tumor did not touch the recurrent nerve

Hospital showed that only 8% of 1235 patients showed size enlargement by 3 mm, and 3.8% of patients showed a novel appearance of lymph node metastases at 10 years of surveillance [11].

All of these studies have one important issue in common: none of the enrolled patients who underwent a rescue surgery following the slight progression of the disease showed a life-threatening recurrence, indicating that it is not too late to perform surgery for low-risk PMC patients after the detection of slight progression signs as mentioned above.

Factors Influencing the Appearance of Progression Signs

The above clinical studies indicate that most low-risk PMCs are indolent and that active surveillance should be the first line of management. They also showed that surgical treatment after the detection of progression signs is not too late. However, there are some factors that influence the progression of PMCs, as indicated below. These factors are not regarded as contraindications for active surveillance, but physicians should pay careful attention to patients with these factors and circumstances.

Patient Age

In our 2014 study, we performed univariate and multivariate analyses to investigate predictors of PMC progression [11]. The results indicated that young patient age (≤40 years) is an independent prognostic factor of PMC progression, tumor growth, and/or appearance of nodal metastasis. In contrast, PMCs in older patients (>60 years) are less likely to progress. These findings are interesting because they are completely at odds with the fact in clinical PTC; old age is a strong prognostic factor especially for carcinoma death. Although clinical PTCs in elderly patients should be treated

carefully, PMCs in elderly patients are excellent candidates for active surveillance. The tumor biology of PMCs in elderly patients seems different from that of clinical PTCs in elderly patients.

In 2014 study, although the number of patients who have undergone this treatment is small, it appears that serum thyroid-stimulating hormone (TSH) suppression to low-normal levels achieved by administering L-thyroxine may be useful for preventing PMC growth, especially for young patients, because none of the young patients whose TSH was set at low-normal levels showed progression.

However, Sugitani et al. reported that the TSH level did not influence the size change of PMCs [12]. Further studies are necessary to elucidate this point.

Calcification and Vascularity Observed by Ultrasound

Fukuoka et al. investigated calcification and vascularity observed by ultrasound during the active surveillance of PMCs, and they found that calcification appeared or became clearer during active surveillance [13]. In addition, the tumors with initially rich vascularity more frequently showed tumor enlargement, but over 60% of the tumors showed a decrease in vascularity. Fukuoka et al. also showed that PMCs in older patients showed stronger calcification patterns and poorer vascularity. These findings in a time-dependent setting might be useful to evaluate the changes in the biological behavior of PMC.

Pregnancy

If pregnancy affects the progression of PMC, it would be better to surgically treat a woman's PMC before she considers becoming pregnant, when possible. Our first report on a small number of such cases showed that 49.4% of PMCs showed size enlargement during pregnancy, but we later found a strong selection bias in that patient series [14]. We carefully checked all of the cases of pregnant patients who underwent active surveillance of their PMCs and published the second report in 2016 [15]: the PMCs of 4 of 51 patients (8%) showed size enlargement, and none showed novel lymph node metastases during pregnancy. Of the four enlarged PMCs, two were surgically treated, and the other two underwent only continued active surveillance, because these tumors did not grow after the patients' deliveries. The two surgically treated patients underwent hemithyroidectomy, and neither has shown recurrent signs post-surgery. We have thus concluded that pregnancy is not a factor precluding PMCs from active surveillance, although surgery may be needed after delivery when a PMC grows.

Surgical Complications

Although surgery for a low-risk PMC is not difficult, various potential complications should be considered. Oda et al. reported that permanent vocal cord paralysis, permanent hypoparathyroidism, and postsurgical hematoma occurred in 0.2%, 1.6%, and 0.5% of patients who underwent immediate surgery for low-risk PMC, respectively [16]. We must note that these incidences are based on the findings of hospitals that specialized in thyroid surgery. If non-expert surgeons perform the surgery for PMC, the incidence of complications would be higher.

In the active surveillance group in the Oda et al. study, 20.7% of the 1.179 patients were administered L-thyroxine (because of hypothyroidism due to chronic thyroiditis) or TSH suppression therapy, whereas 66.1% of the 974 patients in the immediate surgery group received one of those treatments. We must therefore conclude that the rate of unfavorable events in patients who undergo immediate surgery would be much higher than that of patients who undergo active surveillance. This is another reason to use active surveillance of low-risk PMCs as the initial course of action.

Conclusions

Our observation trial of low-risk PMCs was initially an experimental trial without any preceding reports. We therefore proposed two

options to the patients: observation (i.e., active surveillance) and immediate surgery, and the patients chose the option. Evidence has now accumulated supporting the use of active surveillance, and this management was adopted not only in the Japanese guidelines [17] but also in the American Thyroid Association guidelines [18]. Patients can avoid unnecessary surgery and the complications induced by surgery. It is becoming accepted that it is better for patients with low-risk PMC to simply undergo only active surveillance unless they have unfavorable features for this approach. In conclusion, active surveillance should be adopted as the first line of management for low-risk PMC.

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Surgical Treatment of Papillary and Follicular Thyroid Cancer

12

David T. Hughes and Paul G. Gauger

Abbreviations

FNA Fine needle aspirate
PTH Parathyroid hormone

Introduction

Nearly 100,000 thyroidectomy surgeries are performed in the United States each year for both benign and malignant thyroid pathology. Thyroid cancer is the indication for thyroidectomy in about half of these cases [1]. While the majority of thyroidectomies are still performed by low volume surgeons (<25 cases yearly), the literature suggests lower complication rates when thyroidectomy is performed by high-volume surgeons at high-volume centers [2, 3]. There have been recent trends toward more cases being performed by high-volume centers, and this seems especially important in patients with more advanced locoregional disease [4]. Like most cancers, the management of thyroid cancer is best performed by a multidisciplinary team comprised of surgeons, endocrinologists, nuclear medicine specialists, and oncologists. The role of the surgeon is primarily in the initial workup and surgical treatment of thyroid cancer. The majority of patients with differentiated follicular-derived thyroid cancer (papillary and follicular thyroid cancer) require a single surgery; however the appropriate extent of the initial surgery (hemithyroidectomy versus total thyroidectomy, with or without lymph node dissection) is key to preventing persistent disease. The prognosis of papillary and follicular thyroid cancer is excellent; however persistent or recurrent disease can occur in 10–20% of patients and is treated with remedial surgery, additional radioiodine therapy, and/or systemic treatments [1]. This chapter will describe the preoperative considerations, the extent of surgery, the operative approach to thyroidectomy, and the complications related to thyroid surgery for papillary and follicular thyroid cancer.

Preoperative Considerations

Accurate preoperative clinical staging of papillary and follicular thyroid cancer is essential as it determines the appropriate surgical approach for each patient. The extent of disease of the primary tumor and the presence of lymph node metastases

D.T. Hughes, M.D. (✉) • P.G. Gauger, M.D.
Division of Endocrine Surgery, Department of Surgery, University of Michigan, University of Michigan Hospitals and Health Centers,
2920 Taubman Center, SPC 5331, 1500 East Medical Center Drive, Ann Arbor, MI 48109-5331, USA
e-mail: davhughe@umich.edu

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will dictate the appropriate extent of surgery (hemithyroidectomy, total thyroidectomy, lymphadenectomy). Residual lymph node metastasis is the most common etiology of persistent and recurrent thyroid cancer after initial surgery and radioactive iodine treatments and is primarily due to incomplete initial surgery. Preoperative clinical staging relies primarily on physical exam and cervical ultrasound as indicators of both T stage and N stage. Physical exam findings which are predictive of extrathyroidal extension include nodules which are fixed to the overlying strap muscles or underlying trachea and patients with new onset vocal cord paralysis due to recurrent laryngeal nerve invasion. Palpable pathologic lymphadenopathy (usually in the level 3 and 4 lymph node basins) in the setting of known thyroid cancer is generally indicative of lymph node metastasis.

Cervical ultrasound is the primary imaging modality used in the pre- and postoperative setting for thyroid cancer and should be performed in every patient to assess both the primary tumor and cervical lymph nodes (Fig. 12.1). Preoperative ultrasound should include evaluation of the thyroid, the central neck (lymph node level VI), and the lateral neck (lymph node levels II–V). Failure to image the lateral neck can result in missed lymph node metastasis which will lead to persistent disease. Surgeon-performed ultrasound is beneficial as it allows the operating surgeon to evaluate for signs of extrathyroidal extension and the presence and location of nodal metastasis and will help guide the operative plan.

While not always required, cross-sectional imaging, typically with CT with IV contrast, is useful to evaluate the central neck (level VI) and superior mediastinum (level VII) which is often not well visualized on ultrasound. This is especially useful if initial assessment suggests significant regional nodal disease. The findings are very important for planning a thorough initial operation, and the potential for iodinated contrast impacting eventual radioactive iodine scan does not justify not performing this imaging study. CT is also helpful in evaluating patients for tracheal invasion and patients with extensive lymph node metastasis (Fig. 12.2).

Fine-needle aspiration (FNA) biopsy is also important in assessing the primary thyroid nodule and for confirming the presence of lymph node metastasis through cytology and thyroglobulin aspirate washout [5]. FNA of lymph node metastases can often be nondiagnostic or read as negative making inclusion of thyroglobulin aspirate measurement an important adjunct in the assessment of cervical lymph nodes. This is important preoperative information because patients with metastatic lymph nodes in the central or lateral neck should have a compartment-orientated lymph node dissection along with total thyroidectomy rather than expecting radioiodine therapy to eradicate bulky nodal disease which is generally ineffective [1].

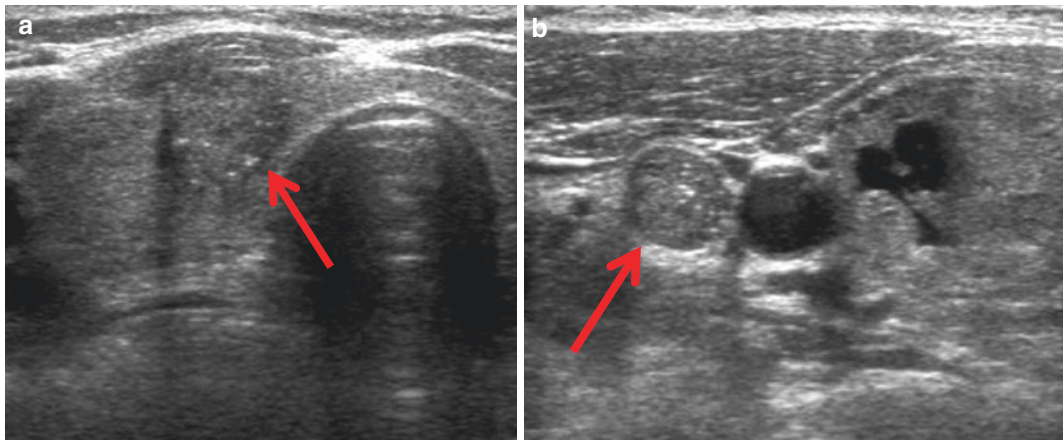

Fig. 12.1 *Red arrow* indicates thyroid nodule (**a**) and lymph node (**b**) with ultrasound characteristics typical of papillary thyroid cancer

Evaluation of vocal cord function is also important prior to surgery for thyroid cancer. Subjective complaints of hoarseness and the surgeon's assessment of the voice can help guide the use of vocal cord assessment. Patient's complaints of voice changes seem less predictive than an experienced surgeon's assessment with regard to vocal cord paralysis, although there should be a low threshold for vocal cord assessment in patients with voice dysfunction [6].

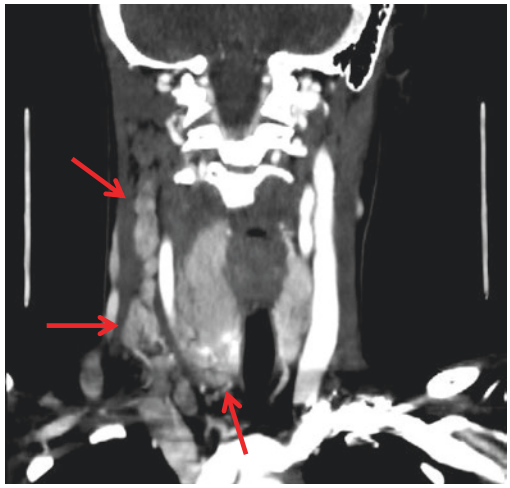

Fig. 12.2 *Red arrows* indicate a primary tumor in the inferior aspect of the right thryoid lobe with multiple, enlarged metastatic lymph nodes in the right lateral neck

Analysis of vocal cord function can be accomplished with several techniques. Mirror laryngoscopy can be performed easily with minimal time and cost; however its utility can be limited by incomplete visualization of the vocal cords in some patients. Laryngoscopy remains the gold standard for the diagnosis of vocal cord pathology. Flexible laryngoscopy will achieve complete visualization of the vocal cords and can be performed in the office, but it does require special equipment (Fig. 12.3). Transcervical ultrasound assessment of vocal cord function has also been shown to be effective however does require some training and can be limited in male patients with laryngeal cartilage calcification (Fig. 12.4) [7, 8]. The use of preoperative vocal cord assessment can be applied on a routine basis for all patients having thyroid surgery or on a case-by-case basis for those patients with voice dysfunction or those with higher risk of vocal cord dysfunction due to thyroid pathology or prior neck surgery. Patients having prior surgeries including prior thyroid surgery, cervical spine surgery, or mediastinal surgery have a risk of recurrent laryngeal nerve injury and should therefore have preoperative vocal cord assessment. Preoperative vocal cord paralysis in a patient with thyroid cancer is generally predictive of extrathyroidal extension of an invasive primary tumor or less commonly due to

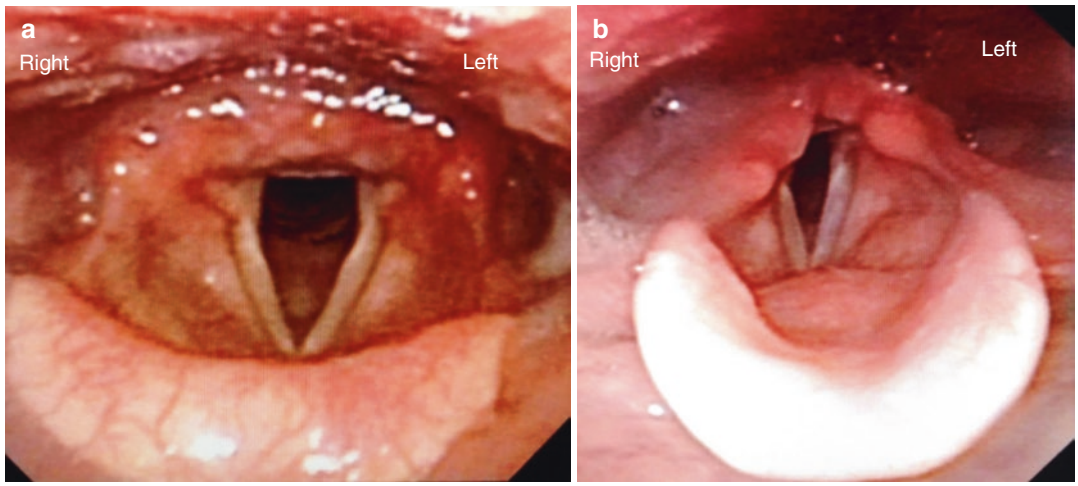

Fig. 12.3 Flexible laryngoscopy. (**a**) Normal. (**b**) Right vocal cord paralysis with right vocal cord in paramedian position, shortening of the vocal cord length and anterior displacement of the arytenoid cartilage

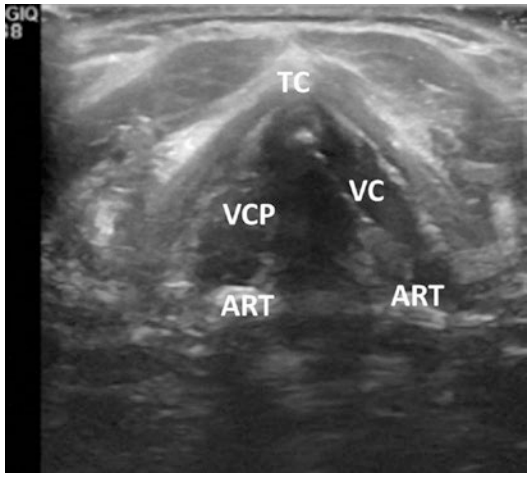

Fig. 12.4 Transcutaneous ultrasound for vocal cord functional analysis demonstrating right vocal cord paralysis with vocal cord in the paramedian position (*TC* thyroid cartilage, *VC* vocal cord, *VCP* vocal cord paralysis, *ART* arytenoid) [Carneiro-Pla D, Miller BS, Wilhelm SM, Milas M, Gauger PG, Cohen MS, Hughes DT, Solorzano CC. Feasibility of surgeon-performed transcutaneous vocal cord ultrasonography in identifying vocal cord mobility: A multi-institutional experience. Surgery. 2014;156:1597–602]

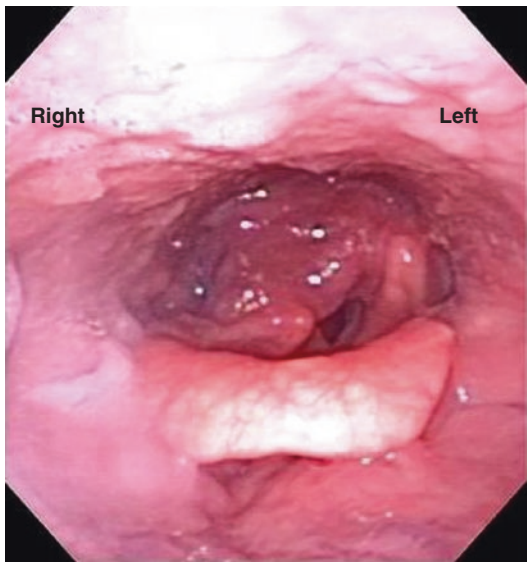

Fig. 12.5 Flexible laryngoscopy with full thickness invasion of thyroid cancer with right vocal cord paralysis

extranodal extension of metastatic lymph nodes in the central neck. In rare circumstances laryngoscopy can also evaluate for full-thickness invasion of the laryngeal structures (Fig. 12.5).

Extent of Surgery: Thyroid Lobectomy vs Total Thyroidectomy

Previous American Thyroid Association Guidelines for the Management of Thyroid Nodules and Differentiated Thyroid Cancer (2009) recommended total thyroidectomy for all differentiated thyroid cancers >1 cm in size regardless of other pathologic features [9]. This recommendation was based on studies which demonstrated lower recurrence rates with total thyroidectomy compared to thyroid lobectomy [10–12]. The new American Thyroid Association Guidelines (2015) now recommend that thyroid lobectomy is sufficient for low-risk, well-differentiated thyroid cancers <4 cm in size without extrathyroidal extension and without lymph node metastasis [1, 13–16]. The specific advantages and disadvantages of this strategy for individual patients should be thoroughly discussed to arrive at the best decision. The advantages of thyroid lobectomy for low-risk papillary and follicular thyroid cancer include the absent risk of postoperative hypoparathyroidism and the general lack of need for thyroid hormone supplementation in patients with otherwise normal thyroid glands (about 15% of patients will require thyroid hormone replacement after thyroid lobectomy) [17]. Total thyroidectomy is still recommended for differentiated thyroid cancers larger than 4 cm, those with extrathyroidal extension, lymphovascular invasion, lymph node metastasis, or distant metastasis. Total thyroidectomy also allows for adjuvant radioiodine therapy which is generally indicated for those patients with more advanced disease. The decision to perform total thyroidectomy or consideration of thyroid lobectomy must be based on accurate and complete preoperative assessment as to the extent of disease. Ultrasound of the thyroid, central neck, and lateral neck should be performed in every patient, and any suspicion of extrathyroidal extension, multifocal disease, or lymph node involvement should lead to total thyroidectomy. Realizing that ultrasound has limited ability to detect involved central compartment lymph nodes, patients with evidence of lymph node metastasis should have a compartment-orientated

lymph node dissection of any involved compartments (central or lateral neck). Selective removal or "berry picking" of involved nodes is not recommended. Any patient with lateral neck lymph node involvement should have at least a central (contralateral VIA and ipsilateral VIA & B) and ipsilateral lateral neck lymph node dissection as most patients with lateral neck lymph node metastasis will also have central compartment nodal disease. When deciding total thyroidectomy versus thyroid lobectomy for low-risk disease, patient preference with regard to thyroid hormone replacement and need for follow-up of any contralateral lobe nodularity should be considered. Total thyroidectomy does allow for thyroglobulin monitoring during thyroid cancer surveillance which may be useful in the detection of persistent or recurrent disease. Total thyroidectomy does carry higher risks of operative complications as compared to thyroid lobectomy, and total thyroidectomy does have a risk of hypoparathyroidism which is absent in thyroid lobectomy. There is generally no role for subtotal lobectomy or subtotal thyroidectomy in the surgical treatment of thyroid cancer, and either complete thyroid lobectomy, total thyroidectomy, or near-total thyroidectomy should be the primary modalities of surgical treatment.

Operative Technique of Thyroidectomy

The operative technique of thyroidectomy for thyroid cancer is similar to that of thyroidectomy for benign disease with the exception of added compartment-orientated lymph node dissection in selected patients. Most thyroidectomies are performed under general anesthesia. Endotracheal intubation does allow for intraoperative monitoring of recurrent laryngeal nerves and external branch of the superior laryngeal nerves. Multiple studies have analyzed the use of intraoperative nerve monitoring during thyroidectomy, and there is no evidence to suggest that nerve monitoring reduces nerve injury rates [18, 19]. However, knowledge of recurrent laryngeal nerve function during total thyroidectomy can be important. A neuropraxia of a unilateral recurrent laryngeal nerve may prompt a surgeon not to proceed with contralateral thyroidectomy, or to proceed with this as a staged procedure, to avoid the possibility of a disastrous bilateral recurrent laryngeal nerve injury with subsequent tracheostomy [20]. Nerve monitoring can be especially useful in cases with extrathyroidal extension or central neck nodal metastases or those having remedial thyroid surgery after previous neck surgery.

The operative technique of thyroidectomy has not changed significantly in recent decades aside from a trend toward smaller incisions, the use of nerve monitoring, and the use of energy devices to aide in dissection and hemostasis. Remote access thyroidectomy (transaxillary, "facelift," etc.) may be a more involved approach with significant dissection involved to access the thyroid and has unique complications compared to the traditional transcervical approach. The benefits of remote access thyroidectomy should be considered purely cosmetic as they avoid an incision in the anterior neck.

Traditional thyroidectomy begins with the patient supine on the operating table. A shoulder roll can be used to provide gentle extension of the neck; however hyperextension should be avoided to prevent posterior neck pain. Positioning the operating table in a supine or Semi-Fowlers/"beach chair" position with a small amount of Trendelenburg may further allow for extension of the neck. Antibiotic prophylaxis is generally not indicated for a typical thyroidectomy, and deep vein thrombosis prophylaxis can be used in selected patients as guided by standard risk stratification schema.

Once the neck is prepped and draped a horizontal, lower neck, collar incision is made, typically between the sternal notch caudally and the cricoid cartilage cranially (Fig. 12.6). Placing the incision in a natural skin crease in the anterior neck helps to provide cosmetically favorable results. After division of the platysma muscle, sub-platysmal flaps are created to provide exposure to the underlying strap muscle from a level above the cricoid cartilage inferiorly to the sternal notch. The median raphe of the strap muscles is

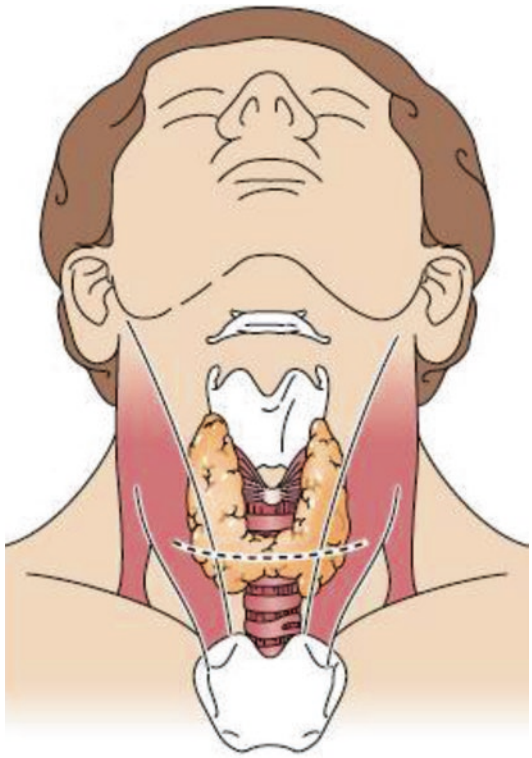

Fig. 12.6 Incision placement for thyroidectomy with or without central neck dissection (Permission: editors, Michael W. Mulholland ... [and others], with 216 contributors; illustrations by Holly R. Fischer. Greenfield's Surgery: Scientific Principles and Practice. Philadelphia, PA: Lippincott Williams & Wilkins, 2006. Print)

then divided, and the sternohyoid and sternothyroid muscles are dissected away from the underlying thyroid and paratracheal space and retracted laterally. Division of the strap muscles is generally not required during thyroidectomy but may be helpful for very large thyroid nodules or goiters. Strap muscle invasion from malignant tumors in the anterior aspect of the thyroid may require excision of the sternothyroid and/or sternothyroid muscles with the intention to obtain a negative margin. Division or resection of the strap muscles, as well as denervation by injury to the ansa cervicalis, generally causes minimal morbidity. If divided for exposure, the strap muscles are usually reapproximated at the termination of the procedure with horizontal mattress sutures.

Once the perithyroidal space is entered, the middle thyroidal veins, if present, are identified as they course over the anterior common carotid artery and can be ligated close to the thyroid capsule. Identification of the recurrent laryngeal nerve(s) should be considered a necessity in every thyroidectomy procedure. Two methods of recurrent laryngeal nerve identification and dissection have been described: proximal to distal (finding the nerve low in the central neck as it emanates from the mediastinum and tracing the nerve cranially as it courses behind the thyroid to eventually insert into the cricothyroid muscle) and distal to proximal (ligating the superior pole of the thyroid first, reflection of the upper thyroid away from the cricothyroid space, and identification of the recurrent laryngeal nerve as it inserts into the cricothyroid muscle and then tracing it caudally until it travels into the mediastinum). Recurrent laryngeal nerve function can be assessed with nerve monitoring either through stimulation of the nerve directly or stimulation of the ipsilateral vagus nerve in the carotid sheath [21]. The technique also facilitates early identification of the key nerve structures as dissection begins. However there are numerous pitfalls in the use of nerve monitoring including both false-positive and false-negative signals; therefore knowledge of how to troubleshoot nerve monitoring problems is essential.

The inferior and superior thyroid arteries should be dissected "high" on the thyroid capsule so as to avoid devascularization or inadvertent removal of the inferior and superior parathyroid glands, respectively. If a parathyroid gland cannot be left in situ or if a normal parathyroid gland appears devascularized, morselization of the gland and re-implantation into the sternocleidomastoid muscle belly should be employed. Frozen section confirmation of parathyroid tissue with a small biopsy of the parathyroid gland can ensure avoidance of inadvertent re-implantation of metastatic lymph nodes. Dissection of the superior thyroid pole and its vessels should occur close to the thyroid with lateral retraction of the superior pole of the thyroid gland so as to avoid injury to the external branch of the superior laryngeal nerve which can have varying anatomic relationship to the superior thyroid vessels. After dissection of the superior and inferior thyroid poles, continued dis-

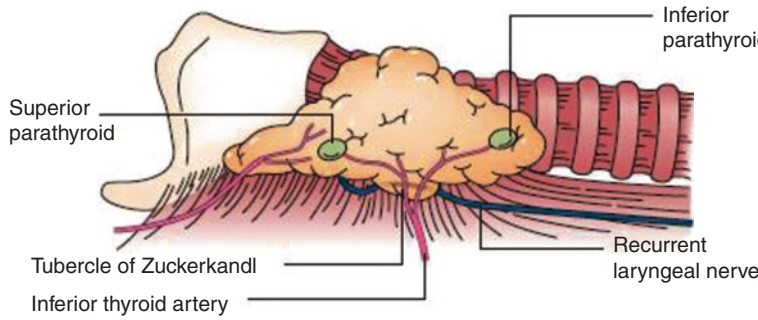

Fig. 12.7 Anatomic relationship of recurrent laryngeal nerve, tubercle of Zuckerkandl, and inferior thyroid artery during thyroidectomy (Permission: editors, Michael W. Mulholland ... [and others], with 216 contributors; illustrations by Holly R. Fischer. Greenfield's Surgery: Scientific Principles and Practice. Philadelphia, PA: Lippincott Williams & Wilkins, 2006. Print)

section along the anterior surface of the recurrent laryngeal nerve posterior to the thyroid gland toward its insertion into the cricothyroid muscle will allow for ligation of the inferior thyroid artery and its branches and reflection of the thyroid lobe anteromedially. Again, care should be taken to ligate distal branches of the inferior thyroid artery "high" on the thyroid at the level of the thyroid capsule to avoid devascularization of the parathyroid glands which typically obtain blood supply from this artery. The relationship of the inferior thyroid artery to the recurrent laryngeal nerve can vary, and continuous visualization of the recurrent laryngeal nerve and gentle dissection and traction on the thyroid gland will help avoid inadvertent ligation or stretch injury of the nerve (Fig. 12.7). The tubercle of Zuckerkandl is an embryologic remnant feature of the thyroid which is a posterior extension of the parenchyma that is close to the ligament of Berry (a fibrous attachment of the thyroid to the trachea near the insertion of the recurrent laryngeal nerve). When present, it often indicates the location of the recurrent laryngeal nerve and the superior parathyroid gland. Division of the Ligament of Berry should be performed with care while dissecting the thyroid away from the genu of the recurrent laryngeal nerve as it inserts into the larynx under the cricothyroid muscle. Adjusting traction to avoid severe nerve angulation at this point is a key fine technical point to avoid stress on the nerve at this genu. Frequently found near the entrance of the recurrent nerve into the larynx is a small artery posterior to the nerve. It usually requires ligation taking care to avoid kinking or impingement of the nerve. Energy devices should either be avoided or used with extreme caution while working adjacent to the nerve. Monopolar electrocautery should also be avoided in close proximity to the nerve, as the path of least resistance to the grounding pad may be through the nerve. The attachments of the thyroid to the anterior trachea can then be divided as the dissection moves medially and posterior to the isthmus of the thyroid past the midline. A pyramidal lobe may extend cranially from the isthmus near the midline and will extend into the thyrothymic tract toward the hyoid bone, and if present the pyramidal lobe should be excised with the specimen. If performing a total thyroidectomy, the contralateral thyroid lobe is removed in a similar manner. A lymph node dissection can be carried out as indicated and is discussed in subsequent chapters.

Special Circumstances in Thyroidectomy for Thyroid Cancer

Extrathyroidal extension of thyroid cancer is an infrequent occurrence; however surgeons performing thyroidectomy for malignancy should be familiar with its management. Preoperative cross-sectional imaging with CT and preoperative laryngoscopy can be helpful in determining the presence of extrathyroidal extension with tracheal invasion if suspected based on physical exam and/

or ultrasound. Management of extracapsular invasion into the overlying strap muscles is relatively straightforward and can be addressed with excision of the overlying strap muscle to achieve a grossly negative margin. Strap muscle excision does not seem to have any effects on postoperative swallowing or voice function [22]. Local tumor involvement of the trachea can be moderate adherence, partial thickness invasion, or full thickness invasion. Tumors adherent to the trachea without evidence of invasion can be shaved off the tracheal cartilage to obtain a grossly negative margin. In partial thickness invasion into the tracheal or laryngeal cartilage, a partial thickness shave resection preserving the cartilaginous support of trachea is appropriate and capable of obtaining a grossly negative margin. Full thickness invasion which requires tracheal ring resection can be repaired primarily up to five tracheal rings (approximately 4 cm) after mobilization of the tracheoesophageal complex. Muscle flap coverage with strap muscle or sternocleidomastoid muscle can be used to cover the repair. Cases with extensive tracheal, esophageal, or pharyngeal invasion, which would require total laryngectomy, are very rare in differentiated thyroid cancer and are more typical of undifferentiated or anaplastic thyroid cancer. Extrathyroidal extension involving the recurrent laryngeal nerve should be suspected in the setting of preoperative unilateral vocal cord paralysis. Intraoperatively, resection of an already nonfunctional nerve should be considered routine in attempts to achieve grossly negative margins. In patients with extrathyroidal extension involving a functional recurrent laryngeal nerve, a shave resection to preserve the nerve anatomically and functionally should be attempted. Recurrent laryngeal nerve monitoring is particularity helpful in these difficult thyroidectomies with extrathyroidal extension.

Postoperative Care

The surgical complications of thyroidectomy include both transient and permanent complications. Transient complications include postoperative hemorrhage, infection, temporary voice changes due to neuropraxia of the recurrent laryngeal or external branch of the superior laryngeal nerve, and temporary hypocalcemia due to hypoparathyroidism. Hemorrhage after thyroidectomy occurs in approximately 1–3% of cases, and most hematomas occur in the first 6–8 h after surgery. Postoperative hematomas can be life-threatening due to airway compromise, and emergent surgical management with hematoma decompression can be lifesaving for those with stridor or significant compression; however this is generally a rare situation. Airway compromise is most commonly due to mucosal edema from venous obstruction due to the hematoma. Attempts at intubation are often unsuccessful, and the required sedation can make ventilation impossible. The initial treatment is evacuation of the hematoma, even if done at the bedside. Usually however, if the patient is ventilating adequately, the patient can be transported to the operating room where more controlled intervention is possible.

Postoperative infections occur in around 1% of cases and may require abscess drainage and/or antibiotic therapy. Recurrent laryngeal nerve injury rates vary from 1 to 15% with lower rates generally seen with higher volume surgeons [23]. Recurrent laryngeal nerve injuries typically present as hoarseness of the voice, inability to generate a strong percussive cough, and aspiration with drinking liquids. Nerve dysfunction can be confirmed with laryngoscopic exam which will demonstrate a nonmobile ipsilateral vocal cord which lies in the paramedian position. Some patients may have subtle voice changes or even no appreciable voice changes with nerve injuries, thus contributing to a likely under-reporting of this complication. Bilateral nerve injuries will cause bilateral nonmobile, paramedian vocal cords which can cause airway compromise, and tracheostomy is often required. Neuropraxias, or stretch injuries, will typically improve over several weeks to months following surgery. Transection of the nerve without reconstruction will result in permanent vocal cord paralysis. Reanastomosis of a transected or resected recurrent laryngeal nerve either primarily or to the ansa cervicalis can have some benefit in voice

quality in about 50% of patients. The graft from ansa cervicalis will not restore volitional control but will help add tone and bulk to the vocal fold and avoid synkinesis [24].

Postoperative hypoparathyroidism is attributed to inadequate parathyroid hormone production by the parathyroid glands after bilateral thyroidectomy. Rates of temporary hypoparathyroidism range from 10 to 30% in some series; however the rates of permanent hypoparathyroidism are much lower in the 1–3% range [25]. Hypocalcemic symptoms include paresthesias of the hands, feet, and perioral areas but may progress to muscle cramping and in rare cases tetany and cardiac arrhythmias. Hypocalcemia is treated with oral calcium supplements (calcium citrate or calcium carbonate) with or without vitamin D (cholecalciferol or ergocalciferol). Calcitriol (1,25-dihyroxycholecalciferol) is an active metabolite of vitamin D which increases the absorption of calcium through the gut and increases the resorption of calcium in the kidney. Calcitriol is effective in the treatment of hypocalcemia when combined with calcium supplementation in doses of 0.25–1 μg daily in divided doses (maximum 2 μg/day). Maintaining normal magnesium levels is also critical to effective treatment of postoperative hypoparathyroidism. Postoperative parathyroid hormone levels shortly after surgery may help guide the appropriate use and dosing of calcium and vitamin D supplements following thyroidectomy [26]. Permanent hypoparathyroidism is defined as a continued requirement for supplementation with low parathyroid hormone levels more than 6 months following surgery. It should be a rare complication, particularly if the surgeon has a low threshold for reimplanting parathyroid glands that appear in any way ischemic. Permanent hypoparathyroidism is treated similarly to temporary hypoparathyroidism but may also include the use of calcium sparing diuretics or injectable parathyroid hormone (PTH) formulations.

Conclusions

Thyroidectomy for differentiated thyroid cancer is associated with excellent oncologic outcomes for most patients and has low complication rates with experienced surgeons. Accurate and complete preoperative assessment to determine the extent of disease both of the primary tumor and cervical lymph nodes is of upmost importance to determine the appropriate extent of surgery and prevent residual disease.

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Lymph Node Dissection for Differentiated Thyroid Cancer

13

Jeff Moley

Introduction

Thyroid cancer is increasing in incidence nationwide [1]. In 2013, 60,220 new cases of thyroid cancer were diagnosed in the United States, with a disproportionate number of females and patients under age 55 affected [2]. It is estimated that in 2016, thyroid cancer in females will outnumber males by approximately 4:1. Studies from Asia report that thyroid cancer has become the most commonly diagnosed cancer in women [3]. Primary management is surgical, and thyroidectomy is recommended [4]. The most common site of spread of thyroid cancer is to cervical nodes, with the central nodal compartment affected most often [5–7]. Despite the rising incidence of thyroid cancer, prognosis remains favorable, reflecting the indolent nature of the disease. Ten-year survival rates for patients with papillary, follicular, and Hurthle cell carcinomas are 93%, 85%, and 76%, respectively (National Cancer database).

There is considerable controversy surrounding the appropriate treatment of papillary thyroid carcinoma (PTC), most of which centers around the extent of thyroidectomy, and the dissection and removal of cervical lymph nodes. Over the past several decades, there have been advocates for extensive surgery and lymph node dissection and, lately, advocates for more limited surgery or even no surgery for some differentiated thyroid cancers. The performance of routine total thyroidectomy and lymph node dissection has been shown to be an effective strategy for medullary thyroid carcinoma, which is not responsive to thyroid suppression or radioactive iodine treatment. PTC, however, is well treated by these adjuvant modalities and, in general, has an excellent prognosis [8]. The benefit of extensive operations for routine cases of PTC without clinical evidence of nodal metastases has not been proven, and this practice is not employed by most surgeons in the United States. Node dissection is generally reserved for patients with clinically detectable adenopathy.

Historically, the operative approaches to those patients with clinically enlarged cervical nodes have included simple excision of involved lymph nodes; modified or functional neck dissection with sparing of the sternocleidomastoid muscle, the jugular vein, and the spinal accessory nerve; and classic radical neck dissection. In the 1950s, Frazell and Foote [9] reported the results of routine radical neck dissection in patients with papillary thyroid carcinoma, a commonly performed procedure at that time for these relatively indolent tumors. In a subsequent report, after further analysis of their data and longer follow-up, they

J. Moley
Section of Endocrine and Oncologic Surgery, Department of Surgery, Washington University School of Medicine, Campus Box 8109, 660 S. Euclid Ave., St. Louis, MO 63110, USA
e-mail: moleyj@wustl.edu; moleyj@wudosis.wustl.edu

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changed their surgical policy for the operative treatment of this malignancy in patients who had no clinically evident lymph node involvement. They calculated that, in order to prevent the development of palpable cervical metastases in a single patient, eight elective neck dissections would have to be performed. Since lymph node recurrence did not appear to affect survival in these patients, they concluded that routine elective radical neck dissection was not justified [9].

Over the past 50 years, the widespread use of routine extensive lymph node dissections for patients with papillary thyroid carcinoma without clinical evidence of nodal disease has diminished, and major controversies in this field remain the extent of the thyroid resection, which is discussed elsewhere in this monograph, and extent of lymphadenectomy.

Lymphatic Anatomy of the Neck

Primary thyroid tumors may invade adjacent structures, including the larynx, trachea, recurrent laryngeal nerve, and esophagus. Once the primary tumor is established, metastasis to regional lymph nodes frequently occurs [10, 11]. There are hundreds of lymph nodes in the neck, and in the normal state, they range in size from a few millimeters to 3–4 centimeters. These nodes are clustered in groups or compartments that are continuous with each other, embedded in fat, and connected by systems of dermal, subcutaneous, and deep lymphatic channels (Fig. 13.1). They are continuous with facial, mediastinal, and axillary node clusters. Spread of thyroid cancer usually, but not always, occurs in a predictable stepwise pattern. The anatomic boundaries of the

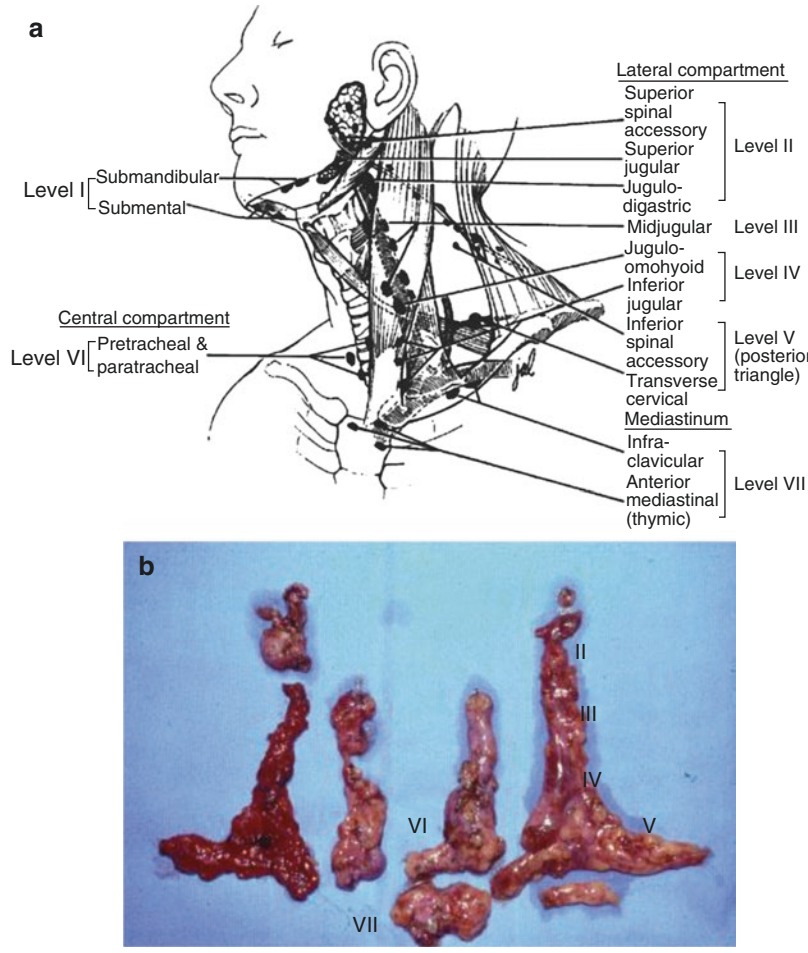

Fig. 13.1 (**a**) Lymph node groups in the neck. From Fialkowski EA, Moley JF. Current approaches to medullary thyroid carcinoma, sporadic, and familial. (**b**) Specimen from a patient following central and bilateral neck dissection. Level II nodes are from the high jugular nodes; level III, mid-jugular nodes; level IV, low jugular nodes; level V, posterior triangle nodes; level VI, paratracheal nodes; level VII, superior mediastinal nodes

central compartment (level VI) are the carotid arteries bilaterally, the hyoid bone superiorly, and the innominate artery inferiorly [5, 12]. In addition to the trachea and esophagus, the central compartment contains the thyroid, parathyroids, thymic horns, recurrent laryngeal nerves, central neck lymph nodes, and fat. Level IV nodes are adjacent to the central compartment, extending from deep to the internal jugular vein, including the pre-scalene fat pad to the lateral border of the sternocleidomastoid muscle. Important structures on the deep aspect of this nodal compartment are the sympathetic chain and thoracic duct medially, the transverse cervical artery and vein, the phrenic nerve, and the brachial plexus laterally. Level III and II nodal groups are anterior to the scalene, extending from the omohyoid muscle to the submandibular gland superiorly. Important structures in this region include the phrenic nerve, the cervical plexus (including the great auricular nerve), and the spinal accessory nerve (SAN) (cranial nerve XI). Both are adjacent to Erb's point. The marginal mandibular nerve and the hypoglossal nerve are also at risk in superior dissections that approximate the submandibular gland and the carotid bifurcation.

Frequency of Node Involvement

In patients with thyroid cancer, lymph nodes in the central compartment (levels VI) are most often involved, followed by levels III and IV on the ipsilateral, and frequently the contralateral, side (Fig. 13.1). Involvement of levels II, V, and VII may also occur. Regional lymph node metastases are present in the majority of patients with palpable primary tumors. Ipsilateral neck dissection, also called "functional" or "modified radical" neck dissection, in which all or portions of levels II, III, IV, and V lymph nodes are removed, should be considered in patients suspected to have locally advanced disease based on clinical exam and imaging.

In most studies that have addressed the issue, the frequency of cervical lymph node metastases in papillary thyroid carcinoma has been reported to be high. Frazell and Foote reported that lymph node metastases were present in 71% of 385 patients with differentiated thyroid cancer [9]. Cody and Shah [13] reported that 22 of 23 patients with locally invasive well-differentiated papillary thyroid carcinoma were found to have metastatic disease in lymph nodes at the time of thyroidectomy and neck dissection. Mizuno and colleagues [14] found lymph node metastases in 89% of 71 patients with papillary thyroid carcinoma treated by thyroidectomy and routine neck dissection. They noted a high incidence of metastases to pretracheal and peritracheal lymph nodes. Sugino and colleagues [15] reported a series of 746 patients with papillary thyroid carcinoma treated by thyroidectomy and modified radical neck dissection. Though it is not possible to calculate the exact incidence of nodal metastases in this series from the data provided, they reported that lymph node metastases were more frequent in younger patients and that distant metastases were more common in older patients. Tisell [16] reported node metastases in 70% of men and 45% of women in his series of operations for papillary thyroid carcinoma (overall incidence of 51% of a total of 195 cases). It is clear, therefore, that lymph node metastases are extremely common in papillary thyroid carcinoma and that, if one routinely performs a lymph node dissection at the time of thyroidectomy for this disease, lymph node metastases will be found on pathological examination.

The pattern of metastatic spread in differentiated thyroid cancer is similar to that seen in medullary thyroid cancer (MTC) [5]. In patients with palpable unilateral intrathyroidal MTC tumors, we found lymph node metastases in 81% in central level VI, in 81% in ipsilateral levels II through V, and in 44% in contralateral levels II through V lymph node groups. In patients with bilateral intrathyroidal tumors, lymph node metastases were present in 78% of central level VI lymph node groups, in 71% of level II through level V lymph nodes ipsilateral to the largest intrathyroidal tumor, and in 49% of level II through level V lymph nodes contralateral to the largest intrathyroidal tumor. This is an alarmingly high incidence of lymph node involvement. In this same series, we found that intraoperative lymph node

assessment by the surgeon had a low sensitivity (64%) and specificity (71%) for detecting positive lymph nodes. Therefore, reliance on intraoperative assessment will miss clinically involved lymph nodes up to one-third of the time. These findings can be applied to differentiated thyroid cancer, which spreads in the same manner. Small deposits of differentiated thyroid cancer, however, are effectively treated by radioactive iodine and thyroid hormone suppression; therefore, surgical removal of all nodal metastatic disease is not as important as in medullary thyroid cancer [8].

Prediction of Involvement of Adjacent Compartments

The burden of lymph node metastasis in the central compartment can help predict lateral compartment involvement. In one retrospective analysis of medullary thyroid cancer, the absence of positive central lymph nodes correlated with a 10% risk of metastatic involvement of ipsilateral level II to V lymph nodes. However, the risk of lateral compartment involvement increased to 77% with 1–3 positive central lymph nodes and to 98% with ≥4 positive central lymph nodes [17, 18]. Contralateral level II–V metastases were observed in 4.9% of cases when no central lymph nodes were positive, in 28% when 1–9 central lymph nodes were positive, and in 77% of cases when ≥10 central lymph nodes were positive. Therefore, the decision to perform lateral neck dissection can be influenced by the extent of central compartment lymph node involvement. If extensive central lymph node metastases are present, even with negative preoperative imaging, serious consideration should be given to performing an ipsilateral functional neck dissection given the high likelihood of lateral lymph node involvement.

Nomenclature of Operations

There are several names for systematic lymph node dissections described in patients with papillary thyroid carcinoma. The standard "radical" neck dissection includes removal of lymph nodes from levels II, III, IV, and V and sometimes level I en bloc with the sternocleidomastoid muscle, internal jugular vein, and spinal accessory nerve. In the past, this operation was performed in conjunction with thyroid lobectomy or subtotal thyroidectomy for differentiated thyroid cancer. Routine removal of paratracheal (level VI) and upper mediastinal nodes (level VII) was often not discussed. In a modified radical neck dissection, the lymph nodes are removed from levels II, III, IV, and V with sparing of muscle, vein, and accessory nerve. The term "functional neck dissection" generally refers to a modified radical neck dissection, but the nodal groups removed are specified. For example, occasionally surgeons do not remove level II or level V nodes during a lateral neck dissection, in which case, the operation could be specified as "functional neck dissection with removal of level III and level IV lymph nodes."

Impact of Lymph Node Dissection on Outcome in PTC

Until recently, most studies have suggested that, although the presence of lymph node metastases in papillary thyroid carcinoma is associated with higher recurrence rates, their presence does not affect survival. Studies of survival in papillary thyroid carcinoma are difficult, because of the indolence of the tumor and because few patients die from the disease. Woolner et al. [19] reported only 18 deaths in 656 patients with papillary thyroid carcinoma who were followed for 40 years. Many studies have reported no influence of lymph node metastases on outcome in patients with papillary thyroid carcinoma. Mazzaferri et al. [20] reported that, although recurrences were more frequent in patients with lymph node metastases, patient survival was not adversely affected. In his study of 576 patients with papillary thyroid carcinoma, there were no statistically significant differences in recurrence or death comparing patients who underwent simple excision of palpable cervical node metastases with those who had systematic modified

radical or radical neck dissection for excision of nodal metastases. Samaan and colleagues [21] compared 340 patients with apparent gland-confined differentiated thyroid carcinoma to 333 patients with lymph node metastases and found no difference in survival. These results were verified by numerous other studies. McHenry and colleagues [22], however, noted higher recurrence rates in patients with lymph node metastases from papillary thyroid carcinoma and recommended routine cervical lymph node sampling with modified radical neck dissection in patients with metastatic carcinoma evident on frozen section. Other authors have advocated a routine aggressive "microdissection" or "compartment dissection" in patients with papillary thyroid carcinoma. Tisell and colleagues, [23] using an approach similar to the microdissection they applied to reoperation for MTC, reported 195 patients treated for papillary thyroid carcinoma. Dissection of the central compartment with excision of pretracheal and paratracheal lymph nodes was routinely performed, and lateral dissection, with removal of levels II, III, IV, and IV nodes, was performed in 25 patients because macroscopically positive lateral nodes were identified. The average operative time was 3.9 h. Radioiodine therapy was given to only seven patients, three because of pulmonary metastases and four because of locally invasive stage III tumors. Only three (1.6%) patients died of thyroid cancer, all of whom had survived for more than 17 years after surgery. One patient (0.5%) had a permanent recurrent nerve injury, and six patients (3.1%) had permanent hypoparathyroidism. These are excellent results and compare favorably with survival rates from other reported series. In Mazzaferri's series, the 10-year mortality following operation for thyroid carcinoma was 0.6% after total thyroidectomy, 1.5% after subtotal thyroidectomy, 1.7% after simple excision of lymph node metastases, and 0.7% after neck dissection. In many other reported series, it is difficult to extrapolate disease-specific mortality rates as a function of the operative procedure performed. In a retrospective series from Japan, Mizuno and coworkers [14] described the routine performance of bilateral cervical lymph node dissection for non-advanced papillary thyroid carcinoma in 71 patients. In an additional 33 patients, sternotomy with mediastinal dissection was performed. The authors found pretracheal and tracheoesophageal lymph node metastases in 51% of the former group and in 48% of the latter. They concluded that such operations would prevent the morbidity of central recurrence with airway or vascular invasion. Scheumann and colleagues [24] reported their experience with routine compartment-oriented node dissection for papillary thyroid carcinoma. They reviewed their institution's experience with this disease and found a significant correlation between lymph node status and recurrence and survival. Their approach in all patients with papillary thyroid carcinoma is to perform a systematic total thyroidectomy and compartment-oriented microdissection of the central neck (levels VI and VII). In patients with macroscopically involved lateral or mediastinal nodes, lateral dissection or median sternotomy with mediastinal node dissection is performed. The authors reported an improvement in recurrence and survival rates, though statistical validation of this conclusion was not provided. In an invited commentary of that study, Blake Cady indicated that the experience of the authors was at odds with almost all recent reports in the world's literature which indicated no influence of lymph node metastases on outcome of surgery for differentiated thyroid carcinoma. He also stated that the findings may be explained by the fact that these patients come from an iodine-deficient area, in which thyroid cancers are known to be more aggressive. Our group has shown that even for patients with persistent cervical lymph node disease after surgery, as seen on posttreatment radioactive iodine scanning, postoperative radioactive iodine therapy results in very high disease-free survival rates [8].

Prophylactic Central Neck Dissection in Differentiated Thyroid Cancer

Surgery, radioactive iodine, and thyroid hormone suppression are the mainstays of treatment for

thyroid cancer. Due to the lack of prospective randomized trials, many of the current guidelines for treatment of well-differentiated thyroid carcinoma remain controversial, including the extent of surgery and management of cervical lymph nodes. The central neck lymph node compartment is defined as tissue between the carotid arteries extending from the vascular pedicle superiorly to the sternal notch and subclavian artery inferiorly [5, 12, 25, 26]. These nodes have been found to frequently harbor metastases. The current National Cancer Comprehensive Network (NCCN) guidelines suggest that if cervical lymph nodes in well-differentiated thyroid cancer are clinically negative for disease, prophylactic central neck dissection can be considered but is not required [27]. Current American Thyroid Association (ATA) guidelines state "prophylactic central compartment neck dissection (ipsilateral or bilateral) may be performed in patients with papillary thyroid carcinoma with clinically uninvolved central lymph nodes, especially for advanced primary tumors (T3 or T4)" [26]. This is a grade C recommendation of expert opinion, and currently no randomized data is available to support that central node dissection impacts survival or recurrence rates in differentiated thyroid cancer. At a recent NIH meeting of thyroid cancer specialists, an informal poll of surgeons indicated that half of those present performed prophylactic central neck dissection routinely, while half did not.

Proponents of prophylactic central node dissection argue that the procedure may decrease recurrence and mortality rates, improves the accuracy of staging, decreases postoperative thyroglobulin levels, and may avoid reoperative surgery [24, 28–30]. Thyroglobulin levels were shown to be improved in patients treated with routine prophylactic central neck dissection [31]. The reported recurrence rates range up to 34% of patients, and among patients with local recurrence, 8% eventually die of thyroid cancer; with distant metastases, 50% die of thyroid cancer. They argue that removing the central neck lymph nodes provides data upon which to base decisions regarding whether or not to treat with radioactive iodine and removes potential sites of recurrence that may require reoperations that have higher complication rates [31].

Several retrospective studies, however, have shown that the presence of central lymph node metastases has little impact on predicting recurrence or survival. A recent meta-analysis of retrospective studies concluded that the addition of a central node dissection to total thyroidectomy has no effect on locoregional recurrence [32, 33]. Also, thyroglobulin levels are unreliable indicators of disease status after treatment and may continue to decline for years after therapy [34, 35]. Our group has shown that even for patients with persistent cervical lymph node disease after surgery, as seen on post treatment radioactive iodine scanning, postoperative radioactive iodine therapy results in very high disease free survival rates [8]. These data argue against the utility of exposing patients to additional surgical prophylactic procedures. Based upon data from randomized clinical trials, prophylactic lymph node dissection has been abandoned in breast cancer [36, 37] and malignant melanoma [38].

Published Guidelines for Treatment of Thyroid Cancer

Guidelines have been developed, published, and updated for most commonly treated cancers including thyroid cancer. The most widely used and cited guidelines for thyroid cancer are those published by the NCCN and the ATA [26, 27]. Published guidelines from high-level professional and government-supported organizations are an increasingly important source of information and guidance for clinicians treating thyroid and other cancer. These guidelines also summarize the current state of knowledge and point out deficiencies in data used to guide clinical decisions. The content of published guidelines is based upon data from published studies that have been vetted and discussed by experts who then compose the text of the guidelines. Current NCCN and ATA guidelines are vague regarding the routine use of prophylactic central neck dissection in early-stage thyroid cancer, because there are no data from prospective clinical trials. The guidelines suggest that the procedure be "considered" or "may be performed."

Technique of Neck Dissection for Thyroid Carcinoma

Preoperative Workup

If the patient is hoarse or if it is a large tumor, awake laryngoscopy should be done to observe cord motion and document abnormalities. If the patient has a vocal cord palsy on one side, special care must be taken with the functioning nerve, because bilateral palsies (even transient ones) often require tracheostomy. Tracheostomy in a patient after a thyroidectomy and central neck dissection is especially dangerous because the tube is adjacent to the innominate artery with no intervening central fat, nodes, and thymus to protect the artery. Innominate blowout may occur. If the patient has a vocal cord palsy on one side, consideration should be given to leaving tissue to cover the innominate artery or to do a unilateral procedure, in which the functioning nerve is not manipulated.

CT of the neck and chest should be done if there is evidence of significant cervical nodal involvement [39]. The presence of distant metastatic disease may influence the surgeon's choice of operation. If distant metastatic disease is detected, removal of the entire thyroid and all disease in the cervical nodes should be done to allow for optimal antitumor effectiveness of radioactive iodine.

Most surgeons in North America rely heavily on preoperative ultrasound imaging to map the extent of lymph node involvement and determine the extent of surgery based on imaging results [40]. Ultrasound with marking of involved lymph nodes should be performed preoperatively. Lymph nodes with metastatic thyroid cancer may have an abnormal appearance, including abnormal overall morphology, loss of fatty hilum, and calcifications. The involved lymph nodes may be marked on the overlying skin, and the surgeon should review the ultrasound (or perform it himself or herself, if able) with the radiologist to be familiar with the findings. A permanent marker should be used and care taken not to wash the marks off in the process of sterile prepping.

Central Neck Dissection

Positioning and Incision

In the operating room, after the induction of general endotracheal anesthesia (which may be done with a nerve-monitoring tube), the patient is placed in a mild relax or "beach-chair" position with the head in mild hyperextension and the arms placed on the lower abdomen with the hands on the anterior superior iliac spines or pubis. This requires pulling the draw sheet around the patient and fastening it together in the midline, creating a "papoose" (Fig. 13.2). Foam padding is placed around the arms to protect from nerve compression. This positioning is necessary because if the

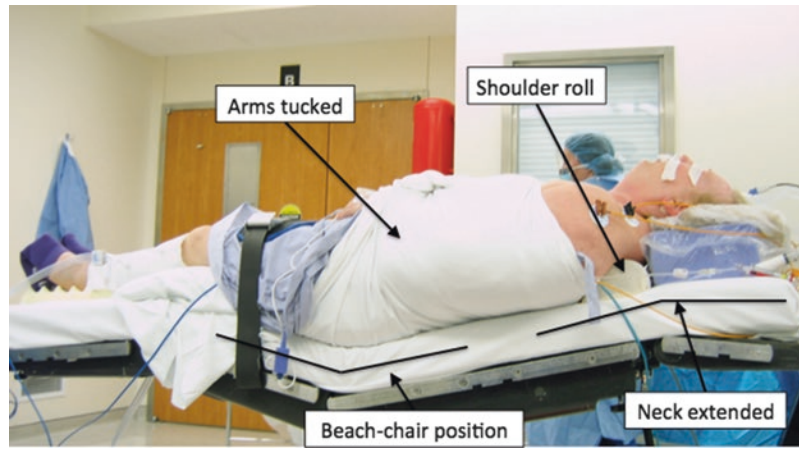

Fig. 13.2 Standard positioning for thyroidectomy, neck dissection

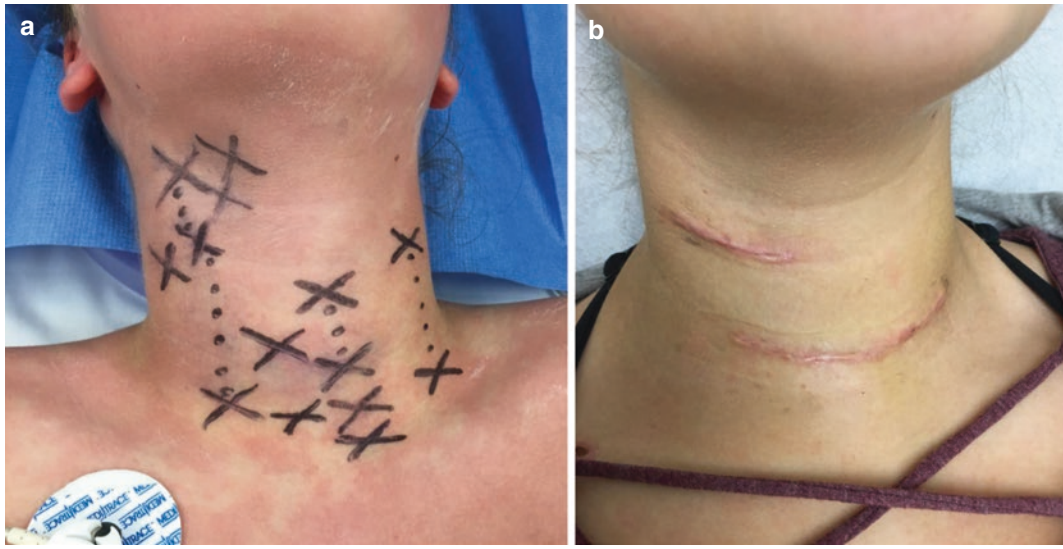

Fig. 13.3 (**a**) Preoperative ultrasound-guided markings of metastatic PTC. (**b**) Same patient 2 weeks post-op showing healed laddered incisions in skin creases (MacFee incision)

arms are tucked at the patient's sides, there may be too much stretch on the brachial plexus, which can cause temporary or permanent numbness and weakness of the hands and arms.

The patient is prepped from the chin to upper chest and draped. The incision is made in a low collar position, ideally overlying the thyroid isthmus, using a preexisting skin crease if one is available (Fig. 13.3). Generally, this operation can be done with a 5–8 cm low collar incision or smaller, if the surgeon is experienced. If a lateral dissection is anticipated, a longer incision should be made, and the incision may be carried up along the posterior border of the sternocleidomastoid muscle. Alternatively, a cosmetically superior approach for lateral dissection is a laddered second incision made in a preexisting skin crease superior and lateral to the low collar incision.

Initial Dissection

Subplatysmal flaps are created in the standard fashion and a self-retaining retractor placed. The strap muscles are then divided in the midline, and on the side of the thyroid tumor, the sternohyoid muscle is separated from the sternothyroid muscle. On the side of the tumor, the sternothyroid muscle is left attached to the underlying thyroid (to provide an additional margin), and the superior and inferior attachments of this muscle are divided (at the thyroid cartilage and the sternum).

Thyroidectomy and Tumor Specimen Mobilization

Superior pole vessels are divided after mobilization medial to lateral to avoid injury to the superior laryngeal nerve which may be visualized during this process. Once the superior pole is taken down, the thyroid is rolled medially and anteriorly. At this point, the procedure departs from what is done in a standard thyroidectomy. The objective is to sweep up the thyroid lobe with surrounding soft tissue and nodal tissue, leaving only the recurrent nerve behind (Fig. 13.4). Attempts may be made to preserve the blood supply to the upper parathyroid, but I usually remove both ipsilateral parathyroids with the specimen and then dissect them out of the specimen if possible, mince them into 1 × 1 mm fragments, and

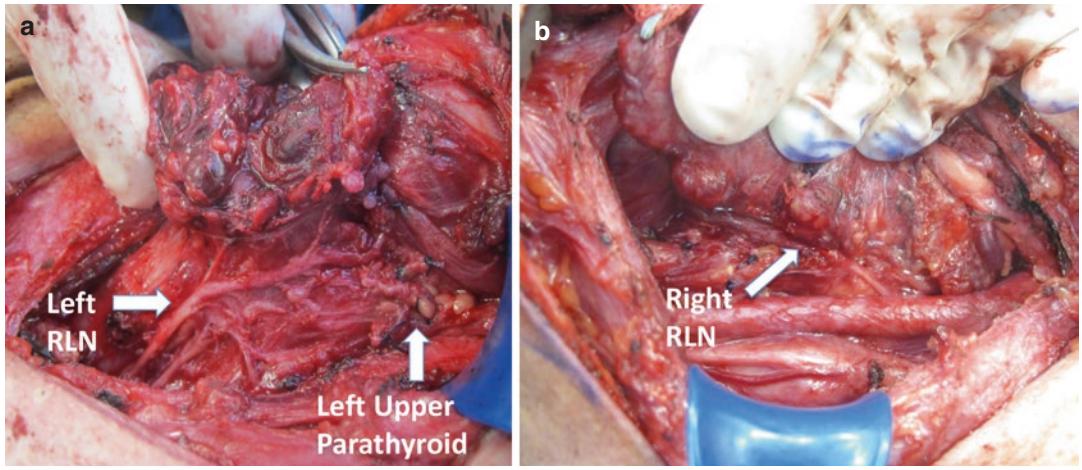

Fig. 13.4 *Left and right* views of thyroidectomy/central neck dissection after mobilization of the specimen. Upper parathyroids are preserved. Lower parathyroids are removed and autotransplanted. Right RLN is partially encased by tumor. Patient's head is to the right

transplant them into individual muscle pockets. Because I am not attempting to preserve the parathyroid blood supply on the side of the tumor, I divide the tissue on the anterior surface of the carotid artery and sweep everything medially. This requires less dissection and fewer vessels to control, but one must be able to identify and transplant the normal parathyroids.

Dissection is carried out on the anterior surface of the carotid artery. If one stays directly on the anterior surface of the carotid, the dissection is quite safe, because the only structures one will encounter are the middle thyroid veins coming off the internal jugular vein, which should be divided. Inferiorly, as the carotid becomes the innominate, the surgeon encounters the thymic horns and associated veins overlying the trachea, which must be divided and swept into the specimen. On the right, the dissection is done to the level of the innominate artery, and on the left the dissection is done to the level of the clavicle, at a point equivalent to the innominate takeoff on the right [41]. Once the central compartment contents are thus mobilized, including the thyroid, parathyroids, central neck nodes, fat, and thymus, dissection is carried out superior to inferior. I find this easiest if done with the (right-handed) surgeon on the left side, using the right hand to perform dissection from above and to cross toward the midline along the innominate artery. The thyroid is mobilized from top down, leaving the sternothyroid muscle attached. In the process, the recurrent laryngeal nerve is identified and preserved, and the upper and lower parathyroids are identified. Soft tissue and vascular attachments to the thyroid are divided, including middle veins and inferior thyroid artery and veins. The nodal packet is swept up off of the recurrent laryngeal nerve and the esophagus to the trachea. It is dissected off of the trachea, leaving only the bare trachea, esophagus, and recurrent nerve centrally (Fig. 13.4). Inferiorly the specimen is swept off of the recurrent laryngeal nerve to the trachea, and the thymic horns are divided with the nodal packet at the level of the innominate artery. Importantly, it is also necessary to mobilize and remove the nodes that reside in the hollow behind the right recurrent laryngeal nerve.

Contralateral Thyroidectomy and Node Dissection

Once the tumor side is completely mobilized, attention is turned to the contralateral side. If this

side has no tumor involvement, both sternothyroid and sternohyoid strap muscles may be mobilized off of the thyroid lobe and reflected laterally. The undersurface of the inner strap muscle is carefully cleaned off so that all fat, nodal tissue, and the thymus are incorporated in the specimen. Again the thyroid superior pole is mobilized and the carotid artery is dissected on its anterior surface inferiorly, and the central compartment containing the thyroid, parthyroids, nodes, and thymus is exposed. If the surgeon prefers to preserve the parathyroids on this side, then a standard parathyroid-preserving thyroid lobectomy should be carried out, leaving the upper parathyroid on an intact vascular pedicle and the lower parathyroid on an intact pedicle in the thyrothymic ligament. Tissue medial and anterior to the thyro-thymic ligament may be swept medially with the thyroid to join the contralateral dissection. The inferior extent of this packet is transected with cautery or a hemostatic device such as the harmonic scalpel, with care to ligate large veins. The entire packet including the thyroid and central neck contents is then oriented with sutures and submitted to pathology, after carefully removing any parathyroids from the tumor-bearing side of the specimen for autotransplantation.

If disease extends inferiorly into the mediastinum, it may be removed through a full or mini-sternotomy. In the mini-sternotomy procedure, the midline sternotomy is carried down to the second or third interspace and is Tee'd off bilaterally to the intercostal space. Care is taken to avoid the internal mammary vessels. Dissection around the innominate vein must be done carefully, and nodal metastases may be present along the sides of the trachea as it descends deep to the innominate vein.

Parathyroid Management

The surgeon must be able to identify the parathyroids, which are removed on the side of the thyroid malignancy, to be transplanted in either the sternocleidomastoid or forearm muscle, depending on the surgeon's preference [42]. The parathyroids on the contralateral side may be preserved in situ or removed and transplanted. Normal parathyroids can be difficult to identify and this requires experience. The ability to identify and autotransplant parathyroid glands is critically important to any surgeon who treats thyroid cancer [41–43]. Hypoparathyroidism is a preventable complication, and its incidence should be extremely low. Parathyroids that are removed during central neck dissection should be placed in cold saline and minced into 1 × 1 mm fragments. These fragments are then autotransplanted into individual muscle pockets (2–3 fragments per pocket) in the sternocleidomastoid muscle or into a muscle of the nondominant forearm. Parathyroid autotransplants will survive in many locations, and surgeons in other nations use different locations, such as the right upper quadrant fat (Sweden) or the pectoralis muscle (Japan). All removed parathyroid tissue should be transplanted. Each pocket is closed with a suture. Transplanting the entire gland in one piece does not work because the parathyroid tissue is not able to absorb oxygen from the surrounding tissue. Tiny fragments in individual pockets have an adequate surface area-to-volume ratio to absorb oxygen from the surrounding tissue and are more likely to survive and grow a new blood supply.

Drains and Closure

A drain is generally placed in the bed of the thyroidectomy and is removed after 1 or 2 days if there is no chyle coming out. The straps are tacked together in the midline, the platysma is closed, and the skin is closed with a running subcuticular and surgical glue or Steri-Strips. Drains are removed on post-op day 1 or 2. Patients usually may be discharged within 1 or 2 days.

Yield

Central neck dissection for thyroid cancer usually yields between 6 and 20 lymph nodes in the specimen, though higher and lower numbers may be seen depending on the patient's anatomy, the thoroughness of dissection, and extent of pathologic examination [5, 12, 41]. When properly done, central neck dissection results in excellent long-term control of disease in the central neck [44, 45].

Complications of Central Neck Dissection

Complications of central neck dissection include hypoparathyroidism and recurrent laryngeal nerve (RLN) injury even when surgery is performed by high-volume and experienced thyroid surgeons [46]. Permanent hypoparathyroidism results from injury to the parathyroid glands and is defined by the requirement of vitamin D and/or calcium supplementation at 6 months and beyond postoperatively. Recent studies have suggested rates of permanent hypoparathyroidism of 1.6–16.2% following total thyroidectomy (TT) with central node dissection as compared to 1.3–6.3% following total thyroidectomy alone [32, 47]. Permanent recurrent laryngeal nerve injury results in vocal cord paralysis or changes in vocal function that persists 6 months and beyond postoperatively. Injury is diagnosed by laryngoscopy, with rates of 1.6–2.3% reported following total thyroidectomy with central node dissection as compared to 1–1.3% following total thyroidectomy alone [32, 47]. Temporary recurrent laryngeal nerve injury results in significant morbidity, especially in patients whose livelihood depends on their ability to speak and be heard [28, 48, 49]. There are higher risks of clinically significant temporary hypoparathyroidism in TT + CND compared to TT alone. Clinically significant temporary hypoparathyroidism is temporary hypoparathyroidism (defined as hypocalcemia requiring supplementation lasting less than 6 months) with the occurrence of serum concentration < 7.0 mg/dL, symptomatic with objectively visible muscle spasms or tetany, requiring IV replacement or calcitriol to control, and requiring readmission or hospitalization. It is estimated that 38% and 64% temporary hypocalcemia in TT and TT + CND, respectively, were clinically symptomatic [50, 51], while the overall prevalence of temporary hypocalcemia (summarized from 11 studies) was 16.2% in TT vs. 31% in TT + CND [32]. Temporary RLN injury is also reported to be slightly higher in TT + CND as compared to TT alone (5.2% vs. 2.9%) [32]. Other local surgical complications have been reported to be higher in patients who have thyroidectomy and central neck dissection compared to thyroidectomy alone [48, 52]. These include hematoma, seroma, chyle leak, and injury to adjacent structures including esophagus and trachea.

The majority of thyroid operations (77%) performed in the United States are not performed by high-volume specialists [53]. Several studies have demonstrated that the rate of hypoparathyroidism and recurrent laryngeal nerve complications is higher when performed by low-volume surgeons who do not specialize in thyroid surgery [54].

Lateral Neck Dissection

If macroscopic lateral lymph node metastases are identified preoperatively or during the operation, bilateral or unilateral modified or functional neck dissections (levels II, III, IV, V) should be performed (Fig. 13.5). Additionally, if central nodal disease is apparent, it is likely that lateral nodes are involved as well, and consideration may be given to performance of a lateral dissection, though, if there is no ultrasound evidence of tumor in the lateral compartment, I would not

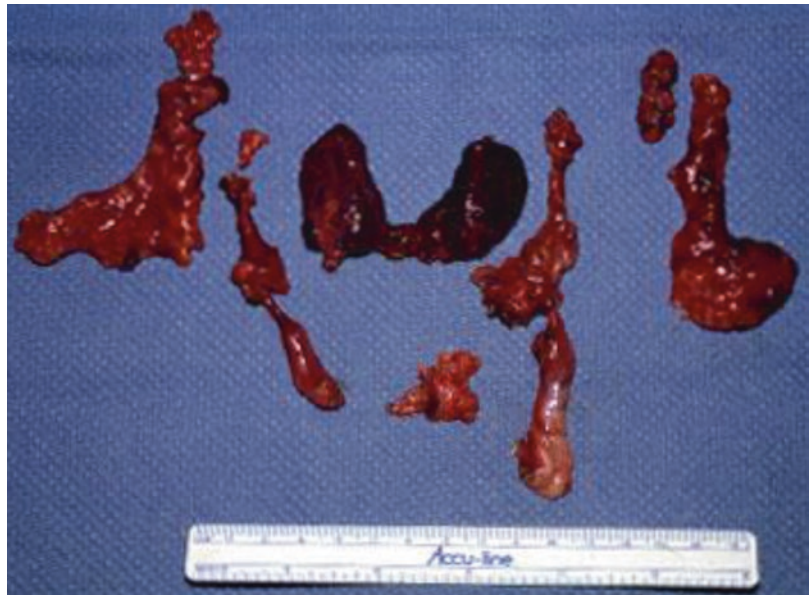

Fig. 13.5 Thyroidectomy/central/lateral neck dissections specimen from a thin young man. Lower parathyroids were removed and autotransplanted

make a larger incision to do this. Radioactive iodine is quite effective at eradicating clinically undetectable nodal DTC metastases [8].

Positioning and Incision

Positioning of the patient is described above. I do not use any different positioning for lateral neck dissection, except to position the anesthesia setup as far from the surgical site as possible, so that the surgeon and assistants can retract from above. The neck incision is started as a low collar incision approximately two finger breadths above the sternal notch (incorporating the thyroidectomy incision) [55]. The extent of the incision depends upon the location of nodes marked by the ultrasonographer as abnormal (Figs. 13.3 and 13.6). The incision may be extended laterally and then superiorly along the posterior border of the SCM to the location of level II lymph nodes (Figs. 13.3 and 13.6). The author prefers a modified MacFee incision for cosmesis, which consists of two laddered parallel incisions preferably located in preexisting skin creases (Fig. 13.3). Extension of the low collar incision superiorly along the posterior aspect of the sternocleidomastoid muscle (SCM) gives good exposure but is inferior cosmetically

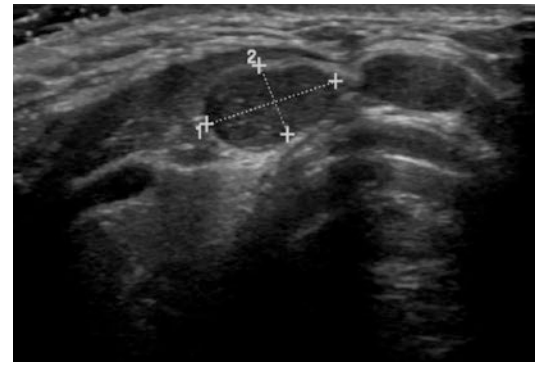

Fig. 13.6 Metastatic thyroid cancer to central lymph nodes anterior to the trachea. The nodes are enlarged, there are microcalcifications and lack of a fatty hilum, and there is an abnormal blood flow pattern

to placement of parallel low collar and upper neck incisions in preexisting skin creases (modified MacFee incision).

Initial Dissection

Subplatysmal flaps are raised. Dissect superiorly to one finger breadth below the inferior border of the submandibular gland and, if necessary, continue dissection on the surface of the SCM (or deep to the submandibular gland fascia) to avoid

injury to the marginal mandibular branch of the facial nerve, which lies superficial and sometimes inferior to the gland. Dissect inferiorly to the level of the clavicle, medially to the internal jugular vein, and laterally just past the anterior border of the SCM. Care is taken to preserve the great auricular nerve and external jugular vein, as they travel superiorly on the anterolateral surface of the SCM, from Erb's point. The fascia investing the SCM is incised at its anterior border. Dissection is carried medially to free the fatty nodal packet from the SCM using electrocautery and stopping when the posterior border of the SCM is encountered. Superiorly, care must be taken to identify and preserve the spinal accessory nerve (SAN), as it enters the SCM. The SCM is retracted laterally using Army-Navy retractors. Mobilization of the pre-scalene nodal packet (levels IV, III, and II) may be done from a medial-to-lateral direction or a lateral-to-medial dissection. The internal jugular vein (IJV) is dissected out circumferentially and is retracted medially with the vagus nerve and carotid artery using a vein retractor. The fat, nodes, and areolar tissue behind the IJV is dissected off of the anterior scalene muscle, with the phrenic nerve identified lying on the anterior surface of the muscle and the brachial plexus exiting at the lateral border of the scalene muscle. Dissection deep to the IJV and carotid arteries may expose the sympathetic chain, which should be avoided. Injury to this structure may result in a Horner's syndrome. The transverse cervical artery and vein run transversely across the anterior scalene muscle and may be ligated if necessary for broad exposure. The phrenic nerve may be tested using a nerve stimulator while watching and feeling for diaphragmatic contracture (hiccup). Injury to the phrenic nerve must be carefully avoided, and the nerve should be visualized often during the dissection.

A common occurrence during dissection in the low neck is a venotomy at the junction of the subclavian vein (SCV) as it joins the IJV. This is usually controlled with prolene sutures. On the left side, the thoracic duct joins the confluence of the left IJV and left SCV and should be identified and carefully avoided. If the thoracic duct is injured, it must be ligated. Thoracic duct anatomy can vary significantly. Routinely identification of the thoracic duct helps to avoid injury. If there is chyle in the surgical bed, there is an injury, and it must be searched for and controlled. Care must also be taken to avoid injury of the brachial plexus, which exits at the poster border of the anterior scalene muscle.

Level II–IV Dissection

The nodal packet is lifted superiorly as the dissection proceeds, further exposing the anterior scalene muscle beneath. The lymph node packet is then retracted medially and released from its posterolateral attachments (the posterior boundary is the plane of the SCM). The cervical plexus is a grouping of nerves that exits the posterior border of the SCM at Erb's point, which is approximately 4–5 finger breadths superior to the clavicle. At Erb's point, the cervical plexus branches into multiple sensory branches to the ear, neck, shoulder, and upper chest. The largest of these branches is the great auricular nerve, which should be preserved. The spinal accessory nerve (SAN) is identified superior to the cervical plexus at the posterior border of the SCM and dissected (without electrocautery) superiorly to where it crosses the IJV. The SAN may be tested using the nerve stimulator while observing trapezius contraction. The node dissection may be stopped at the junction of level II and III if there is no evidence of disease in the more superior nodes. If level II nodes are removed, the posterior belly of the digastric muscle should be identified and traced up to the skull base if necessary. Medial to this, the hypoglossal nerve is identified. With these structures preserved, the fibrofatty lymph node packet is then released from the IJV and carotid artery and sent to pathology for routine examination (Fig. 13.5).

Level V Dissection

If removal of level V nodes (posterior triangle) is planned, subplatysmal flaps should be created

past the posterior border of the SCM, with inferior dissection to the clavicle.

Free the nodal packet away from the brachial plexus and dissect superiorly to the spinal accessory nerve (SAN). The SAN is found immediately superior to the cervical plexus at the posterior border of the SCM, but it courses transversely and inferiorly to the trapezius muscle. It is very important to recognize this and to understand the course of the SAN in the posterior triangle, where it is frequently injured. The SAN is dissected free inferiorly toward its insertion into the trapezius muscle and is preserved. Dissection proceeds inferiorly along of the floor of the neck, carefully identifying and preserving the brachial plexus. These transverse cervical vessels may be preserved or incorporated into the specimen.

The nodal packet is transected at the level of the clavicle and posteriorly at the trapezius.

Closure

Check the level IV dissection bed for evidence of chyle leak, and if seen, ligate the thoracic duct incorporating a small amount of surrounding muscle or fatty tissue (mass ligation). One or two Blake drains (19 French) are connected to self-suction bulbs that are left in place exiting the neck through stab incisions located away from the surgical incision. The platysma is closed with an absorbable suture. After a deep dermal closure, the skin may close with a running or subcuticular stitch and surgical glue and/or tape strips.

Complications of Lateral Neck Dissection

In addition to bleeding and infection, which may occur, complications specific to lateral neck dissection include thoracic duct leak and sympathetic chain injury resulting in Horner's syndrome injury to other nerves including the phrenic, SAN, marginal mandibular nerve, and great auricular nerve. Some sensory nerve disruption/numbness in the neck and shoulder area is seen in virtually all patients due to dissection of the cervical plexus branches. Seroma may also occur but is less common because fluid in the operative bed tends to percolate down into the mediastinum and is rarely a clinical issue. Facial/cerebral edema may occur if both IJVs are taken, and this should not be done. Taking the IJV on one side usually does not result in significant swelling, but attempts to preserve it should be made, especially since the prognosis of DTC is so favorable. Major vascular complications and brachial plexus injury can be catastrophic but are rare. It is important to recognize that if a patient has had previous surgery or biopsy in the area, scarring can significantly impair one's ability to identify critical structures. Postoperative shoulder pain and weakness is common following lateral neck dissection. Physical therapy is recommended for these patients.

Mediastinal Dissection

Several reports have described the routine inclusion of upper mediastinal (level VII) lymph nodes in central (level VI) neck dissections for papillary thyroid carcinoma (Fig. 13.7). In an early report from Japan, Mizuno and colleagues [14] described the routine dissection of paratracheal and upper mediastinal nodes in patients with papillary thyroid carcinoma, occasionally in

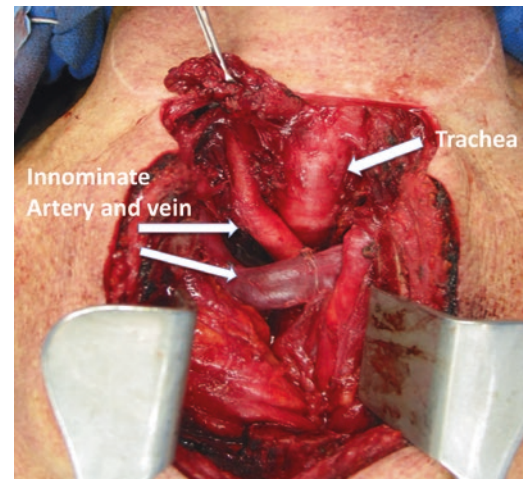

Fig. 13.7 Mediastinal exposure after mini-sternotomy and dissection

concert with a sternotomy and mediastinal dissection. Upper mediastinal nodes are often accessible through a cervical incision, depending on the anatomy of the patient. Sternotomy allows a more thorough clearance of mediastinal nodes and, in some patients, may be necessary for removal of lower peritracheal and upper mediastinal nodes (e.g., in patients with a narrow thoracic inlet). We do not routinely include level VII nodes in central neck dissections unless there is imaging evidence of metastatic involvement to this compartment.

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The Debate *for* Elective Lymph Node Dissection in Papillary Thyroid Carcinoma

14

Nicole Zern and Mark Sywak

Abbreviations

AJCC	American Joint Committee on Cancer
ATA	American Thyroid Association
CND	Central node dissection
PTC	Papillary thyroid cancer
RAI	Radioactive iodine
Tg	Thyroglobulin

Introduction

Papillary thyroid cancer (PTC) metastasizes to cervical lymph nodes in 40–90% of cases, including micrometastases [1]. For this reason, the management of cervical lymph nodes is an important aspect of the surgical care of patients with thyroid cancer. It is well known that a *therapeutic* lymph node dissection should be performed for all patients with clinically involved nodes [2]. However, the role for *prophylactic* or *elective* lymph node dissection is less well defined. In the past two decades, there have been over 30 papers published examining the potential benefits of central compartment node dissection (CND) [3]. Given the preponderance of retrospective data on this topic with inherent bias, there is no consensus opinion as to the role of prophylactic node dissection.

In the American Thyroid Association (ATA) Guidelines [2], Recommendation 36 advocates for consideration of *prophylactic* CND in patients with PTC who have advanced primary tumours (T3 or T4) or clinical evidence of lateral neck nodal spread. Additionally, a prophylactic CND should be considered "if the information will be used to plan further steps in therapy". It is estimated that around 38% of patients with PTC >1 cm have central node metastases despite negative preoperative imaging and normal exam [4]. Positive nodal spread will not only upstage a patient's disease but may also result in modification of dosing of radioactive iodine therapy or change the interpretation of follow-up thyroglobulin levels. For these reasons and others, we will outline why it is useful to perform an *elective* central lymph node dissection for all patients with papillary thyroid carcinoma >1 cm.

Background: Nomenclature

Differentiated thyroid cancer frequently metastasizes to locoregional nodal basins within the neck. In order to fully discuss the role of lymph

N. Zern, M.D. (✉)
Department of Surgery, University of Washington, 1959 NE Pacific Street, Box #356410, Seattle, WA 98195, USA
e-mail: nkzern@uw.edu

M. Sywak, M.B.B.S., F.R.A.C.S., MMed Sci
University of Sydney Endocrine Surgery Unit, Level 3 ASB, Royal North Shore Hospital, Reserve Road, St. Leonards, Sydney, NSW 2065, Australia
e-mail: marksywak@nebsc.com.au

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node dissection in the management of patients with thyroid cancer, we must first describe the nodal basins of the neck and the pattern of metastatic spread.

A consensus statement from the American Association of Endocrine Surgeons, the American Academy of Otolaryngology-Head and Neck Surgery and the American Head and Neck Society released in 2009 [5] described the boundaries of the lymph node compartments within the neck as they pertain to central neck dissection. Conventional nomenclature assigns numeric labels to the cervical nodal compartments to aid in communication while discussing surgical management (see Fig. 14.1). The central compartment contains the Level VI lymph nodes and is the region most frequently involved in papillary thyroid cancer metastases. The boundaries of the Level VI nodal compartment are as follows:

- Superior border: Hyoid bone
- Inferior border: Innominate artery
- Lateral border: Carotid artery bilaterally
- Anterior border: superficial layer of deep cervical fascia
- Posterior border: deep layer of deep cervical fascia

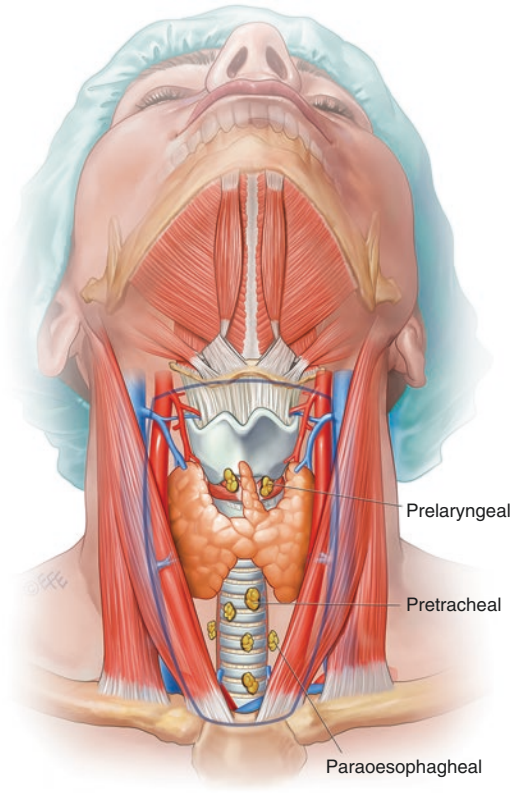

Fig. 14.1 Anatomical boundaries of the central neck compartment

Within the central compartment, there are several groups of lymph nodes that are resected during a central compartment dissection. The *prelaryngeal* nodes are also known as the Delphian nodes and lie just anterior to the cricothyroid membrane near the pyramidal lobe of the thyroid gland. The *pretracheal* nodes lie anterior to the trachea but inferior to the thyroid isthmus. The *paratracheal* nodes are encountered posteriorly to the lateral lobes of the thyroid in close proximity to the recurrent laryngeal nerve. If these nodes are encountered more posteriorly, they are often described as *retropharyngeal* or *paraesophageal* nodes. To perform a complete CND, the prelaryngeal, pretracheal, paraesophageal and paratracheal nodes should all be resected [5].

The extent of surgical management of the central neck compartment is guided in part by preoperative investigations and clinical exam. Dissection of the central neck is commonly described by the indication for nodal resection—*therapeutic* or *prophylactic/elective*. A Level VI dissection is *therapeutic* if lymph node metastases are detected clinically either through preoperative imaging/exam or intraoperative findings. A Level VI dissection is considered *elective* if there is clinically no evidence of nodal metastases. Furthermore, CND should also be described as either *unilateral* or *bilateral*.

If any additional nodal basins are resected at the time of operation, these should also be delineated using appropriate nomenclature. Frequently,

Level VII nodes are included in the resection of the central compartment for thyroid cancer. Level VII nodes are the superior mediastinal nodes that are in direct continuity with the Level VI central compartment. Level VII nodes are located between the suprasternal notch and the innominate vein [6]. Other nodal basins that may be involved by metastatic thyroid carcinoma are the lateral lymph nodes, Level II, III, IV and V. Level I, the submental nodes, are rarely involved. The lateral nodes are more readily accessible for ultrasound evaluation preoperatively than the central compartment and thus may be biopsied if they appear suspicious. This allows for confirmation of metastatic disease prior to surgical intervention, eliminating the need for *prophylactic* lateral node dissection. The most recent ATA guidelines state that lateral neck dissection should only be performed for patients with biopsy-proven metastatic lateral cervical lymphadenopathy (Recommendation 37, [2]).

Background: Patterns of Lymph Node Spread

The spread of thyroid cancer cells in PTC occurs mostly through lymphatics and less often via the haematogenous route. The nearest lymphatic drainage of the thyroid gland is the central compartment nodes (level VI); thus, these have the highest rate of nodal metastases for differentiated thyroid cancer [7]. Tumours located in the upper thyroid pole may spread directly to lateral compartment nodes and "skip" the central compartment. Surgeons should be aware of this pattern of metastasis when planning lymph node surgery.

A retrospective review by Machens et al. in Germany [8] saw a higher incidence of nodal metastases with increasing size of the primary tumour. In this group, 14% of patients with T1 tumours had central compartment metastatic disease, while 45% of the T4 tumours harboured central nodal metastases. The incidence of metastatic disease was increased within ipsilateral central nodes vs. contralateral central nodes (29% vs. 13%), illustrating that thyroid cancer tends to metastasize to the nodes in closest proximity.

Background: Limitations of Imaging and Clinical Exam

Ultrasound is an invaluable tool for the clinical evaluation of patients with thyroid cancer. Ultrasound helps to identify thyroid nodules with characteristics suspicious for malignancy and can be used to delineate which nodules undergo biopsy. Its utility is restricted, however, in the central compartment given anatomical constraints which limit detectability of nodal metastases. One study showed that the sensitivity of ultrasound for detection of nodal disease for papillary thyroid cancer was only 36.7% [9]. It is also more difficult during preoperative physical exam to palpate central nodal metastases given the presence of other structures anteriorly (strap muscles, thyroid gland, clavicles). For these reasons, up to 60% of patients with positive central nodes on final histological assessment histology are undetected clinically prior to operation [10].

Choi and colleagues in Korea [11] performed a retrospective analysis of 589 patients with PTC who underwent both preoperative ultrasound and CT scan to evaluate for nodal disease. All patients underwent a central node dissection at operation. After correlation with final histopathological data, they found that ultrasound had only a 47.16% sensitivity for central compartment metastases, and similarly CT had only a 41.94% sensitivity. Both modalities were much better in evaluating the lateral compartment with sensitivities near 70%. An additional finding in this study was that many of the metastatic nodes within the central compartment were small (<5 mm) thus are unlikely to be detectable on ultrasound which traditionally identifies metastases based on enlargement of the node. This finding was confirmed by Vergez and

colleagues [12] who noted that in patients with positive central node compartment metastases, the largest lymph node measured 5 mm or less in 66% of cases.

It is also well known that surgeons are poor estimators of nodal disease intraoperatively. A well-cited study of surgeon detection of metastatic nodal disease during thyroidectomy for medullary thyroid cancer showed a sensitivity of only 64% [13]. It is common to have enlarged lymph nodes that are reactive to whatever concurrent pathology exists in the thyroid gland (Hashimoto's thyroiditis, Graves disease, etc.), and these enlarged nodes may be mistaken intraoperatively as malignant. With a standard practice of routine CND on all patients, there is no need for reliance on surgeon or imaging detection of nodal metastatic disease. The most reliable method of detecting metastases is surgical resection and histopathologic evaluation.

Benefits of Elective Central Lymph Node Dissection

Decreased Local Recurrence

Performance of a *therapeutic* central node dissection decreases the rate of recurrence of differentiated thyroid carcinoma. The group in Dusseldorf, Germany, showed a decreased rate of recurrence when central compartment dissection was performed at initial operation for both papillary and follicular thyroid carcinomas [14]. Similarly, there is also a decreased rate of recurrence when central node dissection is performed *electively*. Pereira and colleagues in Barcelona reported no recurrence within the central compartment for 43 patients after either therapeutic (15/43) or elective (28/43) CND. Overall, the five patients in this study who developed recurrence (11%) all recurred laterally with no central recurrences after central node dissection at initial operation [15].

A lower rate of recurrence associated with central node dissection has been shown in multiple other studies (see Table 14.1). The group at New York-Presbyterian Hospital noted a recurrence rate of 16.7% in patients without CND vs. only 4.4% in those who underwent CND, although this did not reach statistical significance [16]. Similar to the Barcelona group, they too noted that no patients who underwent CND developed recurrence within the central compartment. Hartl and colleagues in France showed only 2% recurrence for those who underwent CND vs. 12% recurrence in thyroidectomy alone over 5 years, $p < 0.001$ [17]. Both cohorts in this study received similar doses of RAI and had no difference in complication rates.

Several larger studies have also examined recurrence after prophylactic CND. A multicentre study in 2011 by Popadich et al. included endocrine surgical centres in Australia, the United States and the United Kingdom [18]. This retrospective review of 606 patients with PTC >1 cm showed an overall rate of reoperation for recurrence of 5% in Group B (elective CND and total thyroidectomy) compared to 8.4% of patients in Group A, total thyroidectomy alone ($p = 0.11$). When analyzed as recurrence-free survival within the central compartment, there was a statistically signifi-

Table 14.1 Comparison of recurrence rates after CND

Study	Total number of patients (*n*)	Recurrence without CND	Recurrence after CND	*p* value	CND effect on recurrence
Popadich 2011	606	6.1%	1.5%	0.004	REDUCED
Barczynski 2013	640	13.1%	4.2%	<0.001	REDUCED
Hartl 2013	246	12%	2%	<0.001	REDUCED

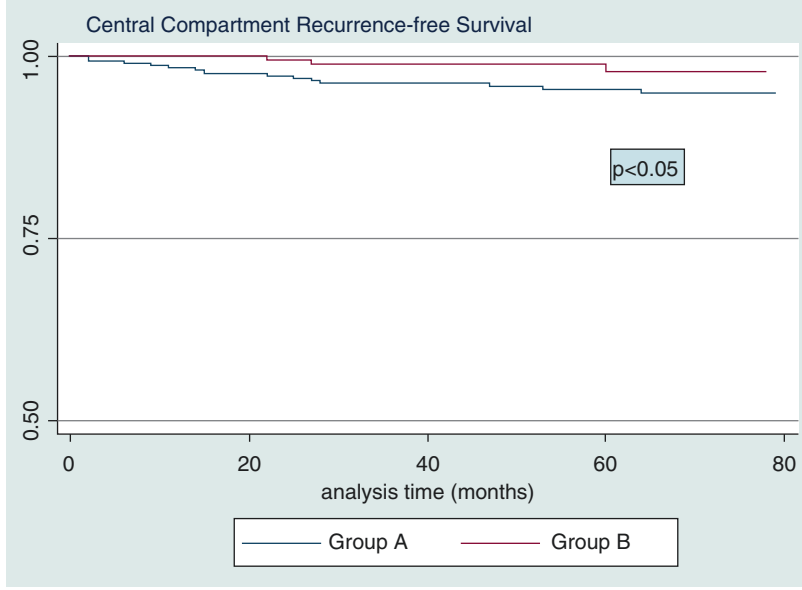

Fig. 14.2 Central Compartment Recurrence-free Survival curves for Group A (total thyroidectomy alone) vs. Group B (total thyroidectomy and CND). Group B (*upper curve*) had fewer reoperations within the central compartment than those in Group A (*lower curve*). Reprinted with permission from Popadich et al. A multicentre cohort study of total thyroidectomy and routine central lymph node dissection for cN0 papillary thyroid cancer Surgery. 2011;150:1048–57

cant improvement for those who underwent elective CND (Group B) as they did not recur within the central compartment (see Fig. 14.2). Furthermore, this study found that in the overall cohort, the performance of 20 prophylactic central neck dissections would prevent one central neck recurrence.

In 2013, Barcyznski et al. published a retrospective review of 640 patients in the British Journal of Surgery [19]. Three hundred and fifty-eight of these patients underwent a prophylactic CND and were compared to 282 patients who did not undergo CND. They found that performance of a prophylactic CND was an independent predictor for improved locoregional recurrence at 10 years postoperatively, Odds Ratio 0.21. They also concluded that patients who underwent prophylactic CND had improved disease-specific survival at 98% over 10 years compared to 92.5% ($p = 0.034$).

Wang and colleagues in the United States conducted a large meta-analysis of 2318 patients looking at the risk of recurrence following prophylactic CND in clinically node-negative patients. While it did not reach statistical significance, there was a lower rate of recurrence in patients with CND than in those without—4.7% vs. 7.9% [20].

Decreased Postoperative Thyroglobulin Level

Thyroglobulin (Tg) level is a clinical marker of recurrent PTC that is closely monitored postoperatively by endocrinologists. An elevated Tg level after thyroidectomy and radioactive iodine ablation indicates the presence of active thyroid tissue within the body. Detectable Tg can come from either remnant thyroid tissue within the neck or from metastatic disease.

An additional benefit to performance of a CND is that clearance of these nodes is associated with a lower Tg level postoperatively. This was first shown by the Sydney, Australia group in 2008 in which a multivariate analysis showed an inverse relationship between the 12-month Tg level and the number of lymph nodes removed at surgery [21]. When data from Australia was combined with the United States and the United Kingdom in the study by Popadich et al., there was a

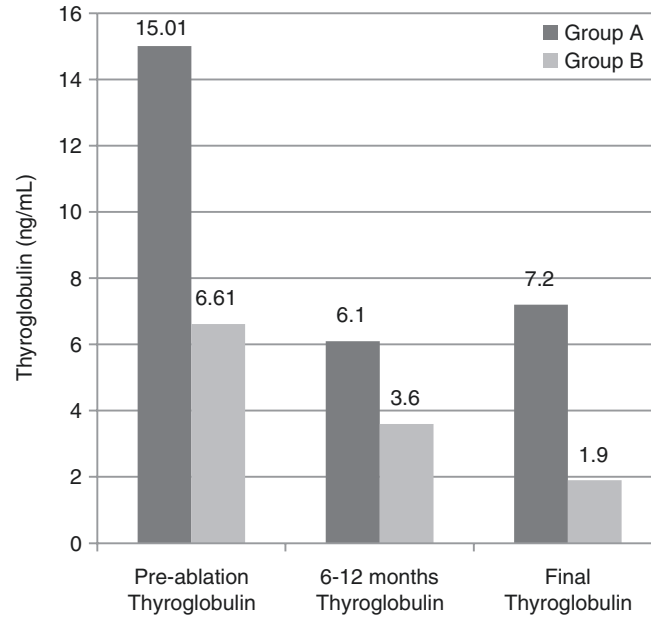

Fig. 14.3 Thyroglobulin levels during follow-up from Group A (total thyroidectomy alone) vs. Group B (total thyroidectomy and CND). Reprinted with permission from Popadich et al. A multicentre cohort study of total thyroidectomy and routine central lymph node dissection for cN0 papillary thyroid cancer Surgery. 2011;150:1048–57

statistically significantly lower Tg level after initial operation in those who underwent CND compared to total thyroidectomy alone. There was also a trend towards a significantly lower Tg after radioactive iodine (RAI) ablation in those with CND (see Fig. 14.3) [18]. The implications of a lower Tg level are significant to both the patient and clinician. A lower Tg level leads to less anxiety about recurrent/persistent disease and less rigorous follow-up investigations.

Modification of Postoperative Radioactive Iodine Therapy

Not every patient with differentiated thyroid carcinoma will undergo postoperative RAI therapy. Endocrinologists use clinical and histopathologic characteristics to determine for which patients RAI is indicated. The most recent ATA guidelines indicate that RAI remnant ablation is not recommended for "low-risk" patients including those with microcarcinoma (Recommendation 51, [2]). However, the presence of clinically evident nodal disease or >5 nodal metastases on histology incurs an ATA "intermediate" risk of recurrence; thus, these patients will likely undergo RAI ablation. As a result, the performance of a CND in which nodal metastases are detected can result in the administration of RAI ablation when it may not have been indicated based on primary tumour characteristics alone.

In a 2009 publication, Bonnet et al. found that elective CND in patients with clinical T1 N0 disease resulted in detection of central nodal metastases in 36.7% of the 115 patients in the study [22]. Based on this knowledge of nodal metastases, 21.7% of patients had a modification in their plan for RAI ablation. Twelve patients received RAI who would not have without known nodal metastases, while 13 other patients had plans for RAI aborted based on negative nodal status.

Accurate Staging and Risk Stratification

Lymph node staging is a component of the management of many malignancies. Despite no clinically apparent nodal disease preoperatively, the standard of care for many malignancies (colorectal adenocarcinoma, gastric adenocarcinoma, etc.) is to resect the draining nodal basins and analyze these histologically to accurately stage the cancer. Thyroid cancer is no different in that knowledge of nodal metastatic disease can influence staging.

The current American Joint Committee on Cancer (AJCC) guidelines for differentiated thyroid cancer [23] stratify patients based on age < 45 years vs. patients 45 years of age and older. For the <45 year old patients, nodal status does not determine stage. All patients under 45 years of age are Stage I unless there are distant metastases, in which case they are Stage II. However, for patients aged 45 years or greater, positive nodal metastases within the central compartment (Level VI) are characterized as N1a disease. The presence of N1a disease places patients into Stage III. Patients are Stage IV if cervical nodal metastases are present outside of the central compartment (Levels I–V and VII, N1b). Thus, knowledge about the nodal status of patients with papillary thyroid cancer can have a significant impact upon staging using the AJCC system.

Additionally, dynamic risk stratification is becoming increasingly used in the management of patients with thyroid cancer. Knowledge of positive nodal metastases helps to re-stratify patients from a low risk of recurrence to a higher risk of recurrence. Conversely, knowing that the central compartment nodes were negative for metastatic disease may downgrade a previously intermediate-risk patient to a low risk of recurrence. Knowledge of nodal status helps to prognosticate to the patient their relative risk of recurrent disease going forward after initial management.

There is also an association between burden of nodal metastatic disease and survival prognosis in thyroid cancer. Overall this has been largely disputed, but there are studies which show worse survival for those with cervical nodal metastases [24]. As such, gaining information about the nodal status of patients will contribute significantly to not only redefining risk of recurrence but in estimating overall prognosis.

Low Risk of Complications

The endocrine surgical group in Sydney, Australia, evaluated the outcomes after elective CND in regard to postoperative complication rates. There was an increased incidence of postoperative temporary hypocalcemia (18% vs. 8%, $p = 0.02$) in those who underwent CND prophylactically. However, there was no significant difference in long-term outcome including a similar low rate of permanent hypocalcemia and recurrent laryngeal nerve injury. There was also no difference in other short-term complications including bleeding and infection [4]. These results were mirrored by the Michigan group in 2010 who also showed a higher rate of temporary hypocalcemia in those with CND (27% vs. 8%) but ultimately no difference long term in either permanent hypocalcemia or nerve injury rate [10].

Lower Risk at Initial Operation than Reoperation

It is an inherent principle of surgery that a reoperation within a previously operated field has a risk of higher complication. Applying this principle, it is reasonable to expect that reoperating within the central compartment of the neck for recurrent thyroid cancer has a higher rate of postoperative complication than initial operation. A review in the World Journal of Surgery from 2007 [7] looked at five studies of reoperation within the central compartment. There was a 0–4% incidence of permanent hypoparathyroidism and a 0–12% incidence of permanent recurrent laryngeal nerve injury (although these may have included intentional nerve sacrifice). After analysis of this data, the group concluded that a CND was safer when performed at the initial operation.

Comment on Level VII Dissection

The cervical Level VII nodes lie inferior to the Level VI central compartment nodes within the superior mediastinum. These two compartments are in direct continuity, and as such, level VII nodes are often included in a central compartment nodal dissection. The role of level VII nodal dissection is not uniformly defined. The AJCC staging system classifies Level VII nodal metastases as N1b (while Level VI nodal metastases are N1a), implying regional spread to the superior mediastinum is similar to regional spread to

the lateral compartments. Furthermore, across various studies different anatomical landmarks are used to define the inferior border of the central compartment with some citing the sternal notch and others the innominate artery. Depending on the definition of the central compartment, Level VII nodes may be included within a CND.

Wang and colleagues in Sydney performed prophylactic removal of both Level VI and VII lymph nodes for patients with PTC and evaluated outcomes [6]. They found that 16% of patients who underwent prophylactic level VII node dissection had macrometastatic nodal disease which would have gone unresected if level VII dissection was not performed. Further follow-up and study is needed to assess for a significant difference in recurrence over time for these patients vs. those with a level VI dissection only.

Role of Prophylactic Lateral Lymph Node Dissection

While not the main focus of this chapter, there has been some similar debate about the role for prophylactic dissection of the *lateral* neck. Ito and colleagues in Japan [25] looked at over 1000 patients who underwent a prophylactic lateral neck dissection in addition to total thyroidectomy with CND. They concluded that if patients have two or more of the following factors, a prophylactic lateral neck dissection is recommended: male gender, age greater than 55, tumour diameter > 3 cm and massive extrathyroidal extension. Prophylactic lateral neck dissection has not been commonplace practice, however, likely because the lateral neck is much easier to examine preoperatively. Rather than subject patients to the added morbidity of a much larger operation with more potential risks, most clinicians opt for surveillance of the lateral neck with dissection only when metastases are confirmed. This is in accordance with the ATA Guidelines Recommendation 37 [2] stating "Therapeutic lateral neck compartmental lymph node dissection should be performed for patients with biopsy-proven metastatic lateral cervical lymphadenopathy".

Conclusion

Given the difficulties in performing a large prospective randomized trial, the debate will likely continue regarding performance of a prophylactic central node dissection for papillary thyroid carcinoma >1 cm. There is evidence to support the following reasons to perform a prophylactic CND on all patients with PTC >1 cm:

- Preoperative ultrasound and clinical exam have poor sensitivity for detection of central compartment nodal metastases.
- Performance of CND decreases local recurrence within the central compartment.
- Performance of CND decreases postoperative thyroglobulin levels.
- Information about nodal status in PTC may change a patient's AJCC stage.
- Information about nodal status may modify the planning of radioactive iodine therapy.
- Information about nodal status may help to predict risk of recurrence (dynamic risk stratification).
- Central node dissection in addition to total thyroidectomy for differentiated thyroid cancer is a safe procedure. There is an increased risk of temporary hypocalcemia but no increased risk of RLN injury or permanent hypoparathyroidism.

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The Debate *against* Elective Lymph Node Dissection in Papillary Thyroid Carcinoma

15

Iain J. Nixon and Ashok R. Shaha

Abbreviations

ATA	American Thyroid Association
DTC	Differentiated thyroid cancer
ECND	Elective central neck dissection
ELND	Elective lateral neck dissection
END	Elective neck dissection
PTC	Papillary thyroid cancer
RAI	Radioactive iodine
Tg	Thyroglobulin

Introduction

We have been asked to set out the arguments against elective lymph node dissection (END) for differentiated thyroid cancer (DTC). To do that, we will first consider what is an END? Then, we will analyze the arguments for and against the practice (Table 15.1). With this approach we hope that the reader will be able to draw conclusions from the evidence presented and combine this with their own experience and complications in order to make appropriate decisions for the individual patients they encounter.

The first point to state in any debate about END for differentiated thyroid cancer (DTC) is that there is currently no prospective evidence base on which to draw any concrete conclusions. That is not to say that the question is not of major concern. Quite the contrary, an increasing number of patients present with DTC [1–10], and therefore clinical decisions must be made in the patient's best interest in every case.

Although the title of this book refers to differentiated thyroid cancers, for the purposes of this debate, we will focus on papillary thyroid cancer (PTC). This is the most common DTC and the histological type which most commonly metastasizes to the lymph nodes of the neck.

Table 15.1 Arguments for and against elective neck dissection

Arguments for elective neck surgery	Arguments against elective neck surgery
Improved staging	Extremely low rates of recurrence if observed
Improved targeting of adjuvant therapy	Excellent survival without elective surgery
Reduced recurrence rates	Procedure morbidity
Reduced need for salvage surgery	Sites of recurrence not routinely addressed in elective setting
Reduced postoperative Tg	
Improved survival	

I.J. Nixon, Ph.D. (✉)
Edinburgh University, Edinburgh, UK
e-mail: iainjnixon@gmail.com

A.R. Shaha, M.D.
Department of Surgery, Memorial Sloan Kettering Cancer Center, New York, NY 10061, USA
e-mail: shahaa@mskcc.org

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Follicular and Hurthle cell carcinomas have lower rates of lymph node metastasis and therefore are not considered for END.

The topic for this debate is a recent one which has developed in the last 10–15 years. Prior to that, thyroid cancer was largely a clinical disease. Now it has become a disease of imaging and biochemical investigation. Evaluation of recurrent disease has changed from clinical to identification of microscopic disease with biochemical tests and ultrasound-guided fine needle aspiration.

The first American Thyroid Association (ATA) guidelines in 2006 made a casual reference to consider ECND in PTC. However, promptly the committee recognized the invalidity of this approach and the high complication rate. Subsequently, the committee revised the recommendation in the updated 2009 guideline to the use of elective nodal dissection in selected patients in the high-risk category with a high probability of occult nodal disease.

What Is an Elective Lymph Node Dissection?

An END is a procedure which excises regional lymph node compartments from the neck when there is no obvious pre- or intraoperative evidence of nodal metastases. This should not be confused with removal of peri-thyroid nodes in conjunction with a thyroidectomy or sampling of lymph nodes in the central or lateral compartment.

Most groups now agree with the definitions that a central END involves levels VI and VII. This extends craniocaudally from the hyoid bone to the innominate vessels and laterally from carotid artery to carotid artery [11]. A lateral END will include levels II-V, with sparing of level I and levels IIb and Va (superior to the accessory nerve) [12].

In modern thyroid practice then, any patient who is considered free of regional disease following adequate preoperative assessment (ultrasound in most cases) will be a candidate for either END or observation of the neck.

Elective Lateral Lymph Node Dissection

If routinely performed, elective lateral lymph node dissection (ELND) for PTC, we see rates of metastatic disease which exceed 20% [13]. However, this has no clinical implication. It is a safe procedure which has gained acceptance within the field of head and neck oncology for squamous cell carcinoma. ELND is recommended for lesions of this type which are treated surgically and have a recognized rate of metastatic disease of >20% in the cN0 setting.

However, although safe, ELND is morbid. Not only is the surgical incision significantly longer than for thyroidectomy alone, but the procedure risks the cervical plexus, the facial and accessory nerve, and the sympathetic chain and results in long-term cosmetic changes to the neck [14–18]. So despite a relatively high yield of metastatic nodes, ELND which was once considered appropriate for PTC [19–22] is now not supported by major international guidelines [23, 24].

In part this change in management relates to the superior accuracy of ultrasound assessment of the lateral neck in comparison to the central neck [25]. However, the reader should remember that at least 20–30% of lateral necks harbor occult disease despite this improved accuracy. Even though over one in five patients with a cN0 lateral neck harbor metastases, very few recur. Those that do can be detected early and almost universally salvaged with neck dissection [26–29]. The reason that ELND has been abandoned is simply that the risks outweigh the benefit.

Arguments for Elective Central Compartment Lymph Node Dissection

Proponents of elective central compartment lymph node dissection (ECND) consider it a low-morbidity procedure and cite advantages of the approach including improved staging information in order to risk stratify and inform adjuvant treatment decisions, reduced rates of salvage surgery which can be challenging, lower rates of

postoperative thyroglobulin (Tg), lower rates of recurrent disease, and improved survival. We will deal with these points individually.

Patients with disease limited to the thyroid (no evidence of metastases) have excellent survival and as such are considered low risk [30]. Such patients have survival rates of 95% at 10 years irrespective of the approach to treatment [31, 32]. Clearly then, even if a survival benefit were associated with more aggressive approach to the N0 neck, the impact would be so low that it would be impossible to prove. Not surprisingly then, it is now accepted that ECND has no role in improving survival for patients with PTC.

For most patients, recurrence rates are a more realistic measure of treatment success. It has been shown that the use of ultrasound and thyroglobulin assessment at 12 months can be used in the process of dynamic risk stratification to describe the response to treatment and quantify the risk of subsequent recurrence. Prospective evidence has been reported which suggested that Tg levels at 6 months are lower following total thyroidectomy plus ECND than for total thyroidectomy alone [33]. However, with time those initial results were not durable, and long-term outcomes show no significant difference in Tg [34]. In addition, in studies where ECND is not performed, ultrasound assessment of the neck during follow-up does not suggest that recurrence rates are significant [35]. When subjected to meta-analysis, the impact of ECND suggests no improvement in rates of recurrence [36]. The overall recurrence rate of 2% is unlikely to be changed with or without ECND as long as the central compartment is evaluated thoroughly at the outset.

Salvage surgery is accepted to carry higher risk to the parathyroid glands and recurrent laryngeal nerve than primary procedures [37]. For that reason, proponents of ECND argue that removal of potentially metastatic, clinically occult disease from the central neck is beneficial in order to prevent the need for future salvage surgery. However, two critical points must be considered before accepting this fact. First, as stated earlier, recurrence rates in this group are vanishingly low in the central neck and have never been convincingly proven to be lower following ECND [26]. Second, although the world's most expert surgical groups have demonstrated that ECND can be performed with low rates of morbidity [38–40], this is not true for the vast majority of surgeons who operate on thyroid cancer [41–43]. The additional morbidity associated with ECND for all patients must be weighed against any assumed outcome benefit on an individual patient basis.

A more nuanced argument for ECND is that the procedure provides additional prognostic information which can be used to more accurately risk stratify patients postoperatively [13]. Indeed, for patients aged 45 years or over, the presence of nodal metastases converts their AJCC staging from early (I/II) to advanced (III/IV) disease [30]. In the American Thyroid Association (ATA) guidelines, the presence of nodal disease corresponds with an increased risk of recurrence [23]. This practice has much in common with staging END procedures which are used in oral cancer, for example. In keeping with more aggressive diseases, not only do some groups use the information as a prognostic tool but as a tool for selection of patients for adjuvant therapy in the form of RAI [13, 39, 44, 45]. However, this must be seen in the context of a far less aggressive disease. As stated above, outcomes are excellent irrespective of the extent of therapy in patients free of metastatic disease and the concept that upstaging patients who have excellent outcomes only serves to increase both patient anxiety and treatment intensity without good reason.

Arguments *Against* Elective Central Neck Dissection

Having examined the reasons behind support for ECND and found flaws on every front, now consider the arguments against ECND.

It is well accepted that PTC metastasizes often and early [46]. This is true for both the central and lateral lymph nodes [13]. In contrast to ELND, which has now been abandoned, controversy still surrounds the central neck. This hinges on the perception that central neck surgery is associated with low morbidity, an opinion which

is outdated [40, 41, 47, 48]. Experienced surgeons in centers of excellence have long argued that central neck surgery can be performed without additional complication in comparison with total thyroidectomy alone [49]. However, the majority of patients are treated outside such centers by surgeons. Indeed, less than 20% of patients in the USA have total thyroidectomy in a center which performs more than 12 such cases per year [50]. It is well recognized that outcomes for thyroid cancer surgery are associated with surgical experience [51, 52]. Ywata et al. found that rates of permanent recurrent laryngeal nerve injury and hypoparathyroidism increased from 1.5% to 5.9% and 2.3% to 11.8%, respectively, when ECND was performed with total thyroidectomy in a center which at least 75 such cases per year [43]. These high rates of morbidity result in significant impact on patients' day-to-day lives in a group who are likely to survive in the long term. Although the rate of occult disease encountered in this study reached 67% in the ECND group, overall recurrence rates were 1.9%. It is critical that the impact of the treatment does not outweigh the impact of the disease. As we always propose, let the punishment fit the crime, and let the treatment not be worse than the disease!

The high rates of occult disease found during elective neck surgery make many clinicians uneasy about observing lymph node basins which are at risk of metastatic involvement. However, such occult nodes are extremely unlikely to progress to present with clinically meaningful "recurrence." With long-term follow-up, overall rates of recurrence in patients with observed central neck are well below 5% [26, 27, 43]. Indeed, postoperative recurrence rates in the central neck itself occurs in <1% of patients who do not undergo ECND. This highlights just how good outcomes are in this patient group [26]. Even for those patients who may be considered at highest risk (e.g., older patients, men, and those with evidence of metastatic nodes in the peri-thyroid tissues removed at surgery), recurrence rates at 5 years do not exceed 4% [53]. One must consider whether a condition with such indolent biology should be treated with a morbid procedure such as ECND.

Clearly, with such low rates of recurrence, even if ECND did prevent recurrence, the difference would be small. So small that when the ATA considered this question, they calculated that around 6000 patients would be needed to reliably prove the impact ECND had on recurrence [54].

This calculation should not be interpreted as evidence that we will never know whether ECND should be performed, quite the opposite. This proves that with such large groups required to reach statistical significance, clinical significance will never justify the practice. Only if the morbidity of the procedure was lower than its impact on outcome would the practice be defensible, and as stated above for all but the most experienced surgeons, this is not the case.

Given the relatively high morbidity of ECND and the low impact on outcome, it is not surprising to find that the procedure is not cost-effective [55]. Not only does the procedure cost around $10,000 but, in addition, the upstaging of low-risk patients which results in increased use of adjuvant RAI incurring yet more costs [13]. In a cost-effectiveness analysis, Zanocco et al. calculated that recurrence rates would have to exceed 10% in order for ECND to break even [55]. It is likely that had contemporary evidence relating to the observation of small-volume recurrences rather than salvage surgery for all been included in this analysis, the calculated rate would have been even higher [56]. Clearly then, cN0 patients do not qualify for ECND on the grounds of cost in a similar way they do not qualify in terms of clinical benefit.

Although it is accepted that revision neck surgery is associated with higher risks than primary procedures [57], salvage surgery is so rarely required in this low-risk patient group that this argument can almost be ignored. Nonetheless, before dismissing out of hand, consider the actual intraoperative findings in salvage central neck surgery. When Clayman et al. reported their findings in 210 patients with persistent of recurrence central neck disease, they found that the majority had disease dorsal to the recurrent laryngeal nerve, deep in the thoracic inlet, or in the region of the vertebral artery [58]. Dissection in such areas carries significant risk in the primary or

recurrent setting, and it is highly unlikely that surgeons would be comfortable addressing these during an ECND. Not only is salvage surgery rare and not avoided by ECND, but when recurrences are analyzed in detail, we see that surgeons would rarely dissect out nodes from the critical areas in which it recurs again arguing against the practice.

Summary

END in differentiated thyroid cancer is used to be considered the standard of care. During the twentieth century, improved appreciation of disease biology in tandem with our understanding of the morbidity associated with lateral neck surgery led to ELND being abandoned. ECND became highly controversial when in 2006 the ATA guidelines stated the ECND should be considered for PTC [59]. This led to increasing rates of ECND internationally. Since that point, the two subsequent updates to the guideline have moved away from this position stating that ECND "may be considered" in 2009 [59] and that "management without ECND may be appropriate" in 2015 [23].

ECND has had ebbing support due to the recognition that the oncological impact is minimal at best. Patients considered cN0 have excellent outcomes, and the concept that upstaging this patient group is advantageous has been discredited both clinically and financially. The historical belief that central neck surgery is not associated with complications has been proven incorrect. In all but the most experienced hands, meaningful clinical outcomes are worse following ECND without an improvement in oncological outcome. All of these points alter the risk-benefit ratio for patients and clinicians considering whether or not ECND should be performed.

Our current practice in the management of the neck in DTC is to get appropriate preoperative imaging with ultrasound and CT scans if necessary and ultrasound-guided fine needle aspiration of suspicious lymph nodes. At the time of surgery, we critically evaluate the central compartment and superior mediastinum for any suspicious lymph nodes. If there are suspicious nodes, we would consider appropriate clearance of that area. We generously use frozen section as a large number of patients in the USA have Hashimoto thyroiditis which may confuse the issue of END.

Conclusion

If you are a high-volume thyroid surgeon with vast experience of central neck surgery and good evidence of extremely low complication rates, *and* you are practicing in a healthcare system with limitless resources, *and* you are treating an elderly male group of patients with advanced primary tumors who have no evidence of metastases in the central neck elective neck surgery, you might consider ECND despite the limited benefit it confers. In all other circumstances, elective lymph node dissection for differentiated thyroid cancer cannot be justified.

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Differentiated Thyroid Cancer: Prognostic and Risk Assessment Systems

16

Jonathan Black and Lawrence Kim

Introduction

Compared to other cancers, differentiated thyroid cancers are often viewed as more indolent in nature, but this is a broad generalization that does not accurately account for the various ways in which differentiated thyroid cancer can present. Small, well-differentiated cancers may be cured with surgery and have very low risk of recurrence or may never progress even without treatment. Conversely, cancers that present with bulky lymph node involvement and distant metastases place the patient at significant risk for morbidity and mortality. Understanding the course of the disease and which factors most closely govern prognosis is essential to appropriately treat patients with differentiated thyroid cancer. Though papillary and follicular thyroid cancers are different entities, there are similarities when it comes to prognosis. Studies have consistently shown that tumor size, age at diagnosis, lymph node involvement, the presence of local invasion, and distant metastases are the greatest predictors of outcome after diagnosis of differentiated thyroid cancer [1]. This chapter will examine these factors in detail to highlight the prognostic implications of each. Over the years, numerous authors have attempted to stratify the risk attributable to the various prognostic factors. This chapter will also describe and compare 16 prognostic scoring models for differentiated thyroid cancer, discussing the merits for each and identifying those with the best prognostic value. The American Joint Committee on Cancer's (AJCC) Tumor Node Metastasis (TNM) scoring system is also included for comparison.

Cancer staging systems such as the TNM system and the thyroid-specific systems discussed herein have been designed to be predictive of mortality. However in recent years, the risk of recurrent disease is increasingly being recognized as equally important in thyroid cancer. Survival rates for differentiated thyroid cancer are higher than many other cancers, but recurrent disease can cause significant morbidity even if it does not lead to mortality. The American Thyroid Association pioneered this approach in their 2009 thyroid cancer guidelines. This is expanded in the 2015 guidelines, which include a three-tiered clinicopathologic risk stratification system to gauge the risk of recurrence. Prediction of recurrence risk may be equally important in selecting treatment strategies such as TSH suppression and use of radioactive iodine. A more complete discussion of assessment of the risk of recurrence can be found in Chap. 18.

J. Black
Department of Surgery, University of North Carolina, Chapel Hill, NC, USA

L. Kim (✉)
Division of Surgical Oncology and Endocrine Surgery, Department of Surgery, University of North Carolina, Chapel Hill, NC, USA
e-mail: Lawrence_Kim@med.unc.edu

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Prognostic Features

Age

Age has been known to be an important predictor of survival in thyroid cancer since at least the 1960s [2, 3]. The earliest widely used prognostic systems, EORTC, AGES, and AMES, all included age as a prognostic factor [4–6]. Differentiated thyroid cancer is unique in that it is the only cancer to have age as a prognostic factor in the AJCC TNM staging system [7]. It is not clear why age is uniquely influential in thyroid cancer. This remains one of the most interesting biological questions in this disease.

Age is, by nature, a continuous variable. Three of the older prognostic systems, EORTC, AGES, and MACIS, all treat age as a continuous variable [4, 5, 8]. Other systems treat age as a categorical variable. Most notably, the AJCC TNM system has used age as a dichotomous variable since the second edition of the *AJCC Cancer Staging Manual* was published in 1983 [7]. In the TNM system, the age of 45 is used as a break point with different staging systems for patients below or above this age. Ganly et al. highlighted some of the limitations of this model. In the current TNM staging, a 44-year-old man with a T1N1b papillary thyroid cancer has stage I cancer with a predicted 5-year survival of 100% at 5 years. That same person with a T1N1b cancer has stage IV disease if they are 46 years old, decreasing the predicted 5-year survival to 51% [9].

Although it has been used for over 30 years, it is unclear why the age of 45 was chosen as the break point. Some have speculated that 45 might have been the median age for study populations of patients diagnosed with differentiated thyroid cancer and thus was chosen as a natural break point [9]. Some will point to the European Organization for Research and Treatment of Cancer's (EORTC) 1979 risk stratification system as being the first to show an increased death rate for patients aged 41–50. However, Byar et al. clearly state in the EORTC paper that they find age to be a better predictor when used as a continuous variable [4]. The AMES system from 1988 used two age cutoffs: 40 for men and 50 for women [6]. Oyer and colleagues have confirmed that patients 45 and older had worse survival, but they also found that survival starts to decline over 35 and gets progressively worse each decade [10]. Bischoff et al. have also demonstrated that the prognosis worsens as you age, though they argue that there is no one inflection point at which the prognosis drops severely. They propose that age 65 be used because this is the point at which their data shows the 5-year expected survival drop below 90% [11]. They are one of several groups who have advocated treating age as a continuous variable rather than a binary one [4, 10, 12].

Several publications have advocated moving the age cutoff from 45 to 55 [12–15]. A recent retrospective analysis examined 1807 patients and found that 55 was a more appropriate cutoff than 45. When 55 is used as the age cutoff, they were able to downstage 213 patients, only three of whom died of their disease [13]. Analyzing the SEER database, Kim et al. found that age greater than 55 was the most important prognostic factor for disease-specific mortality (HR 10.0), while age less than 57 was the best predictor of overall survival (HR 9.0) [14]. Mazurat and colleagues followed a cohort of 2115 patients with differentiated thyroid cancer from 1970 to 2010. Their study had very good follow-up with only 2.1% of patients lost to follow-up over that 40-year period. They too found that age over 55 resulted in decreased disease-specific survival. In their cohort, they found that patients who presented over 55 were more likely to have T3 or T4 tumors, have Hürthle cell histology, and have distant metastases on presentation [12].

It is clear that age plays a vital role in the prognosis of differentiated thyroid cancer. While recent data would suggest that treating age as a continuous variable might make predictive models more robust, the TNM staging system continues to use age >45 as its cutoff. Despite this limitation, the TNM system retains strong correlation between stage and prognosis.

Lymph Node Status

Currently, the 7th edition of the AJCC TNM staging system classifies nodal status into N0, N1a (central neck node involvement), and N1b (lateral

neck node involvement). While some controversy regarding the importance of lymph node status has existed in the past, most recent data supports that the presence of lymph node involvement confers a worse prognosis, especially in older patients [16]. In a large population study published in 2008 using the SEER database performed by Zayfuddin and colleagues, patients with papillary thyroid cancer aged 45 or older with positive lymph node disease had a 46% increased risk of death (hazard ratio 1.46) compared to those who did not. There was no link between positive lymph nodes and an increased risk of death in patients younger than age 45. In that study, lymph nodes were positive in 22% of patients with papillary thyroid cancer compared with only 2% of patients with follicular thyroid cancer. This is understandable since follicular thyroid cancer is much more likely to spread hematogenously. However, for the 2% of patients who did present with positive lymph nodes, the risk of mortality increases significantly. For patients aged 45 or older, the hazard ratio was 2.86, and for those under 45, the risk of death was increased over 11-fold (hazard ratio 11.2) [17]. From these data we can see that patients aged 45 and older with positive lymph nodes have a worse prognosis than node-negative patients, and lymph node metastases in follicular cancer, while rare, portend a significantly worse prognosis. This is especially important for the patients under age 45 since they typically have a better survival.

Early studies viewed lymph node status as a binary entity: either positive or negative. More recently it has become increasingly clear that not all positive lymph nodes are alike. In 2012, the American Thyroid Association published an extensive review of the literature on lymph node status in papillary thyroid cancer [18]. The study found that small volume, microscopic lymph node metastases can be present in up to 80% of patients with papillary carcinoma, but the recurrence rates are low. For patients with a tumor <1 cm in size, recurrence rates were 2–6%, regardless of the extent of lymph node dissection or the use of radioactive iodine ablation. For tumors >1 cm, recurrence rates were similar, 1–6%, when a central neck dissection was not performed. Thus, while present in a majority of cases of papillary thyroid cancer, microscopic lymph node metastases are usually clinically silent and often of no clinical significance. This is in stark contrast to clinically palpable lymphadenopathy. For these patients, the risk of recurrence ranged from 14 to 42%, with palpable nodes in the lateral neck compartments conferring a higher risk of recurrence. Similar to clinically palpable disease, lymphadenopathy detectable by ultrasound also carries an increased risk of recurrence. Again it was seen that the presence of lateral compartment nodes carries a higher risk of recurrence compared to clinically node-negative necks and pathologically proven positive nodes in the central neck.

In addition to the size of the nodes at presentation, the number of nodes is also an independent predictor of recurrence. One study of 148 patients found that the 10-year recurrence for patients with >10 positive lymph nodes was 21%, compared to 7% for 6–10 positive nodes and only 3% for <5 positive nodes [19]. Studies by Ito et al. and Sugitani et al. demonstrate similar results with greater numbers of positive node predictors of both increased recurrence and worse disease-specific survival [20–23].

Laura Wang and colleagues from Memorial Sloan Kettering have extensively studied lymph node status in papillary thyroid cancer. For central compartment lymph nodes (levels 6–7, N1a disease), their work shows that extranodal spread is an independent predictor of recurrence-free survival. Increasing numbers of positive nodes also appear to increase the risk of recurrence, but they hypothesize that this is likely due to association with extranodal spread rather than as an independent predictor [24]. In the lateral neck (levels 2–5, N1b disease), they found that a number of both positive lymph nodes (≥10) and lymph node burden (17%, or at least 1 node positive for every 6 removed) were predictive of recurrence. Additionally, for patients ≥45, extranodal involvement was also predictive of recurrence [25].

The American Thyroid Association Surgical Affairs Committee also suggested that the presence of lymph node metastases could be further

stratified into low- and high-risk groups. Micrometastases, clinically N0 necks, and ≤5 small lymph node metastases characterize low-risk N1 disease with less than 5% chance of recurrence. Conversely, clinically detectable lymph nodes, lymph nodes >3 cm, and the presence of greater than 5 positive lymph nodes are all predictors of higher-risk N1 disease and have a risk of recurrence >20% [18].

In light of these data, it is evident that lymph node status plays a role in the prognosis of differentiated thyroid cancer. Of all the factors included in the TNM staging system, lymph node status appears least frequently in the prognostic scoring systems developed over the years. Of the scoring systems that do include lymph node status, only the Tokyo system accounts for the quality of the nodes, noting that nodes >3 cm conferred a worse prognosis [22]. While the data above are clear that lymph node status is an important prognostic factor in differentiated thyroid cancer, the positive/negative system in which the AJCC currently classifies lymph node status likely does not tell the whole story. Lymph nodes should be viewed on a spectrum that ranges from truly negative or microscopic disease on one end to macroscopic, clinically palpable lymph nodes with extranodal spread on the other.

One difficulty in interpreting lymph nodes as a prognostic feature is that it is highly biased by treatment method. Surgeons have been divided regarding the utility of nodal dissections for clinically negative nodes, especially in the central compartment. Yet regional lymph node metastases in clinically negative nodal basins are exceedingly common in papillary cancer. Wada et al. presented a group of patients with papillary thyroid cancers less than 1 cm [26]. Two hundred and thirty-five patients underwent prophylactic central compartment (zone 6) lymph node dissections and 143 (60.9%) of the patients had positive nodes. One hundred and eighty-five patients also underwent prophylactic lateral lymph node dissections, and 73 (39.5%) patients had positive nodes. Presumably, larger primary tumors would have at least this high a prevalence of positive nodes. Lang et al. reviewed 14 studies comprising 3331 patients, 1592 of whom underwent prophylactic central node dissections [27]. In these studies, the prevalence of positive nodes ranged from 23.5 to 82.4%. Clearly, if prophylactic lymph node dissection is chosen routinely, positive nodes will be found commonly, perhaps leading to upstaging and perhaps more aggressive treatment. Indeed, in the review by Lang, 71.7% of patients who had prophylactic node dissections underwent postoperative radioactive iodine ablation, compared to 53.1% of the patients who did not have the nodal dissection, suggesting that knowledge of positive nodes led to increased RAI use.

Size

While debate still continues as to exactly how much weight to give age and lymph node status as prognostic factors, there is comparatively little discourse on tumor size. As is the case with most cancers, increased size portends a worse prognosis in differentiated thyroid cancers. Most prognostic systems include size as one of their prognostic criteria. In their AMES criteria, Cady and Rossi developed one of the first prognostic systems to include size as a factor, noting that tumors >5 cm placed the patient at an increased risk of disease-specific mortality [6]. Most prognostic systems devised since that time either treat size as a continuous variable [5, 8, 28] or break size into discrete intervals (<1 cm, 1–4 cm, >4 cm) with any tumor >4 cm considered to be predictive of the worst prognosis [29–32].

Ian Hay and colleagues' MACIS system showed that the relative risk of mortality increases 1.4 for each 1 cm increase in size over 1 cm [8]. While size is found to be predictive of disease-specific mortality in numerous multivariate analyses, it may be a less powerful predictor than some of the other prognostic factors. In Yildirim's analysis of 347 patients with differentiated thyroid cancer, the hazard ratio for size treated as a continuous variable was only 1.2, compared to hazard ratios of 2.9 for age and 2.7 for distant metastases [28]. Similarly, in the analysis by Sebastian et al. for the Murcia prognostic system, the odds ratio for survival for tumors >4 cm was 2.7 compared to

odds ratios of 4.8 for age 50 and 17.42 for extrathyroidal spread [32].

Local Invasion and Distant Metastases

Much like size, there is little to no debate over the significance of tumors that spread beyond the thyroid, and metastasis has consistently been shown to carry the worst prognosis. Both local spread into adjacent organs and distant metastases indicate advanced disease and portend lower chance of survival compared to tumors contained within the thyroid gland. Of the 16 scoring systems evaluated in this chapter, all but 2 include some form of extrathyroidal spread as a prognostic factor. Byar et al. in the EORTC system demonstrated that invasion into local structures, which they called T3 disease, carried an almost fourfold risk of death compared to tumors contained within the thyroid. Single and multiple metastases placed the patient at a 3.3× and 20× risk of death, respectively, compared to those patients with no metastatic disease [4]. Subsequent predictive models have confirmed the hazards associated with extrathyroidal disease. In the MACIS scoring system, Hay et al. found that local invasion and distant metastases conferred the highest risk of death with relative risks of 2.9 and 14.8, respectively [8]. Lerch and colleagues found that while age was the greatest predictor of mortality in their cohort of 500 patients, local invasion and distant metastases were both independent predictors of mortality on multivariate analysis with relative risks of 2.98 and 3.85, respectively [33]. In the clinical class prognostic system, Degroot et al. found that their patients with class III disease (local invasion) and class IV disease (distant metastasis) had 87 and 35% 15-year disease-specific survival, respectively, compared to 100% disease-specific survival in their other patients [34]. In their analysis of 1622 patients used to develop the CSMC criteria, Wong et al. found that distant metastases carried the worst prognosis for disease-specific survival with a hazard ratio of 10.26. Age >45 was the next most important factor in their model with a hazard ratio of 8.35, but local invasion was also found to be an independent predictor with a hazard ratio of 2.57 [35]. As might be intuitively expected, local and distant metastases detected at the time of diagnosis indicate either a delay in diagnosis, an aggressive form of differentiated thyroid cancer, or both and confer the worst prognosis in differentiated thyroid cancer.

Gender, Grade, and Histology

Age, lymph node status, size, and extrathyroidal spread have all been confirmed in multivariate analysis by numerous prognostic systems to be independent predictors of disease-specific mortality in differentiated thyroid cancer. As can been seen in Table 16.1, they are the most commonly used factors and each was reviewed independently to give perspective on the relative importance of its contribution to prognosis. Other factors may play a role in the prognosis of differentiated thyroid cancer, but their implications are less clear. Gender was included in three of the earlier prognostic systems [4, 36, 37], but several other systems considered gender and found that it was not statistically significant in multivariate analysis [8, 29, 35]. In studies where gender was significant in univariate analysis but not multivariate, males were found to have worse prognosis than females [29, 35]. This would seem to indicate that males may present later with more advanced disease but tend to have similar survival when matched with females that have a similar cancer burden.

Two of the early prognostic systems reviewed here, EORTC and AGES, both included some kind of tissue or cellular level information as part of their prognostic model [4, 5]. However, their definitions of tumor grade proved difficult to apply broadly to patients at a variety of institutions with different pathologists and reporting standards. The MACIS criteria were derived for just such a reason. Hay and colleagues realized that while tumor grade as described in the AGES criteria was important, it was not universally available and standardized, thus limiting its

Table 16.1 Prognostic factors used in staging systems

	Year	Disease[a]	Study size	Age	Size	Extent/ T-stage	Lymph node status	Metastases	Gender	Grade	Histology	Others	No. of risk groups
EORTC	1979	PTC, FTC, MTC, ATC	507	X		X		X	X		X		5
AGES	1987	PTC	860	X	X	X				X			2
AMES	1988	PTC, FTC	814	X	X	X		X					2
Clinical class	1990	PTC	269			X	X	X					4
MACIS	1993	PTC	1779	X	X	X		X				Completeness of resection	4
SAG	1993	PTC	173	X					X	X			3
Ohio State	1994	PTC, FTC	1355		X	X	X	X				Multifocal disease	4
Noguchi	1994	PTC	2192	X	X		X		X				3
MSK	1994	PTC, FTC	1038	X	X			X		X			3
Munster	1997	PTC, FTC	500			X		X					2
NTCTCS	1998	PTC, FTC, MTC, ATC	1607	X	X	X	X	X					4
UAB/MDA	2000	PTC	208	X				X					3
Murcia	2000	PTC	200	X	X	X					X		3
Tokyo	2004	PTC	604	X		X	X	X					2
Ankara	2005	PTC, FTC	347	X	X			X			X		4
CSMC	2013	PTC, FTC	1622	X		X		X			X		3
TNM	2009	PTC, FTC, MTC, ATC		X	X	X	X	X					4

[a]*PTC* papillary thyroid cancer, *FTC* follicular thyroid cancer, *MTC* medullary thyroid cancer, *ATC* anaplastic thyroid cancer

practicality when trying to develop a universal prognostic system [8]. It should be noted that the MACIS criteria were developed over 20 years ago, and our understanding of tumor biology has grown exponentially since that time. As our understanding of tumor biology continues to evolve, it becomes increasingly clear that factors including the cancer subtypes (papillary tall cell, Hurthle cell, etc.) and specific molecular variants are important in the prognosis of differentiated thyroid cancer. While a number of studies have attempted to correlate a particular molecular marker with prognosis, none have yet been successfully applied across a wide variety of patients and institutions. As we are able to better correlate clinical outcome with particular molecular features, prognostic systems that incorporate these markers will need to be developed.

Prognostic Systems

EORTC 1979

Most point to 1979 for the first published prognostic scoring system for thyroid cancer. In that year, David Byar and colleagues from the EORTC performed a multivariate analysis of 507 patients with thyroid cancer and created a scoring system based on age, sex, histology, T-stage, and the presence or absence of metastasis. They then stratified the patients into five groups and used the observed survival data in their cohort to predict survival [4]. Their patient set included medullary and anaplastic thyroid cancers in addition to papillary and follicular, but it paved the way for the future prognostic systems in differentiated thyroid cancer. Some authors will cite this paper as the reason the age of 45 is used as the cutoff in risk stratification systems [9], but Byar et al. treated age as a continuous variable with patients assigned more points as they got older. They did show increased mortality with increasing age that started in the 41–50 age range, so perhaps that is why age 45 was used by so many of the prognostic systems formulated after theirs.

AGES 1987

Ian Hay and colleagues at the Mayo Clinic next proposed a novel scoring system in 1987. Their system used *a*ge, tumor *g*rade, *e*xtent, and *s*ize to predict survival. It analyzed 860 patients with papillary thyroid cancer and found that patients with an AGES score of 3.99 or less had observed 25-year mortality of 1% for patients who had ipsilateral lobectomy and 2% for patients who had a total thyroidectomy. In contrast, patients with an AGES score of 4 or higher had a 25-year disease-specific mortality of 65% for patients treated with ipsilateral lobectomy compared to only 35% for those who had a total thyroidectomy ($p = 0.06$) [5].

AMES 1988

The Lahey Clinic published their own staging system in 1988, later dubbed the AMES staging system. In their cohort of 814 patients with differentiated thyroid cancer, *a*ge, distant *m*etastasis, *e*xtent, and *s*ize of the primary tumor were predictive of mortality. Age and size were both treated as categorical variables, with size >5 cm and age >41 for men and age >51 for women all predictive of an increased risk of death. Using these criteria, 89.4% of their patients were classified as low risk with a 1.8% risk of mortality, while the other 11% were high risk with a mortality rate of 46% [6].

Clinical Class 1990

Researchers at the University of Chicago were next to publish a risk stratification system dubbed the clinical class staging system. It was based solely on the extent and spread of the disease: class I was intrathyroidal disease, class II cervical node metastases, class III extrathyroidal invasion, and class IV distant metastases. They found that most of the deaths occurred in classes III and IV, with class III conferring a 5.8-fold increased risk of death and class IV a 47-fold increased risk of death. Class II patients were found to have an

increased risk of recurrence but not an increased risk of death. Interestingly, they found that age over 45 and size >3 cm increased the risk of death by 32 and 5.8, respectively, but neither was included in their predictive model [34].

MACIS 1993

Ian Hay and colleagues published a new prognostic system in 1993, just 6 years after the publication of their AGES scoring system. While the AGES system was well validated, many centers did not report grade for papillary thyroid cancer, so the authors wanted a prognostic system that had more general applicability. Their cohort of 1779 patients was divided into two groups sorted by treatment date: 764 who had surgery between 1940 and 1976 and 1065 who had surgery 1965–1989. The first group was used to develop the prognostic model, and the second group was used to test the model. The model incorporated five variables: *m*etastasis, *a*ge, **c**ompleteness of resection, *i*nvasion into surrounding structures, and *s*ize (MACIS). The final formula was 3.1 (if aged < or = 39 years) or 0.08 × age (if aged > or = 40 years), + 0.3 × tumor size (in centimeters), +1 (if incompletely resected), +1 (if locally invasive), and +3 (if distant metastases present). The 20-year disease-specific survival rates for scores of <6, 6–6.99, 7–7.99, and 8+ were 99%, 89%, 56%, and 24%, respectively ($p < 0.0001$) [8].

While it only evaluated papillary thyroid cancer, the MACIS prognostic system has been well validated over the years. Lang et al. analyzed 14 different prognostic staging systems for papillary thyroid cancer developed between 1979 and 2005. They found that the MACIS scoring system most accurately predicted disease-specific survival in their cohort of 587 patients with papillary thyroid cancer [38]. D'Avanzo et al. analyzed 86 patients with follicular thyroid cancer and found that the MACIS scoring system was the most accurate in predicting disease-specific survival in their cohort [39]. Despite being initially developed for papillary thyroid cancer, the MACIS scoring system is applicable to both papillary and follicular cancers and remains one of the best predictive models for differentiated thyroid cancer. In its 2015 guidelines, the American Thyroid Association recommends the MACIS system along with the TNM staging system from the American Cancer Society as its preferred staging and prognostic systems [40].

SAG 1993

In contrast to the MACIS scoring system, the SAG scoring system emphasizes tumor grade as an important prognostic feature. Published by Lars Akslen from the University of Bergen in Norway, he found that histologic grade based on nuclear atypia, tumor necrosis, and vascular invasion was a strong prognostic factor in a cohort of 173 patients with papillary thyroid cancer. His scoring model incorporates *s*ex, *a*ge, and *g*rade, and patients were stratified into three SAG groups. Group 3, made up of male patients over 70 with high-grade tumors, had a significantly higher death rate, 51.5% at 10 years compared to 9.3% and 1.3%, respectively, from SAG II and SAGI [36].

Ohio State Criteria 1994

The Ohio State University system was published by Mazzaferri and Jhiang based on a cohort of 1355 patients from US Air Force and Ohio State University hospitals. It included both papillary thyroid cancer and follicular thyroid cancer. They divided patients into four groups, or stages, based on tumor size, lymph node involvement, multifocality, local tumor invasion, and distant metastases. Stage I patients had tumors <1.5 cm in diameter; stage II, tumor size between 1.5 and 4.4 cm or presence of cervical lymph node metastases or more than three intrathyroidal foci of tumor; stage III, tumors at least 4.5 cm or presence of extrathyroidal invasion; and stage IV, distant metastases. Their staging system is unique in that it incorporates multifocality in addition to the more commonly used factors like size, lymph node status, and metastases. They also report on recurrence rate in addition to cancer-specific mortality. They found that patients with stage II

and stage III papillary and follicular cancers had similar mortality rates for similar disease burden at presentation [29].

Noguchi 1994

Researchers from the Noguchi Thyroid Clinic in Japan published their staging system in 1994 based on a cohort of 2192 patients with papillary thyroid cancer. Their staging system divided men and women into three groups based on gender, age, tumor size, and gross lymphadenopathy. They found that survival for men and women was dependent on different prognostic factors and thus staged them separately. For men, only two factors were found to be predictive: age and nodal status. The low-risk or excellent group included all men younger than 45 and patients up to age 60 without gross nodal metastasis. The intermediate group included patients ages 45–55 with gross nodal metastasis and patients over 60 without gross nodal involvement. The poor group included all patients over 55 with nodal metastasis. Ten-year survival for the three groups was 98.4%, 90.1%, and 74.4%, respectively. For women, tumor size was predictive in addition to age and gross lymphadenopathy. The excellent group included all females up to age 50 plus patients 50–55 without gross nodal metastasis. The intermediate group included patients ages 50–55 with gross nodal involvement, ages 55–65 with no nodal involvement, and age 65+ with no gross nodal involvement whose primary tumors were less than 3 cm. The poor group was any patient over 55 with gross nodal involvement and patients over 65 with a primary tumor >3 cm. Survival for the three groups was 99.3%, 96.4%, and 88.8%, respectively at 10 years [37].

Memorial Sloan Kettering (MSK) 1994

Memorial Sloan Kettering published their prognostic system in 1994 based on a cohort of 1038 patients with differentiated thyroid cancer. Their scoring system takes grade, age, size, and distant metastases into account. Patients were stratified into low-, intermediate-, and high-risk groups according to the following criteria: low-risk patients were those younger than 45 with tumors <4 cm, no distant metastases, and with papillary thyroid cancers. Intermediate-risk patients included those younger than 45 with either distant metastases, tumor >4 cm, or follicular thyroid cancer on pathology or age <45 with no sign of distant metastases, tumors <4 cm, and papillary thyroid cancer. High-risk patients were those 45 with either distant metastases, tumors >4 cm, or follicular thyroid cancer. With a median follow-up of 20 years, disease-specific survival was 99%, 85%, and 57%, respectively. They make it a point to highlight that the intermediate-risk group includes both low-risk patients with high-risk tumors and higher-risk patients with low-risk tumors [30].

University of Munster 1997

Researchers from the University of Munster analyzed 500 patients with differentiated thyroid cancer including almost 40% with follicular thyroid cancer. Patients were stratified into low- and high-risk groups. High-risk patients were those with either a T4 (locally invasive) or M1 (distant metastatic) disease. All others were considered low risk. With a median follow-up of 5 years, there were no disease-specific deaths in the low-risk group and disease-specific survival in the high-risk group was 83%. Age was found to be statistically significant in multivariate analysis with a relative risk of death of 4.67 but was not included in the prognostic system. Lymph node status was evaluated, but on multivariate analysis was not an independent predictor of mortality leading the authors to conclude that the higher mortality of positive lymph nodes seen on univariate analysis is due to the coincidence with local invasion and distant metastases [33].

National Thyroid Cancer Treatment Cooperative Study (NTCTCS) 1998

The National Thyroid Cancer Treatment Cooperative Study was a prospective, multi-institution study involving 14 university centers

and 1607 patients registered from 1987 to 1995. Median follow-up was 40 months. The study included patients with anaplastic and medullary thyroid cancer in addition to papillary and follicular. Differentiated thyroid cancer patients accounted for about 93% of the cohort. Prognostic factors evaluated included age, tumor size, tumor type, extrathyroidal invasion, lymph node, and distant metastases. Patients were stratified into four clinical stages. Factors most predictive of prognosis for papillary cancer included age, size, extrathyroidal invasion, and metastases. For follicular thyroid cancer, age, size, distant metastases, and poor differentiation were predictive. Table 16.2 shows how the patients were stratified into the various stages. Disease-specific survival was 99.8% for stage I, 100% for stage II, 91.9% for stage III, and 48.9% for stage IV [31]. Since its publication in 1998, the NTCTCS staging system has been independently verified and found to be one of the most accurate staging systems for predicting disease-specific survival [35].

UAB/MD Anderson 2000

Published in 2000, this prognostic system evaluated 208 patients with papillary thyroid cancer seen at the University of Alabama at Birmingham and MD Anderson Cancer center. Patients were stratified into low-, intermediate-, and high-risk groups. Age, size, distant metastases, and an aggressive growth pattern (blood vessel invasion, lymphatic invasion, or local invasion) were all found to affect prognosis in univariate analysis, but only age and distant metastases were statistically significant in multivariate analysis. Consequently, only age and distant metastases factor into risk group stratification. Low-risk patients are those less than age 50 with no sign of distant metastases, intermediate risk those over 50 with no sign of distant metastases, and high risk those of any age with distant metastases [41].

Murcia 2000

This prognostic scoring system was developed at the University of Murcia Hospital in Spain and published in 2000. With a mean follow-up of 8 years, it analyzed 200 patients who had surgery for papillary thyroid cancer between 1970 and 1995. The prognostic scoring system included age, tumor size, extrathyroidal spread, and histological variant. Histological variants included solid, tall cell, and poorly differentiated, all of which conferred a worse prognosis. Patients were divided into low-, medium-, and high-risk groups based on score. See Table 16.2 for the scoring equation. The low-risk group had 100% survival at 20 years, while the high-risk group had only a 39% survival at 5 years [32].

Tokyo 2004

Researchers in the division of head and neck pathology at the Cancer Institute Hospital in Tokyo, Japan, published a prognostic system based on 604 patients with papillary thyroid cancer. Mean follow-up was 10.7 years. They used four prognostic factors: age (50 years as cutoff), distant metastases, extrathyroidal extension, and large nodal metastases (≥3 cm). Patients were stratified into low- and high-risk groups. The high-risk group included patients younger than 50 with distant metastases and patient older than 50 with any one of the other three prognostic factors: metastases, extrathyroidal invasion, or large nodal metastases. Ten-year survival for low- and high-risk groups was 99% and 69%, respectively [22].

Ankara 2004

This prognostic system was developed from a cohort of 347 patients with differentiated thyroid cancer. Patients were stratified into four groups: very low risk, low risk, high risk, and very high risk based on age, tumor size, angioinvasion, and distant metastasis. The formula exp[(0.2 × tumor size in cm) + (1 if age more than 45 years) + (0.7 if angioinvasion in primary tumor) + (1 if distant metastasis at presentation)] was used to derive a pretreatment probability of cancer-specific mortality defined as (score)/(1 + score). The four risk groups were defined as

Table 16.2 Methods for risk calculation [38]

Staging system	Calculations and risk groups
EORTC 1979 [4]	Score = age in years + 12 if male + 10 if poorly differentiated FTC + 10 if MTC + 45 if ATC + 10 if T3 + (15 if one metastatic site *or* 30 if multiple metastatic sites)
	Group 1 < 50
	Group 2 = 50–65
	Group 3 = 66–83
	Group 4 = 84–108
	Group 5 > 109
AGES 1987 [5]	Score = (0.05 × age in years if older than 39) + 1 if tumor grade 2 + 2 if tumor grade 3 or 4 + 1 if extrathyroidal invasion + 3 distant spread + (0.2 × size in cm)
	Group 1 < 4.00
	Group 2 = 4.00–4.99
	Group 3 = 5.00–5.99
	Group 4 ≥ 6.00
AMES 1988 [6]	Low-risk group
	1. Younger patients (men <41, women <51) with no distant metastases *OR*
	2. Older patients with intrathyroidal PTC or minor capsular involvement FTC + tumor <5 cm + no distant metastases
	High-risk group
	1. All patients with distant metastases
	2. Older patients with PTC with extrathyroidal spread or tumor >5 cm
	3. Older patients with FTC with major capsular involvement or tumor >5 cm
Clinical class 1990 [34]	Class I = intrathyroidal disease
	Class II = cervical lymph node involvement
	Class III = extrathyroidal invasion
	Class IV = distant metastases
MACIS 1993 [8]	Score = (3.1 if age < 40 *or* 0.08 × age in years) + (0.3 × tumor size in cm) + 1 if incompletely resected + 1 if locally invasive + 3 if distant metastases present
	Group 1 < 6.00
	Group 2 = 6.00–6.99
	Group 3 = 7.00–7.99
	Group 4 ≥ 8.00
SAG 1993 [36]	Score = 1 if male + 1 if ≥ 70 years old + 1 if high grade (vascular invasion, marked nuclear atypia or tumor necrosis is present)
	SAG I = 1
	SAG II = 2
	SAG III = 3
Ohio State 1994 [29]	Stage 1 = tumors <1.5 cm
	Stage 2 = tumors 1.5–4.4 cm or palpable tumor of unknown size or cervical lymph node metastases or multifocal within the thyroid gland (≥3 foci)
	Stage 3 = tumors ≥4.5 cm or locally invasive
	Stage 4 = distant metastases

(continued)

Table 16.2 (continued)

Staging system	Calculations and risk groups				
Noguchi 1994 [37]	Males				
	Excellent risk = age ≤ 45 or age ≤ 60 with no gross nodal metastases				
	Intermediate risk = age 45–55 with gross nodal metastases or age ≥ 60 with no nodal metastases				
	Poor risk = age > 55 with gross nodal metastases				
	Females				
	Excellent risk = age ≤ 50 or age 50–55 with no gross nodal metastases				
	Intermediate risk = age 50–55 with gross nodal metastases or age 55–65 with no gross nodal metastases, or age > 65 with no nodal metastases and tumor size <3.0 cm				
	Poor risk = age > 55 with gross nodal metastases or age > 65 with no gross nodal metastases but tumor size >3.0 cm				
MSK 1994 [30]	Low risk = age < 45 + PTC + tumor <4 cm + no distant metastases				
	Intermediate risk = age ≥ 45 + PTC + tumor <4 cm + no distant metastases *or* age < 45 + (either FTC or tumor >4 cm or distant metastases)				
	High risk = age ≥ 45 + (either FTC or tumor >4 cm or distant metastases)				
Munster 1997 [33]	Low risk = up to T3, M0 (see TNM staging below)				
	High risk = T4 or M1				
NTCTCS 1998 [31]	The disease stage is the highest stage as determined by the following features:				
		Tumor type			
		Papillary carcinoma		Follicular carcinoma	
		Age < 45 years	Age > 45 years	Age < 45 years	Age > 45 years
	Primary tumor size (cm)				
	<1	I	I	I	II
	1–4	I	II	I	III
	>4	II	III	II	III
	Primary tumor description				
	Microscopic multifocal	I	II	I	III
	Macroscopic multifocal or macroscopic tumor capsule invasion	I	II	II	III
	Microscopic extraglandular invasion	I	II	I	III
	Macroscopic extraglandular invasion	II	III	II	III
	Poor differentiation	NA	NA	III	III
	Metastases				
	Cervical lymph node metastases	I	III	I	III
	Extracervical lymph node metastases	III	IV	III	IV

Table 16.2 (continued)

Staging system	Calculations and risk groups
UAB/MDA 2000 [41]	Low risk = patients <50 without distant metastases
	Intermediate risk = patients >50 without distant metastases
	High risk = patients of any age with distant metastases
Murcia 2000 [32]	Prognostic index (PI) = (3 × age score) + (2 × size score) + (6 × spread score) + (2 × variant score)
	Age score = 1 <50, 2 ≥50
	Size score = 1 if 1–4 cm, 2 ≥4 cm
	Spread score = 1 if confined to thyroid, 2 if extrathyroidal invasion
	Histologic variant score = 1 if tall-cell, solid, or poorly differentiated PTC
	Risk groups:
	Low risk <18
	Medium risk = 18–22
	High risk >22
Tokyo 2004 [22]	High risk = patients <50 with distant metastases *or* patients >50 with either large nodal metastases (>3 cm), extrathyroidal invasion, or distant metastases
	Low risk = patients not classified as high risk: patients <50 with no distant metastases *or* patients >50 with no large nodal metastases (>3 cm), extrathyroidal invasion, or distant metastases
Ankara 2005 [28]	Score = exp [(0.2 × tumor size in cm) + (1 if age >45) + (0.7 if angioinvasion is present) + (1 if distant metastasis)]
	Pretreatment probability of cancer-specific mortality = score/(1 − score)
	Risk groups: Very low risk ≤55%
	Low risk = 56–85%
	High risk = 86–95%
	Very high risk ≥96%
CSMC 2013 [35]	Score = 12 if age > 45 + 11 if distant metastases +5 if capsular invasion (T3 or T4 tumor) + 4 if vascular invasion
	Risk groups:
	Low risk <10
	Intermediate risk = 10–19
	High risk ≥20

(continued)

Table 16.2 (continued)

Staging system	Calculations and risk groups
TNM 2009 [42]	T stages
	T0: No evidence of primary tumor
	T1a: <1 cm and confined to thyroid gland
	T1b: 1–2 cm and confined to thyroid gland
	T2: 2–4 cm in greatest dimension and confined to thyroid gland
	T3: >4 cm in greatest dimension and confined to thyroid gland, or any tumor with minimal extrathyroidal extension
	T4a: tumor of any size extending beyond the thyroid capsule to invade subcutaneous soft tissues, larynx, trachea, esophagus, or recurrent laryngeal nerve
	T4b: tumor of any size extending beyond the thyroid capsule to invade prevertebral fascia or encases carotid artery or mediastinal vessels
	N stages
	N1a: metastases to level VI lymph nodes (pretracheal, paratracheal, and prelaryngeal/Delphian lymph node
	N1b: metastases to levels I, II, III, IV, V, VII (cervical or superior mediastinal lymph nodes)
	M0: no distant metastases
	M1: distant metastases
	Staging
	Under 45 years of age
	Stage 1: any T, any N, M0
	Stage 2: any T, any N, M1
	45 years of age and older
	Stage 1: T1, N0, M0
	Stage 2: T2, N0, M0
	Stage 3: T3, N0, M0 *or* T1-T3, N1a, M0
	Stage IVa: T4a, Any N, M0 *or* T1-T3, N1b, M0
	Stage IVb: T4b, any N, M0
	Stage IVc: any T, any N, M1

very low risk ≤55%, low risk 56–85%, high risk 86–95%, and very high risk ≥96%. Ten-year overall and event-free survival were 100/100%, 88/75%, 30/16%, and 5/0%, respectively, for the four groups. The author also developed a post-treatment formula but did not define risk groups in the article [28].

Tumor Node Metastasis (TNM) 7th Edition 2009

The Tumor Node Metastasis model is published periodically by the American Joint Committee on Cancer. The 7th edition took effect for all cancers diagnosed after January 1, 2010, and replaced the sixth edition which was published in 2003. The only difference of note between the 6th edition and the 7th edition was to stratify T1 tumors into T1a (≤1 cm) and T1b (1–2 cm). It is widely used and is the standard by which the various prognostic systems should be judged. The TNM staging system is not without its limitations though and the numerous prognostic models formulated over the years were developed to improve upon the current system. The full TNM staging system is shown in Table 16.2 [42]. In addition to the MACIS scoring system, the TNM system is consistently validated as one of the best prognostic models [40].

Cedars Sinai Medical Center (CSMC) 2013

With the exception of the TNM staging system that is updated on a semi-regular basis, there had been few, if any, new prognostic models for differentiated thyroid cancer until Wong et al. published their prognostic model in 2013. They analyzed a cohort of 1622 patients with differentiated thyroid cancer treated at Cedars Sinai Medical Center in Los Angeles, CA. Median follow-up was 11.8 years. Their model uses a scoring system that assigns points according to the following criteria: 12 points for age >45 years, 11 points for distant metastases, 5 points for capsular invasion (T3 or T4 tumors), and 4 points for vascular invasion. Low-, intermediate-, and high-risk groups were defined as <10 points, 10–19, and 20+, respectively. Ten-year disease-specific survival was 99.4%, 96.6%, and 46.2%, respectively. The authors also compared their prognostic model with 13 other well-known prognostic models and found that their model and the NTCTCS models were most predictive of disease-specific survival [35].

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Role of Radioactive Iodine for Remnant Ablation in Patients with Papillary Thyroid Cancer

17

Nicole M. Iniguez-Ariza, Suneetha Kaggal, and Ian D. Hay

Introduction

The role of radioactive iodine (RAI) for remnant ablation in patients with papillary thyroid carcinoma has been a controversial topic for more than three decades [1–4]. In our chapter, we consider the implications of the recently published American Thyroid Association (ATA) Management Guidelines for adult patients with thyroid nodules and differentiated thyroid cancer (DTC) [2] and hope to clarify for our readers where we currently stand on their Recommendation 51, designed to answer the question of "What is the role of radioactive iodine (RAI) (including remnant ablation, adjuvant therapy or therapy for persistent disease) after thyroidectomy in the primary management of DTC?" Because there is a paucity of published studies specifically addressing the role of RAI and radioiodine remnant ablation (RRA) in patients who have either follicular thyroid cancer (FTC) or Hürthle cell cancer (HCC), we will be restricting our discussion in this chapter to the management of patients with papillary thyroid cancer (PTC), a tumor type which our institution has been carefully studying for more than 30 years [3].

We will plan to consider both low-risk and high-risk PTC patients in this chapter, and in attempting to define an appropriate role for post-surgical RAI in the management of patients presenting with PTC, we will plan to initially address three relevant questions:

1. How did RRA come to be an established part of PTC management?
2. Does RRA improve postoperative outcome in low-risk PTC (classified by tumor size) after complete tumor resection without gross residual disease?
3. If RRA is proven to be ineffective in reducing mortality and recurrence, not only in patients with small PTC tumors but also in all PTC patients with MACIS scores <6, should we be using RRA selectively to treat only the minority of patients with high-risk PTC who have MACIS 6+ disease?

After considering these questions, we will examine the main results from recently published meta-analyses of this controversial subject. Finally, we will carefully examine the evolution over the past two decades of thyroid

N.M. Iniguez-Ariza, M.D.
I.D. Hay, B.Sc., M.B. Ch.B., Ph.D, F.A.C.E., F.A.C.P., F.R.C.P. (✉)
Division of Endocrinology and Internal Medicine, Mayo Clinic and College of Medicine, 200 1st Street SW, Rochester, MN 55905, USA
e-mail: Ariza.Nicole@mayo.edu; hay.ian@mayo.edu

S. Kaggal, B.S.
Division of Biostatistics, Mayo Clinic and College of Medicine, 200 1st Street SW, Rochester, MN 55905, USA
e-mail: Kaggal.Suneetha@mayo.edu

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cancer clinical management guidelines and clarify where we ourselves stand on Recommendation 51 of the 2015 ATA Guidelines [2].

Question 1: How Did RRA Come to Be an Established Part of PTC Management?

History of RAI During 1895 Through 1969

The foundation for the use of RAI in the treatment of thyroid diseases depended largely on advances in science and medicine made at the end of the nineteenth century and the beginning of twentieth century. During that period, it became more readily accepted that (1) the thyroid gland concentrated iodine, (2) tracer substances could be used to analyze biologic functions, and (3) radioactive isotopes could be artificially created.

By end of the nineteenth century, it was believed that the thyroid contained some substance capable of producing marked physiologic effects, and that iodine was a constant constituent of normal and pathologic glands. The German biochemist, Baumann, [5] found iodine in the thyroid gland in 1895 and Kendall, at the Mayo Clinic isolated "the" thyroid hormone (thyroxin) in 1914 using iodine as a marker for the hormone [6]. Joliot and Curie in 1934 discovered artificial radioactivity, [7] with the creation of a new radioactive element, radiophosphorus. Enrico Fermi [8] read the Joliot and Curie paper and tried their experiment, using neutrons instead of alpha particles as a radiation source. He described 22 new radioactive elements, including "radiated iodine," which showed an "intense effect" with a half-life of 30 min.

On November 12, 1936, Karl Compton from the Massachusetts Institute of Technology (MIT) spoke on the subject of "What physics can do for biology and medicine" at Harvard Medical School. He talked about how radioisotopes of many different elements could be made on demand and then used to trace metabolic events in living organisms. At the end of his talk, Saul Hertz from the Massachusetts General Hospital (MGH) apparently asked him whether there might be a radioactive isotope of iodine. Compton replied to Hertz that "yes, iodine can be made artificially radioactive." Soon thereafter, Hertz and Means arranged for physicists at MIT to make the short-lived ^{128}I, thereby permitting study at MGH of its physiology in rabbits. By 1938, they showed that the rabbit's thyroid gland [9] rapidly took up ^{128}I, but because of its short half-life (25 min), there was no hope for using ^{128}I as a potential treatment modality [10].

In 1939, Hamilton and Soley, working at University of California, San Francisco (UCSF), and in Berkeley, California, were able to make several other radioactive iodines, ^{130}I and ^{131}I, with half-lives of 12 h and 8 days, respectively. They were the first investigators to give these isotopes to humans for the study of thyroid physiology. Initially, RAI was used for the study of thyroid physiology, but soon thereafter, the possibility of using RAI as a treatment was considered in the management of both hyperthyroid and thyroid cancer patients.

The earliest study of the uptake of RAI in two cases of carcinoma was reported by Hamilton and colleagues [11] in 1940. In 1942, they described two other cases [12] in which tracer doses of radioactive iodine had been given to the patients prior to the removal of carcinomatous thyroids, but no significant deposition of the RAI in malignant areas was identified in either of these cases. Keston and colleagues [13] subsequently reported the first positive evidence of uptake of RAI by a femoral metastasis from a thyroid carcinoma. The patient was given 10 mCi of RAI, and the metastasis took up about 30%, while the thyroid gland itself took up only about 6% of the total amount administered. With this evidence, the possibility of the use of RAI as a therapeutic agent was suggested, because the metastasis in the femur had fixed such a large proportion of the radioactive material. Subsequently, from the autopsy of this patient, these authors reported that "the bulk of the metastatic tissue was undifferentiated" and the metastasis, which showed consistent uptake of iodine, was the only one which grossly resembled thyroid tissue and which, microscopically, showed well-differentiated tumor [14].

In 1946, Seidlin [15] published details of the successful treatment with RAI of a case of well-differentiated metastatic follicular thyroid cancer

(FTC) with functional metastases causing hyperthyroidism. In 1948, Rawon and coworkers [16] introduced the concept that, after thyroidectomy, there was increased capacity for thyroid metastases to concentrate ^{131}I. They demonstrated that eight patients had significant postoperative increase in RAI uptake in their metastatic lesions, which, prior to thyroidectomy, had shown minimal to no function.

Until 1949, the only counting device for external detection of radioactive substance was the Geiger-Müller (GM) tube, which was very insensitive to penetrating gamma rays from radionuclides such as ^{131}I. This problem was largely overcome by the first scintillation counters developed in 1949–1950 for medical use and constructed by Cassen [17, 18] and his colleagues at UCLA. In 1951, this UCLA group first used a scintillation detector to "scan" RAI distribution in the thyroid, and this made possible the subsequent era of thyroid gamma scans and whole-body radioiodine scanning. By 1951, a decade after the publication of Hamilton's pioneering work [11] with this isotope, the Food and Drug Administration (FDA) finally approved ^{131}I for thyroid patients; this represented the first radiopharmaceutical to be approved for human therapy.

In 1960, Blahd and associates [19] at UCLA published their experience since 1949 with the use of ^{131}I as postoperative therapy for thyroid cancer. Patients received on average therapeutic doses of 100 mCi, but the authors specified that smaller doses might be used to ablate postoperative thyroid remnants, depending upon the size of remnant tissue observed. All of the 26 patients who received ^{131}I therapy had undergone prior thyroid surgery. Fifteen patients in their series had proven metastatic lesions, and 11 patients were treated solely for the purpose of remnant ablation. Blahd's group at UCLA were likely the first to consider that RRA may be used to "complete the thyroidectomy" after an apparently complete surgical resection of primary tumor in localized differentiated thyroid cancer (DTC).

It should be noted that during the period of 1950–1969, only 3% of PTC patients, who had at the Mayo Clinic bilateral lobar resection (BLR) with curative intent, underwent within 6 postoperative months RRA, although during that time RAI therapy was routinely given to both patients who had incomplete primary tumor resection with gross residual disease and those demonstrated to have distant metastases at initial presentation. In other words, at Mayo, for the first two decades after the introduction of RAI as an approved therapy, 97% of PTC patients undergoing definitive, and potentially curative, BLR, typically near-total thyroidectomy (NT) or total thyroidectomy (TT), avoided RAI for remnant ablation.

Early Reports of RAI in Thyroid Cancer During 1970 Through 1981

In 1970, Varma and colleagues, [20] from Beierwaltes' group at Ann Arbor, claimed that ^{131}I administered postoperatively could reduce mortality from thyroid cancer. This study was based on the death rate analysis of 263 patients with PTC or follicular thyroid cancer (FTC) treated with ^{131}I after surgery (intervention group), when compared with the death rates in 50 patients with PTC or FTC treated surgically before the introduction of ^{131}I (control group). In the patients 40 years of age and older, the intervention group had a significantly lower death rate than the surgery-only group. The authors did acknowledge that one possible weakness of their data was that thyroid surgery at their institution may have become more radical since the introduction of ^{131}I in 1947, and a more aggressive operative approach, as directed by the surgical skills of Professor Norman Thompson, may have contributed, at least in part, to the better results observed in the intervention group.

In 1977, Krishnamurthy and Blahd [21] from UCLA again reported on the therapeutic value of postoperative ^{131}I therapy, this time in 54 patients (96% with well-differentiated thyroid cancers, WDTC) treated during a 25-year period. Twenty-four patients (44%) had metastases at the time of ^{131}I therapy, mainly to cervical and mediastinal lymph nodes and less frequently to the bone, brain, lung, and liver. The recurrence rate for

patients with metastases was 56% and in those without metastases was 25%. Seven deaths were attributed to thyroid cancer. The authors noted that no deaths from thyroid cancer occurred when "total ablation was achieved and maintained." They recommended that most patients with WDTC should be considered for postoperative RAI. In reviewing the contemporary management of thyroid cancer, they concluded that "there is as yet no unified single opinion in the medical community as to the best form of therapy for thyroid cancer. Personal philosophy, emotional factors, and the basic medical training play a significant role in the selection of therapy."

In that same year (1977) and again in 1981, Mazzaferri [22, 23] and colleagues reported on a cohort of 576 patients with histologically proven PTC that were treated at the USAF Hospital at Wilford Hall Air Force Base in Texas. In their initial 1977 paper, they described "highly variable" therapy provided to USAF personnel "treated in an individualized manner, reflecting the clinical situation, as well as the experience and bias of the attending physician." In total, 116 patients (20%) were given ^{131}I; 80 had residual nodal disease, 3 had presented with lung metastases, and only 33 (28%) were actually being treated for ablative purposes. In the 1977 report [23], they compared those treated postoperatively with thyroid hormone and ^{131}I to those receiving only thyroid hormone and demonstrated a significant reduction in cumulative percent recurrence in those receiving ^{131}I. Mazzaferri, on the basis of his initial study results, recommended that "ablative doses of I-131 should be employed postoperatively, especially in those with primary lesions that are multiple, locally invasive or larger than 1.5 cm and in those with local and/or distant metastases, provided adequate uptake of radionuclide can be demonstrated."

Clearly, at this point in the literature, the subtle distinctions between RAI therapy and RRA were not being adequately appreciated in this, the first real, study of the efficacy of RAI in a cohort of patients consisting only of pathologically confirmed PTC. In 1981, when his cohort [22] had now a median follow-up of 10 years, Mazzaferri concluded that "treatment with total thyroidectomy, postoperative RAI and thyroid hormone resulted in the lowest recurrence and mortality rates except in those patients with small primary tumors (less than 1.5 cm diameter) in whom less than total thyroidectomy and postoperative therapy with thyroid hormone alone gave results which did not differ statistically from those achieved with more aggressive therapy."

As noted above, at the Mayo Clinic, during the first 20 years (1950–1969) after the FDA approved ^{131}I for therapeutic purposes, RAI was regularly administered to patients either with gross residual disease or who had undergone distant spread, but was not employed in PTC patients undergoing potentially curative bilateral surgery for localized disease. During 1970–1974, only 6% of PTC patients underwent, within 6 postoperative months, RRA after potentially curative bilateral lobar resection (BLR), but by 1980–1989 there had been a tenfold increase in RRA rates [24, 25] to 59%, likely due to the influence of Mazzaferri's 1977 and 1981 reports [22, 23]. RRA in PTC should not be confused with RAI therapy, since, as defined initially by Harry Maxon and more recently by Anna Sawka, RRA "refers to the destruction of residual macroscopically normal thyroid tissue after complete gross surgical resection of cancer" [26, 27].

Question 2: Does RRA Improve Postoperative Outcome in Low-Risk PTC (Classified by Tumor Size) After Complete Tumor Resection Without Gross Residual Disease?

Assignment of PTC risk category at presentation is largely dependent on details readily derived from the contents of initial surgery and pathology reports and, where appropriate, preoperative radiologic imaging of chest and skeleton. Many different potential prognostic variables have been identified, and risk assessment systems developed

[28–36]. Detailed description of these systems is provided in Chap. 16. They can provide guidance on the need for postoperative treatment, including RRA.

Colum Gorman [37] was one of the first Mayo authors to question whether RRA possibly represented in PTC a "questionable pursuit of an unattainable goal," as locoregional recurrences occurred within the thyroid bed or neck nodes in 6 of 69 patients he followed up for up to 5 years. He emphasized the lack of a proven value of postsurgical RRA of presumed normal thyroid tissue and raised the future possibility of a more conservative or "selective" approach to RRA. In an accompanying Journal of Nuclear Medicine editorial entitled "Applying the Radioactive Eraser: I-131 to Ablate Normal Thyroid Tissue in Patients from Whom Thyroid Cancer Has Been Resected," Sisson [38] argued that "extinguishing evidence of thyroid cancer is beneficial, but ablation of normal thyroid tissue is another matter." He even suggested that "wiping the scintigraphic slate clean" did not necessarily eliminate the possibility of future recurrence. And he dared to question the importance of Mazzaferri's 1981 study, [22] in which fewer recurrences followed ^{131}I treatment of presumably normal thyroid residuals, emphasizing that the results were of marginal significance. He highlighted the possibility of second non-thyroid cancer risk following RAI treatment and ended his editorial with a very relevant observation: "to ablate or not to ablate is a question that will haunt us for some time to come."

In 1986, a study by McConahey, Hay, and colleagues [3] of 859 PTC patients treated at Mayo during 1946–1970 found after a median follow-up of 18 years an overall mortality rate at 30 years of only 3% above that expected. These patients were conservatively treated, as only 16% underwent TT and 3% had postoperative RRA. They concluded their manuscript by stating "whether routine remnant ablation can substantially improve the already excellent results of surgical treatment remains, in our assessment, to be proved." In 1990, Hay [39] highlighted the influence of the studies from Michigan [21] and Ohio State [22, 23] on the worldwide use in follicular cell-derived cancer (FCDC) patients of RAI therapy and RRA. He found, however, that, in contrast to Mazzaferri's significantly improved recurrence rates after RAI in 153 ablated PTC patients, in a comparable outcome study of 946 similarly defined Mayo patients, he found no significant differences between bilateral potentially curative surgery ($n = 726$) and the same surgery plus RRA within 6 postop months ($n = 220$), with regard to tumor recurrence ($p = 0.06$), cause-specific mortality (CSM) ($p = 0.25$), or overall mortality ($p = 0.52$). Hay [39] concluded his review by stating that "It is our expectation that further assessment of outcome in appropriately matched patients will permit a more rational use of remnant ablation, and we hope that such data will proved a satisfactory answer to Sisson's haunting question."

In 1994, DeGroot [40] summarized the then present status of RRA in the USA as follows: "Mazzaferri, Young and co-workers provided, nearly 2 decades ago, the first powerful support for the role of radioactive treatment in reducing recurrences and deaths in differentiated thyroid cancer….more recent studies by De Groot and colleagues, and Samaan and coworkers demonstrated, in a careful analysis stratifying patients by extent of diseases, that both more extensive surgery (lobectomy plus subtotal or near-total thyroidectomy) and radioactive iodine treatment reduce the numbers of recurrences and deaths. Hay and co-workers have thrown their support behind more extensive surgery, but have not yet supported routine radioactive remnant ablation." To which Grebe and Hay [41] responded in 1997 by stating that "it is still our stance that we remain unconvinced by the presently available retrospective data describing the efficacy of RAI remnant ablation in differentiated thyroid carcinoma."

In 1998 Wartofsky [42] wrote: "if we place ourselves in the shoes of even a "low risk" patient, would we not willingly accept the consequence of a 30–60 mCi ablative dose of ^{131}I in exchange for the certainty and peace of mind provided by a subsequent negative scan and

undetectable serum Tg level?" In the same article, [42] Schlumberger and Hay talked about a "selective approach" for the use of RAI in patients with PTC and FTC. They stated that RAI was clearly not indicated or not beneficial to patients with small intrathyroidal tumors and that RRA does not influence recurrence rates in patients with node-positive papillary thyroid microcarcinoma but for larger tumors, tumor multifocality, tumor extension beyond the thyroid capsule, or lymph node metastases, the beneficial effects of RAI continued to be debated. They concluded that RRA should be restricted to patients with poor prognostic indicators for relapse or death and representing only a small high-risk minority of DTC patients. In the same year, Morris and colleagues [43] published a survival analysis examining ^{131}I therapy in localized well-differentiated thyroid cancer, based on data from 1969 to 1993 on 1171 patients from the New Mexico Tumor Registry of whom 127 (37%) had received RRA. They concluded that there was no apparent survival benefit associated with RAI following "clinically appropriate" thyroidectomy.

As we have been updating outcome data of our eight-decade Mayo PTC cohort, it has become clear, as shown in Fig. 17.1, that throughout the 80-year period, a third of our

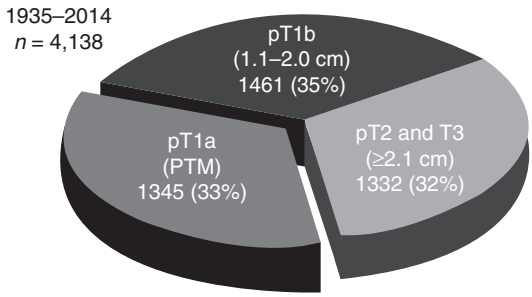

Fig. 17.1 Size distribution of maximal tumor diameter in 4138 adult PTC patients consecutively treated at Mayo during 1935–2014 and demonstrating that one-third of these patients during the eight decades presented with PTM and tumor diameters of 1 cm or less (pT1a)

PTC cases were at presentation 1 cm or less in greatest diameter and would be considered papillary thyroid microcarcinomas [44] (PTM) by the World Health Organization and categorized as pT1a in the current TNM classification approved by the ATA in the 2015 Guidelines [2]. pT1b tumors with 1.1–2.0 cm diameters accounted for a further 35%, while the largest tumors exceeding 2 cm in diameter made up the final 32%. For more than 24 years [44], our group has very carefully analyzed outcome details in pT1 tumors, accounting for almost 70% of our PTC cases. For the remainder of this section of our chapter, we will concentrate on trying to determine whether RRA does have any significant impact on outcome in more than 2/3 of all our PTC cases that are either pT1aM0 or pT1bM0 after complete tumor resection without gross residual disease.

In 2008 we presented and published [45] our experience of treating 900 pT1a tumors over a 60-year period (1945–2004). These patients were followed up for up to 54 years and on average for 17 postoperative years. At last follow-up, only three patients (0.3%) died of PTC. RRA was administered to 17% of the study group and, when reevaluated for efficacy, was found to be 99% successful in terms of negative neck and whole-body RAI scans. Expected and observed all-causes survival were near identical (p = 0.96). CSM rates at 20 and 40 years were 0.1 and 0.7%.

Of 758 patients without distant spread, undergoing BLR with complete tumor resection, 119 (16%) had RRA administered within 6 postoperative months. RRA did not impact tumor recurrence (TR) at local or distant sites, but postoperative ("recurrent") neck nodal metastases (NNM) were more frequently found after RRA, when compared to those treated by BLR only. These higher NNM rates were likely explained because node-positive patients were 10 times more likely to have received RRA. Four percent of node-negative

PTM patients got RRA, and at 20 years TR rates were 0.6% after BLR and 0% after BLR + RRA ($p = 0.79$). By contrast, 38% of node-positive cases got RRA, which did not decrease TR at either local ($p = 0.8$) or distant ($p = 0.7$) sites. Higher TR rates were seen with either multicentric tumors or patients who were node-positive at presentation. Accordingly, for our final analysis of the efficacy of RRA in PTM in our six-decade cohort, we elected to examine four subsets of patients divided according to the number of foci (unicentric vs. multicentric) and presence or absence of NNM at initial surgery.

With unifocal node-negative PTM, RRA did not decrease the <1% risk of nodal recurrence seen after BLR ($p = 0.8$). In multifocal node-negative cases, no recurrences at any site were seen in 101 patients, perhaps implying that multicentricity per se in PTM does not impart a higher risk of TR. In unifocal node-positive disease, RRA did not significantly reduce the 11% TR seen after BLR alone ($p = 0.2$). Finally, in the worst-case scenario of multifocal node-positive PTM, RRA did not in 100 cases significantly decrease the 22% TR rate (all sites) seen after BLR alone. Our 2008 conclusions [45] were that the extent of surgery did not affect TR rates, and RRA did not improve outcome in any subset of patients studied, including those with multicentric tumors or those presenting with NNM at initial surgery.

We recently presented [46] at the 2016 Meeting of the Endocrine Society the results from our experience in managing the 1345 PTM patients shown in Fig. 17.1. Of the 1281 potentially curable cases (no distant metastases and complete surgical resection after BLR), only 165 (13%) had RRA within 6 months of successful BLR. Interestingly, only 1% was ablated in the decade of 1965–1974, but in the decade of 1975–1984, when Mazzaferri's two initial PTC studies [22, 23] were published, this rate rose by more than 20-fold to 23%. However, in the subsequent three decades up to 2014, the rates of RRA dropped progressively from 20 to 16 during 1985–1994 and 1995–2004, respectively, and, most recently, 11% in the last decade of 2005–2014.

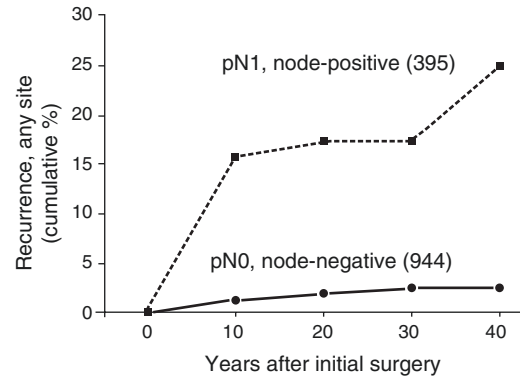

Fig. 17.2 Influence of neck nodal metastases at presentation on cumulative tumor recurrence rates over 40 postoperative years in 1339 patients with localized (M0) papillary microcancers, who had complete primary tumor excision at initial surgery and demonstrating a highly significant ($p < 0.001$) increase (almost tenfold) in those 395 patients who were node-positive (pN1)

Figure 17.2 illustrates, within the eight-decade PTM cohort, the very significant influence ($p < 0.001$) of NNM at presentation on subsequent discovery over 40 postoperative years of so-called "recurrent" NNM. In this recent study, we again concluded that PTM patients have normal life expectancy and typically are cured by adequate tumor resection. More than 99% of our PTM patients treated over eight decades were not at risk of either distant spread or mortality from cancer. The 20-year TR rates were only 7%, almost exclusively in regional (neck) nodes. The extent of initial surgery [46] did not affect locoregional recurrence rates ($p = 0.8$) and, most interestingly, the 30-year TR rates in node-positive cases after lobectomy alone were no different from those seen after BLR or even NT or TT

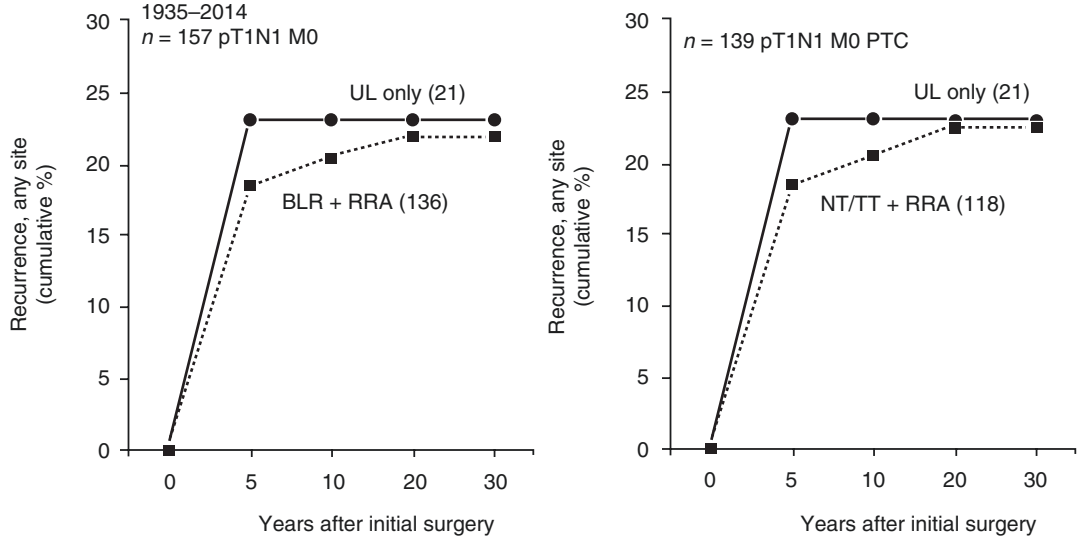

Fig. 17.3 Comparison, within patients with pT1aN1M0 microcarcinoma having potentially curative surgery at Mayo during eight decades (1935–2014), of cumulative tumor recurrence rates over 30 postoperative years and demonstrating that the recurrence risk (at any site, locoregional or distant) after unilateral lobectomy alone was no different (p = NS) from that seen after either bilateral lobar resection (BLR) and RRA (*left panel*) or near-total or total thyroidectomy (NT/TT) and RRA (*right panel*)

followed by RRA ($p = 0.99$). Figure 17.3 demonstrates that in node-positive PTM (pT1N1MO) the 30-year TR rate after UL was insignificantly different from the comparable rates seen after either (left panel) BLR + RRA or (right panel) NT or TT followed by RRA within 6 postoperative months.

In 2009, we had reported to the American Thyroid Association at their annual meeting that neither the 2006 ATA Cancer Guidelines [47] nor a more recently published report by Rosario [48] regarding adjuvant therapy in PTC tumors <2 cm diameter provided convincing data regarding a role for RRA in improving postoperative outcome in PTC patients with AJCC pT1 tumors, especially those pT1b tumors with diameters of 11–20 mm. We suggested [49] that if a prospective trial was to be designed to answer this question, it would likely involve "low risk" (e.g., with MACIS scores <6) tumors in patients aged 21 years or older, with surgically curable T1 disease (i.e., neither T4 nor M1) completely resected by initial successful BLR.

In the prospective retrospective study that we presented, [49] our aim was to define outcome in a cohort of 765 adult (aged 21 or older) patients with MACIS <6 pT1M0 PTC treated during the 35 years after the introduction of RRA and before the current era of ultrasound-guided neck nodal biopsies, recombinant human TSH-stimulated thyroglobulin (Tg) testing and near-routine central compartment neck nodal dissection. The 765 patients (545F; 220M) underwent BLR during 1950–1985 for tumors that were completely resected and were neither locally invasive at initial neck exploration nor distant spread at initial presentation.

Median patient age in this 1950–1985 cohort was 45 years (range 21–72), mean tumor size 12 mm (49% <11 mm); 24% were multicentric and 30% node-positive. Mean follow-up was 27 years (longest 55); 23% for >35 years. One hundred and seventy (22%) received RRA. 35-year occurrence rates for CSM, local recurrence (LR), regional nodal metastases (RNM),

and distant metastases (DM) were 1.1, 2.2, 5.0, and 1.6%, respectively. Comparable rates for Group A (n = 375 PTM with pT1a tumors <11 mm) were 0.6, 1.8, 4.5, and 0.5%. For Group B (n = 390 pT1b tumors of 11–20 mm diameter), rates were higher at 1.6, 4.3, 5.5, and 2.6%, respectively. RRA's impact was assessed by comparing survival to each of these four endpoints in patients undergoing BLR alone versus those receiving BLR + RRA within 18 postoperative months. The 35-year CSM rates in Groups A and B were after BLR 0.6 and 1.6% and after BLR + RRA insignificantly different ($p > 0.75$). Similarly, survival rates to LR, RNM, and DM were no different in ablated patients than after BLR alone in both Groups A ($p > 0.07$) and B ($p > 0.33$).

It was our principal conclusion [49] from this study that the results confirmed the excellent prognosis of AJCC pT1 tumors treated by BLR and did not identify a significant reduction in either mortality or recurrence rates in those patients with T1 PTC tumors selected for RRA.

Question 3: If RRA Is Ineffective in Reducing Mortality and Recurrence in PTC Patients with MACIS Scores <6, Should We Be Using RRA Selectively to Treat Only the Minority of Patients with High-Risk PTC, Who Have MACIS Scores of 6 or More?

In an attempt to quantify the influence of RRA on outcome in low-risk PTC after adequate initial surgery, we performed in 2002 [25] and again in 2006 [50] analyses on 1163 MACIS low-risk PTC (scores <6) patients, who had undergone NT or TT during 1970–2000 for tumors confined to the neck that were completely excised at initial neck exploration. 498 (43%) of these patients had RRA within 6 months of the initial surgery. Those who received RRA were more likely to have had NNM at presentation ($p < 0.001$). Of 636 node-negative patients, 195 (31%) received RRA. However, of 527 node-positive patients, 303 (57%) were ablated.

At 20 postoperative years, the CSM rate for the surgery alone patients was 0.4%, and for the NT/TT and RRA group, it was insignificantly different at 0.6% ($p = 0.64$). At 20 years, the TR rate was actually significantly higher in the ablated group (14% vs. 9%; $p = 0.008$), likely reflecting the tendency to more readily ablate node-positive patients. When the patients were divided into node-negative and node-positive groups, there were no statistically significant differences in outcome (CSM and TR) between those having surgery alone and those who also received postoperative RRA. Interestingly, there were no deaths from PTC in the 636 node-negative cases and only two in the node-positive group.

For the node-negative patients, the 20-year TR rates were 3.4% after surgery alone and 4.3% after surgery and RRA ($p = 0.80$). For the node-positive group, who clearly had much higher TR rates, the CSM rates at 20 years were 1.2% after surgery alone and 0.9% after RRA ($p = 0.99$). The 20-year TR rates only differed by 0.4%, being 19.5% for surgery alone and 19.9% for surgery and RRA ($p = 0.66$). Clearly, it was our 2006 conclusion [50] that RRA did not significantly improve the outcome (either CSM or TR) in low-risk (MACIS scores <6) PTC patients previously treated with initial NT or TT with curative intent. This conclusion obviously became a pivotal part of our Mayo policy [51] for managing patients with low-risk PTC published in 2007.

As we prepared for this chapter and were working on updated outcome results from our eight-decade Mayo PTC cohort, we considered it relevant to extend the years of our MACIS <6 cohort a further 14 years to encompass those low-risk PTC patients who were surgically treated definitively, with or without RRA, in the years of 2001–2014. This added a further 911 patients to

a new total cohort of 2074 adult MACIS <6 patients, of whom 760 (37%) underwent RRA within 6 months of NT or TT with curative intent. The principal details of the 20-year CSM and TR rates are included in the accompanying Table 17.1.

Table 17.1 Lack of influence of RRA on outcome in 2074 MACIS <6 low-risk PTC patients (without distant metastases) treated at Mayo during 1970–2014 by NT/TT with complete tumor excision

Low risk	20-Year mortality		20-Year recurrence	
(MACIS < 6) 1970–2014	NT/TT alone	NT/TT and RRA	NT/TT alone	NT/TT and RRA
All patients (%) (n = 2074)	0.3	0.7	8.7	18.2
	P = 0.09		P < 0.001	
Node-negative (%) (n = 1159)	0	0.5	3.9	4.6
	P = 0.11		P = 0.34	
Node-positive (%) (n = 915)	1.0	0.9	19.1	26.3
	P = 0.53		P = 0.08	

Figure 17.4 illustrates the differences in TR over 20 postoperative years between ablated and not ablated patients in the entire study cohort of 2074 low-risk PTC patients (left panel), the 1159 node-negative cases (middle panel) and the 915 node-positive patients (right panel). As expected, in the node-positive patients, most recurrences (83%) were situated in regional neck nodes. There were no significant differences between the ablated and the not ablated groups in terms of either local recurrences (p = 0.34) or distant metastases (p = 0.49), generally considered [3, 32] to be postoperative events associated with an increased risk of CSM. Interestingly, the recurrence rate in regional nodes was insignificantly higher (p = 0.05) in the 496 ablated patients, and this was felt to be attributable to significantly higher numbers of NNM found in those patients selected for RRA. The cumulative recurrence rates over 20 postoperative years in the 915 node-positive cases for all three anatomic locations

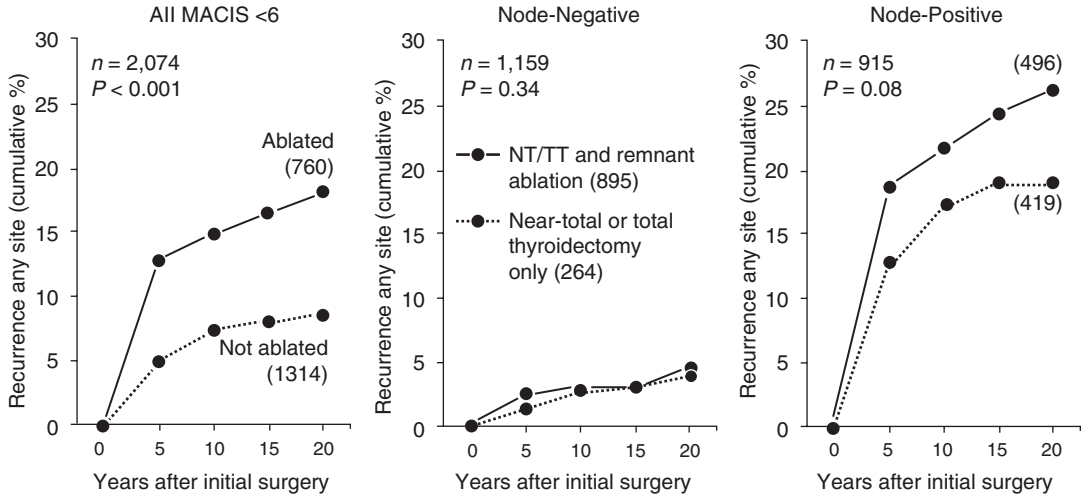

Fig. 17.4 Influence of RRA on tumor recurrence (any site) over 20 postoperative years in 2074 MACIS <6 PTC patients, who had no distant metastases and had undergone complete tumor resection after initial potentially curative surgery with NT/TT during the 35-year period of 1970–2014 (*left panel*), in 1159 pN0 node-negative patients (*middle panel*) and in 915 pN1 node-positive patients (*right panel*). Recurrence rates were higher (p < 0.001) in ablated patients (*left panel*), but were insignificantly different (p = NS) in either node-negative (*middle panel*) or node-positive patients (*right panel*)

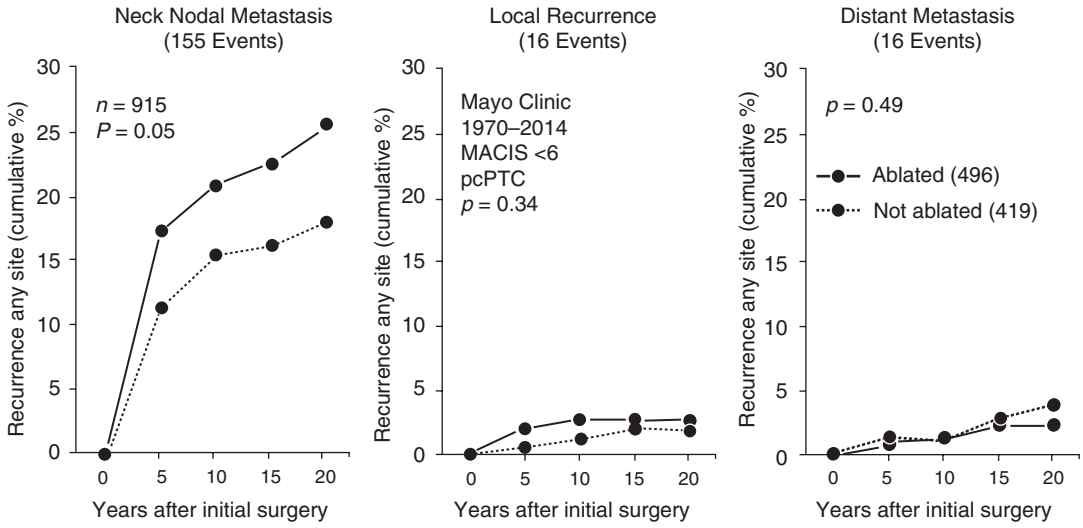

Fig. 17.5 Lack of influence of RRA administered within 6 postoperative months, when compared to NT/TT + RRA, in 915 potentially curable MACIS <6 node-positive PTC patients consecutively treated at Mayo during 1970–2014 on rates of cumulative tumor recurrence at regional (*left panel*), local (*middle panel*), and distant sites (*right panel*)

(regional, local, and distant) are illustrated in Fig. 17.5.

The results of these two studies defining the lack of impact of RRA on outcome in MACIS <6 low-risk PTC have helped convince us that RRA can probably be avoided in, not just the 68% of PTC patients who have pT1 tumors but also the 84% who have MACIS scores <6 and have tumors localized to the neck and having complete primary tumor excision at initial definitive surgery.

Era of Systematic Reviews and Meta-Analyses

That remarkable source of knowledge, Wikipedia, informs us that "conceptually, a meta-analysis uses a statistical approach to combine the results from multiple studies in an effort to increase power (over individual studies), improve estimates of the size of the effect and/or to resolve uncertainty when reports disagree." Given the rancor expressed in the past 30 years over the vexed question of the efficacy of RRA in low-risk PTC, it is not perhaps surprising that multiple authors have jumped at the chance of "resolving uncertainty when reports disagree."

Mayo-trained Anna Sawka started this type of study in 2002–2003, while she was working at McMaster University in Hamilton, Ontario. She began by screening 1543 unique references and ended up by studying in great detail those 23 references [27] that "met all inclusion criteria," one of them from Mayo [25]. Her conclusion [27] from a systematic review of the 1966–2002 literature was that "the effectiveness of RAI ablation decreasing recurrence and possible mortality in low-risk patients with well differentiated thyroid carcinoma, although suspected, cannot be definitively verified by summarizing the current body of observational patient data." She expressed the opinion [27] that "only a long-term randomized controlled trial may definitely resolve this issue" and concluded that "in the meantime, the decision for RAI ablation must be individualized, based on the risk profile of the patient, as well as patient and physician preference, while balancing the risk and benefit of such therapy."

Four years later, Sawka published [26] an "updated systematic review" which included data from 20 studies from the original review [27], the original review itself, and seven newer studies from 2002 to 2007. Again, she was unable to identify any long-term randomized controlling trials examining outcomes after RRA; she therefore restricted her review to observational data. Her conclusion in 2007 was that "upon carefully examining the best existing long-term observational evidence, the authors could not confirm a significant, consistent, benefit of RRA in decreasing cause-specific mortality or recurrence in early stage WDTC." She observed [26] that "in an age of freely available information, patients themselves may have strong opinions about accepting or declining RRA and it is important for physicians to be sensitive to such concerns. The current reality is that decision making about RRA in early stage thyroid carcinoma is a complex, evolving issue and long term higher quality evidence is needed to inform future clinical practice."

In a more recent systematic analysis of the 1966–2008 peer-reviewed literature, published in 2010, Sacks [52] from Cedars-Sinai reported "that the preponderance of evidence suggests that RAI treatment is not associated with improved survival in patients with low-stage or low-risk DTC. The data concerning recurrence rates following RAI treatment in this group of patients were less conclusive." On the basis of her analysis, she recommended the adoption of a risk group categorization, based on AJCC TNM staging and the MACIS score, and proposed a management guideline based on a patient's risk: very low, low, moderate, and high. Her final conclusion was that "a majority of very low-risk and low-risk patients, as well as select cases of patients with moderate risk, do not demonstrate survival or disease-free survival benefit from postoperative RAI treatment, and therefore we recommend against postoperative RAI in these cases."

Finally, in 2015, an Italian systematic review [53] by a group of investigators from Rome and led by Cooper, the lead author of the 2006 [47] and 2009 [54] ATA Guidelines, concluded that, when compared to earlier meta-analyses [26, 52] of literature until 2007–2008, "our review of the more recent literature (2008–2014) clearly shows no advantage of RRA in low-risk patients, but it was unable to provide conclusive data for or against RRA in preventing disease recurrence in intermediate risk patients." They recommended from their analysis that "a careful evaluation of tumor pathological features and patient characteristics and preferences should guide RRA decision making." They expressed hope that the two presently ongoing European prospective randomized trials (the French Estimabl2 study and the British IoN study) will "provide valuable data to inform this issue." They recommended that "an undetectable serum Tg, especially in a high-sensitivity Tg assay, and negative neck US 6–12 months after surgery should enable many low risk and intermediate risk patients to be categorized as being 'free of disease', despite not having undergone RRA," thereby supporting a position remarkably close to that proposed in the 2007 description of the current Mayo management [51] of patients with low-risk PTC.

Evolution of Management Guidelines During 1997–2016

In the first AACE Clinical Practice Guidelines for the Management of Thyroid Carcinoma [55] published in 1997, it was stated that "RRA is used to complete the initial therapy in a patient whose FCDC has been completely resected—that is, when no gross residual disease is reported at the conclusion of the primary neck exploration. RRA is a procedure that is offered to patients who have undergone "potentially curative" surgical treatment and should not be confused with RAI therapy, in which larger administrated doses of I-131 are used in an attempt to destroy persistent neck disease or distant metastatic lesions." In the section under the heading of "adjuvant therapy," it was stated that "other investigators, however, have not advocated RRA in low-risk PTC patients because of lack of evidence of improved

outcome. The issue of RRA in low-risk patients remains unsettled; a case-by-case decision is recommended, guided by clinical judgement and experience."

In 2006, the ATA Taskforce stated in their management guidelines [47] that the reported advantage of reducing tumor recurrence and cause-specific mortality in PTC "appears to be restricted to patients with larger tumors (>1.5 cm) or with residual disease after surgery, while lower-risk patients do not show evidence for benefit". However, rather than advocating a selective use of RRA for only higher-risk patients, the ATA recommended [47] with a B rating that RRA be performed in "patients with stage III and IV disease (AJCC 6th edition), all patients with stage II disease younger than age 45 years (Any T Any N M1), most patients with stage II disease 45 years or older (T2NOM0) and selected patients with stage I disease, especially those with multifocal disease, nodal metastases, extrathyroidal or vascular invasion and/or more aggressive histologies."

Under these 2006 ATA Guidelines, of patients having an initial NT or TT with curative intent, it was estimated [56] that approximately 70% of PTC patients would be submitted to RRA "although all current staging and scoring systems would identify the high-risk minority, who could potentially benefit from RRA to be only about 15–20% of PTC cases." Hay [56] suggested that "since neither the Mayo [25, 50] nor the NTCTCSG [57] data can demonstrate improvement in either tumor recurrence or cause-specific mortality rates with RRA in low-risk patients, such an escalation of aggressive postoperative adjunctive therapy can hardly be justified. Indeed, one must seriously doubt whether the proposed increased use of RRA and the increasing evaluation of rhTSH-stimulated thyroglobulin levels will either be cost-effective or lead in future years to improved outcome results for patients with PTC, the commonest endocrine cancer."

Only 3 years later, Cooper and his ATA Taskforce issued Revised Guidelines [54] and here it was recognized that "the first dose of RAI may also be considered adjuvant therapy because of the potential tumoricidal effect on persistent thyroid cancer cells." In Recommendation 32, the strength of evidence for the efficacy of RRA in reducing CSM and TR, with the exception of M1 disease, varied from B to E. On the basis of reviewed contemporary data, the ATA advised that CSM and TR rates were likely after RRA to be reduced only in patients of 45 years or older with pT3 disease or in any patient with pT4 or M1 disease. They therefore recommended RRA "for all patients with known distant metastases, gross extrathyroid invasion of the tumor regardless of size, or primary tumor size >4 cm." For sure, they did not recommend RRA for either intrathyroidal PTM (pT1a) or patients without evidence of NNM at presentation. They advised, with a C recommendation rating, a "selective use" of RRA in patients "with 1–4 cm thyroid cancers confined to the thyroid who have documented lymph node metastases, or other high risk features when the combination of age, tumor size, lymph node status, and individual histology predicts an intermediate to high risk of recurrence or death from thyroid cancer."

A novel feature of the 2009 Guidelines [54] was the description of a "three-level stratification" system for the assessment of the risk of recurrence. Using this risk adapted paradigm, [58] the ATA defined high-risk patients as those with distant metastases, incomplete tumor resection, or gross extrathyroid invasion (otherwise known to Mayo authors as the "MCI of MACIS" [33]) and leaving behind the continuous [33] variables of **A**ge and **S**ize to the AJCC/IUCC staging! ATA low-risk patients had complete tumor resection, no "local or distant metastases," and "no tumor invasion of locoregional tissues or structures." Also, low-risk tumors could not have aggressive histology, vascular invasion, or RAI uptake outside of the thyroid bed on a first post-treatment whole-body RAI scan: all in all, a rather complex definition for low-risk PTC! Those who were neither high nor low were termed intermediate and had to have "any of the following": (1) microscopic invasion of tumor into the perithyroidal soft tissues at initial surgery, (2) cervical lymph node metastases or ^{131}I

uptake outside the thyroid bed on the RxWBS done after thyroid remnant ablation, or (3) tumor with aggressive histology or vascular invasion.

Citing the reference of Tuttle and Leboeuf [58] from 2008, the ATA Guidelines stated that "appropriate management requires an ongoing assessment of the risk of recurrence and the risk of disease-specific mortality as new data are obtained during follow-up." The 2009 Guidelines [54] did, however, during Dr. Mazzaferri's last term on the task force, stop short of including the risk adapted paradigm of Tuttle [58] into one of its 80 recommendations. Seven years later, the 2015 Guidelines [2] had now adopted the "three-level stratification" scheme; Recommendation 48 announced that "the 2009 ATA Initial Risk Stratification System is recommended for DTC patients treated with thyroidectomy, based on its utility in predicting risk of disease recurrence and/or persistence." In the Modified Initial Risk Stratification System outlined in Fig. 4 of the paper, the three tiers are somewhat simplified in that high risk implies gross invasion, incomplete resection and distant spread, low risk encompasses "intrathyroidal DTC," and intermediate risk includes "aggressive histology, minor extrathyroidal extension (MEE) and vascular invasion." A novel feature was the inclusion of the number and size of NNM in the risk classification. Thus, low risk was 5 or less NNM of <0.2 cm, intermediate risk was >5 involved NNM (0.2–3 cm), while high-risk included NNM with maximal diameters exceeding 3 cm. The ATA writing group did admit that "the incremental benefit of adding these specific prognostic variables to the 2009 Initial Risk Stratification system has not been established," perhaps implying that we will not have to wait another 7 years to see how these novel variables perform.

Current Role of RAI

In the Recommendation 51 of the 2015 Guidelines [2] which defined the role of RAI in the primary management of DTC, the recommendations depended largely on the novel ATA postoperative risk stratification. Thus, RAI adjuvant therapy was routinely recommended for ATA high risk, RRA was not routinely recommended for ATA low risk, and RAI adjuvant therapy "should be considered" for ATA intermediate risk. The ATA writers went on to clarify this position by stating that "given that the ATA risk classification is relatively new and the majority of studies examining therapeutic efficacy of postsurgical RAI remnant ablation or therapy (adjuvant or for persistent disease) have been performed with attention to traditional mortality risk stratification systems such as AJCC/TNM system, MACIS, NTCTCSG or others…we have also categorized some of the results of our evidence review according to the AJCC/TNM risk of mortality stratification system because this system has been in use longer in our field."

If one carefully examines Table 14 on page 56 of the 2015 Guidelines, [2] the most important columns relate to the bodies of evidence suggesting that RAI improves CSM or TR rates and the answer to the question: "Postsurgical RAI indicated?" Patients with tumors 1 cm or less (uni- or multifocal), who are pT1a N0 or NX M0 or MX, are the only subset with No No No, and patients with gross ETE or with distant metastases are the only examples of Yes Yes Yes. Patients with tumor size >1–4 cm (T1b or T2 N0 or NX M0 or MX) are not routinely advised to have RAI, but such therapy may be considered if microscopy reveals either aggressive histology or vascular invasion. With larger but node-negative tumors >4 cm diameter (T3N0MO), the data is conflicting and the ATA advises consideration of other adverse features. When it comes to MEE or T1-3 N1a or N1b disease, there is apparently no evidence that RAI reduces CSM and conflicting data regarding TR rates; thus, the ATA advises "Consider—Generally favored due to higher risk of recurrent disease." As if this situation was not complicated enough, the ATA writers state that "in addition to standard clinicopathologic features, local factors such as the quality of preoperative and postoperative US evaluations, availability and quality of Tg measurements, experience of the operating surgeon, and clinical concerns of the local disease management team may also be considerations in postoperative RAI decision-making."

Conclusions

So, having considered how RRA came to become an established part of PTC management, having looked at the results of multiple Mayo studies demonstrating the lack of efficacy of RRA in low-risk PTC, and having reviewed the meta-analyses of our international colleagues and the management guidelines of our specialist societies, where do we personally stand on the issue of RRA in the management of patients with PTC? As we stated in our introductory remarks, we are in no doubt that RAI therapy should be used regularly in the setting of patients who have incomplete tumor resection with gross residual disease and those who present with or subsequently develop distant spread with demonstrable uptake of RAI in metastatic lesions. We are convinced that RRA should not be employed in the management of PTM (pT1a) and indeed remain unconvinced that tumors between 11 and 20 mm, presently considered as pT1b, benefit from RRA after a potentially curative surgery.

Our recently published study of pT3 PTC [59] and the work of others seem likely to result in the AJCC in the near future downstaging PTC patients with "microscopic ETE" [2], and, therefore, such patients should not, in our minds, be given RRA. We worry somewhat about the ATA recommendation for routine RAI in PTC patients of any tumor size with gross ETE (ATA high-risk T4 AnyN AnyM). In that particular setting, we would think that application of the MACIS score could be highly relevant and that, in this circumstance, patients with local invasion, who have had complete surgery and lack distant spread, may not of necessity undergo RAI therapy.

We are in no doubt that the development of so-called recurrence in NNM is highly dependent on the nodal status of the patient at presentation, and it will be of interest in future years to see whether the neck nodal recurrence rate will significantly fall as nodal dissection [60] becomes a near routine part of the initial surgical approach to PTC. Our own experience with ultrasound-guided percutaneous ethanol ablation (UPEA) [61–63] of persistent or recurrent NNM has led us to believe that RRA rarely completely eliminates neck nodal burden, despite the "scintigraphic slate" being wiped clean [38]. Accordingly, in the setting [50, 51] of a young woman with stage I node-positive PTC who has had an initial surgery consisting of NT or TT with central compartment exploration [64, 65] and has at 3–6 postoperative months both a negative neck ultrasound scan and a near undetectable serum Tg on thyroxine suppressive therapy, one doubts whether such a patient would obtain further benefit from RRA. Clearly, the size and number [66] of NNM may prove to be relevant in this consideration and the role of extranodal extension [2] in the NNM of PTC requires much more study. However, the presence of NNM at presentation in a PTC patient would not, in our assessment, lead in 2017 at Mayo to RRA being "generally favored." Rather, such a patient would be followed up with regular neck US and serum Tg measurements, and if further NNM were to be found, surgery or UPEA at our institution would generally be favored over RAI therapy.

In general, we are delighted that successive ATA Management Guidelines are moving toward a more selective use of RRA in PTC management. As stated above, we favor RAI for distant metastases and persistent disease after incomplete primary tumor resection. We are enthusiasts for the MACIS prognostic scoring system and have now in our institution almost a quarter century of experience in staging and scoring PTC patients in the postoperative period and using such information to help make decisions as to the need, or not, for RRA. Currently, we typically consider RRA in the minority (about 15%) of PTC patients who have a MACIS score of 6 or more. Naturally, clinical experience, individual bias, prior medical training, and patient circumstances may lead us currently to be ablating a slightly larger fraction of our PTC patients, perhaps closer to 25–30%, in any 1 year. However, repeated

analysis of our eight-decade cohort data leads us to believe that as we have avoided RRA in the management of our MACIS <6 patients with low-risk PTC, we have not seen any worsening of either CSM or TR rates, and we have been encouraged by the improving outcome that we have seen in our high-risk PTC patients with MACIS scores of 6+. We optimistically hope that these trends continue and that the 2020 ATA Management Guidelines for treating adult PTC patients will be even more conservative.

Conflict of Interest None of the authors state that they have any conflicts of interest.

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18 Considerations in Thyrotropin-Stimulating Hormone Suppression in Individuals with Differentiated Thyroid Cancer

Jennifer M. Perkins

Therapy and Risk Stratification

In general, first line therapy of differentiated thyroid cancer (DTC) includes surgical resection. For lower-risk intrathyroidal tumors with no clinically involved lymph nodes, a hemithyroidectomy may be performed vs. a total thyroidectomy for higher-risk/larger tumors or any tumors with known involvement of central or lateral compartment lymph nodes or distant metastases. Then depending on stage, and risk, radioactive iodine (RAI) may or not be employed for those that have undergone total thyroidectomy. Generally, RAI is not recommended for those who have undergone only hemithyroidectomy. The American Thyroid Association (ATA) also recommends TSH suppression goals based on stage, risk of recurrence, and existing comorbidities as discussed below.

Prior to discussing goals of TSH suppression therapy, it is important to understand the new ongoing dynamic risk stratification recommended by the ATA during initial and long-term follow-up. First, patients should be put into either low risk, intermediate risk, or high risk. The ATA defines these as follows:

J.M. Perkins, M.D., M.B.A.
Duke University Health System,
30 Medicine Circle, DUMC 3452, Durham, NC 27710, USA
e-mail: jen.perkins@duke.edu

ATA low-risk patients include papillary thyroid cancer with all of the following:

- No local or distant metastases.
- All macroscopic tumor has been resected.
- No invasion into locoregional tissues.
- Tumor does not have aggressive histology including tall cell, insular, columnar cell carcinoma, Hürthle cell carcinoma, or follicular cell carcinoma (FTC).
- No vascular invasion.
- No I131 uptake outside the thyroid bed if a I 123 or I 131 scan is done.
- Clinical N0 or ≤5 pathological N1 micrometastases (<0.2 cm in largest dimension).
- Intrathyroidal, encapsulated follicular variant of PTC.
- Intrathyroidal, well-differentiated FTC with capsular invasion and no or minimal <4 foci, vascular invasion.
- Intrathyroidal, papillary microcarcinoma, unifocal, or multifocal, including V600E BRAF mutated if known.

ATA intermediate-risk patients include:

- Microscopic invasion into the perithyroidal soft tissues (minimal extrathyroidal extension ETE)
- Cervical lymph node metastases or I131 uptake outside the thyroid bed on posttreatment scan done after thyroid remnant ablation

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- Tumor with aggressive histology or vascular invasion (e.g., tall cell, insular, columnar, Hürthle cell, hob nail, or FTC).
- Papillary thyroid cancer with vascular invasion
- Clinical N1 or >5 pathological N1 with all involved LNs <3 cm in largest dimension
- Intrathyroidal, PTC, with primary tumor 1–4 cm and V600 E BRAF mutated if known.
- Multifocal papillary microcarcinoma with extrathyroidal extension and BRAF 600E mutated (if known)

ATA high-risk patients include:

- Macroscopic tumor invasion into the perithyroidal soft tissues (gross ETE)
- Gross residual tumor
- Distant metastases
- Postoperative thyroglobulin suggestive of distant metastases
- Pathologic N1 with any metastatic LN ≥ 3 in largest dimension
- FTC with extensive vascular invasion (>4 foci)

(Adapted from the new American Thyroid Association Guidelines, [1]).

Surveillance in the First Year

How we choose surveillance should depend on the original pathology and risk stratification of the patient. At the outset, we have a static risk assessment to guide initial therapy and early follow-up recommendations. As patients move through the first year and beyond following initial therapy, providers need to provide dynamic risk stratification based on available data and continually reassess the clinical data to reevaluate their management plans. Our newest guidelines recommend putting patients into categories of excellent response, biochemical incomplete, structural incomplete, and indeterminate.

Excellent response implies negative imaging and either undetectable suppressed thyroglobulin (Tg) or TSH-stimulated Tg < 1 ng/mL. Patients who achieve an excellent response will have a 1–4% risk of recurrence and a <1% disease-specific death risk [1]. Patients who achieve this typically can undergo a decrease in intensity and frequency of follow-up and the degree of TSH suppression [1].

Patients who experience a biochemical incomplete response are characterized by negative imaging and a suppressed Tg > 1 ng/mL or a stimulated Tg > 10 ng/mL or a rising Tg antibody level. At least 30% of these patients will spontaneously evolve to NED (no evidence of disease), 20% will achieve NED after additional therapy, 20% will develop structural disease, and <1% will experience disease-specific death [1]. Patients in this category who have stable or declining serum Tg levels should undergo continued observation with ongoing TSH suppression in most patients. Rising Tg or Tg antibody values should prompt additional investigations and potentially additional therapies [1].

Patients who fall into the category of structurally incomplete response will exhibit structural or functional evidence of disease with any Tg level +/− Tg ab. Patients in this category will continue to have persistent disease despite additional therapy 50–85% of the time. The disease-specific death rate may be as high as 11% with locoregional metastases and 50% with structural distant metastases. Patients with structural incomplete response may undergo additional treatments or ongoing observation depending on multiple clinicopathologic factors including size, location(s), rate of growth, RAI avidity, pet avidity, and specific pathology of the structural disease [1].

Indeterminate response includes patients with nonspecific findings on imaging studies or faint uptake in thyroid bed on RAI scanning, nonstimulated Tg detectable, but less than 1 ng/mL, stimulated Tg detectable but less than 10 ng/mL, or Tg antibodies stable or declining in the absence of structural of functional disease. Of these patients, 15–20% will have structural disease identified during follow-up. In the remainder, the nonspecific changes are either stable or resolved. Less than 1% will experience disease-specific death. Patients in this category should undergo continued observation with appropriate serial imaging of the nonspecific lesions and serum Tg monitoring. Nonspecific findings that become suspicious over time should be evaluated further with additional imaging or undergo therapy [1].

Thyroglobulin measurement in the serum and cervical neck ultrasound are cornerstones of surveillance. Measurement of serum Tg is an important modality to monitor patients for persistent or recurrent disease. Following initial therapy, patients at low risk of recurrence and death can be followed with a suppressed Tg every 6–9 months in the first 2 years with no need to obtain a stimulated Tg value if there are no other suspicious clinical concerns [2]. These patients should get at least one follow-up neck ultrasound [2] keeping in mind that surveillance ultrasounds in this low-risk population are more likely to have false-positives and lead to more procedures, including follow-up ultrasound, FNA, and more patient anxiety.

How to Use Risk Stratification for Long-Term Follow-Up

Most recurrences of DTC occur within the first 5 years after initial treatment; however, recurrences may occur even decades later, particularly in patients with PTC [3]. Long-term follow-up is guided by the evaluation of how the patient responded to therapy in the first 1–2 years of original diagnosis [4] (Table 18.1). At each subsequent visit, patients should be classified as having one of the following clinical outcomes to direct long-term surveillance [4, 5]:

Table 18.1 Clinical implications of response to therapy: a reclassification in DTC patients who have undergone total thyroidectomy and RAI remnant ablation

Category	Definitions	Clinical outcomes	Management implications
Excellent response	Negative imaging and either: suppressed Tg <0.2 ng/mL or TSH stimulated Tg <1 ng/mL	1–4% recurrence	An excellent response to therapy should guide an early decrease in the intensity and frequency of follow up and degree of TSH suppression
		<1% disease specific death	
Biochemical incomplete response	Negative imaging and suppressed Tg >1 ng/mL or Stimulated TG > 10 ng/mL or Rising Tg ab levels	At least 30% spontaneously evolve to NED	If associated with stable or decreasing Tg levels, should lead to ongoing observation with ongoing TSH suppression in most patients
		20% achieve NED after additional therapy	Rising Tg or Tg abs should prompt additional investigations and potential additional therapies
		20% develop structural disease	
		<1% disease specific death	
Structural incomplete response	Structural or functional evidence of disease	50–85% continue to have persistent disease despite additional therapy	Ongoing observation or additional treatments depending on multiple clinicopathologic factors including size, location, rate of growth, RAI avidity, ^{18}FDG avidity, and specific pathology of the structural lesions
	With any Tg level +/− Tg ab	Disease specific death rates up to 11% with loco-regional metastases and 50% with structural distant metastases	
Indeterminate response	Nonspecific findings on imaging studies	15–20% will have structural disease identified on follow up	Continued observation with appropriate serial imaging of the nonspecific lesions and serum Tg monitoring. Nonspecific findings that become suspicious over time can be further evaluated with additional imaging or biopsy
	Faint uptake in thyroid bed on RAI scan	In the remainder, nonspecific changes are stable or resolve	
	Non stimulated Tg detectable but <1 ng/mL	<1% disease specific death	
	Stimulated Tg detectable but <10 ng/mL or Tg abs stable or declining in the absence of structural or functional disease		

Adopted from the new ATA thyroid cancer guidelines [1]

- Excellent response: no clinical or biochemical or structural evidence of disease
- Biochemical incomplete response: abnormal thyroglobulin levels in the absence of localized disease
- Structural incomplete response: persistent or newly identified locoregional or distant metastases
- Indeterminate response: nonspecific biochemical or structural findings that cannot be classified as either benign or malignant confidently

When defining an excellent response or a biochemical incomplete response, the extent of the initial therapy is key. In patients whom have undergone total thyroidectomy and RAI remnant ablation, an excellent response is defined as a stimulated Tg value of <1 ng/mL or a highly sensitive non-stimulated Tg of <0.2 ng/mL with negative imaging, commonly a normal postoperative neck ultrasound. In patients who underwent total thyroidectomy without subsequent RAI therapy, a non-stimulated Tg value of <1 ng/mL is considered an excellent response. In patients treated with less than total thyroidectomy, non-stimulated Tg values less than 20 ng/mL are considered an excellent response. This equals about 50% of the Tg expected from a normal thyroid. Any Tg value above these ranges is considered biochemical incomplete response in the absence of confirmed structural disease.

Patients classified as having an excellent response to therapy should have a decrease in the intensity of their surveillance and frequency of follow-up. They should have their TSH goal raised to 0.5–2 mU/L and be seen for physical exam and non-stimulated Tg levels yearly with surveillance neck ultrasound at 3–5 year intervals. Patients originally classified at ATA intermediate or high risk who then achieve an excellent response to therapy may benefit from closer follow-up and more intense suppression for a few more years.

Patients whom demonstrate a biochemical incomplete response to therapy defined as an abnormal Tg in the absence of structurally identifiable disease should continue to be monitored every 6 months with ongoing TSH suppression and yearly neck ultrasound for several more years. Patients with stable or declining Tg values should continue routine surveillance and TSH suppression, while those with rising Tg should prompt additional imaging modalities and evaluation.

Patients deemed to have a structural incomplete response to therapy could require additional imaging or therapy depending on several clinical factors including location, rate of growth, Positron emission tomography (PET) fluorodeoxyglucose (FDG) or RAI avidity, and pathology.

Patients with an indeterminate response to therapy defined as a nonspecific biochemical or structural imaging should continue on mild TSH suppression (0.1–0.5 mU/L) with 6 month follow-up visits for 2–3 years with yearly neck ultrasound. After that time, most patients can be reclassified [4, 5].

Goals of TSH Suppression Therapy

After total thyroidectomy, thyroxine therapy is required for all patients to maintain TSH levels whether or not radioactive iodine is given or not. Partial thyroidectomies may or may not require thyroxine therapy. Several studies have been conducted to better predict who will require thyroxine therapy following a hemithyroidectomy. Those with preexisting Hashimoto's thyroiditis or elevated TSH prior to surgery have a higher risk. Kandil et al. evaluated over 50,000 people who had undergone hemithyroidectomy, and a TSH >2.5 mU/L had a relative risk of 3.16 and a 95% confidence interval of 2.03–4.90 for postoperative hypothyroidism [6].

Studies have postulated that levothyroxine also can limit potential TSH stimulation of tumor growth by keeping the TSH suppressed. The American Thyroid Association guidelines for the treatment of thyroid cancer recommend that ATA low-risk disease patients who still have low levels of thyroglobulin maintain a serum TSH between 0.1 and 0.5 mU/L until the patient demonstrates an excellent response to therapy, which usually occurs in the first 6–12 months. At that point, the TSH can be kept between 0.5 and 2.0 mU/L. This latter level is also recommended

in patients who have undergone lobectomy only for their low-risk disease. There are few studies that assess TSH goals in patients who have undergone lobectomy only [7]. In ATA low-risk patients who have undergone remnant ablation and have undetectable levels of thyroglobulin, their TSH goal should be 0.5–2 mU/L. For ATA intermediate-risk disease, the serum TSH should be 0.1–0.5 mU/L [10]. Obviously, a patient's comorbidities may dictate that lower doses be utilized such as active heart disease, other coinciding terminal illness, or bone loss. Once patients remain disease free for 5–10 years, the TSH can be allowed to come into the normal range [4]. Newer guidelines released in 2016 recommend utilizing both patient morbidities with patients' prognostic indicator (excellent response, indeterminate, biochemically incomplete and structurally incomplete) to determine the ideal TSH suppression goal [1] (Fig. 18.1).

During long-term follow-up, if patients demonstrate a structurally incomplete response to therapy, the goal TSH should be below 0.1 mU/L [1]. In patients who demonstrate a biochemically incomplete response, the TSH should be kept between 0.1 and 0.5 mU/L keeping in account the Tg trend, the Tg level, the ATA risk classification/risk of original pathology, and the risk of suppression. Patient who have high-risk disease at presentation but have demonstrated an excellent structural and biochemical response, consideration can be given to keeping the TSH suppressed to 0.1–0.5 mU/L for the first 5 years of surveillance [1]. For ATA low-risk patients who have demonstrated an excellent biochemical and structural response or those who have not undergone remnant ablation or total thyroidectomy, the TSH should be kept 0.5–2 mU/L in the setting of negative neck ultrasound and a Tg that is not rising [1].

The data supporting TSH suppression to below the normal range impacting thyroid cancer morbidity and mortality has remained controversial. In part, this is due to the lack of large,

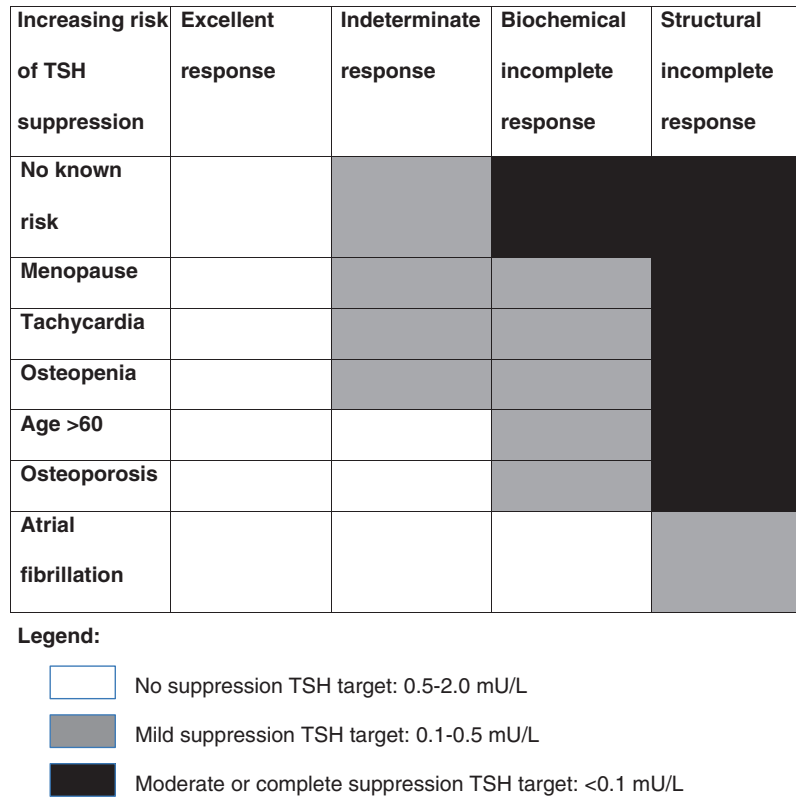

Fig. 18.1 TSH suppression targets for long-term therapy in DTC patients (Adapted from: [1])

randomized, prospective trials proving a benefit of TSH suppression in recurrence or survival. There is a lack of general consensus as to what degree of suppression is needed across stages to best reduce thyroid cancer-related death and recurrence if any. It is thought that most well-differentiated thyroid carcinomas express TSH receptors on their cell membrane and respond to TSH stimulation by increasing the expression of several thyroid-specific proteins such as thyroglobulin and thus increasing rates of cell/tumor growth [8]. Goitrogens, iodine deficiency, and partial thyroidectomy promote the development of thyroid cancer, but these tumors can be prevented by the oral administration of levothyroxine or by hypophysectomy, both of which reduce or suppress the secretion of TSH [9]. Differentiated thyroid cancer has functional TSH receptors (TSHRs), and thyroid cancer cells in primary culture respond to TSH stimulation by activating the cyclic-AMP cascade that promotes cell growth [10]. TSHRs and other thyroid-specific proteins are not well expressed in poorly differentiated thyroid cancers [11]. The first study published describing the regression of papillary thyroid cancer in two patients treated with thyroid extracts was published by Dunhill in 1937 [12]. Decades later, Mazzaferri and Jhiang published a retrospective analysis of 30 years of follow-up data showing that patients treated with thyroxine therapy had 25% fewer recurrences and 50% fewer cancer deaths than those who did not receive LT4 therapy and who had serum TSH levels within the hypothyroid range [13]. Based on these findings and others, TSH suppression became a cornerstone of therapy in patients with differentiated thyroid cancer. Although earlier studies found that TSH suppression below physiological levels has reduced thyroid cancer recurrence and disease-specific mortality, this has remained controversial and not well studied by large randomized controlled trials. There are risks to long-term suppression including iatrogenic thyrotoxicosis, bone loss, arrhythmia, angina, psychiatric concerns, and others. Sugitani and Fujimoto evaluated 441 patients with a proven diagnosis of papillary thyroid carcinoma who were randomized to receive TSH therapy to <0.01 mU/L or to not receive any TSH suppression. They excluded patients with tumors less than 1 cm or patients too high risk to undergo suppression (already with heart disease, or bone loss). At 5 years of median follow-up, disease-free survival and recurrence did not differ among these two groups [14]. Carhill et al. performed a multi-institutional disease registry evaluating 4941 patients with DTC. Of these, 88% had PTC, 8% had follicular thyroid cancer (FTC), and 4% had Hürthle cell carcinoma (HCC). Median follow-up was 6 years but ranged from 0 to 25 years. TSH suppression was graded as TSH undetectable, TSH subnormal but detectable, TSH normal range, and TSH above normal range. In all stages, moderate TSH suppression (subnormal but detectable) was shown to have improved overall and disease-specific survival, and even in the presence of distant metastases, TSH suppression (undetectable) was not found to improve overall survival above modest TSH suppression. This suggests there may be no benefit across any stage to suppress TSH to an undetectable level [15]. Wang et al. studied 771 patients with ATA low- or intermediate-risk DTC to see if a median TSH <0.4 mU/L vs. a median TSH >0.4 mU/L improved recurrence over a median follow-up of 6.5 years. Osteoporosis incidence was evaluated in women only. They found that suppression of a TSH <0.4 mU/L did not change recurrence rates in low- to intermediate-risk patients with DTC but did increase osteoporosis incidence in women [16]. Studies have shown that doses of levothyroxine that reduce circulation TSH to <0.4 mU/L reportedly induce maximum suppression of serum Tg [17] suggesting that increasing the degree of TSH suppression beyond this point may not further decrease tumor function [18]. Others have found that serum Tg continues to decline when TSH is further suppressed to levels that are undetectable <0.01 mU/L [19]. These findings have added to the controversy of optimal TSH suppression levels in patients with thyroid cancer.

Morbidity Associated with TSH Suppression

For many decades, all patients with thyroid cancer following thyroid surgery were put on thyroid hormone suppression to suppress TSH to undetectable levels without much appreciation of the consequences, nor good data to support this universally. Over time, our assays for TSH became more sensitive with our third-generation assays detecting a TSH to <0.01 mU/L. We now have a better understanding that with suppression comes the price of morbidity including bone loss, arrhythmia, particularly atrial fibrillation, psychiatric concerns, and symptoms of hyperthyroidism. We also have better understanding of long-term mortality and the generally favorable prognosis in most patients with DTC. Given this, it is imperative for the clinician to weigh the risks and benefits of thyroid hormone suppression and discuss with their patients at each ongoing visit. Below is a discussion of several morbidities associated with long-term TSH suppression.

Bone Loss

Bone loss has been a known and well-studied concern in patients with overt and subclinical hyperthyroidism, particularly in elderly and postmenopausal female patients; however, the relationship between TSH suppressive therapy and osteoporosis remains unclear. Since patients with DTC often undergo TSH suppression as part of their therapy, it is important to consider the effects on bone metabolism and clinically significant bone loss in this cohort. Particularly in postmenopausal women, several studies have reported a negative effect of long-term TSH suppression on the bone mineral density of patients with DTC [20, 21], while other studies have not confirmed such a negative effect [22, 23]. A systematic review analyzed 21 clinical studies on this issue and suggested that postmenopausal women with subclinical hyperthyroidism are most at risk for osteoporosis, whereas no increased risk was observed in men or premenopausal women [24]. Many investigations, however, have mostly been designed as cross-sectional studies or longitudinal studies with small cohorts, and there is a lack of large-scale prospective controlled trials.

Bone mineral density (BMD) analysis is important because it is correlated with the risk of fracture in postmenopausal women [25]. Wang et al. retrospectively examined a total of 771 patients (569 women) with ATA low or intermediate DTC with a mean age of 48 +/− 14 years who underwent thyroidectomy between the years 2000 and 2006. They were followed for a median of 6.5 years. The cohort was divided into two groups, a median TSH of >0.4 mU/L or <0.4 mU/L. Primary outcomes were structural recurrence of thyroid cancer, postoperative development of atrial fibrillation, and osteoporosis (the latter in women only). A total of 5.6% of patients recurred (43/771) and 3.9% (29/739) developed osteoporosis. The rates of recurrences were similar among the two groups, but patients suppressed to a TSH of <0.4 mU/L were at a higher risk for osteoporosis (HR 2.1, $p = 0.05$) compared to those patients with a TSH of >0.4 mU/L [21]. Gomes de Melo et al. performed a cross-sectional study that assessed BMD and risk factors for decreased BMD in 109 postmenopausal women under TSH suppression for DTC therapy. They compared this cohort to age-matched euthyroid women as a control. They found that low body mass index and low TSH levels were correlated with lower BMD, but there was no increased prevalence of osteopenia or osteoporosis compared to the age-matched, euthyroid controls [26]. Sugitani and Fujimoto performed a randomized controlled trial in female patients with PTC. They were randomized to suppressive therapy or non-suppressive therapy. The mean TSH in the suppressed group was 0.07 mU/L ($n = 144$) and 3.14 mU/L ($n = 127$) in the non-suppressed group. They measured annual lumbar spine BMD. They found that there was significant decreases in T scores within the first 1 year postoperatively in the suppressed group in women ≥50 years old but not

those <50 years of age. In the non-suppressed group, there was no significant decline in lumbar spine BMD until 5 years postoperatively [27]. One can appreciate that risk factors for lower BMD, and fracture risk should be taken into account along with benefits of TSH suppression when treating patients for DTC.

Atrial Fibrillation and Cardiovascular Considerations in DTC Patients

Hyperthyroidism is a well-established risk factor for the development of atrial fibrillation (AF) [28] and other cardiovascular morbidity/mortality. Even subclinical hyperthyroidism has been shown to have a greater risk of AF in patients over the age of 60 [29]. Abonowara et al. evaluated 136 patients with a mean age of 52 years (85% female and mean follow-up 11 years) to evaluate the risk of developing AF. The mean TSH was 0.17 mU/L, and 14 patients were found to have AF. The mean age of those patients with AF was 61.6 years vs. 51.4 years in those patients who did not develop AF. The prevalence of AF in this study was 10.3% in DTC patients over the age of 60, which is over 17.5% higher than the rate of published data for the incidence of AF in the same age group [30]. In addition to AF, other important cardiovascular risk factors can develop in young and middle-aged patients undergoing long-term TSH suppression therapy including increased heart rate, increased left ventricular mass, increased mean arterial pressure, and diastolic dysfunction [31]. Since the survival rate of most patients with DTC is high, several investigators are interested in the harm of the long-term effects of TSH suppression and therapies for DTC. Klein Hesselink et al. retrospectively followed 524 DTC patients that were age and sex matched to controls and found that patients with DTC had an increased risk of cardiovascular and all-cause mortality (hazard ratios 3.35, CI: 1.66–6.74 and 4.40 95% CI, 3.15–7.21, respectively) even after adjusting for age, sex, and cardiovascular risk factors. The TSH level was predictive for cardiovascular mortality, and the adjusted HR was 3.08 for each tenfold decrease in geometric mean TSH level [32].

Psychiatric and Cognitive Concerns

Thyroid disease and psychiatric disorders are both common in the general population [33]. Many have tried to associate hypothyroidism with depression and hyperthyroidism with anxiety in clinical practice; however, mixed results have been reported regarding these associations, and several confounders have been identified [34]. Several studies have shown a worsened quality of life with subclinical hyperthyroidism (similar conditions to that of TSH suppression in DTC patients) based on quality of life scoring symptoms, but some studies have not concluded the same [35–37]. The Danish General Suburban Population Study showed that patients with subclinical hyperthyroidism had a small risk of depression. This study included 14,787 individuals, and those with suppressed TSH values were those below a TSH of <0.4 mU/L. The prevalence of depressed individuals was 8.07% in the suppressed TSH group vs. only 5.8% in the normal TSH group [38]. Bensenor et al. showed that subclinical hyperthyroidism was positively associated with panic disorder and negatively associated with anxiety disorder, although this was no longer significant after adjustment for multiple comparisons illustrating that there are a myriad of confounders [39]. Moon et al. performed a cross-sectional study looking at 50 DTC patients over the age of 65 who had received TSH suppressive therapy for at least 5 years and compared them to 90 control subjects matched for age, sex, and education. There was no difference between depression scores nor any neuropsychiatric testing among the two groups demonstrating the long-term safety of TSH suppression on the cognitive function in the elderly DTC patients [40].

Symptoms of Hyperthyroidism

TSH suppressive therapy can also be associated with signs of hyperthyroidism including insomnia, racing heart, tremor, palpitations, diarrhea, excessive sweating, anxiety, heat intolerance, and weight loss. Several studies have shown that TSH suppressive doses of levothyroxine can impair quality of life as measured by psychological, social, and physical items, particularly when the

serum TSH is undetectable [31]. Although patients may not qualify for psychiatric diagnoses due to these, nor have coexisting psychiatric conditions, it is crucial to screen for symptoms of TSH suppression that could substantially impair quality of life at each visit. The clinician must then weigh this information in decision-making along with their risk of thyroid cancer in the present or risk of recurrence in the future. Further studies understanding patient-related outcomes based on long-term TSH suppression therapy could help guide clinicians on how to best monitor and treat patients undergoing suppressive therapy in the future.

Summary and Conclusions

DTC is growing in incidence, but overall most patients have an excellent prognosis. We have a better understanding of how to dynamically risk stratify patients at each ongoing clinical visit in order to tailor therapy and surveillance to their individual needs to avoid unnecessary surveillance and morbidity to our patients. TSH suppression has always been a cornerstone to therapy after thyroid surgery, but now we have improved guidelines and directions as to the level this should be undertaken that balance scientific evidence and risks of morbidity in doing so. TSH suppression goals should be addressed at each visit after taking into consideration the side effects, potential harms, and assessment of ongoing benefit to avoid bone loss, cardiac detriments, psychiatric concerns, and overall symptoms of hyperthyroidism.

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19 Imaging Modalities in the Diagnosis of Recurrent or Metastatic Thyroid Cancer

Jorge Daniel Oldan, Jenny Hoang, and Terry Zekon Wong

Introduction

Differentiated thyroid cancer (DTC) is typically a slow-growing malignancy, with a 5-year survival rate of 98%. With 64,300 new cases in 2016 but only 1980 deaths, it has a much better prognosis than many other cancers. Distant metastatic disease at initial presentation is relatively uncommon, representing 4% of newly diagnosed cancers, so metastatic disease is more often seen after prior treatment; however, up to 27% of diagnosed patients have regional nodal disease at presentation, though it has relatively little effect on survival, with 5-year survival in regional nodal disease dropping only to 97.8%. It affects people of all ages, with the median age of diagnosis of 51 and about three times as many women as men [1].

The imaging of thyroid cancer takes a multimodality approach, and this is particularly the case for the workup of recurrent and metastatic disease. Ultrasound can be used to look for regional nodes or evaluate palpable lesions. Cross-sectional imaging such as computed tomography (CT) and magnetic resonance [MR] can look for disease in the neck as well as throughout the body. Total body iodine scans with low-dose ^{123}I or ^{131}I can be used for evaluating residual functioning tissue following total thyroidectomy prior to radioiodine ablation and can also be used to detect nodal and distant metastatic disease in high-risk patients; some iodine-avid metastases may not be visible on CT or MR imaging. In high-risk patients, total body iodine (TBI) scans can help determine the appropriate ^{131}I dose for radioablation. TBI scans can also be used to evaluate patients suspected of having recurrent disease following ablation (e.g., rising serum thyroglobulin). Tumors that are not visible on TBI in spite of elevated thyroglobulin may have become less well differentiated and may no longer metabolize iodide. These patients may benefit from fluorodeoxyglucose positron emission tomography/computed tomography (FDG-PET/CT) scanning, since FDG accumulates in dedifferentiated tumors.

This chapter describes the role, technique, and imaging findings of patients with known or suspected recurrent or metastatic disease in patients with well-differentiated thyroid cancer. Knowledge of the strengths and limitations of the available imaging options will help the clinician optimize the management of patients with well-differentiated thyroid cancer.

J.D. Oldan (✉) • T.Z. Wong
Diagnostic Radiology, University of North Carolina-Chapel Hill Hospitals, Chapel Hill, NC, USA
e-mail: joldan@med.unc.edu; tzwong@med.unc.edu

J. Hoang
Diagnostic Radiology, Duke University Medical Center, Durham, NC, USA
e-mail: jennykh@gmail.com

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General Imaging Considerations

The primary treatment for well-differentiated thyroid cancer is surgery (total thyroidectomy). Total body iodine scans are not helpful prior to total thyroidectomy, as any tumor uptake will be eclipsed by the intense normal thyroid activity. Ultrasound can be used to characterize local disease and evaluate nodal metastases, as well as assist in biopsy guidance. CT and MRI are typically not used unless distant metastatic disease is suspected or in unusual cases of bulky local disease. If CT is used, intravenous contrast should be avoided if subsequent radioiodine imaging and/or treatment is anticipated. Iodinated contrast will suppress iodine uptake for a minimum of 4–6 weeks.

In the *initial* postoperative period (2–4 weeks following total thyroidectomy), the role of imaging is to determine whether any thyroid tissue (residual gland or tumor) has been left in the thyroid bed and if there is adenopathy or distant metastatic disease; nuclear medicine studies with iodine are key at this point as they can detect small amounts of residual functioning thyroid tissue and are not susceptible to the usual postoperative changes that can complicate the interpretation of US, MR, and CT. Examples of the use of total body iodine (TBI) imaging (with SPECT) are shown in Figs. 19.1 and 19.2. Patients with low-risk thyroid cancer may not require postoperative radioiodine imaging or ablation. In patients at higher risk for recurrent or metastatic disease, radioablative doses of ^{131}I sodium iodide may be given with TBI imaging before and/or following the radioiodine therapy.

After ablating with radioactive iodine, patients are usually followed with thyroglobulin levels to detect recurrence. For routine follow-up, ultrasound is recommended at least once and possibly more often, whereas TBI is usually only per-

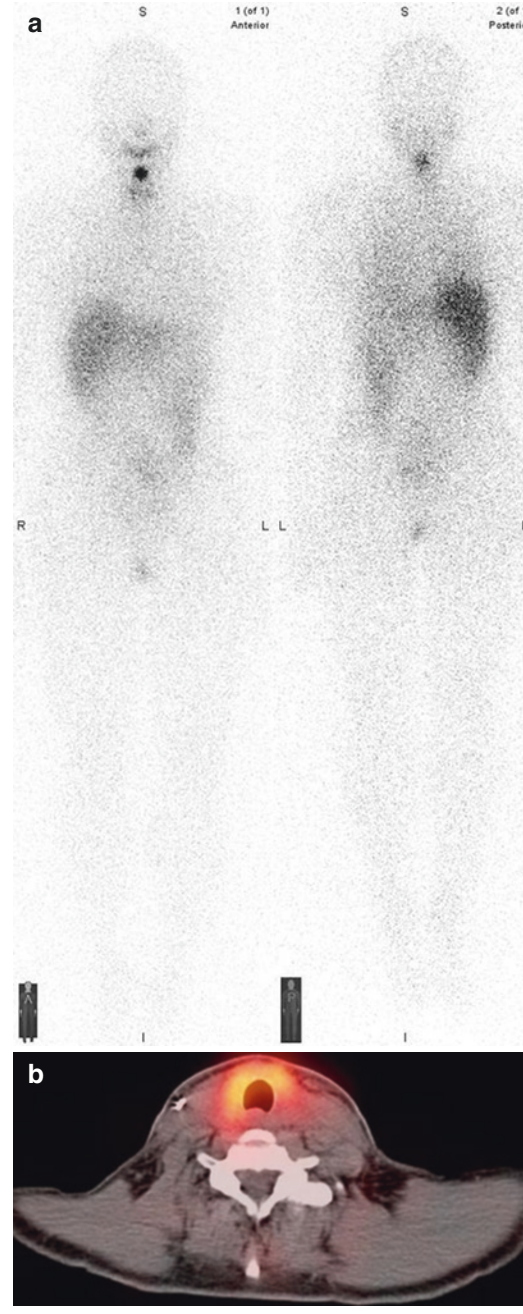

Fig. 19.1 A 40-year-old female with papillary thyroid carcinoma and positive nodal metastases on dissection. TBI (**a**) with SPECT (**b**) showing uptake in the neck, which localizes to the thyroid bed. No new metastases were found

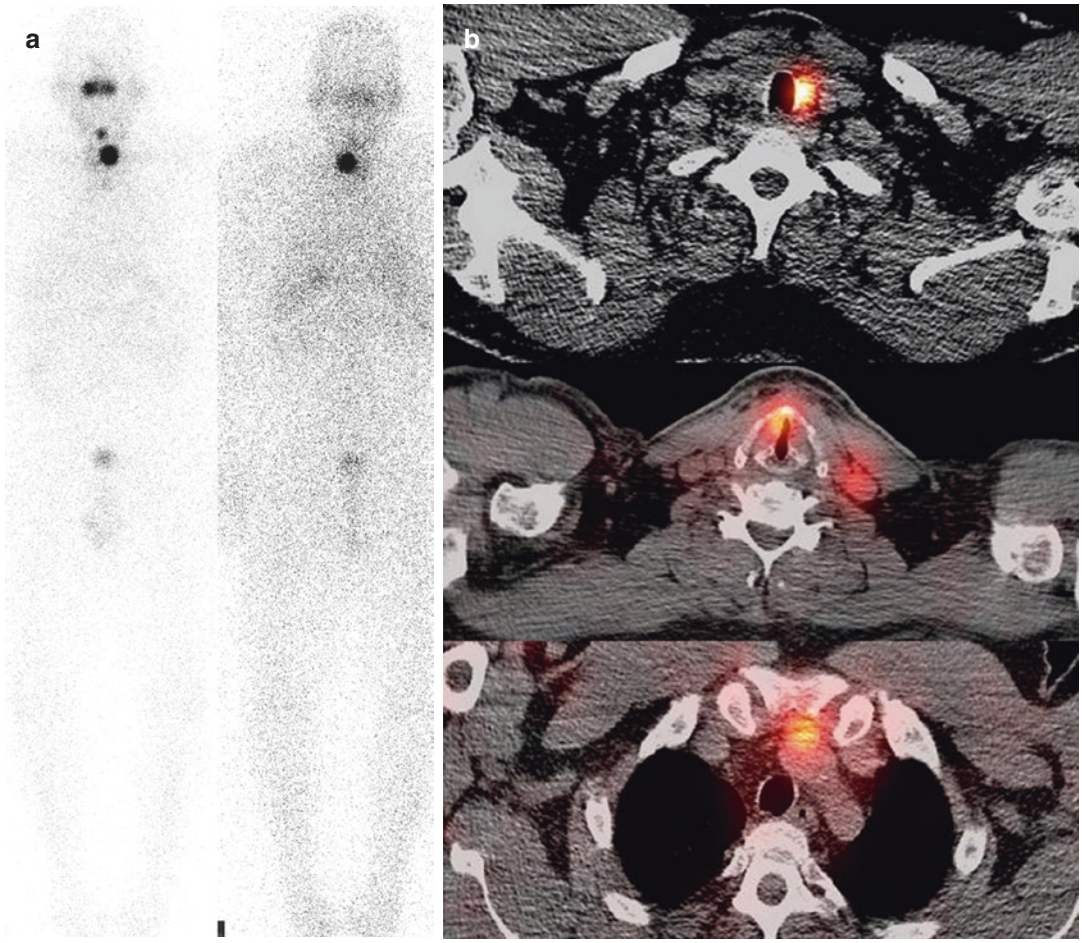

Fig. 19.2 A 60-year-old man with postablation scan for follicular carcinoma localized to the thyroid. TBI (**a**) with SPECT (**b**) shows spread to local nodes in the neck and chest

formed once as long as the scan is negative—and that only if the patient is high risk. There is no role for CT or MR in routine follow-up of these patients.

Should serum thyroglobulin rise, imaging may be indicated to evaluate recurrent disease. TBI is usually performed first to localize any iodine-avid lesions. If there is elevated thyroglobulin but TBI scan is negative, FDG-PET/CT may be useful to detect non-iodine-avid disease. TBI and FDG-PET imaging are felt to be complimentary, with radioiodine imaging more sensitive for well-differentiated disease and FDG imaging more sensitive for detecting tumors after they dedifferentiate.

US, CT, and MRI are useful if there is clinically palpable disease or concern for invasion into surrounding neck structures.

Specific Modalities in Imaging

Ultrasound

Primary Role: Local Metastasis and Recurrence

Ultrasound has a prominent role in the initial workup of the primary tumor, in forming a picture of the thyroid and detecting suspicious nodules, and in guiding FNA (fine-needle aspiration) of suspicious nodules. It can also detect nodal recurrence in the neck. Ultrasound scanning is convenient and less expensive compared to CT, MRI, or PET and does not involve ionizing radiation. However, ultrasound imaging is highly operator dependent, and the skill and experience of the technologist and interpreting physician play an important role.

Preoperative Evaluation

Ultrasound examination is recommended for detecting the presence of suspicious cervical nodes in the central or lateral compartments for all patients being investigated for a thyroid nodule or being prepared for thyroidectomy [2], as well as for all patients with cytologic findings positive for malignancy [3] (Table 19.1). Ultrasound is not effective for evaluating distant metastases from thyroid cancer, which may involve the lung and bone.

Nodal metastases can be identified in 25–50% of patients depending on the technique [4–6]. Micrometastases may be present in a greater number of patients, 53–90% according to some studies [6, 7], although these are of questionable clinical significance—subclinical nodes have a much lower probability of recurrence [8]. Ultrasound may detect about 37% of nodes [9] in older studies, identifying adenopathy in 24–27% of patients [9, 10] and changing management in 20–40% [11–13]. A meta-analysis of 13 studies performed through 2010 gave an overall sensitivity of 72% with a specificity of 98%; sensitivity was better in the lateral compartment than in the central on a per-lesion basis (72% vs. 45%, with overall per-lesion sensitivity of 63%) [14]. More recent work yields similar results, with three studies of at least 100 patients giving 23–41%

Table 19.1 Applications by modality

Modality		Applications
Ultrasound		Follow-up at 6–12 months and "periodically" thereafter
		Evaluation of palpable or symptomatic abnormalities
		Guides biopsy if nodes over 8–10 mm
CT/MR	Neck and upper chest	Bulky and widely distributed nodal disease not well seen by ultrasound
		Investigation of entire aerodigestive tract for invasion
		Rising thyroglobulin with negative US
	CT chest	High-risk DTC with Tg > 10 ng/mL or rising antibodies
	CT/MR abdomen	High-risk DTC with Tg > 10 ng/mL and negative neck and chest imaging
	MR skeletal survey	
	MR brain	Concern for tumor swelling with radioiodine ablation therapy
TBI +/− SPECT		Follow-up at 6–12 months for intermediate- to high-risk patients (SPECT if positive finding)
FDG-PET/CT		High-risk patients with Tg > 10 ng/mL and negative TBI

sensitivity in the central compartment [15–17]. Sensitivity in the lateral compartment (presumably not blocked by the thyroid gland) is again better, at 70–78% [15, 17], although it may be somewhat lower at level V [18] and seems to vary with operator experience [19].

When nodes are found, ultrasound can also be used to suggest the probability of malignancy of a lymph node. Typically, a benign node is oval with a hyperechoic stripe and has vascular flow in the center of the node [3]. Conversely, a round shape, microcalcifications, a cystic appearance, and peripheral vascularity suggest malignancy. Nodes over 1 cm are more likely to be malignant. These features differ in their importance, with features such as microcalcifications and cystic aspect being more specific and features such as peripheral vascularity and hyperechogenicity and the absence of an echogenic hilum being more sensitive [20, 21]. Ultrasound-guided FNA of sonographically suspicious nodes of at least 8–10 mm in short axis is recommended [2]. In addition, patients with significant, posterior or inferiorly located, or poorly visualized adenopathy, fixation to surrounding structures of nodes, or suspicion for significant extrathyroidal extension may benefit from cross-sectional imaging [3].

Unfortunately, ultrasound can also detect many smaller nodes of uncertain significance, and it is not clear which ones will grow (or whether growth indicates morbidity). A survey of 166 patients with suspicious nodes of an average size of 1.3 cm outside the thyroid bed followed over 3.5 years found that only 20% grew, and none cause morbidity or mortality; unfortunately, no sonographic feature predicted growth [22]. Pathological studies give rates of nodal metastasis of 70–90% to the central compartment [23] and 64% in the lateral [24]; however, regional recurrence rates are much smaller, and these nodes may not affect overall, disease-free, or disease-specific survival [23]. At least one study of 560 patients showed that ultrasound-detectable metastases to the lateral compartment predicted a worse relapse-free survival, whereas pathologically detectable nodes only did so if the tumor was at least 2 cm [24]; another using the same series showed that ultrasound was not sensitive for central compartment nodes but that these did not affect disease-free survival anyway [25]! Lateral nodes larger than 3 cm or numbering more than 5 appear to be particularly worrisome in one study of 621 patients [26]. The clinical significance of smaller nodes, however, remains unclear.

Ultrasound can also detect signs of local invasion, such as invasion of muscles [27], or other dangerous complications such as tracheal invasion [28] or invasion or encapsulation of local vessels such as the common carotid artery or internal jugular vein; invasion of vessels at the microscopic level (which is important histologically in discriminating follicular carcinoma from adenoma) is not detectable by ultrasound [27].

There is substantial evidence demonstrating that CT can detect nodes where US cannot. CT was shown to be more sensitive than US (77% vs. 62%) on a "per-level" analysis of 37 patients [29], was more sensitive in the central compartment in a study of 299 patients (though ultrasound was more accurate for extrathyroidal extension and intrathyroidal disease) [30], and added sensitivity to US for the central compartment in a study of 162 patients [31] and even to the lateral compartment (66% vs. 51%) in a study of 169 patients [32].

Postoperative Imaging

Ultrasound is often used after surgery as well. It is generally performed significantly after surgery (6–12 months), to allow postoperative

changes time to resolve [3]. However, it has been used in the immediate postoperative setting or even during surgery, commonly in Europe, to check the lateral compartments if no preoperative ultrasound is available or if postablation scans or elevated thyroglobulin levels relative to postablation scans suggest spread of disease [20]. A study of 731 patients, all with lymph node involvement, who had ultrasound just after surgery and before radioiodine ablation showed a 95% NPV for persistent disease at 41 months, suggesting it may in fact be useful in high-risk cases [33]. Another study of 72 patients who had surgeon-performed ultrasound found a change in management in 57% of cases [10]. As such, it may show utility if there is a particular reason to suspect local disease has been missed on initial evaluation.

Recurrence

Ultrasound plays a key role in evaluation for recurrent disease; a negative ultrasound is required to define absence of persistent tumor and hence excellent response to therapy [2]. Visualization improves in the central compartment due to the removal of the thyroid [3]. It can be used to detect recurrent neck nodes and guide FNA for aspirations in cases of suspected recurrent disease.

Generally, it is recommended to wait at least 6 months after surgery to reexamine the neck with ultrasound [to allow postoperative changes to resolve] [34]. Current recommendations are to ultrasound the thyroid bed and central and lateral neck compartments at 6–12 months and then periodically depending on thyroglobulin levels and recurrence risk; low-risk patients with remnant ablation, a negative ultrasound, and negligible levels (<0.2 ng/mL or <1 ng/mL with TSH stimulation) do not need follow-up ultrasound [2].

Evidence for the use of ultrasound in the detection of recurrent disease is also quite strong. Ultrasound had a sensitivity of 94%, compared with 57% for thyroglobulin levels and 45% for WBS, in a study of 494 patients followed up over a mean of 54 months [35]. In 80 patients with papillary microcarcinoma (too small for RAI), ultrasound was able to identify three patients with nodal metastases, one of whom was thyroglobulin negative [36]. Notably, however, specificity may not be that high—many thyroid bed nodules never increase in size—a study of 191 patients found only 9% had an increase in size over 5 years [37], and another of 59 patients found recurrences were difficult to distinguish based on sonographic findings [38], and many can simply be followed.

As with the initial evaluation for metastatic disease, a cystic appearance or hyperechoic foci and peripheral vascularization are malignant, whereas a hyperechoic hilum and central vascularization suggest a benign node. A round shape or loss of the hilum and a hypoechoic appearance are not sufficient to indicate a biopsy is needed [39]. In addition to the sonographic appearance, clinical data should be considered as well. Risk of recurrence is higher with more metastatic nodes at initial presentation, as well as with extravascular extension [40] and with macroscopic nodal disease [8]; one study of 545 patients showed no significant increase in recurrence for microscopic nodal disease [41].

It is not clear if detection of metastases below 8–10 mm is of any clinical utility. If nodes are suspicious and at least 8–10 mm, fine-needle aspiration biopsy for cytology, with thyroglobulin measurement in the aspirate fluid, should be performed; thyroglobulin over 10 ng/mL in the aspirate is very suspicious (unless the patient has not been treated with RAI). Surgery is usually recommended with macroscopic disease only [3]. Smaller or

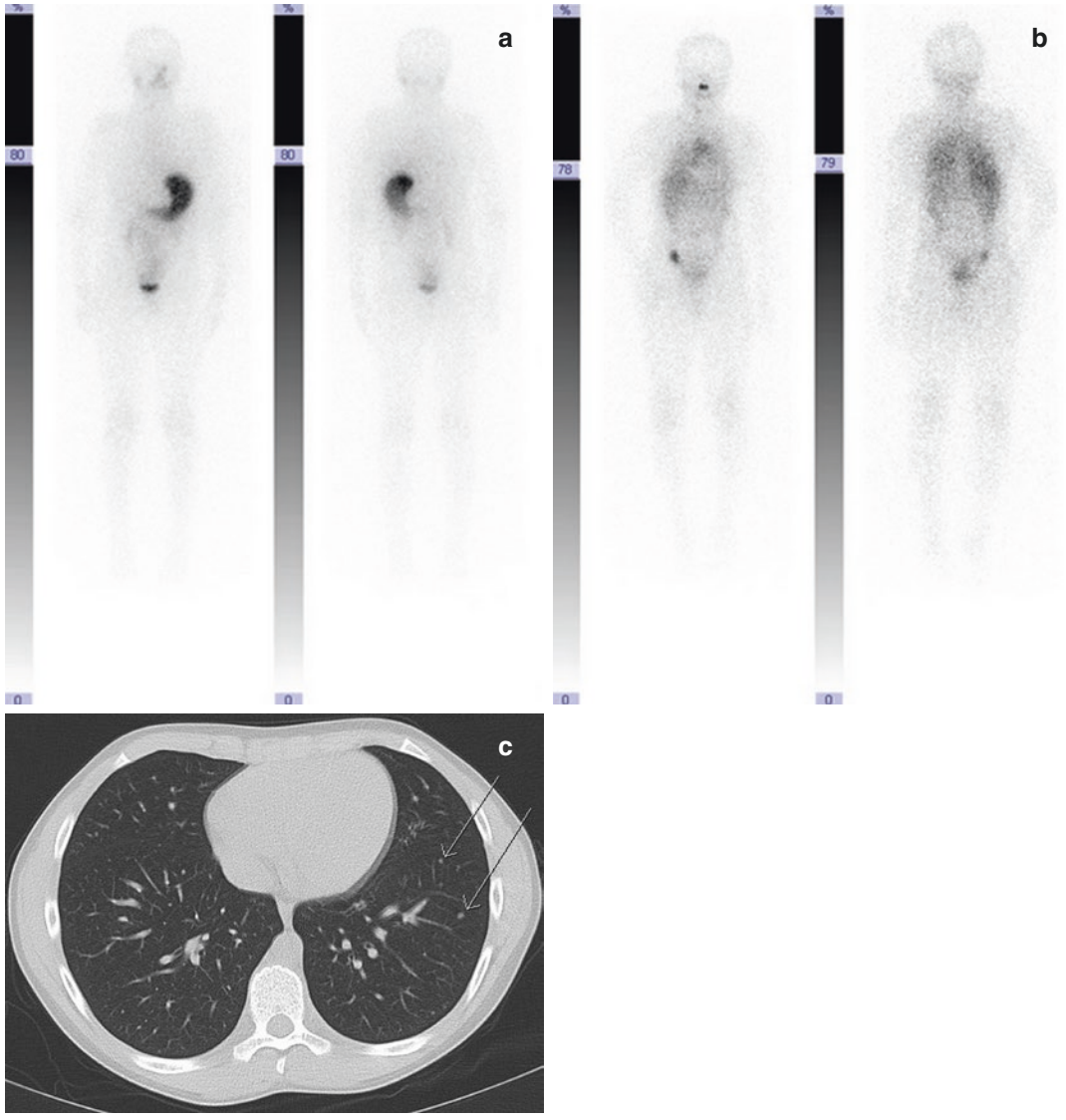

Fig. 19.3 A 10-year-old boy with preablation (**a**) and postablation (**b**) scans for thyroid carcinoma. Preablation scan shows no metastases, whereas postablation scan shows diffuse lung uptake. Chest CT (**c**) confirms miliary metastases (*arrows*)

less suspicious nodes can usually be monitored [2]. An example of a typical node is shown in Fig. 19.3.

If surgery is desired, present cutoffs for reoperation are 8 mm (short-axis diameter) in the central compartment and 10 mm in the lateral compartments [2]; even multiple revision surgeries have decreased thyroglobulin levels [41]. As with any surgery, other factors such as proximity to adjacent vital structures and (given the location in the neck) effects on vocal cord function, as well as patient comorbidities and primary tumor

factors, should be considered as well [2]. In cases where reoperation is desired, surgery must be planned using medical imaging of some sort, in order to determine the location of the target. Together with CT, ultrasound can provide an effective presurgical map [31].

Ultrasound can also guide other forms of locally directed therapy, such as ethanol injection [42] or radiofrequency [43] or laser [44] ablation.

Nuclear Medicine

Primary Role: Detection of Residual and/or Metastatic Disease After Therapy and Detection of Disease in High-Risk Patients Afterward

There are two major nuclear medicine studies used in thyroid imaging, total body iodine (TBI) scintigraphy with radioactive iodine (^{123}I or ^{131}I) and positron emission tomography (PET) with fluorodeoxyglucose (FDG-PET). Whether to use TBI or FDG-PET depends largely on the anticipated level of differentiation of the cancer. More well-differentiated cancers tend to concentrate iodine but be less avid for FDG; poorly differentiated cancers tend to be less able to concentrate iodine (being less functional as thyroid tissue) but more avid for FDG (having increased anaerobic metabolic rate and upregulation of the GLUT1 glucose transporter) [45, 46]. As a result, cancers may be (and often are) visible on one scan and not on the other, and a previously iodine-avid, FDG-non-avid cancer may dedifferentiate in the process of metastasizing and become iodine-non-avid, FDG-avid cancer [47]. This is known as the "flip-flop" phenomenon, and there is a large amount of data demonstrating poorer prognoses in iodine-non-avid, FDG-avid cancers [48]. Generally, thus, TBI is used earlier in the course of disease when the tumor is assumed to still be iodine avid, and PET used later if it no longer appears to be taking up iodine.

FDG-PET/CT is best done with dedicated head and neck imaging, including images where additional time is spent scanning the head and neck and different reconstruction algorithms are used. This may add to the sensitivity and specificity for recurrent thyroid carcinoma in an otherwise negative workup [49].

Preoperative Staging

As previously mentioned, TBI is usually deferred until after thyroidectomy. While FDG-PET/CT is frequently used for initial staging of highly aggressive and rapidly spreading cancers such as lymphoma or melanoma, FDG-PET/CT is currently not recommended for initial staging of differentiated thyroid cancer [2], given the slow growth (and good differentiation) of most thyroid cancers, based on a study of 26 patients with initial staging of thyroid cancer where FDG-PET/CT showed no advantage over ultrasound and contrast-enhanced CT and showed a low sensitivity of 30% [50]. More recent work shows that a highly FDG-avid primary tumor is more likely to have metastases, but overall detectability remains low [51].

Postoperative Scanning: Preablation Scanning and Stunning

Following total thyroidectomy for well-differentiated thyroid cancer, the prognosis is related to the surgical pathology findings, as well as demographic factors such as age. The next step is often ablation of the residual functioning tissue (whether normal thyroid or tumor) with radioactive iodine (RAI). The dosage and other aspects of planning may depend on the amount (if any) of remnant tissue and whether any metastases are present. A common way of looking for remnant tissue and metastases is a preablation scan, where a low dose of RAI is given, enough to allow visualization of any iodine-avid metastases, but (hopefully) not enough to sensitivity of remaining thyroid tissue to RAI ablation.

According to ATA recommendations, postoperative (pretherapeutic) diagnostic RAI WBS can be useful if the extent of the thyroid remnant or residual disease cannot be ascertained from the surgical report or neck ultrasonography and when results may have clinical relevance (either altering decision to treat or dose of RAI).

Recommended activity is 1.5–3 mCi of ^{123}I or 1–3 mCi of ^{131}I sodium iodide. In selected cases, SPECT/CT may be useful in further localizing areas of uptake [3].

There is substantial evidence that preablation TBI can alter clinical management, resulting in management changes in 25–53% of cases [52, 53], by detecting unsuspected regional metastases in 28–35% of cases and distant metastases in 4–8% of cases and by helping to differentiate between nodes and thyroid remnant in others [54].

However, there is concern that the prior diagnostic dose of radioactive iodine may decrease the effectiveness of the radioactive iodine ablation, an effect known as "stunning." The evidence on this remains mixed and contradictory. There are studies showing that a prior ^{131}I diagnostic scan decreases the effectiveness of subsequent ^{131}I ablation [55], possibly with a dose-dependent effect with 3 mCi being worse than 1 mCi [56], although 1 mCi may still decrease the success of the ablation [57]. Other studies show no change at 1 mCi [58] or at 3–5 mCi [59] or even at 5 mCi. One potential solution is to use ^{123}I for the preablation TBI, which theoretically should be at less risk for causing stunning as it is not a beta emitter and will therefore not deliver significant radiation dose to the thyroid. The literature is again split: one study suggests there is no difference in ablation failure rate between doing the diagnostic scan with ^{131}I and ^{123}I [60] (2 mCi of ^{131}I), whereas yet another suggests a 3 mCi of ^{131}I diagnostic scan does decrease ablation success rate vis-à-vis an ^{123}I scan [61]. More recent work suggests apparent stunning on scans (a decrease in visible uptake) may not reflect outcome [62]. Guidelines suggest that therapeutic activity should be administered within 72 h of the diagnostic scan to avoid stunning [2], so a plan as to whether therapeutic activity is likely should be formulated ahead of time. More recent work suggests that, in addition to doing the scan within 3 days, waiting 1 week also decreases the effects of stunning [63].

SPECT/CT

SPECT/CT is an imaging technique used to better localize foci of iodine uptake. A rotating camera obtains 3-dimensional images of an area of the body in the fashion of a CT scanner, at the expense of half an hour of imaging time and a small amount of radiation from a low-dose CT used for image processing and anatomic localization. The current evidence suggests that performing SPECT/CT is in fact useful, at least as regards workup of a focus of activity detected on initial TBI, and it is currently recommended by guidelines for this purpose [3]. A study of 38 patients with a mixture of preablation and postablation scans showed SPECT/CT was able to resolve the cause of uncertain findings as nonmalignant in 80% of cases, avoiding unnecessary radioiodine therapy [64]. Another of 48 patients showed a preablation SPECT/CT scan changed postsurgical staging in 21% and proposed dose in 48% [65]. A study of 53 mostly preablation patients found incremental value in 48% of cases [66].

There is some argument for performing SPECT/CT as a *routine* part of a preablation scan, usually in higher-risk patients. A study of 79 patients who received SPECT/CT showed an increase in specificity from 68 to 100%, with sensitivity rising from 41 to 50% [67]. A prospective study of 320 patients who received SPECT/CT with their preablation scans showed a change in management in 29% of patients and a change in risk stratification in 15% [68]. A recent study of 83 patients showed preablation SPECT/CT had incremental value in 40% of cases [69]. However, even a low-dose CT carries at least some additional radiation, and this must be balanced against the likelihood of metastasis, particularly in low-risk patients who may not receive ablation. (The SPECT is done using the radiation from the original scan and does not carry any additional dose.)

Postablation TBI Scan

After the patient has received a therapeutic dose of radioactive iodine for ablation, ranging from 30–200 mCi depending on risk factors and disease burden, the activity from the ablation dose can be used for a post-therapy TBI scan. Because of the high administered dose, the postablation TBI may display metastases not visible on prior diagnostic

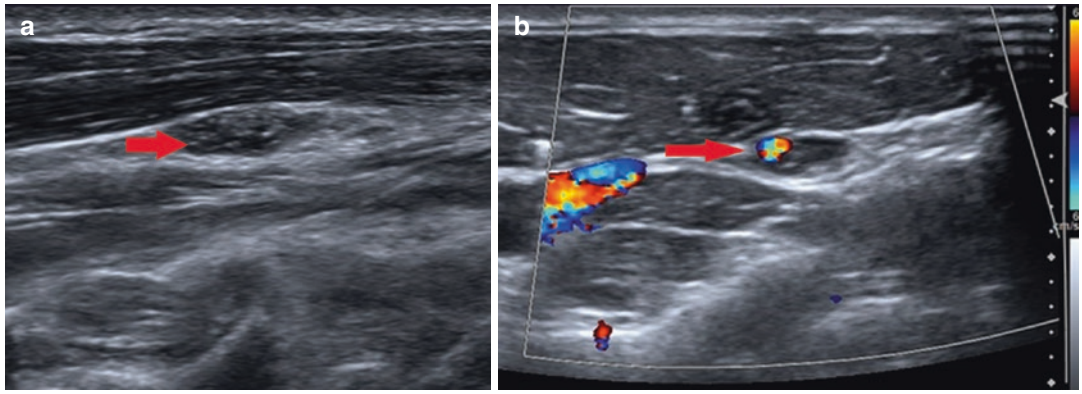

Fig. 19.4 1.2 × 1.1 cm level III node with microcalcifications (*arrow*, **a**) and peripheral vascularity (*arrow*, **b**), suspicious for malignancy. Patient was a 25-year-old male with prior history of thyroidectomy and radioiodine ablation. The decision was made to follow this node

doses. TBI may be useful after RAI remnant ablation or treatment, to inform disease staging and document the RAI avidity of any structural disease [2]. Images are usually taken 3–10 days after the administration of the radioactive iodine dose (the literature has ranged from 2 to 12).

There is evidence supporting routine utilization of TBI scans following radioablative therapy, primarily from single-center retrospective studies [70–75], mostly showing some variable increment of additional findings (anywhere from 6 to 50%) over and above a pretherapy scan. As many of these were performed on high-risk patients, the overall rate of residual or metastatic disease detected could be quite high, ranging from 20 to 84% [71, 73, 74], confirming the need for at least *one* scan in patients high risk enough to require ablation. An example of additional findings visible on the post-therapy scan is seen in Fig. 19.4.

One question under active investigation is whether SPECT/CT should be added to a post-therapy scan. The evidence here suggests that SPECT/CT is useful. Again, it is often performed on an as-needed basis for a detected focus of radioiodine uptake on a whole-body scan and usually shows improvement in diagnosis and/or management. SPECT/CT had a specificity of 95%, as opposed to 55% for planar TBI, in a study of 140 patients [76]. In one study of 41 patients with 53 scans with diagnostic uncertainty on planar TBI, it localized additional nodal disease in 29% and additional distant metastases in 21%, changing treatment decisions in 24% of patients [77]. Another study of 66 patients with locally advanced or metastatic disease, 23 of whom received SPECT/CT for inconclusive planar scans, found that SPECT/CT clarified the location or nature of metastases in 85 and 83% of patients, changing management in 47% of patients who received it [78]. Another study focusing specifically on inconclusive cases found changes in therapy in 25% of 25 cases [79]. Another study of 71 patients, mostly postablation, showed improvement in diagnosis in 57% of patients [80]. There is some evidence that imaging at 7 days may display metastases not visible at 3 [81].

However, for routine use, the case is somewhat less clear-cut, although it overall appears to favor the use of SPECT/CT. An early prospective study of 55 patients showed it clarified the 16% of indeterminate cases and correlated better with follow-up than planar SPECT [82]. A positive postablation SPECT/CT was a strong predictor of future recurrence (HR 65.2) in a single-center trial of 170 patients, with an estimated 78% sensitivity and 100% specificity [74]; another study of 81 patients showed a patient with a positive SPECT/CT was about ten times more likely to have abnormal TBI 5 months later; however, only 15% of patients with positive scans actually had uptake at 5 months [83]. A study of 109 patients, both post-surgical and with concern for recurrence, with intermediate- or high-risk disease who received SPECT/CT found that the need for additional cross-sectional imaging was reduced in 20% of patients and changed the ATA risk classification

in 6% of cases. Non-iodine-avid lesions were detected on CT in 22% of cases, though some of these, such as subcentimeter lung nodules, were of unclear long-term significance [84]. Another study of 147 patients found that SPECT/CT changed staging in 6% of patients and management in 2% of patients [85]. Conversely, another study of 187 patients showed that SPECT/CT found additional nodal metastases in 9% of patients initially assumed to have only remnant uptake, whereas it proved there were no nodes in 40% of patients assumed to have nodes on planar scan [86]. Another study of 94 patients found that SPECT/CT improved localization in 21% and changed management in 23% of patients [87]. Another retrospective study similarly showed a change in management in 20% of patients [88]. Another of 93 patients showed a change in management in 20%, with frequent downstaging [89].

Iodine binds to common dental metals, and SPECT/CT may be useful in differentiating this incidental uptake from disease [90, 91].

PET/CT in Initial Staging of Less Well-Differentiated Cancers

FDG-PET/CT is presently not recommended in well-differentiated thyroid cancer for initial staging. However, it may be useful for staging of more poorly differentiated cancers, both papillary and follicular cell with adverse histology and less differentiated types such as invasive Hürthle cell carcinomas [2]. A study of 286 patients with intermediate- to high-risk carcinoma showed a change in management in 14% of patients [92]. A study of 90 patients with either metastasized or extensive high-risk differentiated thyroid carcinoma found a total change in management in 21% of patients [93], and a 3-year follow-up found an 85–91% NPV for recurrence [94]. Another study of 197 patients with differentiated thyroid cancer showed a 67% sensitivity on a per-lesion basis, with a 70% sensitivity and 91% specificity for lateral neck nodes [95]. Another of 38 patients with aggressive histology, mostly tall cell or poorly differentiated, showed additional lesions on FDG-PET/CT over TBI scan in 41% of cases [96].

FDG-PET/CT has also shown to be effective for initial staging of Hürthle cell tumors; a study of 44 patients found 95% sensitivity and 95% specificity [97], and a smaller study of 17 patients for both initial and recurrent cancer showed 90% sensitivity [98]. For poorly differentiated thyroid cancer, which is intermediate between differentiated thyroid cancer and anaplastic thyroid cancer, there is suggestion that FDG-PET/CT is more avid, with uptake in 86% of a group of tumors [47] and 69% sensitivity in the previously mentioned group of 38 patients [96].

Given its avidity for more aggressive tumors, a positive FDG-PET/CT is a poor prognostic factor. A study of 202 thyroid cancer patients 6 months after initial treatment showed a positive PET/CT was a strong prognostic factor for decreased overall survival (HR 6.1) [99].

There is one study showing it may even be of use in determining whether radioiodine therapy will be effective: a study of 141 patients who received at least two ablations found FDG-avid metastases were less likely to demonstrate a good biochemical response and had poorer long-term survival [100].

Surveillance and Recurrence: Whole-Body Scintigraphy and SPECT/CT in Follow-Up

After surgery and RAI followed by TBI, the patient must be followed up to exclude recurrence. Whether this requires further TBI depends on the patient's risk profile. After the first posttreatment TBI performed following RAI remnant ablation or adjuvant therapy, **low-risk and intermediate-risk patients** with an **undetectable thyroglobulin** on thyroid hormone with **negative antithyroglobulin antibodies** and a **negative ultrasound** do not require further evaluation with TBI [2, 101]. A meta-analysis of ten studies comprising 1959 patients suggested that a TSH-stimulated thyroglobulin test was sufficient to exclude recurrent disease (in the absence of antithyroid antibodies) and hence TBI was not needed [102]. A study of 315 patients had similar findings [103]. Indeed, the study is of low sensitivity if there is no uptake outside the thyroid bed on the initial scan [104].

However, for **high-risk and higher intermediate-risk patients**, diagnostic TBI (after either hormone withdrawal or rhTSH) 6–12 months after adjuvant radioiodine ablation therapy can be useful and can be done with ^{123}I or low-activity ^{131}I. Some recommended indications include uptake outside the thyroid bed on post-therapy TBI, large thyroid remnants which can obscure small nodes, and antithyroglobulin antibodies (making following the patient with thyroglobulin alone difficult) [2].

Total body iodine scans are also used for localization when a specific reason for suspecting recurrence exists, specifically if thyroglobulin becomes elevated (suggesting an iodine-concentrating, differentiated tumor). If thyroglobulin is elevated but TBI is negative, PET/CT is recommended to detect a dedifferentiated tumor. An example of iodine-negative, FDG-positive metastases is shown in Fig. 19.5.

Most of the foregoing evidence on SPECT/CT of postablation scans also applies to recurrent

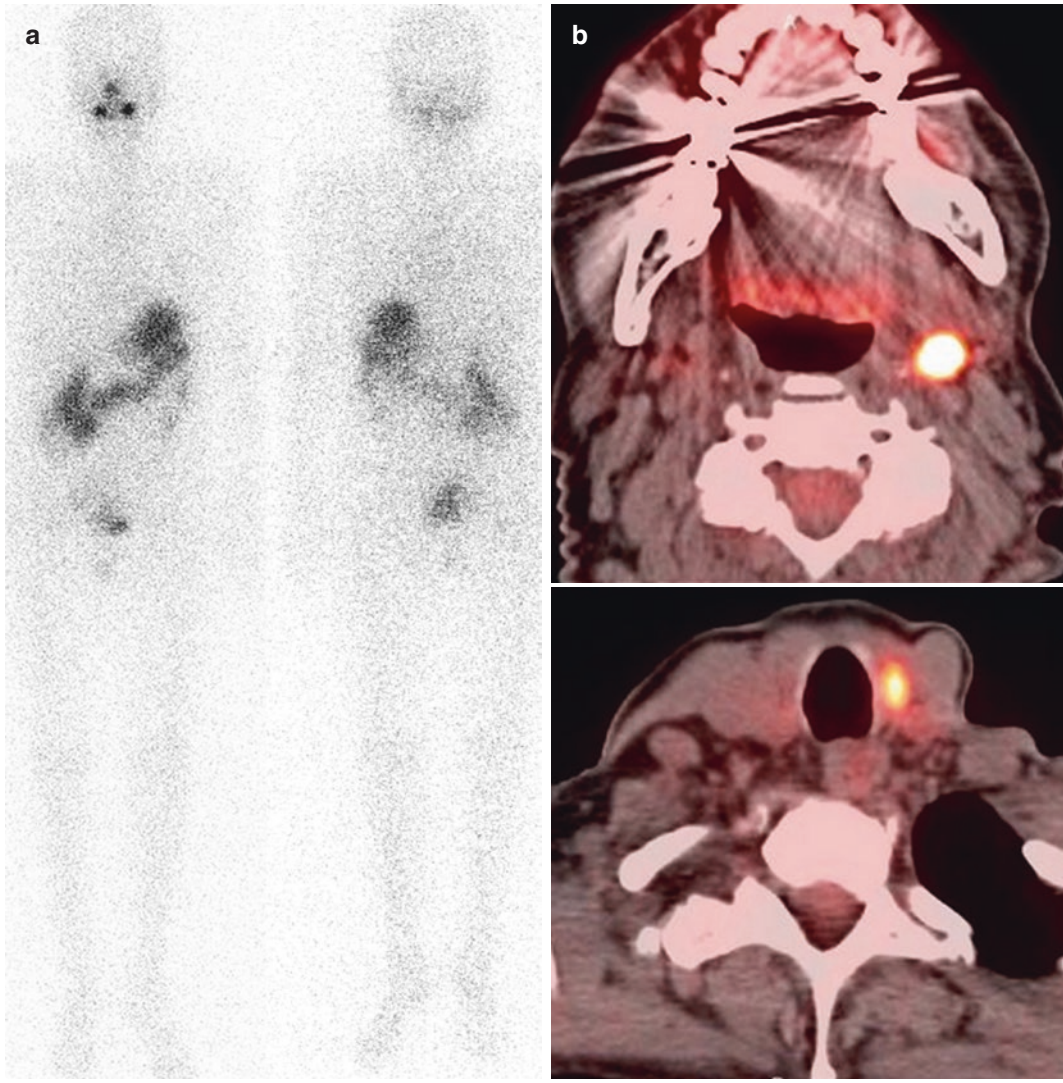

Fig. 19.5 This was a 1-year follow-up scan of a 59-year-old woman with thyroid carcinoma with nodal metastases who had been treated with surgery and radioiodine ablation. Iodine scan (**a**) is negative, but stimulated Tg was 24 ng/mL, and FDG-PET (**b**) shows local metastases (later confirmed by biopsy)

disease. A few studies of the utility of SPECT specifically in recurrent disease have been done. At least one study of 87 patients found that SPECT/CT found evidence of disease in 9% of the total who would have otherwise gone untreated [105]. Another of 117 consecutive patients, most with recurrent disease, showed it avoided unnecessary treatment in 20% of cases, modified treatment in 36% of positive cases, and had at least some incremental value in 67% of cases [106].

PET/CT: TENIS and Beyond

If TBI is negative *and* serum Tg is over 10 ng/mL, FDG-PET/CT scanning is recommended [2]. (This is sometimes referred to as TENS or TENIS—thyroglobulin elevation with negative scintigraphy.) A 2007 meta-analysis of 20 studies of FDG-PET for recurrent thyroid cancer comprising 789 patients showed an overall 83% sensitivity (ranging from 50 to 100%) and 84% specificity (ranging from 42 to 100%) [107]; this was confirmed by a 2016 meta-analysis of 18 studies showing a 90% sensitivity and 80% specificity [108]. More recent studies confirm these values (84% sensitivity, 79% specificity) [109]. There is some evidence ultrasound may be more specific than TBI in the investigation of lateral neck nodes in the TENIS situation [110].

FDG-PET/CT is generally *not* recommended in patients with TSH-stimulated Tg < 10 ng/mL due to low sensitivity [10–30%], unless there are other factors that may cause a low thyroglobulin—for example, aggressive, poorly differentiated tumors that fail to secrete thyroglobulin or antithyroglobulin antibodies that prevent accurate measurement of thyroglobulin levels [2]. However, the latest meta-analysis of 34 studies of FDG-PET for recurrent thyroid cancer gave a pooled sensitivity and specificity of 79%, which included a variety of indications, so this may change with time [111]. It changes management in anywhere from 14 to 78% of cases of suspected recurrent thyroid cancer [112]. Another type of high-risk cancer for which FDG-PET/CT is also effective in the recurrent setting is Hürthle cell cancer; one of the few studies done specifically on recurrent Hürthle cell patients, on 17 patients, showed a 92% sensitivity and 80% specificity [113].

FDG-PET/CT scanning may also be considered as a prognostic tool in patients with metastatic disease and as an evaluation of posttreatment response following therapy of metastatic or locally invasive disease [2].

As with many other tumors, a high FDG uptake has prognostic value—largely negative, as it reflects a poorly differentiated carcinoma. Four hundred patients with DTC showed that FDG avidity was a strong negative predictor for survival [114]; another of 43 patients showed number of lesions and total lesion glycolysis were poor prognostic factors as well [115]. Another study of 80 patients with both FDG-PET/CT and radioiodine scans showed that FDG uptake was predictive for poor survival, whereas radioiodine uptake was prognostic for stable disease [116]. A negative FDG scan in the setting of TENIS syndrome appears to be a favorable prognostic indicator, although it complicates diagnosis [117]. One study of 54 patients with well-differentiated thyroid carcinomas in incidentally detected thyroid nodules, however, suggests it *does not* have prognostic value over and above standard factors such as age and stage [118], so this advantage may be restricted to the metastatic setting. Other metrics besides uptake such as heterogeneity have occasionally been used [119].

PET/CT may also be used for response assessment in chemotherapy, usually with a decline in FDG avidity representing response. It has been used to track response to experimental drugs in BRAF V600E-mutated tumors [120] and sorafenib [121] and sunitinib [122] in iodine-refractory tumors, as well as isotretinoin treatment [123]. Ga68 somatostatin receptor agonists have been used to assess response to somatostatin receptor-expressing tumors [124].

One question is whether stimulation with Thyrogen (rhTSH) helps the detection of FDG-avid cancers. A study of 108 lesions in 63 patients showed an increase in the number of lesions detected, but not in the number of patients with disease; additionally, there was a change in management in only 6% of cases [125]. A

meta-analysis of seven studies including 168 patients did show an increase in the number of patients found with lesions (OR 2.45) and number of lesions (OR 4.92), although again management only changed in 9% of cases [126]. There is one study of 47 patients suggesting that higher stimulated thyroglobulin levels may indicate whether the test will be of any use, with true positive tests rare below 8 μg/nL [127].

Other Nuclear Tracers: A Work Still in Progress

An area of active research is the use of a positron-emitting isotope of iodine, ^{124}I, which provides the advantages of coincidence PET imaging and would have higher image quality than current TBI SPECT scans. ^{124}I-PET/CT is more sensitive, identifying as many as 50% more foci of uptake than radioiodine [128], identifies findings seen on later high-dose ^{131}I post-therapy scans [129], and may be able to assess response to therapy in tumors that are not FDG avid [130]. However, ^{124}I is not yet commercially available.

Apart from ^{124}I, there is some early evidence (a study of 11 patients) that sodium fluoride PET and/or bone scan with SPECT may be more accurate than FDG-PET/CT for bone metastases specifically [131]. Planar bone scan is less sensitive [132]. Somatostatin receptor tracers do not appear to be as effective [133], although if positive they may indicate patients responsive to peptide receptor therapy [124]. Fluorothymidine is less sensitive than FDG [134].

CT and MRI

Primary Role: Investigation of Suspected Recurrent Disease Throughout the Body

Role

The majority of patients do not have preoperative imaging with CT or MRI because ultrasound adequately evaluates the primary tumor and nodal disease. The only reason to image with other cross-sectional modalities, such as CT and MRI, is concern for local invasion or if there is high suspicion for extensive nodal metastases outside the lateral neck (Fig. 19.6). The detection of these findings can change operative approach or preclude curative intent surgery.

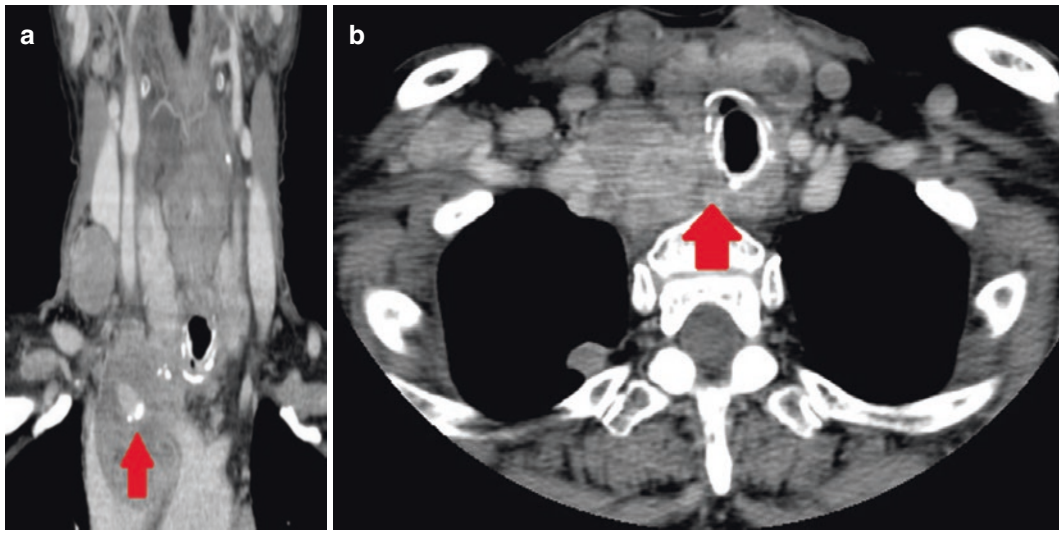

Fig. 19.6 A 79-year-old woman with metastatic papillary thyroid cancer at presentation. Enhanced CT shows a large right superior mediastinal nodal mass which surrounds the arteries (*arrow*, **a**) and possibly invades into the trachea (*arrow*, **b**). There were also pulmonary and bone metastases

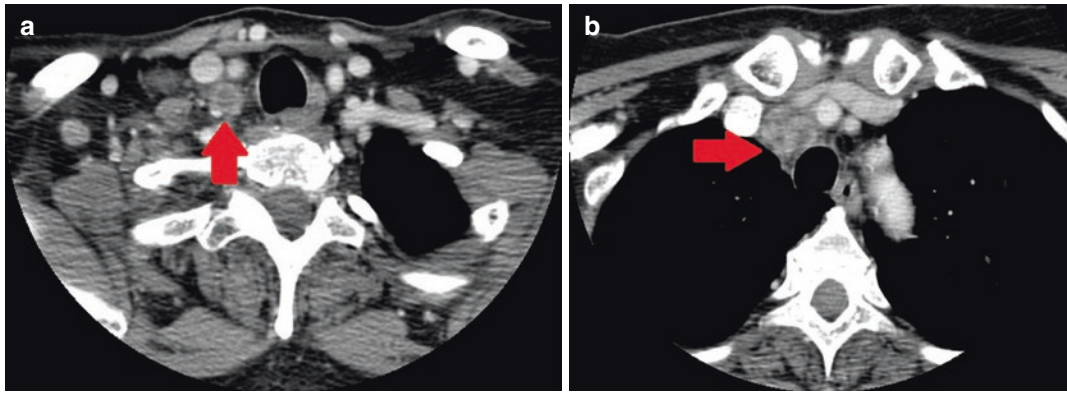

Fig. 19.7 A 64-year-old woman with a history of papillary thyroid cancer and rising thyroglobulin levels. Enhanced CT shows right level IV and superior mediastinal lymph nodes (*arrows*) with ill-defined margins and necrosis. The superior mediastinal nodes could not be visualized with ultrasound

CT and MRI of the neck and upper chest are not first-line modalities for recurrent disease, but they do contribute to the imaging of patients in three scenarios. First, CT could be performed in the setting of rising or elevated thyroglobulin or antithyroglobulin antibodies and negative ultrasound and radioiodine study. Many institutions may use PET/CT as the first-line study in this scenario. Second, CT or MRI of the neck should be considered in the setting of bulky and extensive recurrent nodal disease where ultrasound may not completely delineate disease and when there is concern for invasive recurrent disease (Fig. 19.7) [2]. Finally, when metastases are not resected due to small volume or patient morbidity, follow-up imaging for monitoring can be performed with CT and MRI.

A dedicated CT of the chest can be performed in high-risk DTC patients with elevated or rising thyroglobulin levels [2]. Cross-sectional imaging of other sites such as the brain or abdomen should only be performed if there are symptoms referable to those organs. Chest radiography is generally not used here.

Imaging Technique

Neck ultrasound has higher spatial resolution to detect morphological abnormalities in the lymph nodes and is more sensitive and specific for small nodal metastases compared to CT and MRI. However, ultrasound is limited for deep structures and sites that are shielded by air and bone. CT and MRI are preferred for the detection of metastases outside in the deep neck or mediastinum. Deep locations include the central compartment (level VI) and the retropharyngeal and retroesophageal groups. CT is advantageous compared to MRI because MRI is limited for detection of pulmonary metastases. MRI does not have the spatial resolution to visualize small metastases, and there is respiratory motion artifact since the images cannot be acquired in a breath-hold.

In the past there were concerns about iodinated contrast agents delaying subsequent whole-body scans or radioactive iodine, but this has now been shown to be unfounded. Recent studies show water-soluble iodinated contrast agents are generally cleared within 4 weeks in most patients so post-thyroidectomy patients requiring radioiodine therapy can be scanned with radioactive iodine within 1 month of the contrasted CT [135, 136].

Imaging Findings

The criteria of an abnormal lymph node on CT and MRI are lymph node size; commonly used cutoff is greater than 1 cm in short axis. However, size cutoffs are not a reliable marker of malignancy. Small nodes can harbor small metastases that do not expand the node, and, conversely, benign nodes can commonly be enlarged due to

hyperplasia or inflammation. The choice of size cutoff simply changes sensitivity and specificity for detection of nodal metastases. Morphological changes in the node are far more useful. These changes include cystic components, calcification, intense enhancement, or proteinaceous or hemorrhagic content appearing as hyperdensity on CT and T1 hyperintensity on MRI [137].

Conclusion

The evaluation, treatment, and follow-up of thyroid cancer require a multidisciplinary imaging approach. Each modality has a role to play. Preoperatively, ultrasound can assess for metastases, and CT and MR may assess complicated cases. Immediately after surgery but before ablation, radioactive iodine can be used to assess for remnant thyroid tissue (which may suggest reoperation) or metastatic disease (which may affect the dose of radioactive iodine given). After ablation, the radioactive iodine can be used to image for metastatic disease as well. In follow-up, ultrasound and often whole-body scintigraphy are useful; should whole-body scintigraphy become discordant with thyroglobulin levels, FDG-PET/CT can be used instead. Finally, MR and CT have a role in evaluating morphology and extent of suspected invasive disease and follow-up of known metastasis.

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Operative Treatment of Recurrent or Metastatic Disease

20

Kristin L. Long and Nancy D. Perrier

Operative Treatment of Recurrent or Metastatic Disease

Well-differentiated thyroid carcinoma (WDTC) is reported to recur in upward of 30% of patients, and the detection of disease in the cervical lymph nodes is the most common manifestation [1]. In the majority of cases, surgical treatment is employed for the purpose of disease elimination. Careful planning of re-operative interventions for recurrent, persistent, or metastatic disease is mandatory and requires a thoughtful multidisciplinary approach.

Detecting and Defining Recurrence

Patients previously treated for WDTC should undergo dedicated surveillance, with a minimum of annual high-resolution neck ultrasound (US) and laboratory assessment of thyroid function and tumor markers. According to the 2015 American Thyroid Association Guidelines, thyroid-stimulating hormone (TSH), as well as serum thyroglobulin (Tg) and anti-thyroglobulin antibodies (TgAb), should be measured annually, and perhaps more frequently in high-risk patients, with a purpose of detecting disease recurrence at the earliest possible opportunity [2]. The guidelines define a disease-free status as a patient demonstrating no clinical evidence of tumor, no imaging evidence of tumor by radioactive iodine (RAI) imaging and/or neck ultrasound, and low serum thyroglobulin levels during TSH suppression in the absence of circulating TgAb [2]. If any of these criteria are not met, the patient must be considered to have recurrent or persistent disease, and the need for surgical intervention should be evaluated.

Employing the same strategies used to define initial disease burden preoperatively, high-resolution cervical ultrasound can be used to survey for even subtle evidence of abnormal tissue in the neck. Residual thyroid tissue, in situ parathyroid glands, and central and lateral neck lymph nodes (both normal and abnormal) can be characterized with modern ultrasound. Disease measuring only a few millimeters can be evaluated and, if enlarging or suspicious, can be verified with US-guided fine-needle aspiration biopsy. Evidence of abnormal lymph nodes on ultrasound should be documented and measured precisely. Typically, in order to avoid confusion with expected postsurgical changes, postoperative

K.L. Long, M.D.
Department of Surgery, Section of Endocrine Surgery, University of Wisconsin School of Medicine and Public Health, 600 Highland Avenue K4/744, Madison Wisconsin 53792, USA
e-mail: longk@surgery.wisc.edu

N.D. Perrier, M.D., F.A.C.S. (✉)
Department of Surgical Oncology, MD Anderson Cancer Center, 1400 Pressler Street, FCT 17.6014, Houston, TX 77030, USA
e-mail: Nperrier@mdanderson.org

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imaging is not performed until 6 months after the initial surgical intervention, but may be warranted sooner if palpable abnormalities are detected on physical exam.

Serum assessment such as thyroid function tests is not routinely assessed until a minimum of 6 weeks after thyroidectomy, and tumor markers are often not evaluated until 6 months postoperatively, depending on the preoperative level of disease and postoperative pathologic features. Serum Tg is considered the most sensitive marker for the presence of WDTC after total thyroidectomy and is the most concerning for disease progression when a rapidly rising trend is documented [3].

After confirmation of disease presence, a more specific definition of the disease burden must be formulated. Patients who have previously demonstrated no evidence of disease with US and serum Tg and subsequently present with abnormal labs or imaging findings are considered to have recurrent disease. Local recurrence implies that the disease has been demonstrated in the thyroid bed; regional recurrence refers to disease in the central or lateral lymph nodes of the neck; and distant disease or metastases encompass the presence of thyroid carcinoma outside of the neck. If the patient has never been found to have a normal US or undetectable serum Tg levels in the postoperative period, they are categorized as having persistent disease. Both patients with persistent disease and those with newly documented recurrent disease should be evaluated by a surgeon for consideration of further therapy.

Nonoperative Treatment Strategies for Recurrent Disease

Active Surveillance

Current ultrasound examinations have begun to detect even sub-centimeter evidence of recurrent disease, which prompts multidisciplinary teams to carefully evaluate the necessity of surgical resection. Some have advocated a strategy of active surveillance, or "delayed intervention," where small lesions that do not appear to be growing or demonstrate no imminent invasive threat to nearby vital structures are conservatively monitored without immediate surgical intervention. Support for this strategy rests on the fact that, even with very experienced surgical teams and preoperative localization techniques, sub-centimeter lesions in a re-operative field can be difficult or impossible to identify at the time of operation [4]. Central neck lymph nodes smaller than 0.8 cm and lateral nodes smaller than 1 cm may be observed if stable [1]. Patients considered for active surveillance must have access to experienced care teams, must be reliable and consistent with follow-up, and must be active in the decision-making process for this care strategy. Disease that is considered nonoperative or unresectable may also be managed with systemic therapy, which is discussed thoroughly in other chapters.

Ablation

In patients who are not considered surgical candidates, or who refuse surgical intervention, ablative techniques such as radiofrequency ablation (RFA) or ethanol ablation (EA) have been described for select patients with isolated disease. RFA, which uses heat generated by high-frequency oscillating currents to cause local tissue destruction, and EA, which relies on injection of up to 1 mL of 95% ethanol directly into the tissue, have both demonstrated safety and efficacy, with subsequent tumor volume reduction of greater than 50% [5–7]. Despite these advancements, surgical resection remains the gold standard for treatment of recurrent disease [8].

Preoperative Planning for Surgical Resection

Once recurrent disease is confirmed and surgical resection is deemed necessary, certain preoperative measures must be undertaken. Staging evaluation, including computed tomography of the neck and chest, should be considered for

comprehensive preoperative planning. Likewise, formal voice and vocal cord evaluation should be performed in any patient with a history of prior neck surgery to document vocal cord mobility, position, and vibratory wave. Review of any prior operative and pathology reports is mandatory, to evaluate initial burden of disease, as well as unexpected pathologic findings including inadvertently resected parathyroid glands. Patients with multiple comorbidities or poor functional status will require perioperative medical clearance and optimization. Anticoagulation should be stopped if medically feasible.

When pursuing surgical resection of isolated, small disease, intraoperative ultrasound may be used for improving localization. In our practice, nerve monitoring is routinely considered when the ipsilateral recurrent laryngeal nerve is at risk for injury.

Surgery and Technical Considerations

Recurrence in Thyroid Bed and Central Compartment

Disease may recur or persist in the thyroid bed and, in this location, may involve the trachea, recurrent laryngeal nerve (RLN), esophagus, or larynx [4]. Review of preoperative CT scan images can provide valuable information regarding extent of disease and invasion of surrounding structures. If no evidence of invasion exists, resection of disease from the thyroid bed may only involve removal of the gross tumor with exquisite attention devoted to identifying and preserving the RLN and remaining parathyroid glands. Inspection from the cricoid cartilage to the sternal notch will be necessary to ensure no remaining thyroid tissue, such as a pyramidal lobe or superior pole remnant, exists.

Disease within the central compartment can be found in a variety of locations. Most commonly, disease is found near the RLN, both anteromedial and posterolateral in location, as well as at the RLN inlet (Fig. 20.1). Recurrence can also be found in a thyroid remnant near the tubercle of Zuckerkandl, Delphian nodes, remaining central (level VI and VII) nodes, and along the posterior aspect of the strap muscles [9]. The propensity for persistent disease along the recurrent laryngeal nerve may result from inadequate initial dissection [10]. The most common complication following repeat central compartment dissection is long-term hypoparathyroidism from failure to maintain viable parathyroid tissue with an intact vascular pedicle, although this occurs only in a small subset of patients [9].

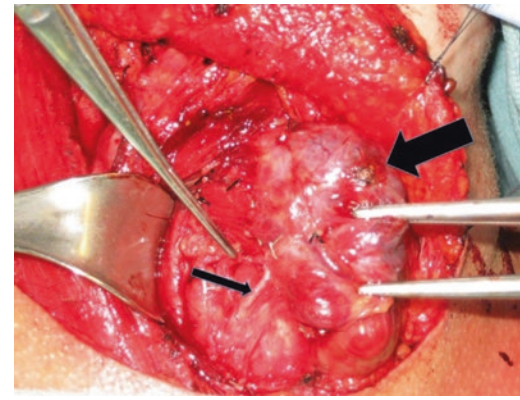

Fig. 20.1 Gross tumor involvement of the recurrent laryngeal nerve. *Thin black arrow* points to recurrent laryngeal nerve. *Thick black arrow* denotes the bulky lymph node disease encasing the nerve

Recurrence in the Lateral Compartment

While central compartment recurrences may include lymph node disease as well as gross primary tumor recurrences, disease in the lateral neck is composed almost exclusively of lymph node metastases [11]. This may occur in the setting of a previously undissected field, where microscopic disease may not have been detectable at initial operation, or it may present as an isolated recurrence after a formal component-oriented lateral neck dissection. Factors such as initial tumor multifocality, extrathyroidal extension, and tumor size do not appear to be related to a higher risk of lateral neck disease; however, aggressive histological variants (tall cell, insular, and columnar types) do place patients at a higher

risk of recurrence in the lateral neck [11]. Similarly, documented disease in the central lymph nodes at the time of first operation also predisposed patients to the development of metastatic disease in the lateral neck [11].

Re-operative procedures are often performed with lateral extension of the prior cervical scar. The incision should be large enough to allow complete visualization of the lateral neck compartments after creation of generous subplatysmal flaps. Hyperextension of the patient's neck, along with including the earlobe, chin, and sternum in the sterile field as landmarks, can facilitate identification of key structures in the re-operative neck. Excision of the lateral neck contents from level II to level IV and, in some instances, level V is necessary. Most often, vital structures are preserved, although a unilateral resection of the internal jugular vein (IJV) may be indicated if intimately involved with tumor. Nodal tissue both anterior and posterior to the IJV and along the carotid sheath should be removed. Any surgical clips from prior operative procedures should be removed, and use of clips should be avoided as they create significant artifact on imaging and hinder detailed delineation of anatomy, particularly in high-resolution computed tomography images. Retraction and, in rare cases, division of the sternocleidomastoid muscle (SCM) will facilitate exposure of the lateral neck contents. Multiple consensus statements now concur that selective node removal, or "berry picking," represents an oncologically inadequate procedure and is not recommended. A compartment-oriented lateral neck dissection (CLND) is indicated in cases of recurrent thyroid carcinoma. Specimens removed from the neck should be oriented on a template and photographed to document disease location (Fig. 20.2).

After completion of the surgical procedure, many surgeons elect to leave a closed-suction drain in place in the neck. Variability exists among surgeons, but many routinely leave drains after lateral neck dissection until the patient has eaten a full solid meal. The drain output and character is evaluated, and if it remains minimal and serosanguinous in nature, it is often removed on the morning of postoperative day 1. Particularly in re-operative lateral neck operations, evaluations for lymphatic or chylous leaks are recommended. Upon completion of dissection, increased Valsalva maneuvers can be performed to assess for chylous leaks.

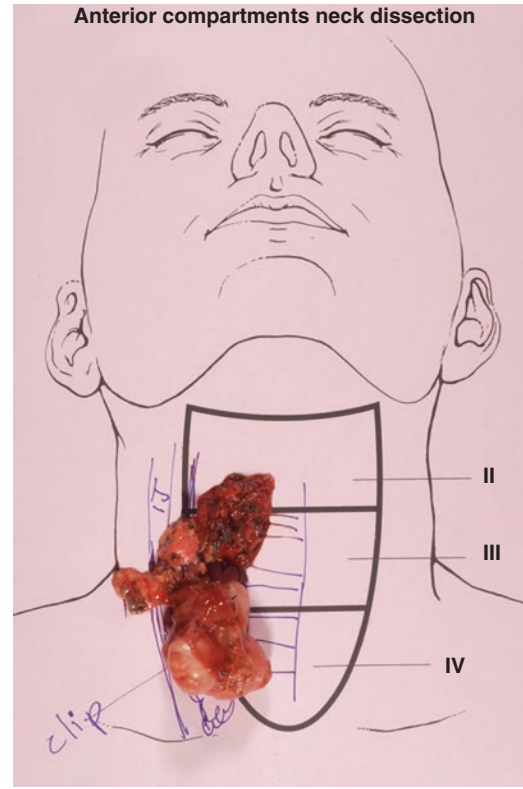

Fig. 20.2 Template demonstrating resected lymph node disease as found in the central and lateral neck. The use of such templates can be extremely helpful for surgical trainees, pathologists, and others to fully appreciate the extent of disease and to objectively document the areas resected

Locally Advanced and Structurally Invasive Disease

Involvement of the Recurrent Laryngeal Nerve

Differentiated thyroid carcinoma frequently recurs near the course or insertion of the recurrent laryngeal nerve. Failure to thoroughly inspect and resect lymph nodes or tissue immediately posterior to the nerve or its branches can

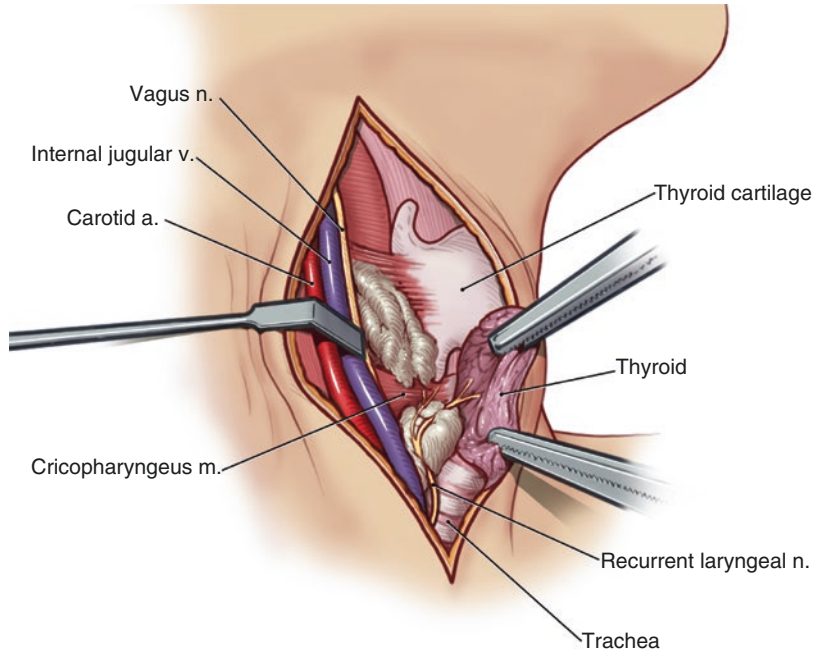

Fig. 20.3 Illustration of recurrent disease in lateral neck lymph nodes both behind the jugular vein and encasing the recurrent laryngeal nerve

lead to sites of recurrence. On occasion, tumor can encase the RLN, and this may be suspected preoperatively in patients presenting with hoarseness (Fig. 20.3). Frequently, the tumor may be circumferentially dissected free from the nerve or may be meticulously shaved off the intact nerve. If a patient has evidence of a functioning nerve and complete resection of disease elsewhere is not possible, or if a patient has evidence of distant metastatic disease, shaving tumor off of the RLN in order to preserve function is, in fact, preferable [12]. In other cases, however, sacrifice of the nerve may be mandated to render the patient disease-free. If a large portion of the nerve must be sacrificed, the patient will be left with a deficit. This again highlights the importance of knowing the preoperative functional status of both vocal cords and counseling the patient in detail regarding possible nerve involvement, resection, and potential for tracheostomy tube placement if both nerves are rendered nonfunctional. If only a small portion of the RLN is resected, immediate reapproximation with fine, permanent monofilament suture (7-0 Prolene or smaller) may aid in the restoration of some motor function over time. In many re-operative cases, but in particular those involving resection or significant dissection on the RLN, the surgeon should remain immediately available during extubation and emergence from anesthesia to ensure appropriate airway patency. Further procedures, including vocal cord injections or medialization procedures can also assist in functional improvement after nerve sacrifice.

Tracheal Invasion

Tumoral invasion of the trachea can often be identified on preoperative CT scans and can therefore be anticipated in preoperative planning. Depending on the depth of invasion, as well as the functional/nutritional status of the patient and the integrity of the surrounding tissue, some tumors may again be simply shaved off the tracheal wall. In these cases, frozen section analysis is useful for confirmation of negative margins. On occasion, isolated or segmental resection of a small portion of tracheal wall may need to be resected along with the tumor. In these cases, primary repair is often performed with simple, interrupted absorbable monofilament suture. Disease recurrence with significant tracheal involvement may necessitate circumferential tracheal resection

and require complete reanastomosis of the tracheal ends. These cases may require advanced mobilization and release maneuvers with a multiteam operative approach and may include placement of a Grillo stitch suturing the patient's chin to their chest to eliminate tension on the new anastomosis. Recent studies have suggested that aggressive but organ-preserving extirpative surgery in cases of aerodigestive tract invasion provides excellent locoregional disease control and preserves function and quality of life [13].

Esophageal Invasion

Recurrent differentiated thyroid carcinoma can also invade the esophagus. As with cases of tracheal invasion, esophageal invasion can require either partial-thickness or full-thickness resection. Resection of esophageal musculature can be performed in a relatively straightforward fashion, with primary suture repair and buttressing. Transmural involvement may likely require much more invasive resection and reanastomosis and, as with tracheal surgery, should involve appropriate disciplines. If resection of esophageal musculature is anticipated, a nasogastric tube should be placed in the esophagus prior to the start of the surgical procedure. The completeness of the surgical resection is a key determinant of overall outcome, and efforts should be made to clear the patient of gross disease with preservation of function [14].

Extended Lymph Node Disease

When recurrent lymph node disease is identified along the jugular chain, several additional locations must be evaluated. In particular, when nodal disease is found along the upper IJV, the possibility of retropharyngeal nodal involvement must be examined. Although difficult to access, many instances of retropharyngeal node disease can be safely resected without advanced maneuvers [15]. Likewise, the possibility of upper mediastinal node disease should be explored when patients present with significant nodal recurrences in the central compartment. Disease recurrence itself is a predictor for the presence of superior mediastinal node involvement [16]. Often, resection of the superior mediastinal nodes can be accomplished via transcervical approach. Anterior retraction of the sternum and meticulous dissection of the retrosternal space can provide excellent visibility of the area of the innominate vein. Resection of nodes lower than the innominate artery will require mediastinoscopy or sternotomy.

Distant Metastatic Disease

Only a small portion of patients with differentiated thyroid carcinoma will ultimately develop distant metastatic disease, with rates between 1 and 23% in the literature [17]. The most common site of distant metastatic disease is the lung, followed by the bone and then other solid organs including the liver and brain. Metastatic disease, while rare, does decrease survival rates for patients with WDTC [18]. Disease identified in the lung can be either micronodular (most common) or macronodular and, often unresectable, is treated with systemic therapy including RAI (Fig. 20.4). Bone disease is also frequently multifocal and may be treated with multiple modalities, including systemic therapy, RAI, or focused stereotactic radiation. In some cases, metastatic

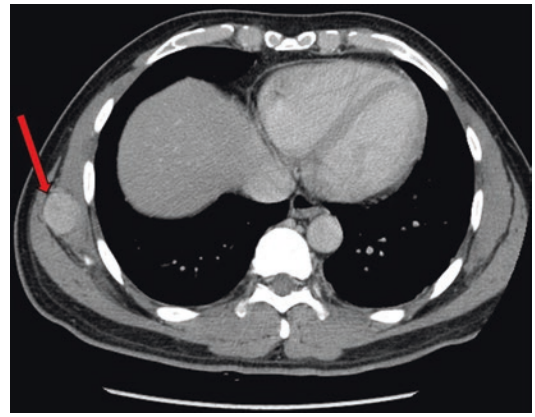

Fig. 20.4 Isolated metastatic deposit in the right lateral chest wall musculature (denoted by *red arrow*) in a patient with papillary thyroid cancer

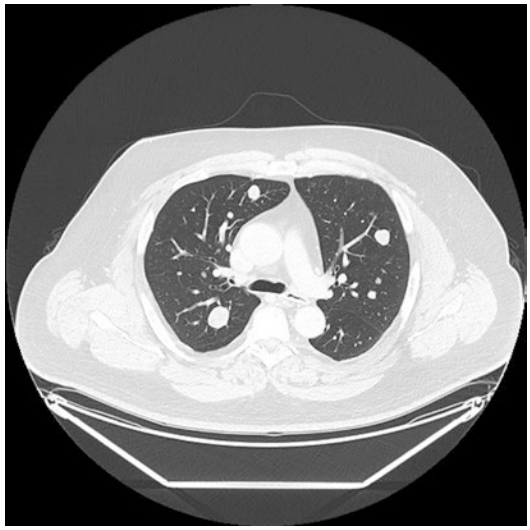

Fig. 20.5 Bilateral lung metastases of papillary thyroid cancer

disease will be refractory to RAI treatment, and other options must be considered.

Surgical resection in the setting of distant metastatic disease can be utilized in select cases. When an isolated focus of disease that is amenable to surgical excision is identified, it should be resected. This will provide an opportunity to regain local control, clearing the disease and effectively "resetting the clock" for the likely future requirement of systemic therapies (Fig. 20.5).

Patients may present with evidence of distant metastatic disease at initial diagnosis. In these cases, resection of the primary tumor is often necessary for locoregional control and to enhance the effectiveness of systemic treatments (including RAI) aimed at the distant sites of disease. Certain sites of metastatic disease may also pose a threat to the functional status of the patient and may require surgical treatment other than resection (such as kyphoplasty for stabilization of diseased vertebrae in cases with advanced bony metastases).

Postoperative Considerations and Complications

After surgical intervention for recurrent differentiated thyroid cancer, patients may suffer from several possible complications. In the setting of any re-operative neck procedure, the presence and function of parathyroid tissue must be confirmed prior to a patient being discharged from the hospital. Detectable PTH (parathyroid hormone) must be present to confirm function. If persistently undetectable, calcium and vitamin D in full replacement doses will be necessary. If transient, the hypoparathyroidism can be managed with calcium supplementation alone. The patient must also demonstrate appropriate RLN function, including adequate voice, breathing, and swallowing. Aggressive physical therapy can be employed for exercises to prevent pain-related muscle atrophy or frozen shoulder. Pain must be well controlled on oral analgesia, and the patient must be able to tolerate a diet. If closed-suction drainage was placed at the time of surgery, it should be removed when serous output has decreased to less than 25 mL over 12 h and the presence of a chyle leak has been ruled out. If drains are removed prior to hospital discharge, patients must be instructed on signs and symptoms indicative of possible problems. Swelling of the neck incision can represent benign seroma formation, common after extensive re-operative dissections. However, it could also represent acute hematoma formation or lymphatic/chyle leaks, which would require aggressive treatment and intervention. Patients must be aware of symptoms of hypocalcemia, as even well-preserved and viable parathyroid tissue can be hypofunctional after surgery. Finally, patients must be monitored for wound healing to ensure no signs of infection develop. In most cases, patients will be ready for discharge in the day following the operation to convalesce at home. Neck surgery, even in the re-operative setting, is generally well tolerated by most patients and presents with minimal morbidity. After the acute phase of healing, patients with recurrent or metastatic disease will require close monitoring and further treatment in the setting of a multidisciplinary team with extensive experience in the treatment of differentiated thyroid cancer. Even in the setting of recurrent disease, if appropriately and aggressively treated, survival rates of patients with differentiated thyroid cancer remain excellent.

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Local and Systemic Treatment of Unresectable Disease

21

Naifa Lamki Busaidy and Tania Jaber

Papillary thyroid cancer is the most common subtype of thyroid cancer. Although incidence of the disease is increasing, survival rates are excellent, with 10-year survival around 90%. However, approximately 15–30% of patients with papillary thyroid cancer are found to have metastases (half of them at initial presentation), most commonly seen in the lungs (50%), bones (25%), both lungs and bones (20%), or occasionally in other sites (5%). Many of these patients can be treated, but complete remission is only seen in one third [1]. When progression is seen after initial treatment with thyroidectomy and radioactive iodine, other options remain. Surgical resection of locoregional disease (in selected patients) generally offers the best chance of cure; however, reoperation is generally riskier than initial surgery due to scar tissue formation. If resection is not an option due to the extent of disease, involvement of critical structures, or patient refusal, radioactive iodine treatment is generally recommended. However, advanced disease is frequently refractory to therapy with radioiodine; studies are underway of several therapies that may resensitize tumor to iodine. External beam radiotherapy (EBRT) may be employed to treat either locoregional recurrence or distant metastatic disease. TSH suppression remains an important part of therapy. Lastly, therapy with tyrosine kinase inhibitors (TKIs), either approved by the Food and Drug Administration [FDA] or as part of a clinical trial, may be recommended in symptomatic patients with progressive metastatic disease [2].

N.L. Busaidy (✉) • T. Jaber
Department of Endocrine Neoplasia and Hormonal Disorders, The University of Texas MD Anderson Cancer Center, 1400 Pressler, Unit 1461, Houston, TX 77030, USA
e-mail: nbusaidy@mdanderson.org; TJaber@mdanderson.org

Radioactive Iodine

Radioactive iodine therapy can play an important role in the treatment of advanced differentiated thyroid cancer. It is first-line therapy postoperatively in patients with RAI-avid disease, and its use should be exhausted prior to the initiation of systemic therapies such as TKIs. However, its use is limited, as a significant portion of metastatic differentiated thyroid cancer (DTC) is radioiodine refractory. It is important to ensure that patients are optimally prepared prior to RAI—that the TSH is adequately stimulated, that they have not had recent contrast (with urine iodine checked if necessary), and that they have followed a low-iodine diet—so that they are not falsely identified as refractory. Empiric treatment with RAI in patients with nonavid disease is not generally recommended as it has little benefit but still exposes patients to adverse effects, especially with high cumulative doses [3]. Higher doses are generally used in metastatic disease—in our center, we

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generally give 100 mCi in patients with nodal disease, 150 mCi in patients with lung metastases, and 200 mCi in patients with bone or brain metastases. Some centers use a dosimetric approach, but the data has not shown a clear benefit versus empiric dosing [4]. Doses higher than 150 mCi should be avoided in elderly patients.

RAI should be repeated multiple times, every 6–12 months, in patients with pulmonary micrometastases as long as the disease remains RAI avid. Complete remission is more frequently seen in this group than in any other subset of patients with metastatic disease [5]. The use of RAI in pulmonary macronodular metastases may shrink RAI-avid lesions or decrease the Tg but is rarely associated with complete remission [5]. RAI may be used in RAI-avid bone metastases but rarely leads to remission, and other therapies should also be considered (including surgery, EBRT, and/or bisphosphonates) [6].

Preparation with Recombinant Human TSH (rhTSH) Versus Thyroid Hormone Withdrawal (THW)

rhTSH preparation prior to radioactive iodine is useful in some cases compared to THW. rhTSH is FDA approved to prepare low-risk DTC patients with no evidence of metastatic disease for remnant ablation; use in patients with metastatic disease is considered off-label. Some patients require rhTSH rather than THW—for example, patients with central hypothyroidism or patients with comorbidities in whom prolonged hypothyroidism would be risky and inadvisable. Multiple studies have shown non-inferiority of rhTSH compared to THW, but there is insufficient data to recommend its routine use in all patients with metastatic disease [7–11].

Adverse Effects of RAI

Adverse effects of RAI are uncommon and dose dependent. They include damage to the salivary glands leading to xerostomia and dental caries, obstruction of the nasolacrimal duct leading to excessive tearing and increased risk of infection, increased risk of secondary malignancies, and dysphagia. The use of sour candies is frequently recommended in order to prevent sialadenitis; however, studies regarding its efficacy are mixed, with most showing mild benefit and a few showing harm. Pain from acute sialadenitis may be treated with ice. Patients with dry mouth may benefit from cholinergic agents to stimulate salivary flow [12]. These patients should also work closely with a dentist to minimize the risk of caries, dental decay, and tooth loss. Nasolacrimal duct obstruction is most commonly seen in patients receiving high cumulative doses of RAI, and patients reporting epiphora following RAI should be promptly evaluated by an oculoplastic surgeon [13]. The risk of developing a secondary malignancy related to RAI therapy is present but very small. Age-appropriate cancer screening is recommended, with no need for additional screening [14–18]. RAI may have significant effects on reproductive function. A quarter of women become transiently amenorrheic following treatment with RAI. RAI concentrates in the lactating breast; breastfeeding and pumping should be stopped at least 3 months prior to administration of RAI. Pregnancy should be delayed 6–12 months after administration of RAI due to theoretical increased risks of miscarriage, infertility, and fetal loss. RAI may cause a temporary reduction in sperm count in males but generally is not associated with fetal anomalies, miscarriage, or permanent infertility unless the patient has received high cumulative doses.

TSH-Suppressive Therapy

TSH-suppressive therapy is an integral part of the management of advanced PTC. Although there have been no prospective randomized controlled trials examining the most effective degree of suppression in patients with advanced disease, most studies point toward a survival benefit with TSH suppression [19–21]. No survival benefit of TSH suppression has been shown in patients with low-risk disease [22].

TSH suppression is associated with several adverse outcomes. One study showed a 3.3-fold increase in cardiac mortality in patients with

DTC, independent of age, sex, and cardiovascular risk factors, which was further increased with TSH-suppressive therapy. This is likely related to increases in atrial fibrillation, decreased diastolic function, and increased left ventricular mass [23]. Beta-blockers may be used to decrease the risk, especially in elderly patients, and may also be useful in controlling symptoms of anxiety or palpitations that some patients may experience [24]. TSH suppression in postmenopausal women has been associated with increased risk of osteopenia and increased risk of hip fracture; no association is seen in men or in premenopausal women [25, 26]. Postmenopausal women should be appropriately treated with vitamin D, calcium, and (if indicated) therapies such as bisphosphonates or denosumab for osteoporosis to minimize bone loss associated with TSH suppression.

The most recent American Thyroid Association (ATA) guidelines introduced a new classification system used to risk-stratify patients to identify appropriate TSH goals, in which the decreased risk of disease progression is weighed against the potential adverse effects of TSH suppression [2]. Patients with excellent response show no structural or biochemical evidence of disease and have a 1–4% risk of recurrence. Patients with biochemical incomplete response show negative imaging with detectable thyroglobulin (Tg) or rising Tg levels; 20% will develop structural disease, 30% will spontaneously achieve no evidence of disease (NED), and 20% will achieve NED with further therapy. Patients with structural incomplete response have evidence of disease on imaging; 50–85% will remain with persistent disease despite therapy. Patients with indeterminate response have nonspecific imaging findings or low but detectable Tg or Tg antibody; 15–20% will have structural disease identified.

Patients with structural or biochemical incomplete response should have their TSH suppressed to <0.1 indefinitely. Patients with indeterminate response should keep their TSH between 0.1 and 0.5. Patients with high-risk disease but excellent response should have TSH suppressed to 0.1–0.5 for up to 5 years, after which they can be maintained at 0.5–2.0. Patients with low-risk disease and excellent response do not require TSH suppression and should be maintained in the lower half of the reference range (0.5–2.0). These goals may be relaxed based on individual patient risk factors as described above, including atrial fibrillation, osteoporosis or osteopenia, age >60, tachycardia, and/or menopausal status (Table 21.1).

Table 21.1 Matrix showing TSH suppression goals in reference to treatment response and risks of suppression

Risk Factors of TSH Suppression	Excellent	Indeterminate	Biochemical Incomplete	Structural Incomplete
No Known Risk	None	Mild	Complete	Complete
Menopause	None	Mild	Mild	Complete
Tachycardia	None	Mild	Mild	Complete
Osteopenia	None	Mild	Mild	Complete
Age >60	None	None	Mild	Complete
Osteoporosis	None	None	Mild	Complete
Atrial Fibrillation	None	None	None	Mild

None.TSH goal 0.5-2 mU/L
Mild. TSH goal 0.1-0.5 mU/L
Complete. TSH goal <0.1 mU/L

External Beam Radiotherapy

External beam radiotherapy is a useful option in advanced DTC, particularly when the disease is iodine nonavid. It is most commonly used to treat surgically unresectable locoregional disease, as an adjunct to surgery if pathology shows high-risk disease with extranodal extension or soft tissue invasion, or to shrink surgically unresectable disease that threatens important local structures (trachea, larynx, esophagus, or great vessels).

Most data shows benefit to EBRT in the treatment of high-risk incompletely resected locoregional disease [27–29]. Several older studies, however, suggested lack of efficacy, and this has led to controversy regarding its utility [30, 31]. Much of the available data is taken from institutional case series, with varying selection criteria; many of the studies predate the use of intensity-modulated radiation therapy (IMRT) and other newer modalities of radiation that spare more of the normal tissue. Currently, most EBRT is administered via either IMRT or stereotactic body radiotherapy (SBRT). In IMRT, three-dimensional imaging (CT, MRI, and/or PET) is used to determine the size and shape of the radiation beam in order to target the tumor while sparing nearby structures. In SBRT, multiple radiation beams are finely collimated to deliver a higher dose of radiation to a single point, and many fewer sessions are needed [32]. The location of the thyroid poses a particular challenge in the use of EBRT, as tumor and lymph nodes lie in very close proximity to critical structures (such as the aerodigestive system or great vessels) and are at high risk for complications.

Acute toxicities following EBRT include dermatitis, xerostomia, dysphagia, mucositis, hoarseness, dysgeusia, and fatigue. Most are self-limited, although occasionally they may persist. Late effects are more commonly seen with 3DRT versus IMRT. Esophageal stricture may necessitate placement of a temporary or permanent percutaneous endoscopic gastrostomy (PEG) tube. Laryngeal stricture may require temporary or permanent tracheostomy [33, 34]. Late toxicities are rarely seen with IMRT, compared with rates of up to 10% seen with conventional irradiation (3DRT) [35]. EBRT can interfere with healing of recently operated tissues and may exacerbate the xerostomia and respiratory issues caused by radioactive iodine.

Treatment of Metastatic Disease

The incidence of thyroid cancer continues to be on the rise and has increased faster than that of any other solid-organ malignancy. The reported increase is more than 5 % per year in both men and women, partially owing to overdiagnosis attributed to increased imaging of the neck area. The estimated number of new cases for 2016 is 64,300: 14,950 in males and 49,350 in females. Thyroid cancer remains the fifth most common cancer diagnosed in women [36].

While earlier detection has been on the rise, the number of deaths from thyroid cancer has also been increasing with an estimated 1980 deaths per year—910 in males and 1070 in females [36].

Treatment of newly diagnosed DTC aims at a curative approach for this type of cancer. The recurrence risk varies however depending on patient factors, stage at diagnosis, and histologic type. The risk of recurrence is highest for patients whose age is less than 20 or more than 60. Tumors larger than 1.5 cm at diagnosis and those with the presence of extrathyroidal extension also confer a higher risk. The presence of more than five metastatic lymph nodes or clinically apparent N1 disease confers a risk of recurrence greater than 20%. Certain histologic types such as tall cell variant or sclerosing variant have also been associated with an increased recurrence risk [37].

Recurrent Neck Disease

The locoregional recurrence rates for well-differentiated thyroid cancer can vary between 15 and 30% [37–40] and depend partially on the extent of the initial surgery. The decision to observe versus intervene depends on the extent of disease as well as the rate of growth in trying to balance the risks of a second neck surgery.

Small-volume local disease both in the central and lateral neck demonstrates minimal growth in

70–90% of the time [41, 42]. This can be managed conservatively with observation. Bulkier recurrent disease is best managed surgically with a compartment dissection approach of the affected neck even though this may not mean biochemical cure [37, 43]. If metastatic disease is present synchronously, then surgery should only be considered if recurrent local disease is compromising vital structures such as the airway, esophagus, or the recurrent laryngeal nerves [37, 44, 45]. If the disease is unresectable, then EBRT may be an option as previously discussed in this chapter.

Distant Metastases

Even metastatic and radioiodine-refractory DTC can have a long indolent phase whereby the rate of progression of disease does not confer an urgency to initiate treatment [44]. The decision to delay treatment allows patients to continue to lead a good quality of life without the side effects and monitoring schedule of systemic treatment. More importantly, the drugs available to treat such disease—the tyrosine kinase inhibitors (TKIs)—have not yet been shown to prolong overall survival.

In such instances, and if the disease burden does not threaten any vital structures, then the disease can be monitored with serial biochemical and radiologic studies. Tg and thyroglobulin antibody (TgAb) trends can be followed over time. Radioactive iodine scans can also be obtained. In the face of rising Tg and/or TgAb and negative nuclear scans, radioiodine-refractory disease should be considered. In such instances, alternative imaging modalities should be used to monitor radiologic progression of disease, such as comprehensive neck ultrasound and CT scans of the chest. Depending on the clinical scenario, MRI of the brain and/or spine, bone scans, and fluorodeoxyglucose positron emission tomography (18FDG-PET/CT scan) can be considered.

It is important to note that the use of the same imaging modality to monitor progression of disease is paramount. It is also important to use a standardized method for comparison, and the most widely use method at this time is the RECIST (Response Evaluation Criteria in Solid Tumors) criteria. Progressive disease is defined as a 20% increase in target lesion size. Partial response is defined as a 30% decrease in target lesion size. Stable disease is defined as any change in between those values. A comparison of different RECIST criteria versions is listed in Table 21.2.

Treatment of distant metastases also depends on the site involved and can further be delineated based on locations as follows:

1. Lung: Lung metastases are the most common site of distant metastases from thyroid cancer. In asymptomatic patients with indolent disease that is not threatening vital structures, serial imaging is recommended. In the setting of localized pulmonary metastases, surgery or EBRT may be considered. If the disease remains radioiodine sensitive, then targeted treatment with I131 radioactive therapy is recommended. However, in refractory disease that is rapidly progressing or threatening vital structures, then consideration for systemic therapy should be given.
2. Bone: The bone is the second most common site for distant metastasis in DTC and is seen in 2–13% of DTC patients [46]. It is often a sign of poor prognosis indicating the widespread and aggressive nature of the disease. They are often symptomatic and confer an increased morbidity and mortality due to skeletal-related events (SREs) such as pathologic fractures, spinal cord compression, and pain. In prior studies of patients with DTC and bone metastases, 51–78% of patients developed at least one SRE [47, 48]. The effective treatment of bone metastases is challenging and consists of RAI therapy if the metastasis is radioiodine sensitive, surgery, and/or EBRT. EBRT is especially considered in instances where the bone metastases are conferring significant pain or threatening a fracture and/or compression. Antiresorptive agents such as bisphosphonates or RANKL inhibitors are also useful in pain control and stabilization.

Table 21.2 Summary of RECIST criteria versions 1.0 and 1.1 [113]

	RECIST 1.0	RECIST 1.1
Target lesions (1)	Measurable target lesions:	Measurable target lesions:
	– Unidimensional measurement	– Unidimensional measurement
	– ≥20 mm with conventional techniques	– Tumor lesions, ≥20 mm with conventional techniques and ≥10 mm with spiral CT
	– ≥10 mm with spiral CT	– Malignant lymph nodes, >15 mm
	– Maximum number:	– Maximum number:
	– 5 per organ	– 2 per organ
	– 10 total	– 5 total
Nontarget lesions (2)	Size <1 cm, cystic lesions, bone lesions without soft tissue component, serous effusions, leptomeningeal disease, lesions in an irradiated area	Lymph nodes: 10–15 mm
		Non-lymph nodes: Size <1 cm, bone lesions without soft tissue component, serous effusions, leptomeningeal disease
Objective response	1. CR, disappearance of all target lesions at ≥4 week. PR, ≥30% decrease at 4 week. PD, ≥20% increase or new lesions. SD, neither PR or PD criteria met	1. CR, disappearance of all target lesions at ≥4 week. PR, ≥30% decrease at 4 week. PD, ≥20% increase and overall 5 mm net increase or new lesions. SD, neither PR or PD criteria met
	2. CR, disappearance of all nontarget lesions and normal tumor markers at ≥4 week. PD, unequivocal progression or new lesions. Non-PD, persistence of ≥1 lesion or abnormal tumor markers	2. CR, disappearance of all nontarget lesions and normal tumor markers at ≥4 week. PD, unequivocal progression or new lesions or new positive PET scan. Non-PD, persistence of ≥1 lesion or abnormal tumor markers
Overall response	– Best response: recorded in measurable disease from start of treatment to progression or recurrence	
	– Non-PD in nontarget lesions reduces CR in target lesions to overall PR	
	– Unequivocal new lesions are PD	

CR complete response, *PR* partial response, *PD* progressive disease, *SD* stable disease

3. Brain: Brain metastases from thyroid cancer are rare, and the optimal treatment is controversial. Seen in less than 1.5% of thyroid cancers [49], the prognosis is poor, with average survival less than 1 year after diagnosis. I131 radioactive iodine treatment is rarely used and may worsen edema surrounding the metastatic lesion(s), so if it is used, administration of prophylactic steroids must be considered. Solitary lesions may be treated with surgical resection or stereotactic surgery. Extensive disease may be treated with whole-brain radiation therapy.
4. Liver: Liver metastases from DTC are also rare and are seen in around 5% of DTC patients [50]. At the time of discovery of the liver metastases, most patients exhibit other widespread disease, and the treatment in that case is systemic therapy. In some instances, radiofrequency ablation or chemoembolization may be considered [51–53]. Surgical resection may be an option if risks of surgery are acceptable in a patient with widely metastatic disease.

Systemic Therapy

Systemic therapy should be considered in a subset of patients that meet certain criteria for initiation. In asymptomatic patients, progressive disease over a 12-month period, especially if the disease is deemed to be RAI refractory as will be discussed later, is an indication for treatment. Symptomatic

patients and patients with bulky disease that threaten vital structures should also be considered when local therapies alone are not enough.

Traditional Chemotherapy

Doxorubicin is the only Food and Drug Administration (FDA)-approved cytotoxic agent for DTC. Response rates however are dismal, and its use in metastatic DTC has become obsolete, especially in the face of the newer targeted TKIs.

Other cytotoxic agents such as paclitaxel, bleomycin, cisplatin, carboplatin, and etoposide have had poor outcomes as well, with minimal (if any) improvement in response rates. Combination chemotherapy with doxorubicin and cisplatin has been shown to increase toxicity without an improvement in response [54, 55].

TKIs

Signaling Pathways

Over the past decade or so, advancements in identifying molecular mechanisms of thyroid cancer tumorigenesis and progression have led to the recognition of specific mutations enabling the development of molecular-targeted therapy in DTC. Elucidating downstream signaling pathways of the Ras/Raf/MAPK and PI3K-AKT pathways has allowed for the identification of oncogenic mutations that have prognostic implications in DTC (Fig. 21.1).

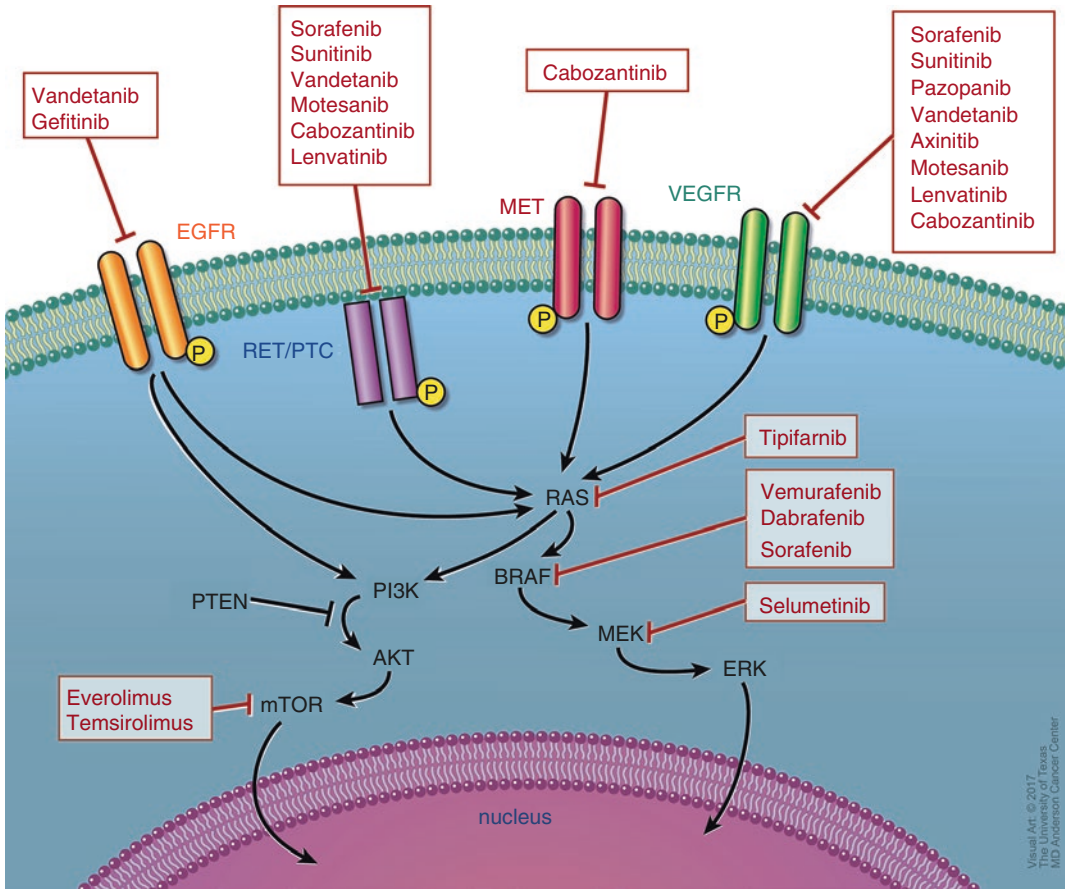

Fig. 21.1 Receptor pathways and targets of clinically available inhibitors

In the MAPK signaling pathway, extracellular signals activate Ras, which in turn activates BRAF. Activated BRAF activates MEK through phosphorylation, and activated MEK in turn phosphorylates ERK to activate it. This leads to intranuclear translocation of activated ERK to regulate transcription of genes involves cell differentiation and survival. BRAF mutations are most commonly seen in DTC and found in up to 40% of primary tumors and 70% of recurrent ones [56, 57]. Among those, BRAF V600E accounts for more than 90% and has been associated with more aggressive and refractory disease [58–61]. RET/PTC and RAS mutations occur in 30–40% of tumors and have also been associated with worse prognosis [62, 63].

In the PI3K-AKT pathway, downstream signaling activates mTOR which is an inhibitor of apoptosis. Angiogenic factors are also upregulated in DTC enabling the use of multitargeted therapies against vascular endothelial growth factor receptors (VEGFRs) and endothelial growth factor receptors (EGFRs) [64–66].

There are currently only two FDA-approved TKIs for DTC, but many others are under investigational trials. The decision to start treatment with TKI should be limited to patients with disease that is either symptomatic or rapidly progressive (growing by at least 20% annually). Consideration should be given to baseline assessment of symptoms prior to initiation of treatment and during therapy [2, 67–69].

Available FDA-Approved TKIs for DTC

Lenvatinib (Lenvima)

Approved in February 2015, 2 months before its goal date, for the treatment of metastatic and progressive DTC that is refractory to radioactive iodine treatment, it is an oral multi-TKI against VEGFR, RET, and FDFR. The recommended starting dose is 24 mg orally once daily.

In the initial multicenter phase II trial, 58 patients with metastatic and progressive DTC were enrolled and received treatment with lenvatinib. Of those, the partial response rate was 50%, and progression-free survival (PFS) was 12.6 months. Subgroup analysis revealed even better PFS rates for patients whose tumors contained a RAS mutation [70].

In the subsequent phase III SELECT trial which was an international, randomized, double-blinded trial, 392 patients with progressive, metastatic, radioiodine-refractory DTC were assigned to receive lenvatinib versus placebo in a 2:1 ratio [71]. The primary endpoint of this trial was PFS, and secondary endpoints evaluated response rates, overall survival, and safety. In the lenvatinib group, the median PFS was 18.3 months versus 3.6 months in the placebo group with a HR of 0.21 (99% CI, 0.14–0.31). This prolongation in PFS was also seen in patients who had been previously treated with one TKI. In terms of response rates, complete response was seen in four patients treated with lenvatinib compared to none in the placebo group. A partial response was noted in 63.2% of patients. Overall survival was not reached, perhaps because patients initially assigned to placebo were allowed to cross over to the treatment group only after demonstration of disease progression [72]. In a subgroup analysis, however, overall survival was reached in the subset of patients older than 65 years of age on treatment with lenvatinib [73].

Most common adverse events seen with lenvatinib were hypertension (68%), fatigue (59%), diarrhea (59%), and loss of appetite (50%). Serious and fatal adverse events, although rare, included thromboembolic events, liver and kidney toxicity, hemorrhagic stroke, and gastrointestinal perforation. The rate of discontinuation of the study drug due to adverse events was estimated at around 14% [72, 74].

Sorafenib (Nexavar)

Approved in 2013 for the treatment of metastatic and progressive DTC that is refractory to radioactive iodine treatment, it is an oral multi-TKI whose targets include BRAF, VEGFR1, and VEGFR2. The recommended daily dose is 400 mg twice a day, to be continued until no clinical benefit is seen or until unacceptable toxicity occurs.

Sorafenib had previously been approved for treatment of renal cell carcinoma (RCC) in 2005 and hepatocellular carcinoma in 2007. Its most recent approval for DTC in 2013 was based on

the DECISION trial which was a multicenter, double-blinded, placebo-controlled phase III trial [75]. Four hundred and seventeen patients with locally recurrent or metastatic, progressive DTC refractory to radioactive iodine treatment were enrolled and randomized 1:1 to receive sorafenib 400 mg twice daily or a matched placebo. Baseline characteristics were not different among both groups. Approximately 50% of the patients were male with a median age of 63 (range 24–82). Among the thyroid cancer patients, 57% had papillary, 25% had follicular, and 10% had poorly differentiated carcinomas. Ninety-six percent of all patients had distant metastases, and most common metastatic sites, in order of their occurrence, were the lung (86%), bone (27%), and liver (14%).

The results showed a statistically significant improvement in the median PFS in the sorafenib group (10.8 months) as compared to the placebo group (5.8 months) with a hazard ratio (HR) of 0.59 (95% CI 0.45–0.76; $p < 0.0001$).

In terms of safety, adverse events occurred in over 98% of the sorafenib group as compared to 88% of the placebo group. There were no serious adverse events, and the most frequent ones observed were hand-foot skin reactions (76%), diarrhea (69%), and rash/desquamation (50%).

There were multiple phase II trials leading up to the DECISION trial that have shown favorable results. The first published phase II trial included 30 patients, 27 of which had DTC [76]. All patients received sorafenib 400 mg twice daily for a median duration of 6.7 months. The partial response (PR) rate by RECIST criteria was 23.3% and stable disease (SD) noted in 53.3% patients. The median PFS in patients who had DTC was 21 months as compared to 18 months in the entry cohort.

Another phase II study included 41 patients with PTC and showed PR in 15% with a median PFS of 15 months [77]. Another long-term outcome study looked at sorafenib treatment for a median period of 9.2 months (range 0.1–39 months) with a median follow-up of 25 months (range 3.5–39 months). Initial response rates were better in the first 6 months of the study as compared to the end of the study with 31% of patients having PR at 6 months compared to 15% only at the end of follow-up [78].

Table 21.3 Multitargeted kinase inhibitors under study

Drug	Target	Phase	RR (%)	PFS (months)
Multi-KIs				
Sunitinib	PDGFR, VEGFR, RET, c-kit	II	31	12.8
Pazopanib	PDGFR, VEGFR, c-kit	II	49	11.7
Vandetanib	RET, VEGFR, EGFR	II	8	11.1
Cabozantinib	MET, VEGFR2, RET	I	53	–
BRAF inhibitors				
Dabrafenib	BRAF	I	29	11.3
Vemurafenib	BRAF	II	35	15.6

Off-Label TKI Use

After the recognition that a range of tyrosine kinases is involved in the pathogenesis of thyroid cancer, several multitargeted kinase inhibitors are under study in multiple phase I and II trials (Table 21.3). Common targets include VEGFR, PDGFR, and RET. PFS in these trials has ranged from 9.3 to 18 months [79–86].

Vandetanib (Caprelsa)

Approved for treatment of metastatic unresectable medullary thyroid cancer (MTC), it is a TKI that targets RET, VEGFR, and EGFR. It has been studied in DTC in a phase II trial involving 145 patients with metastatic, radioiodine-refractory disease [83]. Patients were randomized to receive vandetanib 300 mg once daily or placebo and were followed for a median of 19 months. At the end of follow-up, median PFS was 11.1 versus 5.9 months in the vandetanib group as compared to the placebo group (HR 0.63, 95% CI 0.54–0.74). No difference was noted however in partial response rates or overall survival rates. Most commonly observed adverse events were QT prolongation and diarrhea.

Sunitinib (Sutent)

Approved for the treatment of advanced RCC, sunitinib targets multiple VEGFRs as well as RET/PTC subtypes 1 and 3. It has also been studied in open-label phase II trials in patients with progressive DTC at a dose of 50 mg daily for 28 days followed by 14 days of no treatment per cycle. In one study, the partial response rate was 13% [87]. In another study, that rate was 17% [88]. In another trial, sunitinib was given continuously at a dose of 37.5 mg daily. The partial response rate was 25% [89]. Most commonly noted adverse events include fatigue, diarrhea, hand-foot syndrome, and hypertension.

Pazopanib (Votrient)

Also approved for the treatment of advanced RCC, pazopanib is an inhibitor of all VEGFR subtypes only. It has no effect on the RET or BRAF kinases, and its actions in thyroid cancer are limited to its antiangiogenic effects [90]. In a phase II trial, 37 patients with progressive DTC were started on pazopanib 800 mg daily. The partial response rate was 49%, and the PFS rate at 1 year was 47% [82]. The most commonly noted adverse events were hypertension, elevated liver enzymes, and mucositis.

Vemurafenib (Zelboraf)

Approved for the treatment of metastatic melanoma, vemurafenib is a BRAF kinase inhibitor and has been tested in BRAF-positive advanced DTC. In an open-label, multicenter phase II trial, 51 patients with progressive unresectable radioiodine-refractory DTC with a positive BRAF V600E mutation were enrolled and started on vemurafenib 960 mg orally twice daily [86]. There were two cohorts in this study, a TKI-naïve cohort and another cohort whose patients were previously treated with a TKI. The partial response rate in the TKI-naïve cohort was 35% with a median PFS of 15.6 months, while the partial response rate in the previously treated group was 26% with a median PFS of 7 months only. Commonly noted adverse events included rash, fatigue, and alopecia. In another center's experience, 17 patients received vemurafenib and had a partial response rate of 47% [91].

Dabrafenib (Tafinlar)

Also a BRAF kinase inhibitor approved for the treatment of unresectable metastatic melanoma, dabrafenib has been studied in BRAF-mutated DTC. In a phase I trial of 14 patients with BRAF-mutated DTC, the partial response rate was 29% [85]. This drug has also been studied in resensitization to RAI therapy which will be discussed later in this chapter. It is also currently being studied in multiple clinical trials in combination with MEK inhibitors.

Sequential Administration

There is little data regarding sequential administration of TKIs in patients with progressive DTC and how these patients respond compared to treatment-naïve patients. In a small retrospective review, patients with progressive DTC on sorafenib were then treated with sunitinib. In one patient refractory to sorafenib, there was a 38% tumor reduction on second-line sunitinib [92]. In another trial comparing response to lenvatinib in treatment-naïve patients versus patients treated with prior VEGFR kinase inhibitors, the response rate in the treatment-naïve group was 54% compared to 41% in the previously treated group, suggesting continued activity of lenvatinib despite prior treatment [71]. In another trial evaluating the role of vemurafenib in BRAF-mutated DTC in pretreated patients and treatment-naïve patients, the partial response rate was also lower in pretreated patients (26%) compared to treatment-naïve patients (35%) [86].

Another retrospective review evaluated the efficacy of salvage therapy in patients with advanced DTC who failed first-line sorafenib treatment [93]. Salvage therapy included treatment with sunitinib, pazopanib, cabozantinib, lenvatinib, or vemurafenib in 17 patients who had previously failed sorafenib. Partial response rates were 41% in the salvage group compared to 13% in the sorafenib-only group. Median overall survival rates were also significantly longer in the salvage group (58 months) compared to the sorafenib-only group (28 months).

Given the mixed treatment responses in pretreated patients compared to treatment-naïve

patients, more studies are required to evaluate the optimal sequencing of TKI use in progressive DTC.

Adverse Effects

Commonly seen adverse events specific to each TKI have been noted above. Certain adverse events that pertain to the drug class as a whole will be discussed below.

Hypertension. This is the most common adverse effect associated with TKIs with angiogenic effects. While its severity is dose related, certain studies have shown that it is a marker of efficacy as blood pressure over 140/90 was associated with improved survival [94]. According to the Angiogenesis Task Force of the National Cancer Institute Investigational Drug Steering Committee's guidelines for management of TKI-induced hypertension, it is recommended that the goal blood pressure should be less than 140/90 prior to and during treatment with TKIs [95]. The choice of antihypertensive agent should be individualized. Patients should monitor their blood pressure daily and doctors weekly until goal blood pressure is achieved. Stopping the TKI or reducing the dose may be needed if blood pressure goals are not met.

QT Interval Prolongation on EKG. A baseline EKG and electrolyte panel should be performed in all patients being considered for a TKI. While all TKIs can cause QT prolongation, vandetanib carries a "black box" warning to QT interval prolongation, torsades de pointes, and sudden death. It is thus contraindicated with anyone with a history of or at high risk for those. Electrocardiograms should be performed at baseline, after 2–4 weeks, and every 3 months thereafter. Careful consideration to initiation of other drugs that may prolong QT interval should also be made.

Congestive Heart Failure. Although infrequent, TKIs have been associated with myocyte toxicity and both systolic and diastolic heart failure. Hypertension can also exacerbate this failure. Baseline evaluation with an echocardiogram should be considered, and periodic monitoring thereafter depends on patient symptomatology and clinician judgment. Standard heart failure therapy should be initiated if indicated. Discontinuation or interruption of the TKI should be considered if medical treatment fails to control the symptoms.

Renal Adverse Events. The main concern with TKI use is proteinuria, and it is recommended that baseline renal function and urinalysis be performed at baseline and periodically thereafter. Discontinuation of therapy is recommended for grade 4 proteinuria.

Hepatic Adverse Events. Manifested as an increase in liver enzymes, TKI-associated hepatotoxicity may be severe and even fatal with some reported cases of liver failure. Baseline liver function tests and monitoring at a monthly interval thereafter are recommended. It is recommended that patients with baseline elevation in transaminases greater than 2.5 times the upper limit of normal or development of grade 3 hepatic adverse events or higher be excluded from initiation or continuation of TKI therapy [67].

Hematologic Adverse Events. All TKIs have the potential to cause bone marrow suppression, thrombosis, and hemorrhage. They should not be initiated in patients with fresh surgical wounds or scheduled surgery within 1 week. Careful consideration of risks and benefits should be given prior to initiation in patients with history of hemoptysis or a bleeding disorder or patients on anticoagulation. Baseline blood cell counts are recommended at baseline and at every visit and may be needed to be done more frequently in higher-risk patients.

Dermatologic Adverse Events. Usually appearing in the first 6 weeks of treatment, the most commonly seen events are hand-foot reactions and rash. Dose modification or interruption may be required.

Endocrine Considerations. TKIs have been noted to interfere with levothyroxine absorption and can induce hypothyroidism [96]. Patients usually require a higher dose of thyroid hormone replacement once initiated on TKI therapy. Thyroid function tests should be monitored frequently and adjustments made as needed.

Based on the above adverse events, a careful history and laboratory evaluation of patients considered for systemic therapy should be performed. Consideration and careful documentation of baseline performance status, symptoms, and laboratory values should be performed and

recorded. Table 21.4 summarizes the recommended studies at baseline and during treatment with TKI. These finding can be documented in a form resembling that in Fig. 21.2 [67].

Table 21.4 Baseline and surveillance studies in TKI therapy

Baseline and surveillance labs/imaging	
CBC	Basic metabolic panel
Coagulation profile	Liver function tests
Thyroid function tests	LDH
EKG	Urinalysis
Beta HCG (if applicable)	

RAI-Refractory Disease

Definition

RAI-refractory disease is determined when one of the following is established:

PATIENT USE ONLY *(please check if you have had one or more of the following symptoms):*

☐ Rash (on skin or hands/feet) ☐ Burning of the mouth ☐ Fever ☐ Shortness of Breath ☐ Hoarseness
☐ Increased Blood Pressure ☐ Nausea/Vomiting ☐ Diarrhea ☐ Weakness/Fatigue ☐ Weight loss

Patient Signature Print Name

PHYSICIAN USE ONLY:

Toxicity	0	Grade 1	Grade 2	Grade 3	Grade 4
ANOREXIA	No	☐ Loss of appetite, without alterations in eating	☐ Oral intake altered without sig wt loss	☐ Assoc w/ sig wt loss; requires IVF/TPN/TF; inadequate oral intake	☐ Life threatening
BLEEDING	No	☐ Mild; No Intervention	☐ Sxs, gross bleeding; intervention needed	☐ Transfusion, Interventional radiology, OR, hemostasis	☐ Life threatening
DIARRHEA	No	☐ Increase <4 stools/day over baseline	☐ Increase of 4-6 stools/day over BL; not interfere w/ADLS; IV fluids < 24 hrs	☐ Increase of ≥7 stool/day; or incontinence; IVF> 24hrs; hospitalization	☐ Life threatening
DRY MOUTH	No	☐ Symptomatic, no dietary alteration	☐Symptomatic & significant PO intake decreased	☐ Symptoms causing inability to eat adequately	-
DYSPHAGIA	No	☐ Sxs, but able to eat	☐Sxs; altered eating; IV fluids < 24 hrs	☐ Sxs; severely altered eating. IV, TPN, TF > 24 hrs	☐ Life threatening Obstruction etc
FATIGUE	No	☐ Fatigue relieved by rest	☐ Moderate fatigue not relieved by rest, limiting some ADLs	☐ Fatigue not relieved by rest limiting self care ADLs	☐ Bedridden/ disabling
FEVER/RIGOR	No	☐ 38-39°C; 100.4–102.2°F	☐ 39. 1–40°C; 102.3–104°F	☐ >40 °C; >104 °F for <24hrs	☐ >40 °C; > 104 °F >24hrs
HAIR LOSS	No	☐ Thinning or Patchy	☐ Complete		
HAND-FOOT SYNDROME	No	☐ Numbness, tingling, paresthesia, painless swelling or erythema of hands and/or feet or discomfort not interrupting usual activities	☐ Painful erythema & swelling of hands &/or feet &/or discomfort affecting subject's activities	☐ Moist desquamation, ulceration, blistering or severe pain of hands &/or feet &/or severe discomfort causing inability ADLS or work	-
HOARSENESS	No	☐ Mild or intermittent; fully understandable	☐ Moderate or persist, repetition but understandable	☐ Severe including predominantly Whispered speech	-
HYPERTENSION	No	☐ PreHTN (SBP 120 - 139 mm Hg or DBP 80 - 89 mm Hg)	☐ Stage 1 HTN (S8P 140-159 mm Hg or DBP 90-99 mm Hg); medical intervention indicated; recurrent or persistent (>= 24 hrs) symptomatic increase by >20 mm Hg (diastolic) or to > 140/90 mm Hg if previously WNL; monotherapy indicated	☐ Stage 2 HTN (SBP>=160mm Hg or DBP >=100 mm Hg); medical intervention indicated; > 1 drug or more intensive therapy than previously used indicated	☐ Life threatening consequences (e.g., HTN crisis), urgent intervention indicated
MUCOSITIS	No	☐ Erythema of mucosa	☐ Patchy ulceration, pseudomembrane.	☐ Confluent ulceration, pseudomembrane	☐ Tissue necrosis life threatening
NAUSEA	No	☐ Loss of appetite with no change in eating	☐ Oral intake decreased without weight loss or dehydration	☐ Inadequate caloric or fluid intake; IVF/TPN/FT or hospitalization indicated	-
PAIN	No	☐ Mild pain	☐ Mod pain, limiting ADLs	☐ Severe pain, limiting self care ADLs	☐ Disabling
RASH	No	☐ Macular/papular eruption or erythema without associated sxs.	☐ Rash with pruritus or other sxs, localized desquamation or other lesions covering >50% BSA	☐ Severe, generalized macular/ papular erythroderma, vesicular eruption; or desquamation covering ≥50% BSA	☐ Generalized bullus, exfoliative or ulcerative dermatitis
VOMITING	No	☐ 1 episode in 24hrs >Baseline	☐ 2-5 in 24hrs over Baseline; IV fluids < 24hrs	☐ ≥6 in 24hrs over Baseline; or needs IVF > 24hrs	☐ Life threatening
WEAKNESS	No	☐ No sxs. Weakness on exam	☐ Sxs, interfer with function, but not ADL	☐ Sxs & interfere with ADL	☐ Life threatening
WEIGHT LOSS	No	☐ 5 to <10% from baseline; intervention not indicated	☐ 10 - <20% from baseline	☐ ≥20% from baseline	-

Baseline Weight: _____ Current Weight: _____ Blood Pressure: _____ ECOG Performance Status: _____

Fig. 21.2 Endocrine-targeted therapy adverse event record. *ADL* activities of daily living, *BSA* body surface area, *BL* baseline, *HTN* hypertension, *ECOG* Eastern Cooperative Oncology Group, *IVF* intravenous fluids, *PO* oral, *Sxs* symptoms, *TF* tube feeds, *TPN* total parenteral nutrition

- No iodine uptake at known sites of metastases (found on cross-sectional imaging)
- Progressive disease despite RAI treatment with confirmed uptake
- Disease progression within 1 year after treatment with RAI
- Cumulative RAI dose >600 mCi

Loss of Iodine-Concentrating Ability

Certain mutations have been associated with more aggressive RAI-refractory thyroid cancer and usually include mutations in the MAPK signaling pathway and the mTOR pathway and mutations in VEGFRs.

The BRAF V600E mutation has also been implicated in RAI-refractory disease owing perhaps to its association with a more aggressive course. The RAI refractoriness in BRAF V600E-mutated thyroid cancer cells has been thought to be related to reduced expression of the Na/I symporter (NIS) that mediated iodine uptake [97, 98]. Animal studies have shown reduced mRNA levels for all thyroid-specific genes involved in iodine metabolism in BRAF mutant tumors including NIS, thyroglobulin, and thyroid peroxidase genes [97]. Furthermore, using a MEK inhibitor to suppress the BRAF/MEK/MAP kinase pathway in BRAF mutant rat thyroid and PTC cells restored the expression of those genes [98].

In a retrospective human study, 67 PTC patients were evaluated. Cancers with mutations of the BRAF V600E mutation were associated with more recurrences at the end of the 3-year follow-up period. These recurrences were in most RAI refractory [99].

Redifferentiation Therapy in Iodine-Refractory Disease

Given that the prognosis of metastatic DTC diminishes significantly as compared to localized DTC with an estimated 10-year survival rate of 42% only, older patients with lung or bone metastases or radioiodine-nonavid disease have even lower survival rates, estimated to be at 10% [44]. As such, efforts have concentrated on agents that may help restore iodine avidity in hopes of being able to use such targeted treatment in metastatic disease and improve outcomes.

Failed Agents

Retinoids

In vitro studies have shown that retinoids have beneficial effects in thyroid carcinoma including increased NIS mRNA expression and iodide uptake in some thyroid cancer cell lines. This is thought to be due to the fact that the promoter of the NIS gene has a retinoic acid response element:

(a) 13-*cis*-Retinoic acid

Isotretinoin, or 13-cis-retinoic acid, is a ligand for the retinoic acid receptor (RAR) which plays a role in the NIS gene. Its efficacy in reversing RAI refractoriness has been studied in metastatic thyroid cancer.

In one study, 25 patients were treated with a 3-month course of isotretinoin at a dose of 1 mg/kg/day [100]. After finishing treatment, a diagnostic I131 whole-body scan (WBS) was done. The age range of the patients was 37–86 with a median age of 66. Ten out of the 25 patients had PTC. Out of the 25 patients, only 4 had increased uptake on the WBS, and only in 3 patients, the uptake was considered to be dosimetrically relevant.

In another study, 16 patients were treated with 8 weeks of isotretinoin at a dose of 1.5 mg/kg/day [101]. A CT scan and a diagnostic I131 WBS were obtained before treatment, and a repeat WBS was obtained 2 weeks after completing treatment. The median age of the patients was 66, and 9 out of the 16 patients had PTC. Only one out of the 16 patients had increased uptake, but it was thought to be dosimetrically irrelevant.

(b)Bexarotene

Bexarotene is a retinoid X receptor activator which is also involved in the NIS gene expression. Its use to reverse RAI refractoriness in metastatic thyroid cancer has been studied in a trial involving 12 patients who were treated for 6 weeks with bexarotene 300 mg orally daily [102]. Cross-sectional imaging and diagnostic thyrogen-stimulated I131 WBS were obtained

prior to starting treatment, and a repeat diagnostic thyrogen-stimulated I131 WBS was obtained after completing treatment. The age range of the 12 patients was 36–71 with a median age of 49. Five out of the 12 patients had PTC. Eleven patients completed the study, and 8 out of the 11 had a partial response to treatment. Out of those, seven patients had increased uptake on cross-sectional imaging but not on the WBS. Furthermore, the increased uptake was not noted at all metastatic sites suggesting a mixed response.

Romidepsin

Romidepsin is a histone deacetylase (HDAC) inhibitor that has been studied in RAI-refractory disease. HDAC inhibitors have been shown to have apoptotic activity in anaplastic thyroid cancer cells [103, 104]. In vitro studies have also shown them to increase RAI uptake [105, 106].

Twenty patients with metastatic DTC were treated with intravenous romidepsin at dose of 13 mg/m^2 at days 1, 8, and 15 of 28-day cycles [107]. Cross-sectional imaging was obtained at baseline and every two cycles. A diagnostic thyrogen-stimulated I131 WBS was obtained after two cycles of treatment. The median age of the patients was 64, and eight patients had PTC. Only 2 out of the 20 patients had increased uptake. One of those two patients showed increased uptake after 12 cycles of treatment and was then treated with I131 but had progressive disease at 3 months. The other patient showed increased uptake after two cycles and was also treated with I131 and also progressed at 3 months.

Rosiglitazone

Rosiglitazone is PPAR gamma agonist, and its use to reverse RAI refractoriness in metastatic thyroid cancer has also been studied. Twenty patients with a median age of 57 were treated with rosiglitazone 4 mg orally daily for 1 week then 8 mg orally daily for 7 weeks [108]. Sixteen out of the 20 patients had PTC. A diagnostic thyroid hormone withdrawal I131 WBS was obtained after completing the 8 weeks of treatment. Only five patients had increased uptake that was thought to be clinically insignificant and incomplete.

Promising Agents: BRAF/MEK Inhibitors

BRAF and MEK inhibitors have been studied in mouse models expressing the BRAF V600E mutation. Inducing this mutation in thyroid cells resulted in poorly differentiated thyroid tumors and inability to incorporate RAI. Treatment with a BRAF or MEK inhibitor partially restored RAI sensitivity [109]. As such some of these agents were studied in humans and yet others are currently under study.

Sorafenib

The use of sorafenib to reverse RAI refractoriness in metastatic thyroid cancer has been studied.

In one study, 32 patients were initially recruited to undergo treatment with 26 weeks of sorafenib at a dose of 400 mg orally twice daily [110]. Cross-sectional imaging and a diagnostic I131 WBS were obtained within 4 weeks of starting treatment and after completing the treatment. Twenty-two patients completed the study. The median age of patients was 65 with 12 patients out of 32 having PTC and 10 of those had the BRAF V600E mutation. Nineteen patients had a clinically beneficial response with 8 patients having partial response and 11 patients with stable disease. Only 1 patient out of the 22 who completed the 26 weeks of treatment had slight increase in RAI uptake that was thought to be clinically irrelevant.

Selumetinib

Selumetinib is a MEK1 and MEK2 inhibitor that has also been studied in RAI-refractory metastatic thyroid cancer. Twenty patients with median age of 61 were treated with selumetinib at a dose of 75 mg orally twice daily for 4 weeks [111]. Cross-sectional imaging was obtained prior to and after completing the treatment with I124 PET scans. If the repeat I124 study showed a significant uptake, then those patients were treated with I131. Out of the 20 patients, 9 had BRAF mutations and 5 had NRAS mutations. Twelve patients had increased uptake, eight of whom reached dosimetry threshold for treatment. Interestingly all five patients with NRAS mutations had shown increased uptake and were subsequently treated.

Dabrafenib

Dabrafenib is a BRAF inhibitor, and its use in reversing RAI refractoriness in metastatic thyroid cancer has been studied. Ten patients with BRAF V600E-mutated metastatic DTC were treated with dabrafenib 150 mg orally twice daily for 25 days [112]. I131 WBS was obtained prior to and after completing the treatment. If there was new or improved uptake, then dabrafenib was continued for 17 more days followed by treatment with 150 mCi of I131. Out of the ten patients, six showed increased uptake and all six were treated. At the 3-month restaging visit, a third of the patients had partial response, and two thirds had stable disease.

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Surveillance Strategies After Initial Treatment of Differentiated Thyroid Cancer

22

Deepa Kirk

Abbreviations

CT	Computed tomography
DTC	Differentiated thyroid cancer
dWBS	Diagnostic whole-body scan, or diagnostic whole-body radioiodine scan
FDG	18F-Fluorodeoxyglucose
FDG-PET	18F-Fluorodeoxyglucose/positron emission tomography
FTC	Follicular thyroid cancer
HAMA	Human anti-mouse antibodies
HRQoL	Health-related quality of life
IMA	Immunometric assay
LCMS	Liquid chromatography-tandem mass spectrometry
LID	Low-iodine diet
LTT	Less than total thyroidectomy
MRI	Magnetic resonance imaging
PET	Positron emission tomography
PTC	Papillary thyroid cancer
QoL	Quality of life
rhTSH	Recombinant human TSH
RIA	Radioimmunoassay
TgAbs	Antithyroglobulin autoantibodies, or thyroglobulin antibodies
Tg-FNA	Thyroglobulin in the aspirate fluid
THW	Thyroid hormone withdrawal
TT	Total thyroidectomy
WBS	Whole-body scan, or whole-body radioiodine scan

D. Kirk, M.D.
Division of Endocrinology, Department of Medicine,
University of North Carolina School of Medicine,
300 Meadowmont Village Circle, Suite 202,
Chapel Hill, NC 27517, USA
e-mail: dkirk@med.unc.edu

Background

Following the initial treatment of differentiated thyroid cancer (hereafter referred to as "thyroid cancer" or DTC) with surgery and often radioiodine ablation, the focus shifts to monitoring for residual or recurrent disease. Historically, patients with papillary and follicular thyroid cancer (PTC and FTC, respectively) were monitored with assessment of symptoms, regular physical exams, periodic diagnostic whole-body scan (dWBS) with radioiodine after withdrawal from thyroid hormone, and first-generation thyroglobulin measurements. Disease was often clinically or structurally evident by the time it was identified [1, 2]. Moreover, as patients had to be withdrawn from their thyroid hormone replacement for up to 6 weeks before performing dWBS, thyroid cancer surveillance required repeated, prolonged periods of iatrogenic hypothyroidism. For the majority of individuals with thyroid cancer, this protocol resulted in decreased quality of life for several months surrounding the time of dWBS, as well as the expected medical consequences of hypothyroidism including fatigue, constipation, and fluid retention [3].

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Since the 1990s, methods for detecting residual or recurrent thyroid cancer have become increasingly sensitive, allowing for detection of disease well before symptoms or signs arise. Currently, the two most commonly utilized tests for surveillance—measurement of serum thyroglobulin and imaging of the neck and cervical lymph nodes with high-resolution ultrasound—can capture almost all patients with residual or recurrent disease [4–6]. Positron emission tomography (PET) scanning may permit detection of disease that is poorly radioiodine avid and/or located outside the neck and can be used to localize such disease and monitor its response to therapy [7]. Moreover, "stimulated" surveillance studies (primarily dWBS and stimulated thyroglobulin) have become significantly less cumbersome for many individuals with thyroid cancer due to the advent of recombinant human TSH (rhTSH), which can be used in place of thyroid hormone withdrawal in most cases [8]. Improved prognostication schemes have allowed lower-risk patients and patients with excellent responses to treatment to forgo dWBS and stimulated testing altogether. These patients can often be followed with periodic neck ultrasound and suppressed serum thyroglobulin measurements alone [4, 5].

The improved sensitivity of surveillance techniques has raised several important new challenges, chief among them are (1) how to determine if minor abnormalities in test results are due to real disease and (2) what to do with proven low-level or "subclinical" disease. This dilemma is not unique to thyroid cancer. Similar questions arise in other areas of medicine in which disease is identified at increasingly earlier stages [9]. But the dilemma is particularly germane to the care of patients with differentiated thyroid cancer, as any remaining or recurrent disease is often indolent or slowly progressive and as overall mortality remains extremely low. Detecting subclinical persistent disease or early-stage recurrence, or even the possibility of disease, risks subjecting patients to the morbidities of additional testing and treatment, with a low likelihood of improving clinically meaningful outcomes or mortality in low-risk and perhaps even some intermediate-risk patients [10]. Even if treatment is deferred in favor of observation, patients may suffer psychological and financial consequences of frequent testing [11, 12]. Deciding whether to observe or treat patients with low-level disease is beyond the scope of this chapter. However, we will address strategies to optimize detection of disease in high-risk patients while minimizing over-testing in lower-risk groups and those with excellent responses to therapy. Unless otherwise indicated, the terms low risk, intermediate risk, and high risk used in this chapter refer to the risk categories proposed by the American Thyroid Association (ATA) in 2009 and updated in 2015 [13].

Goals and Guiding Principles of Surveillance

The goals of surveillance for individuals with DTC include:

1. Identification of recurrent or persistent disease before the development of disease-related symptoms or signs
2. Identification of recurrent or persistent disease when it can be treated with low-risk, less invasive intervention (as opposed to delay in detection that might lead to a higher-risk, more invasive intervention with greater treatment-related morbidity)
3. Reduction in mortality, which is particularly relevant to higher-risk patients

As mentioned previously, the challenge lies in knowing which patients will derive clinically meaningful outcomes—reduction in morbidity and/or mortality—from finding disease recurrence at an earlier stage. In general, higher-risk patients, including those with more advanced disease at presentation, more aggressive histologic variants, and older age at presentation, benefit the most from early detection of disease and by implication from more aggressive surveillance protocols [10, 13]. Other chapters address in greater

detail what treatments have been associated with improved outcomes in subsets of thyroid cancer patients. But most available data for meaningful clinical endpoints in thyroid cancer treatments is retrospective, or derived from prospective cohort studies; randomized controlled trials are not available except in advanced cancer patients with shortened lifespans in whom the impact of treatments on disease-free progression and survival can be studied in a reasonable time frame [14].

Thus, it is critical that providers who care for thyroid cancer patients be familiar with the characteristics of the surveillance tests being ordered and counsel patients about the possible results in an anticipatory fashion. With every test ordered, the ordering provider(s) should discuss in advance the next steps in the case of positive, negative, indeterminate, or conflicting results. For patients with known but slowly progressive disease, the frequency and type of monitoring, as well as thresholds for intervention, should be determined in conjunction with a multidisciplinary team, typically including endocrinology, surgery, nuclear medicine, oncology, and/or radiation oncology. The benefits of intervention (whether additional treatment or intensified surveillance) for concerning findings should be weighed against the risks, not just for the treatment or surveillance methods in question, but for the particular patient being monitored.

The remainder of this chapter is organized into two parts.

Part I will review principles and components of stimulated testing and describe the available surveillance options in turn. Interpretation, advantages, and limitations of each surveillance method will be discussed. Table 22.1 summarizes the key aspects of this discussion for reference.

Part II will describe the rationale for and potential harms of surveillance and the general approach based on initial risk stratification and subsequent response to initial therapy.

Table 22.1 Summary of surveillance methods for differentiated thyroid cancer

Surveillance method	Description	Advantages/benefits	Disadvantages/limitations
Thyroglobulin (Tg)	Protein product of thyroid follicular cells	Most sensitive method for detecting the presence of disease, particularly after stimulation with rhTSH or THW	Wide variability between assays
	Measured in the serum by IMA, RIA, or LCMS. IMA is most common commercial method	Specific marker of thyroid follicular cells	TgAb interference occurs in up to 25% DTC patients, precluding reliable interpretation
		Degree of elevation and rapidity of rise (doubling time) is a rough indication of disease burden particularly in differentiated disease	Does not localize disease
Neck ultrasound (neck US)	High-frequency sound waves are transformed into high-resolution 2-D digital images of the thyroid bed and cervical lymph node compartments	No radiation exposure	Operator dependent
		Best method for detection of structural disease in cervical lymph nodes or thyroid bed	Clinical significance of small abnormal lymph nodes or residual tissue in thyroid bed is unclear, especially in low-risk patients with low or undetectable Tg
		Easily coupled with FNA for suspicious lesions	

(continued)

Table 22.1 (continued)

Surveillance method	Description	Advantages/benefits	Disadvantages/limitations
Whole-body scan (WBS)	Nuclear medicine planar imaging is obtained after administration of an isotope of radioiodine (I-123 or I-131)	Functionally localizes iodine-avid areas of thyroid cancer or thyroid tissue	Less sensitive than serum thyroglobulin and neck ultrasound for low-level disease
		Can be coupled with SPECT to correlate function and anatomy of areas of interest	Will not identify non-iodine-avid disease
			Requires preparation with TSH stimulation and LID
Computed tomography (CT)	X-ray attenuation is used to calculate the value of pixelism, which becomes translated into an image	Anatomically localizes structural disease	Ionizing radiation exposure
		Particularly useful for bulky or posterior neck disease or metastases to lung and mediastinum	Iodinated contrast exposure
Magnetic resonance imaging (MRI)	Body tissues that contain hydrogen atoms (e.g., in water) are made to emit a radio signal which are detected by the scanner. Search for "magnetic resonance" for physics details	Anatomically localizes structural disease	Expensive compared to CT
		Particularly useful for bulky or posterior neck disease or metastases to brain, bone, and liver	Contraindicated in patients with metal implants or cardiac pacemakers
		No ionizing radiation	
Positron emission tomography (PET)	Nuclear medicine imaging is obtained after administration of radiolabeled glucose (18-FDG)	Can functionally localize radioiodine-avid and non-avid disease within or outside the neck	Blood glucose cutoff to perform the study may complicate testing in patients with uncontrolled diabetes or hyperglycemia
		Useful for prognostication as well as disease detection	FDG-avid areas may not be thyroid cancer (risk of false positives)
		Can be coupled with CT to correlate function and anatomy of areas of interest	

Part I: Surveillance Methods

Stimulated Testing

General Principles and Rationale

Surveillance for differentiated thyroid cancer can be performed under unstimulated or stimulated conditions. Unstimulated testing refers to testing that is performed while the patient continues to take thyroid hormone at replacement or TSH-suppressive doses. Hence, unstimulated testing is also known as testing "on suppression." Stimulated testing refers to testing that is performed after thyroid hormone withdrawal (THW) for a time period sufficient to raise endogenous serum TSH > 30 mIU/L[1] [17, 18] or after administration of exogenous recombinant human TSH (rhTSH or Thyrogen®) [19]. These methods of stimulation are known as withdrawal-based testing and rhTSH-based (or Thyrogen®-based) testing, respectively. The purpose of stimulated

[1] A TSH goal of >30 mIU/L is commonly used in preparation for treatment with radioiodine or diagnostic testing and is endorsed by major thyroid organizations, but the exact TSH associated with the best DTC ablation or detection rates has not been definitively established [13, 15, 16]. Some data suggests that a TSH of >25 mIU/L may be adequate [8].

testing is to increase the sensitivity of the surveillance method in question, i.e., the likelihood of finding residual or recurrent disease.

Of the surveillance methods described below, whole-body iodine scanning is the only test performed solely under stimulated conditions. The sodium-iodine symporter responsible for uptake of iodine into thyroid follicular or epithelial cells is directly stimulated by TSH [20]. Residual thyroid cells—normal or cancerous—are therefore unlikely to take up radiolabeled iodine unless TSH is raised endogenously or administered exogenously. Moreover, it is also recommended that a period of dietary iodine restriction with low-iodine diet (LID) be undertaken prior to whole-body iodine scanning, again to facilitate uptake of radiolabeled iodine into any remaining thyroid cells. Data for LID is less robust than that for raising the TSH, but the potential for enhancing sensitivity of WBS is felt to outweigh the relatively limited harms (primarily inconvenience and unpalatable diet) of dietary iodine restriction [21].

Serum thyroglobulin can be measured on suppression or after stimulation. The sensitivity of thyroglobulin for detection of disease is greater with stimulation, since TSH stimulates the release of the thyroglobulin protein from thyroid epithelial or follicular cells into the bloodstream [4]. With the advent of "ultrasensitive" thyroglobulin assays, stimulated thyroglobulin testing can be deferred in many low-risk patients with no clinical or radiographic evidence of disease with undetectable thyroglobulin on suppression [22]. But for patients at intermediate or high risk for thyroid cancer recurrence, or those with a moderate to high pretest probability for recurrence, stimulated thyroglobulin measurement remains a powerful tool for detection [4].

Anatomic imaging studies—which include neck ultrasound and cross-sectional imaging (CT, MRI)—do not change based on serum TSH. Hence, there is no need to perform these tests under stimulated conditions. Positron emission tomography (PET) scanning, a functional imaging technique that visualizes uptake of a radiolabeled analog of glucose (^{18}F-FDG) into areas with high metabolic activity, may demonstrate improved sensitivity under stimulated conditions. Elevated TSH is known to induce expression of glucose transporters in thyroid follicular cells, resulting in greater visualization on PET [23]. This effect, however, is not as pronounced as the effect of elevated TSH on the sodium-iodine symporter. Thus, raising serum TSH is not essential for PET, in contrast to the conditions required for whole-body iodine scanning [7]. The decision to recommend stimulation with THW or rhTSH prior to PET should be based on the individual clinical scenario. Patients who are already undergoing THW or rhTSH in preparation for stimulated thyroglobulin and WBS, and in whom PET is also needed, would not experience any additional logistical or preparation burden for a stimulated PET and might benefit from improved diagnostic yield. Likewise, patients in whom disease was previously detected on stimulated PET may need to be followed with repeat stimulated PET to adequately assess response to therapy on an analogous exam.

Figures 22.1 and 22.2 provide detailed timelines for preparation of DTC patients for stimulated testing with THW or rhTSH, respectively.

THW Versus rhTSH

Evidence for THW in general, as well as for various withdrawal protocols, comes largely from patients being prepared for treatment with radioiodine rather than from patients being prepared specifically for diagnostic or surveillance testing. In early observational studies, endogenous elevation of TSH to >30 mIU/L appeared necessary for thyroid remnants to significantly concentrate administered radioiodine [17]. More recently, two randomized controlled trials reported that either directly stopping levothyroxine for 4–5 weeks or substituting levothyroxine with liothyronine for the initial 2–3 weeks resulted in similar short-term quality of life and hypothyroidism symptom scores; and in patients being prepared for treatment, rates of successful ablation were similar [18, 24]. One of the RCTs included patients being prepared for diagnostic scanning, but the number of patients was very small, and the ability to detect residual or recurrent disease or persistent thyroid tissue was not specifically studied [24].

Time from diagnostic RAI dose	4–5 week prior	3–4 week prior	2 week prior	3–5 days prior	Day of diagnostic RAI dose	24–48 h later	After dWBS, if no treatment is planned
Step number	1. Stop LT4 + start LT3 (if transition to LT3 is desired)	2. Stop LT4 (if transition directly from LT4 to THW is desired)	3. Start LID (and stop LT3 if patient is taking LT3)	4. Obtain serum TSH*, Tg, and TgAb	5. Administer diagnostic dose of I-123 or I-131	6. Obtain dWBS	7. Resume regular diet and LT4

Fig. 22.1 Sample timeline for THW-based testing. *If TSH is <30, repeat in 3–5 days and defer dWBS until TSH is ≥30; also repeat Tg and TgAb when TSH is ≥30. *Note*: Steps 3, 5, and 6 can be omitted if only a stimulated Tg is desired, i.e., without dWBS. *THW* thyroid hormone withdrawal, *RAI* radioiodine, *LID* low-iodine diet, *LT4* levothyroxine, *LT3* liothyronine, *dWBS* diagnostic whole-body scan

Time from diagnostic RAI dose	2 week prior	48 h prior	24 h prior	Day of diagnostic RAI dose	24–48 h later	72 h after second rhTSH injection	After dWBS, if no treatment is planned
Step number	1. Start LID	2. rhTSH 0.9 mg IM	3. rhTSH 0.9 mg IM	4. Administer diagnostic dose of I-123 or I-131	5. Obtain dWBS	6. Obtain serum Tg and Tg Ab	7. Resume regular diet

Fig. 22.2 Sample timeline for rhTSH-based testing. *Note*: Steps 1, 4, and 5 can be omitted if only a stimulated Tg is desired, i.e., without dWBS. *rhTSH* recombinant human TSH, *RAI* radioiodine, *LID* low-iodine diet, *dWBS* diagnostic whole-body scan

The extremely favorable prognosis of most cases of DTC, coupled with the rapidly increasing incidence and detection of low-risk tumors since the early 1990s, intensified interest in surveillance protocols that were safe and better preserved quality of life. Specifically, there was a need for methods to raise serum TSH without inducing clinical hypothyroidism. Bovine TSH proved effective but was abandoned due to the development of allergic reactions as well as TSH-neutralizing antibodies [25]. Reduction of daily levothyroxine to half the usual dose was proposed but not confirmed in large series. Moreover, this approach attenuated but did not entirely avoid the consequences of clinical hypothyroidism [26].

The large-scale production of recombinant human TSH became possible after the β-subunit coding of the TSH gene was cloned, allowing for overexpression of the encoded TSH protein in a cell system [27–29]. (TSH is a pituitary glycoprotein composed of an α-subunit shared by the pituitary gonadotropins FSH and LH and a hormone-specific β-subunit.) Recombinant human TSH has the same biologic properties as native TSH and an identical amino acid sequence, but is less glycosylated and has more sialic acid. While these differences result in a lower affinity of rhTSH to the TSH receptor compared to endogenous TSH [27], preclinical in vitro and animal studies demonstrated that rhTSH increased serum T4 and T3 and stimulated radioiodine uptake into thyroid cells [30, 31]. Additional studies showed that rhTSH was a potent stimulus for T4, T3, and thyroglobulin release in normal human subjects [32, 33].

Initial clinical trials of rhTSH in DTC patients included several phase I/II studies for dose-finding and pharmacokinetics [34], followed by two phase III studies which established its safety and efficacy in this population [19, 35]. The first phase I/II study was completed in 1994 in 19 patients following thyroidectomy. It showed that rhTSH administration at doses of 0.9–3.6 mg for 1–3 days produced iodine scans of equal quality and with similar number of abnormal uptake sites in 63% of subjects. Serum thyroglobulin more than doubled in 73% after rhTSH, though the absolute rise in TSH was lower after rhTSH compared to THW in most subjects [34].

The first phase III study was conducted between 1992 and 1995 across multiple centers in the USA. One hundred twenty-seven thyroid cancer patients underwent two ^{131}I whole-body scans, the first after rhTSH (0.9 mg IM for two consecutive days) while remaining on levothyroxine and the second after withdrawal from thyroid hormone. Compared to THW, preparation with rhTSH was associated with significantly fewer symptoms of hypothyroidism, but in 29% of patients was less sensitive for detecting residual or recurrent disease by ^{131}I whole-body scan. The study may have been limited by the high percentage of negative scans (51% of patients) and scans with uptake in the thyroid bed only (72% of those with a positive scan), as well as by variation in the diagnostic dose of ^{131}I and a lack of inclusion of serum thyroglobulin as an endpoint [35].

The second phase III study, performed across multiple centers in the USA and Europe, addressed some of these limitations. It was designed to compare two different dose regimens of rhTSH, as well as compare rhTSH-stimulated results to THW-based results. A total of 229 thyroid cancer patients were randomized; those in arm I received two injections of 0.9 mg on two consecutive days, and those in arm II received three injections of 0.9 mg 3 days apart. Serum thyroglobulin was included as an endpoint, both alone and in combination with WBS. The dose of ^{131}I was fixed at 4 mCi and scanning procedures were standardized. Peak serum TSH concentrations occurred 24 h after the last rhTSH injection in both groups, though elevation of TSH persisted for longer in arm II than in arm I (9 days versus 4 days). Peak thyroglobulin levels occurred 3 days after the last rhTSH injection in arm I and 1–3 days after the last rhTSH injection in arm II. In both groups, the peak thyroglobulin was lower after rhTSH than after THW. Overall, 89% of patients had concordant scans, 16% had superior scans after THW, and 4% had superior scans after rhTSH. There was no difference between the two dosage regimens of rhTSH, suggesting the more convenient two-dose regimen could be used. The combination of serum thyroglobulin and WBS after rhTSH identified 100% of patients with metastatic disease and 93% with uptake in the thyroid bed. Moreover, a thyroglobulin cutoff of 2 ng/mL predicted thyroid bed uptake in 52% of patients and metastatic disease in 100%. Similar to prior studies, rhTSH preparation resulted in a much better quality of life, and it did so without causing significant side effects or anti-rhTSH antibodies [19].

On the basis of these studies, rhTSH was approved in the USA in 1998 and Europe in 2001 as a diagnostic tool in patients being tested for persistent or recurrent well-differentiated thyroid cancer [36]. Since its approval, multiple published studies have confirmed its efficacy and safety. As compared to THW-based regimens, rhTSH-based preparation has been associated with significant improvements in multiple quality of life measures [37, 38] and in some cases (particularly the elderly and those with underlying medical illness that are exacerbated by hypothyroidism) avoidance of the significant medical consequences of THW [39]. Another advantage of rhTSH compared to THW is the shorter duration of exposure of any remaining cancer cells to high levels of TSH, with potential to minimize the risk of residual tumor growth [40]. Indeed, suppression of TSH with supraphysiologic doses of thyroid hormone is one of the mainstays of long-term management of DTC. It thus follows that limiting exposure to elevated TSH levels might be beneficial.

Given similar rates of disease detection in most patients, and clearly improved quality of life with use of rhTSH compared to THW, under what circumstances might THW be selected instead of rhTSH to prepare a patient for stimulated surveillance studies? There have been several reports of acute swelling of known thyroid cancer lesions after rhTSH [41, 42], presumably due to the rapid surge in TSH that resulted in clinical compromise. Thus, THW might be considered if there is a strong suspicion for residual or recurrent disease in or near critical structures. Examples include metastases to the brain or near the spinal cord or skeletal metastases in weight-bearing bones susceptible to fracture. However, swelling at such sites, particularly in patients with a history of large-volume or bulky disease, is not unique to rhTSH stimulation. It is well known to occur after endogenous TSH stimulation with THW as well. Fortunately, serum thyroglobulin and imaging studies on levothyroxine suppression are usually already positive in patients with significant residual disease, or the clinical history and past treatment record indicate patients who are at higher risk. In such cases, administration of glucocorticoids prior to stimulation with rhTSH or THW may prevent or mitigate tumor expansion [43].

Financial or logistical circumstances may favor THW over rhTSH in select situations. On a societal level, the high cost of rhTSH may be balanced or offset by the decrease in morbidity and increase in productivity (e.g., fewer missed work days) associated with avoiding prolonged hypothyroidism. Several but not all studies examining this issue have concluded that rhTSH for these reasons represents good value for money, with the benefit to patients and society obtained at modest net cost [38, 44–46]. On an individual level, however, rhTSH is not affordable to everyone. rhTSH is expensive, with costs and insurance reimbursement rates varying widely among different countries. In the USA, for example, patients without insurance or those with high out-of-pocket costs of medication may be unable to afford rhTSH injections [45].

From a logistical perspective, the extra clinic or hospital visits required for rhTSH-based preparation may not be feasible, particularly if the patient's primary residence is located far from the site of rhTSH administration. Patients, who tolerate THW well but cannot attend four visits within a single week for rhTSH injections, WBS, and thyroglobulin measurement, may opt for THW since the scan and stimulated thyroglobulin can be obtained with only two visits [8]. Finally, while not a reason in itself to select THW over rhTSH, it should be noted that rhTSH-based surveillance is more time sensitive than THW-based withdrawal. Diagnostic dose of ^{131}I should be given 24 h after the second rhTSH injection (with images obtained 48 h after the ^{131}I), and measurement of stimulated thyroglobulin should be done approximately 72 h after the second rhTSH injection [8]. If the patient misses any of these critical appointment times, rhTSH must be readministered (which may not be feasible due to cost) before obtaining WBS and stimulated thyroglobulin. By contrast, patients withdrawn from thyroid hormone may undergo WBS and serum thyroglobulin measurement any time after the serum TSH reaches >30 mIU/L, allowing for greater flexibility in case of unanticipated delays. Similarly, if there is a high suspicion for residual disease necessitating a therapeutic dose of ^{131}I, preparation with THW may be preferred, since the therapeutic dose could be administered soon after the diagnostic WBS and thyroglobulin results are available. For patients prepared with rhTSH, an additional two injections of rhTSH (or subsequent THW) would be needed to treat any disease detected on surveillance testing.

Overall, rhTSH-based preparation for stimulated surveillance studies is preferred over THW in most situations. A good understanding of the specific advantages and limitations to each approach allows for identification of patients who may benefit (or are unlikely to suffer significant harm) from THW, thus facilitating a patient-centered approach that includes informed decision making.

Low-Iodine Diet

It is recommended that patients follow a low-iodine diet (LID) prior to whole-body radioiodine scanning for treatment or diagnostic

purposes, to facilitate increased uptake of radioiodine into any remaining thyroid cells. This recommendation is based primarily on observational studies of patients who followed an LID in preparation for remnant ablation or treatment with ^{131}I [21]. No studies have specifically examined the efficacy or safety of LID in patients undergoing surveillance WBS.

Of 8 studies examined in a systematic review, in most cases, patients were restricted to < 50 mcg of dietary iodine per day for 1–2 weeks, though the duration of the LID varied from 4 days to 4 weeks. All LIDs studied were associated with significantly lower urinary iodine excretion, as well as increase in ^{131}I uptake into residual thyroid or tumor, compared to diets free of iodine restriction [21]. In two of the studies included in the review, using an LID for 2 weeks resulted in an approximate 50% reduction in mean urinary excretion compared to the same diet for 1 week [47, 48]. (A subsequent study published after the review paper showed that a 3-week LID did not result in any further reduction in mean urinary excretion compared to a 2-week LID [49].) Only one study in the review paper examined LID in combination with rhTSH administration; the remainder used LID in conjunction with THW [21, 47]. While urinary iodine excretion significantly decreased after 2-week LID with rhTSH, the reduction was not as robust as the same 2-week LID with THW [47]. The addition of diuretic therapy to LID did not appear to further lower urinary iodine measurements in the one study that measured urinary iodine with and without concurrent ethacrynic acid [50].

No investigators have specifically studied whether using an LID for remnant ablation or treatment improves long-term disease recurrence or mortality. There is some evidence that remnant ablation is more successful with LID, but data is conflicting and for the most part derived from retrospective analyses that used historical controls [51, 52]. In terms of safety, only one study included in the systematic review reported on side effects of LID, noting that the only complaint from participants was the "boring" nature of the diet [53]. No other adverse effects were noted. However, multiple cases of severe, potentially life-threatening hyponatremia following an LID have been reported [54, 55]. Most such cases involve elderly patients who were withdrawn from thyroid hormone, frequently in the presence of metastases to the lung or brain and in some instances treated simultaneously with thiazide diuretics. Duration of diet was also greater than 1 week in the majority of cases where hyponatremia developed [56].

In summary, despite the inconvenience of LIDs, the demonstrated reduction in urinary iodine excretion and increase in radioiodine uptake supports their use for 1–2 weeks prior to surveillance WBS. For elderly patients, particularly those with known thyroid cancer metastases, measures should be undertaken to minimize the risk of dangerous hyponatremia, including avoidance of co-administered diuretics, possible limitation of LID to 1 week, and consideration of stimulation with rhTSH instead of THW. It is also important to communicate to patients that "low-iodine" diet does not imply a "low-sodium" diet; non-iodized salt is permitted and can mitigate the risk of hyponatremia. Descriptions of low-iodine diets and general instructions can be found at several websites, including that of the American Thyroid Association (http://www.thyroid.org/low-iodine-diet/) and the Thyroid Cancer Survivors' Association (http://www.thyca.org/pap-fol/lowiodinediet/).

Finally, ascertaining exposure to high amounts of iodine in the weeks to months preceding WBS—through vitamins, dietary supplements, or iodinated contrast medium including that given during contrast-enhanced CT scan or cardiac catheterization—is particularly important. If such exposures have occurred, an LID for a few weeks will be insufficient for adequate radioiodine uptake. The WBS would need to be delayed until the exogenous iodine load has been excreted, which could be assessed by serial measurements of urinary iodine excretion or waiting at least 4–6 weeks. Although studies of patients with intact thyroid glands have shown that total body iodine stores are increased for several months following iodinated contrast exposure, a study conducted in thyroid cancer patients following thyroidectomy demonstrated that the urinary iodine excretion returned to normal by 4 weeks [57].

Serum Thyroglobulin

Thyroglobulin is the precursor glycoprotein from which thyroid hormone is synthesized, following iodination of its tyrosine residues and coupling of mono- and diiodotyrosines. It is co-secreted into the circulation from the normal thyroid epithelial cells along with thyroid hormone. It is also produced by almost all differentiated thyroid cancer, but not by other tissues or cancers. Thus, a detectable thyroglobulin indicates the presence of functioning thyroid epithelial cells, either from normal thyroid tissue or from a follicular cell-derived thyroid cancer. Its absence is generally reassuring for DTC remission, cure, or stability, depending on the clinical risk status of the patient [20].

There are several reasons why serum thyroglobulin has emerged as the most powerful tool in the long-term follow-up and surveillance of differentiated thyroid cancer. It is the most sensitive method for detection of disease, particularly when measured after stimulation with rhTSH or THW; it retains high specificity in patients who have undergone thyroidectomy and remnant ablation; and it correlates with the extent of tumor or disease burden in many cases [58].

Most thyroglobulin assays currently in use are "second-generation" assays that have functional sensitivities of ≤0.1 ng/mL, compared to earlier "first-generation" assays with functional sensitivities of 1 ng/mL [5]. Multiple studies have shown that a single stimulated thyroglobulin of <0.5–1.0 ng/mL in the absence of interfering antibodies carries a high likelihood—approximately 98–99.5%—of remaining disease-free on long-term follow-up [59–61]. By contrast, a stimulated thyroglobulin of >2 ng/mL is highly sensitive for identifying individuals with persistent disease [60]. Low-level stimulated thyroglobulin levels, i.e., those that are detectable but between 0.2 and 2 ng/mL, are generally followed over time if there is no clinical or radiographic evidence of disease. In such cases, the overall risk status of the patient and the trend in the thyroglobulin over time are important factors in determining the frequency and intensity of subsequent follow-up and the threshold for additional treatment [59, 62]. Progressive increases in thyroglobulin or short doubling time suggests that the remaining disease is likely to become clinically apparent [63, 64].

Very low or undetectable thyroglobulin values on suppression in assays with functional sensitivities of 0.1–0.2 ng/mL may obviate the need to obtain stimulated thyroglobulin values [65–67]. Suppressed thyroglobulin of <0.1 ng/mL in one study using a sensitive assay was associated with an rhTSH-stimulated thyroglobulin of >2 ng/mL in only 2% of cases [22]. Minimally detectable thyroglobulin values on suppression—in the range of 0.2–0.3 ng/mL—are associated with a higher but still overall low risk of stimulated thyroglobulin rising to >2 ng/mL. More importantly, the chance of finding clinically relevant disease in such patients is very low [65, 68]. How then are we to utilize modern-day assays that detect extremely low levels of circulating thyroglobulin and still preserve enough specificity to avoid unnecessary subsequent testing and possibly even treatment? Receiver operator curves have demonstrated that thyroglobulin levels on suppression of 0.2–0.3 ng/mL are associated with an optimal balance of sensitivity and specificity for detecting persistent disease [69]. Thus, patients with suppressed thyroglobulin levels in this range, negative thyroglobulin antibodies, and low clinical suspicion of disease may be followed without stimulated testing. For higher levels of thyroglobulin on suppression, in the range of 0.3–1 ng/mL, stimulated testing is still recommended since 20% will have a stimulated thyroglobulin of >2 ng/mL, and approximately one-third of these patients will be found to have persistent or recurrent disease [70].

Beyond its primary role in disease detection, thyroglobulin may also be useful for estimating residual disease burden in some patients. It has been estimated that 1 g of normal or differentiated neoplastic thyroid tissue increases the serum thyroglobulin by ~0.5 ng/mL when TSH is suppressed to <0.1, by ~1 ng/mL when TSH is normal, and by 2–10 ng/mL after rhTSH stimulation [71, 72]. This relationship has been studied primarily in individuals with clinically significant, macroscopic disease and in particular those with

metastases. It is uncertain to what degree low levels of residual or persistent disease, e.g., microscopic disease in the cervical lymph nodes, will quantitatively raise thyroglobulin.

There are several important limitations to the use of serum thyroglobulin in the long-term follow-up of thyroid cancer patients. One is the continued variance in thyroglobulin assays among different laboratories, resulting in significant differences in thyroglobulin values measured on the same sample. Substantial variance can be seen regardless of type of assay used, including immunometric assay (IMA, the most commonly used), radioimmunoassay (RIA, less widely available, and perhaps less sensitive with low-level disease), or more recently liquid chromatography-tandem mass spectrometry (LCMS, least used at present) [5, 73, 74]. To limit potential variance, it is recommended that IMAs and RIAs be calibrated against the CRM-457 international standard. However, even with standardization, assays from different laboratories can differ by up to twofold, presumably due to the heterogeneity of the thyroglobulin protein and differences in the epitopes targeted by each assay. The clinical implication of this variation is that serum thyroglobulin levels in an individual patient should be measured longitudinally in the same laboratory whenever possible [5]. If serum thyroglobulin concentration must be measured in a different laboratory, for example, due to institutional change in methodology or patient relocation to a new care provider whose laboratory uses a different assay, the initial thyroglobulin level measured on the new assay should be treated as the patient's new baseline. Any discordance from prior measurements should not be taken as absolute evidence of a true change in clinical status, but rather interpreted in light of the entire clinical picture.

The most challenging limitation encountered in serum thyroglobulin testing is the presence of antithyroglobulin autoantibodies (TgAbs), which are detectable in approximately 10% of the normal population [75] and around 25% of patients with differentiated thyroid cancer [76, 77]. These autoantibodies can cause false-negative or false-positive thyroglobulin results, depending on assay used, making thyroglobulin an unreliable marker of thyroid cancer in patients who harbor them. It is unclear why the prevalence of these antibodies is higher in patients with thyroid cancer than in normal individuals. Individuals with history of autoimmune thyroid disease, or with the background of Hashimoto's thyroiditis on surgical pathology, are more likely to be TgAb positive [78]. In addition to TgAb, heterophile antibodies (primarily human anti-mouse antibodies or HAMAs) can also interfere with thyroglobulin measurement. The prevalence of HAMA is much less common (~ 0.5%) in thyroid cancer patients compared to TgAb and when present tends to falsely elevate the measured thyroglobulin level on immunometric assays. HAMA is not routinely measured but can be ordered if there is clinical suspicion, for example, if a low-risk, TgAb-negative patient with DTC and previously negative thyroglobulin is found to have a newly elevated serum thyroglobulin without any other evidence of recurrence [5, 79].

Unfortunately, there is no method that entirely overcomes interference from TgAb or HAMA. IMA is the assay type that is most affected. In the presence of TgAb, the thyroglobulin level on an IMA is usually falsely undetectable or low [80]. Thus, an "undetectable" thyroglobulin by IMA in a TgAb-positive patient cannot be interpreted as absence of disease. A detectable thyroglobulin level on IMA generally indicates that thyroglobulin is present, but its true concentration may be underestimated. Evidence for the use of "recovery assays" to detect potential interference in TgAb-positive patients is conflicting, so their use is generally discouraged [79, 80]. RIAs are less prone to interference from TgAb, but can still be affected. Unlike IMAs, however, RIAs usually produce falsely elevated thyroglobulin results if they are affected by TgAb [81–83]. Detectable thyroglobulin on RIA in a TgAb-positive patient therefore should not be used as the sole factor for determining the presence of residual thyroid tissue or tumor.

Most recently, an LCMS assay for thyroglobulin has been developed and may be able to accurately measure thyroglobulin even in the presence of thyroglobulin antibodies. Longer-term data regarding these assays' sensitivities,

correlations with immunoassays, and relationship to disease remission or persistence will help determine their role in the follow-up of differentiated thyroid cancer [84].

In the meantime, following the trend (i.e., the concentration) of thyroglobulin antibodies over time in patients who are antibody positive is useful. Thyroglobulin antibodies should be quantified using the same laboratory assay whenever possible because there is substantial variation in their measurement among different assays, just as occurs with measurement of thyroglobulin itself [79]. Progressively decreasing levels of thyroglobulin antibodies may indicate disease remission, or at least a low or declining tumor burden. Thyroglobulin antibodies usually become undetectable at a median of about 3 years in initially antibody-positive patients who remain disease-free [85, 86]. By contrast, increasing thyroglobulin antibody levels, or the emergence of thyroglobulin antibodies in a patient who was previously thyroglobulin antibody negative, raises concern for recurrent disease.

A final limitation to the use of thyroglobulin is its low production by some thyroid cancers, often but not always those with more aggressive histology or those that have become dedifferentiated. Sometimes low tumoral thyroglobulin production can be predicted preoperatively, for example, if a patient with known thyroid cancer has an unexpectedly normal or low-normal serum thyroglobulin even before thyroidectomy [72]. In other instances, poor thyroglobulin production by remaining tumor is suspected based on clinical or radiographic grounds, for example, if residual tumor is detectable on an imaging study in the absence of significantly elevated thyroglobulin. Patients whose cancers are "poor thyroglobulin producers" require more frequent surveillance by imaging studies.

Neck Ultrasound

The cervical lymph nodes are the most common site of spread outside the thyroid gland for papillary thyroid cancer. The majority of patients with PTC have cervical node involvement at the time of diagnosis, though in many cases these are not apparent preoperatively or at the time of initial surgery and often do not change the overall patient prognosis. This is particularly true of nodal micrometastases (those <2 mm) [87–89]. Likewise, ~90% of all recurrences of PTC occur in the cervical lymph nodes; and cervical lymph node recurrences have been reported in ~30% of patients. The central neck lymph nodes are more commonly involved than those in the lateral neck, but both central and lateral neck lymph node involvements are far more common than distant metastases in PTC [90]. The prevalence of cervical lymph node metastases is much lower in follicular thyroid cancer, on the order of 10%, and more commonly with the Hürthle cell subtype of FTC [91]. As papillary cancer comprises the great majority of DTC, an imaging modality that accurately identifies central and lateral lymph node metastases is essential in the surveillance of thyroid cancer patients.

Cervical ultrasonography has emerged as the most sensitive imaging method for detecting cervical lymph node metastases. Indeed, it has become the primary structural imaging modality for patients with differentiated thyroid cancer [13, 15, 16]. Using a high-resolution probe, with frequency of ≥10 MHz, abnormal lymph nodes as small as 2–3 mm can be detected [6]. No specific patient preparation in terms of diet and laboratory values is needed. Additional advantages compared to other imaging techniques include its noninvasive nature, lack of associated exposure to radiation, and permitted use in patient populations in whom radiation-emitting or contrast-based studies may be contraindicated (including pregnant and breastfeeding patients or those with advanced kidney disease). Moreover, it is the only imaging modality that can readily be coupled with fine-needle aspiration of any identified suspicious lesions [92].

If abnormal small cervical lymph nodes <5–7 mm in short axis are detected, close observation is generally recommended, as such lymph nodes may remain stable for long periods of time [93, 94]. Further, surgical resection may fail to produce a biochemical remission in up to 73% of patients [95]. If abnormal cervical lymph nodes measuring ≥8–10 mm in size are detected, fine-needle aspiration is general recommended,

assuming that confirmation of disease would lead to change in management. In 80% of cases of cervical lymph node metastases, cytology is confirmatory. The diagnostic yield is improved when measurement of thyroglobulin in the aspirate fluid (Tg-FNA) is performed in addition to cytology [96, 97]. Tg-FNA samples are typically obtained by washing 1 mL of normal saline through the needle used for fine-needle aspiration into a sterile plain tube or container, after the contents of the biopsy needle have been placed onto a slide for cytology. The ability to measure thyroglobulin in the aspirate fluid is especially advantageous in patients with circulating thyroglobulin antibodies. Unlike serum thyroglobulin measurement, the measurement of thyroglobulin in cervical lymph node fluid is not affected by circulating thyroglobulin antibodies [98]. A thyroglobulin level of 1–10 ng/mL in aspirate fluid is considered suspicious for malignancy, and a value of >10 ng/mL is highly likely to represent DTC that has spread to the aspirated lymph node [99, 100].

Features concerning for recurrence in the thyroid bed include ovoid shape of a lesion in the longitudinal plane (and taller than wide in the transverse plane), hypoechogenicity, microcalcifications, irregular borders, and increased vascularization [101]. Features most concerning for cervical lymph node metastases include cystic appearance, microcalcifications (hyperechoic punctuations), and peripheral vascularization [15]. These lymph node findings have specificities in the range of 80–100%, thereby justifying fine-needle aspiration when present individually or in combination in a lymph node measuring 8 mm or larger [102]. Lymph nodes that have lost their normal hyperechoic fatty hilum, and those that are round in shape or hypoechoic, are considered suspicious, but in the absence of other concerning features are less specific for malignancy. Thus any one of these latter findings, if present in isolation, does not automatically warrant fine-needle aspiration [13, 15, 103].

It is critical that abnormalities on neck ultrasound be interpreted in the context of the patient's clinical picture and pretest probability of disease. In low- and intermediate-risk patients with an undetectable serum thyroglobulin, the risk of lymph node recurrence is <2% [15]. Minor abnormalities are more likely to represent false-positive findings than true disease in this population, and even in the case of true disease, the clinical significance of small recurrences <8–10 mm is unclear [104]. A substantial portion of patients in this category may experience stability or regression of the abnormal cervical nodes over time, bringing into question the benefit of intervention, and supporting a strategy of continued observation. On the other hand, abnormal lymph nodes in patients with detectable or elevated thyroglobulin are more likely to grow or become clinically significant over time, warranting at minimum attempts at diagnostic aspiration [105].

The main limitation of cervical ultrasound is its dependence on the skill of the operator. A thorough ultrasound exam must include evaluation of the thyroid bed as well as the central and lateral cervical lymph node compartments. Individuals performing ultrasound should be specifically trained and experienced in thyroid disease and pathology, including imaging of the postoperative neck, in order to approximate the high sensitivity of neck ultrasound reported in the literature [92]. Traditionally, dedicated sonographers within radiology departments performed most neck ultrasounds. However, with the rising use of neck ultrasound in thyroid cancer surveillance, and the growing recognition that abnormal findings may be best interpreted in the context of the patient's entire clinical picture, endocrinologists and surgeons who care for thyroid cancer patients are increasingly performing their own office-based neck ultrasounds. Office-based ultrasound also allows for "real-time" manipulation of the probe, with improved ability to identify abnormalities that are concerning for recurrence and distinguish them from less concerning findings such as postoperative scar or suture-related granuloma [106]. If abnormal findings are reported from a center with less thyroid disease experience, or normal findings are reported in the setting of a high clinical suspicion for recurrence, the images should be reviewed by a center or provider with specific training in thyroid cancer and a high volume of DTC patients.

Whole-Body Scanning

Iodine-131 has occupied a central diagnostic and therapeutic role in the management of patients with differentiated thyroid cancer since its discovery in 1938. It is taken up by normal thyroid as well as most differentiated thyroid cancer cells, emitting ~10% of its energy and dosage via gamma radiation that can be visualized by gamma camera. [The other 90% of its dosage undergoes beta decay, which does not contribute to visualization but does cause destruction of immediately surrounding tissue at higher doses.] Another radioisotope of iodine, ^{123}I, emits primarily gamma radiation and is thus used for diagnostic but not treatment purposes. It has a shorter half-life and may produce superior images, but since it is more difficult to create compared to ^{131}I, it is also more expensive [107]. Regardless of the isotope used, diagnostic doses are usually in the range of 2–5 mCi, and diagnostic whole-body scan to visualize remaining thyroid tissue in the thyroid bed, neck, or distant sites is performed approximately 24 h (for ^{123}I) or 48 h (for ^{131}I) later. Planar images are produced [58].

The main advantage of dWBS as a functional imaging technique in the surveillance of DTC is its potential to identify the location of any remaining thyroid tissue, including neoplastic tissue, throughout the body. It is especially useful in determining whether known or suspected persistent or recurrent disease is radioiodine avid, allowing for prognostication and treatment planning [58]. When planar imaging is combined with SPECT/CT, functional and anatomic imaging can be superimposed, significantly increasing both the sensitivity and the specificity of the dWBS. Normal thyroid remnants may be better differentiated from lymph node metastases due to the presence of anatomic landmarks on SPECT/CT. Similarly, SPECT/CT can help determine lung versus rib uptake, as well as physiologic accumulation of ^{131}I in the gastrointestinal tract or bladder versus pathologic pelvic lesions [108, 109].

On the other hand, dWBS remains significantly less sensitive compared to serum thyroglobulin or cervical neck ultrasound, in particular for the detection of low-level disease [110–112]. Current evidence suggests that low-risk patients with no uptake outside the thyroid bed on post-treatment WBS (at 1 week after initial radioiodine treatment or remnant ablation), undetectable serum thyroglobulin and thyroglobulin antibodies while on thyroid hormone, and negative neck ultrasounds can forgo dWBS at the time of subsequent surveillance testing, since it is unlikely to yield additional useful information. Diagnostic WBS is usually still indicated in the follow-up of patients at intermediate or high risk for recurrence and for low-risk patients who do not fulfill the above criteria. Patients with large thyroid remnants, generally those demonstrating >2% uptake of the administered radioiodine dose, may also benefit from dWBS at the time of stimulated surveillance testing, since residual thyroid tissue can obscure visualization of cervical lymph node disease [113, 114].

Disadvantages of dWBS, in addition to its low sensitivity compared to serum thyroglobulin and cervical neck ultrasound, include the need for pre-procedure preparation with TSH stimulation by either thyroid hormone withdrawal or rhTSH stimulation, as well as with LID. The process of TSH stimulation carries risks of hypothyroid symptoms (for THW) and possible growth or swelling of remaining thyroid cancer (for either THW or rhTSH) [41, 115]. Both the TSH stimulation and LID components of preparation can be logistically challenging for patients. Further, patients are also exposed to radiation with dWBS. While the exposure is far less compared to therapeutic doses of radioiodine, the doses of ^{131}I administered for dWBS may cause "stunning" of remaining thyroid tissue, rendering these foci less amenable to uptake of future therapeutic doses of ^{131}I. When there is a concern for possible "stunning," ^{123}I can be used in place of ^{131}I for dWBS [116, 117]. Finally, aggressive or dedifferentiated forms of thyroid cancer—precisely the forms which are the most important to detect and treat—often lose their ability to concentrate iodine and are at high risk of being missed on dWBS. In some of these cases, an empiric high (or therapeutic) dose of ^{131}I can lead to detection of thyroid cancer location on the

1-week posttreatment WBS, but the clinical benefit to patients is unclear [118, 119].

CT and MRI

Since neck ultrasound coupled with serum thyroglobulin will detect most cases of persistent or recurrent disease, cross-sectional imaging with computed tomography (CT) or magnetic resonance imaging (MRI) is not necessary in the standard follow-up of most patients with differentiated thyroid cancer. These tests do, however, play important roles in several situations. CT scanning of the chest and neck is recommended when thyroglobulin is rising and neck ultrasound is negative, particularly in high-risk patients or when thyroglobulin exceeds 10 ng/mL [13]. Helical or spiral CT of the chest is the most sensitive test for detecting lung metastases, as it can detect micrometastases in the lung as small as 2 mm. It can be performed without contrast for parenchymal lesions. The addition of contrast allows for assessment of the mediastinum as well as the neck [120, 121]. In cases of known or suspected bulky neck disease, CT of the neck with contrast can complement neck ultrasound, as it can better delineate the extent of disease behind the trachea and in the mediastinum [120, 122]. Moreover, if neck CT was performed at baseline for a patient with bulky or posterior lymph node involvement at presentation, CT should be a part of the initial surveillance strategy, so as to allow direct comparison to prior images and follow response of specific disease foci to treatment.

MRI is also suitable for imaging of the neck and mediastinum and may be preferred over CT when there is concern about iodinated contrast administration [123–125]. Providers may seek to avoid iodinate contrast (1) when radioiodine treatment or diagnostic whole-body scanning is anticipated in the near future, as either would need to be deferred for at least 4 weeks after a contrast CT study [57], or (2) if preexisting renal dysfunction predisposes a patient to iodinated contrast-mediated kidney injury. MRI may also be preferred when aerodigestive tract disease is a possibility, as some studies indicate it is superior to CT scanning in this situation [126, 127].

If no abnormality is found in the neck or chest (the first and second most common sites of DTC spread, respectively) to explain a rising thyroglobulin, again focusing on high-risk patients or patients in whom thyroglobulin exceeds 10 ng/mL, MRI of the brain, MR skeletal survey, and/or MRI or CT of the abdomen should all be considered to localize the site of thyroglobulin production [20]. MRI is the most sensitive tool for detecting liver lesions and also for differentiating metastases from benign entities such as angiomas, cysts, or benign nodules [128].

There is no clear-cut rule for which imaging modality—CT, MRI, or PET (see below)—should be performed in patients who require or would likely benefit from additional surveillance beyond the "first-line" tests of serum thyroglobulin and cervical ultrasound. The decision is made based on a number of factors, including but not limited to suspected or most likely site of residual/recurrent disease, method by which extrathyroidal disease was first detected (if applicable), anticipated need for diagnostic or therapeutic iodine in the near future, preexisting renal disease, relative costs of each imaging technique, and access to these imaging modalities.

FDG-PET Scanning

FDG-PET imaging is a functional nuclear medicine test in which PET scanning is used to localize the uptake of 18F-fluorodeoxyglucose (FDG) following its intravenous injection. Metabolically active tissue utilizes glucose to a greater degree than inactive tissue, a principle that underlies the rapid expansion and now routine use of FDG-PET in staging and monitoring throughout oncology [7]. Unlike many other malignancies, however, most differentiated thyroid cancer is slow growing and lacks high levels of metabolic activity. Thus, FDG-PET is not a first-line staging or surveillance tool for most patients with DTC. In fact, the sensitivity of FDG-PET even in patients with a modestly elevated thyroglobulin is low, ranging from <10% to at most 30% in patients with a stimulated thyroglobulin of <10 ng/mL [129, 130].

However, FDG-PET is useful for detection of disease in high-risk DTC patients with serum thyroglobulin >10 ng/dL and negative radioiodine scans. The first report of localization of thyroid cancer by FDG-PET, published in 1987 [131], and several subsequent larger series of patients with DTC [132–134], all showed that FDG-concentrating lesions were more aggressive in their growth pattern than those that concentrated only radioiodine and that an inverse relationship between FDG avidity and radioiodine avidity existed for most of the detected lesions. This relationship may be explained by loss of the ability to transport and/or organify iodide but a gain in glucose transporter expression in aggressive thyroid cancers, leading to reduced visibility on ^{131}I scanning while simultaneously increasing visibility on FDG-PET [7]. Dietlein et al. found that FDG-PET was 82% sensitive for localizing disease in patients with significantly elevated serum thyroglobulin concentrations and negative radioiodine scans [135]. Multiple subsequent studies confirmed these findings, and a study by Wang et al. demonstrated an approximate 92% positive predictive value of FDG-PET in thyroglobulin-positive, radioiodine scan-negative patients [136]. Sensitivity is higher with greater degrees of dedifferentiation and larger tumor burden. Sensitivity has also been reported to be particularly high (92%) in Hurthle cell cancer, perhaps related to the extremely high concentrations of mitochondria in Hurthle cells [137–139]. Most thyroid cancer lesions missed by FDG-PET are due to small-volume cervical lymph nodes, which may be detected by high-resolution neck ultrasound.

The addition of TSH stimulation, either by THW or rhTSH, modestly increases the sensitivity of FDG-PET. Biologically, this effect can be attributed to the ability of TSH to increase glucose uptake and metabolism in thyroid cells [23]. In published studies, TSH stimulation has led to the identification of additional FDG-avid lesions compared to unstimulated conditions, but generally has not made a difference in finding versus not finding any FDG-avid lesion, and overall has led to a change in management in only 6–9% of cases [129]. An additional benefit of TSH stimulation, beyond the detection of additional foci of FDG-avid DTC, is a possible improvement in the ability to distinguish FDG-PET-positive thyroid cancer tissue from lymph nodes or other FDG-avid tissues, i.e., increasing the test's specificity [140, 141]. On the basis of available data, TSH stimulation should be considered on a case-by-case basis, but is not essential for the use of FDG-PET as a surveillance tool in thyroid cancer.

Beyond its role in surveillance, FDG-PET is useful in several aspects of thyroid cancer management that are addressed in other chapters. These include initial staging of high-risk thyroid cancer and prognostication, planning therapy for known disease, targeting cancers at highest risk of progression, and following treatment response.

Drawbacks to use of FDG-PET as a surveillance tool include its expense, as well as its relatively poor specificity compared to more thyroid tumor-specific modalities such as radioiodine scan. The specificity can be improved by combining FDG-PET with CT (FDG-PET/CT), which may, for example, allow reactive lymph nodes to be distinguished from cancerous ones, but there is still a frequency of up to 39% for false-positive lesions with FDG-PET in published series [121, 140]. For this reason, it is important to confirm a positive finding on FDG-PET with fine-needle aspiration (using cytology and Tg-FNA) before proceeding to treatment.

Part II: Rationale for Surveillance and Recommended Approach

Having reviewed the individual characteristics, utility, and limitations for the main biochemical and imaging tools used in thyroid cancer surveillance, we now turn our attention to the evidence base for surveillance including the potential harms and optimal approaches in clinical practice.

Rationale for Surveillance and Potential Harms

The first question is whether surveillance positively impacts outcomes, including survival or

disease recurrence. There is no randomized trial, prospective study, or even retrospective study of surveillance versus no surveillance on outcomes in DTC patients. Thus, any positive impact of surveillance on survival or recurrence must be extrapolated from studies of treatment effects. That is, patients in whom treatment is associated with increased survival or decreased recurrence should be preferentially targeted for early detection of disease, so that disease may be identified at a stage where treatments are more likely to be effective. The specific surveillance methods and frequency of testing should be tailored based on patient and tumor characteristics, in order to maximize the positive predictive value of testing while minimizing the risk of false-negative results. The concept of risk-based testing is discussed in more detail in the subsequent section.

What about the harms associated with surveillance? A number of studies have evaluated quality of life (QoL) and health-related quality of life (HRQoL) after DTC. Initial studies reported a modest decrease in HRQoL, but many of the studies were small, used inconsistent instruments to measure HRQoL, and/or relied on tools developed for other populations [3, 142, 143]. A large-scale, cross-sectional assessment of thyroid cancer survivors, reporting on the initial 1174 patients recruited into a prospective cohort study of thyroid cancer survivors (the North American Thyroid Cancer Survivorship Study, or NATCSS), subsequently was performed and directed specifically toward QoL issues surrounding thyroid cancer diagnosis, treatment, and long-term management. Mean overall QoL was decreased (5.56/10, with 0 being the worst) in thyroid cancer patients; but greater reductions in QoL were found with issues surrounding surveillance. Fear of future diagnostic tests, a second malignancy, or thyroid cancer recurrence received scores of 4.89, 3.77, and 4.17, respectively. QoL remained low for many years after diagnosis and did not correlate with stage of disease, meaning patients with low-stage, low-risk disease did not report less anxiety or impact on QoL. Strikingly, the QoL for thyroid cancer survivors was lower than previously reported QoL for survivors of colorectal cancer, breast cancer, and malignant glioma—malignancies with worse survival rates and more invasive treatments than thyroid cancer [144]. The same group reported in another study that QoL in patients with thyroid cancer was similar to that of other cancers with worse survival including gynecologic cancer. Younger patients reported worse QoL outcomes than older patients [11].

A population-based, nationwide, cross-sectional cohort study performed in Sweden based on their national cancer registry found that even long-term HRQoL in DTC survivors (at 14–17 years after initial diagnosis) was lower than the general population for general health, vitality, social functioning, and mental health. All patients diagnosed with DTC in Sweden between 1995 and 1998 were identified for this study, with a high percentage (79%) responding to a QoL questionnaire in 2012. Only 7% of this group had experienced a recurrence, but 48% reported concerns about having a recurrence. Patients concerned about a recurrence reported lower HRQoL than those without concerns about recurrence in five out of eight domains [12].

Why would HRQoL for DTC be comparable or lower than other malignancies with worse prognosis and more invasive treatments, and why would this effect last for so long after diagnosis even when patients remain disease-free? There are several potential reasons. The relatively young age at diagnosis of many DTC patients and the female preponderance is unique compared to the majority of adult non-gynecologic malignancies, leading to a disproportionate impact on employment, family planning, reproduction, and other areas in which young women are particularly vulnerable. The lifelong and at times intense nature of surveillance clearly also plays a role [11, 144].

In addition to its negative impact on QoL, thyroid cancer surveillance imposes a significant financial burden on patients. Bankruptcy rates for cancer patients in general have been reported to be 2.2–3%, approximately twice as much as the general population [145, 146]. However, a study examining bankruptcy rates of cancer patients in western Washington State from 1995 to 2009 found that thyroid cancer patients suffered a

higher incidence of bankruptcy than any other cancer type studied, at 9.3 for 1000 person-years. This incidence rate was just above the rate for lung cancer, but substantially greater than that of uterine cancer, leukemia/lymphoma, colorectal cancer, melanoma, breast cancer, and prostate cancer. The hazard ratio for bankruptcy for thyroid cancer patients was 3.46 compared to patients without cancer [145]. The authors hypothesized that thyroid cancer patients may be at higher risk for lost wages due to loss of productivity associated with surgery, radioiodine ablation, and extended hypothyroid state in some patients. Moreover, due to the mean young average age of thyroid cancer patients, they likely had greater debt to income ratios and less access to non-employment-based health insurance (e.g., Medicare) or income sources (e.g., social security benefits). Given the duration of the study period, and the fact that a substantial portion of bankruptcy filings occurred between year 1 and year 5 after diagnosis, surveillance costs together with the initial costs of diagnosis and treatment likely contributed to financial decline of these patients [145].

Monitoring for thyroid cancer is also expensive on a societal level. The estimated overall cost for care of well-differentiated thyroid cancer in 2013 in the USA, for all patients diagnosed after 1985, was $1.6 billion. This amount was comparable to the cost of other solid tumors with worse survival, including cervical, gastric, and esophageal cancer. Over one-third of the total cost (37%) was attributable to the cost of surveillance. Based on incidence trends at the time, the authors projected that costs for DTC care in the USA in 2030 would exceed $3.5 billion [147].

Wang and colleagues performed the first known cost-effectiveness analysis of posttreatment papillary thyroid cancer surveillance, based on data from 2932 patients who underwent thyroidectomy for DTC between January 2000 and December 2010 at Memorial Sloan Kettering Cancer Center [148]. A total of 1087 of these patients were included for analysis after excluding those with non-papillary histology, secondary cancer diagnoses, management outside of the head and neck department, less than total thyroidectomy, and without a recurrence if followed for less than 36 months. Patients were classified as low risk (362 patients, or 33.3%), intermediate risk (561 patients, or 51.6%), or high risk based on ATA categories. Costs of surveillance were determined with fee schedules of the Centers for Medicare and Medicaid Services and included costs of thyroglobulin and thyroglobulin antibody tests, office visits in the first 36 months of follow-up, and all related imaging studies (and biopsy if performed). A total of 69 recurrences occurred in the first 36 months of follow-up, including 3 in the low-risk group (0.8%), 44 in the intermediate-risk group (7.8%), and 22 in the high-risk group (13.4%). The cost of surveillance per patient, as might be expected, was lowest in the low-risk group and higher for the intermediate- and high-risk group. However, the cost *per recurrence* was more than six times higher for the low-risk group ($147,819) than for the intermediate- and high-risk groups ($22,434 and 20,680, respectively). The large difference between the low-risk group and the intermediate- and high-risk groups persisted in sensitivity analyses that projected costs if recurrence rates were three times higher than actually occurred or if ultrasound frequency was three times higher than actually occurred [148]. It is likely that the true costs of surveillance were underestimated, as testing done outside Memorial Sloan Kettering was not captured, indirect costs such as time off work and transport were not included, and costs from private insurers' fee schedules were not considered. Regardless, this study highlights the high cost to benefit ratio of conventional surveillance practices in low-risk thyroid cancer patients and underscores the need for reduction of surveillance intensity in this population.

Recommended Approach to Surveillance Based on Risk Status

Given the limited data on the benefits of surveillance in most DTC patients, and the potential for harm in one or more domains, it is critical that the intensity of surveillance be matched to the patient's estimated risk of mortality or recurrence.

The ultimate goal of surveillance is to maximize detection of disease in the minority of patients whose survival may be affected and those who are at high risk of clinically significant disease recurrence, while avoiding unnecessary surveillance in low-risk patients. Several staging systems have been available for predicting survival and entry into cancer registries [149–151]. However, risk categories for recurrence have more clinical utility for deciding intensity and frequency of surveillance. Therefore, the first step in planning a surveillance strategy is to establish the patient's risk category for recurrence based on results of surgical pathology and, if applicable, the results of pre- and/or post-therapy whole-body iodine scanning. The risk stratification system proposed in the ATA 2009 thyroid cancer guidelines is commonly used. It has been validated in multiple retrospective studies and appears to help predict recurrence even in patients who have not undergone radioiodine remnant ablation. Several other prognostic variables to further refine risk stratification were suggested in the revised 2015 guidelines, though the additional benefit of these variables has not been established yet [13].

The risk category—low, intermediate, or high—should guide intensity and type of follow-up through approximately the first year following initial treatment. Thereafter, based on the response to therapy, as gauged by suppressed thyroglobulin, neck ultrasound, stimulated thyroglobulin, and dWBS when indicated, the response to initial therapy can be classified as excellent, biochemically incomplete, structurally incomplete, or indeterminate [13]. A suggested approach to surveillance based on initial risk status, and in the event of subsequent excellent response to therapy, is provided in Tables 22.2 and 22.3, respectively. Patients who have biochemically incomplete, structurally incomplete, or indeterminate responses to therapy will require greater intensity of surveillance and additional treatment when appropriate. This topic is discussed in other chapters.

Patients who are initially low risk with an excellent response to treatment have an extremely low recurrence rate. One recent study of 932 total patients at a single center in Poland found a recurrence rate of only 0.2% in patients with low initial risk status and excellent response to treatment [152]. The authors proposed based on their data that patients in this category be discharged from further follow-up at a cancer center. Indeed, as a number of other studies have demonstrated a similar extremely low rate of persistent/recurrent disease in these patients [10, 153], it would seem reasonable to transition care of these patients to local endocrinologists or other care providers who can manage thyroid hormone replacement, follow clinical exams, and order additional testing as needed based on change in clinical status. Serum thyroglobulin on suppression could be measured periodically for the first 3–5 years after treatment.

Though guidelines from several organizations suggest that periodic neck ultrasound also be considered in low-risk patients, recent data suggests that such an approach may be overly aggressive and yield very low rates of structural disease detection. Analysis of a large database from Memorial Sloan Kettering Cancer Center showed that only three structural recurrences were identified in low-risk patients by neck ultrasound from 2003 to 2012, despite a 5.3-fold increase in the number of ultrasound examinations per patient-year of follow-up in the same time period. There were no disease-related deaths [154]. A previous study from the same institution reported a 67% false-positive rate of surveillance neck ultrasound in 171 low-risk patients over a median follow-up of 8 years, leading to additional testing without identifying clinically significant disease. Only two structural recurrences were identified in this group of patients, one of which was associated with rising thyroglobulin level [104]. Thus, routine continuing use of neck ultrasound is likely not warranted in low-risk PTC patients with excellent response to therapy in whom serum thyroglobulin is a reliable marker of disease (i.e., thyroglobulin antibody-negative patients).

A retrospective study recently raised the question of whether even intermediate-risk patients who meet these criteria could forgo stimulated testing and perhaps routine neck ultrasound. The study included 578 patients, of whom 47.2%

Table 22.2 Suggested initial surveillance for DTC

Initial surveillance based on ATA 2009 risk category (first 12–24 months after treatment)						
	Tg on LT4 suppression	Tg with stimulation	US	dWBS	CT/MRI	FDG-PET
Low risk	6 months	Once at 6–18 months	6 months	Not needed if unstimulated Tg is <0.2 ng/mL and neck US is negative	Not needed in the absence of elevated Tg or clinical suspicion	Not needed in the absence of elevated Tg or clinical suspicion
	12 months		12 months			
	18–24 months		+/−24 months[a]			
Intermediate risk	6 months	Once at 6–18 months	6 months	Consider at time of stimulated Tg testing	Not needed in the absence of elevated Tg or clinical suspicion	Not needed in the absence of elevated Tg or clinical suspicion
	12 months		12 months			
	18–24 months		24 months[a]			
High risk	q 3–6 months	12 months	6 months	Consider at time of stimulated Tg testing	Consider based on clinical situation	Consider as prognostic tool; consider if WBS is negative with Tg > 10
			12 months			
			24 months			
With LTT and no RAI	Consider periodic testing	No	6 months	No	No	No
			12 months			
			24 months			
With TgAb+	q 6–12 months	12 months	6 months	12 months	Consider based on clinical situation and TgAb trend	Consider based on clinical situation and TgAb trend
	Follow TgAb level over time		12 months			
	Consider RIA or LCMS if initial testing was with IMA		24 months			

[a]If unstimulated Tg has been undetectable, and there is no clinical evidence or suspicion for disease, the 24-month ultrasound can be deferred in most low-risk patients. Some data suggests the same may also be true for intermediate-risk patients with the same characteristics

Table 22.3 Suggested longer-term surveillance for DTC for those with excellent response

Longer-term surveillance for those with ATA excellent response to therapy[a] (following the first 12–24 months after treatment)						
	Tg on LT4 suppression	Tg with stimulation	US	dWBS	CT/MRI	FDG-PET
Low risk	q 12 months, consider extending to q 24 months after first 3–5 years	Not needed	Consider deferring routine US if Tg remains negative and otherwise NED, at least for very-low-risk patients	Not needed	Not needed	Not needed
Intermediate risk	q 12 months, consider extending to q 24 months after first 3–5 years	Not routinely needed	q 2 year for 3–5 years, then consider deferring further routine US if Tg remains negative and otherwise no evidence of disease	Not routinely needed	Not needed	Not needed
High risk	q 12 months	Consider at least one additional set of stimulated studies, based on initial clinical presentation	q 12 months for 3–5 years, then tailor frequency to clinical situation	Consider at time of stimulated testing	Not routinely needed; can consider based on initial clinical presentation	Not routinely needed; can consider based on initial clinical presentation
With LTT and no RAI	q 12–24 months	No	q 12 months for 3–5 years, then tailor frequency to clinical situation	No	No	No

LTT less than total thyroidectomy

[a]Excellent response is defined as (1) Tg on suppression <0.2 ng/mL or Tg with stimulation <1 ng/mL and (2) no evidence of disease on appropriate imaging tests Patients with persistent thyroglobulin antibodies, even with no other evidence of disease, should not be classified as excellent response. These patients can be classified as having an indeterminate response (if antibody levels are declining) or biochemical incomplete response (if antibody levels are rising)

were low risk and 52.7% were intermediate risk, all with unstimulated Tg ≤ 0.2 ng/mL and no clinical or radiographic evidence of disease after initial therapy. Structural recurrence was low (12 patients total or 2% of the study population) over a median of >5 years of follow-up, and most of the structural recurrences (10 out of 12) were accompanied by a rise in thyroglobulin to >0.2 ng/mL. Of the two structural recurrences that occurred in patients with undetectable thyroglobulin values, only one was detected by neck ultrasound. The authors therefore proposed that measurement of unstimulated thyroglobulin with a second-generation assay in patients with low or even intermediate-risk PTC might be sufficient for long-term follow-up in TgAb-negative patients with excellent response to initial therapy. They recommended a neck ultrasound at 5 years for intermediate-risk patients who presented with relevant lymph node involvement [155].

Patients classified at greater than low risk initially, those with low initial risk but subsequent evidence of disease persistence/recurrence, and those with low initial risk but indeterminate response to treatment require some form of extended or lifelong follow-up. Though the vast majority of these patients will not die from their disease, a significant portion will develop recurrence, with a smaller subset demonstrating clinically significant recurrence (i.e., some evidence of structural disease, not just thyroglobulin elevation). Moreover, though most cases of residual/recurrent disease are detected in the first few years after initial treatment, recurrence of DTC can occur many years and even decades later. One caveat to the relatively high rates of structural recurrence (around 30%) in the original studies that followed thyroid cancer patients over decades is that these patients were treated 30–40 years ago, when most patients presented with palpable primary tumors or clinically evident lymphadenopathy [2, 156]. Studies of patients treated more recently suggest that rates of structural recurrence are significantly lower (between 3 and 10%), in part due to increasing diagnosis of small tumors and subclinical disease, and also because persistent/recurrent disease is usually detected in the first few years after treatment [10, 153, 157, 158]. The likelihood of persistent or recurrent disease manifesting as structural disease rather than isolated thyroglobulin elevation is lowest for low-risk patients (20–30%) and increased for intermediate-risk (49–71%) and high-risk (79–81%) patients [10, 159, 160].

The concept of dynamic risk assessment—continually reassessing risk over time—should be stressed when deciding on appropriate surveillance for an individual patient. Risk may need to be reclassified based on interim findings during follow-up or lack thereof [10]. If, for example, a patient has aggressive histology and extrathyroidal spread at presentation, but subsequently is found to have negative suppressed and stimulated thyroglobulin values, negative whole-body scans, and normal neck ultrasounds—essentially no biochemical or structural evidence of disease—the initial "high-risk" status could be modified to "high risk with subsequent excellent response to therapy." Not only could the degree of TSH suppression be decreased in such patients, but the schedule for surveillance could be transitioned to annual measurement of thyroglobulin on suppression and annual neck ultrasound, much like patients originally classified as low risk. Conversely, an initially low-risk patient who subsequently develops a rising thyroglobulin and/or abnormalities on imaging requires a more intensive schedule of surveillance following any indicated therapeutic intervention(s).

As more data accumulates regarding long-term outcomes (over decades) in patients who have been diagnosed and treated in the modern era of ultrasensitive thyroglobulin assays and high-resolution neck ultrasound, we may be able to further liberalize surveillance recommendations for low-risk individuals who constitute the largest and most rapidly expanding group of thyroid cancer patients and for select intermediate- and high-risk patients who demonstrate an excellent response to therapy.

Recommended Approach to Surveillance in Patients Without Total Thyroidectomy and/or RAI

The increasing detection of low- and very-low-risk thyroid cancer has led to a growing number of thyroid cancer patients who may be considered for thyroidectomy (TT) alone without radioiodine or with less than total thyroidectomy (LTT, including lobectomy or near-total thyroidectomy) without radioiodine. Guidelines from several organizations now support consideration of TT alone without radioiodine for low- and some intermediate-risk patients, as well as LTT without radioiodine for very-low- or low-risk patients [13, 15, 16]. The revised 2015 ATA guidelines state that lobectomy alone can even be the initial surgical approach for low-risk DTC measuring up to 1–4 cm in size, substantially expanding the potential pool of DTC patients who may retain a significant portion of their normal thyroid [13]. The intention of this marked shift from previous recommendations is to avoid the potential complication of total thyroidectomy when it is unlikely to confer any meaningful recurrence or survival benefit.

However, patients who have undergone TT without radioiodine or LTT may pose a dilemma for surveillance. Serum thyroglobulin, at least in absolute terms, is difficult to interpret in the presence of remaining thyroid remnant and particularly in the presence of a remaining thyroid lobe. Neck ultrasound may not readily distinguish between residual normal thyroid tissue and residual/recurrent thyroid cancer in patients who have not received radioiodine; and it may detect additional nodules of unknown malignant potential in patients with a remaining thyroid lobe. There is data to suggest that thyroglobulin and ultrasound still play important roles in monitoring these patients for recurrent disease, primarily by (1) following trends in serum thyroglobulin on levothyroxine suppression and (2) tracking serial sonographic size and appearance of remaining thyroid bed tissue or intrathyroidal nodules [6, 161, 162].

In 290 low- and intermediate-risk patients who have undergone TT without radioiodine ablation or treatment, the serum thyroglobulin on levothyroxine was usually <1 ng/mL or <2 ng/mL and stable on follow-up. In patients with thyroglobulin values initially >2 ng/mL, the thyroglobulin usually decreased over time without additional therapy. By 5–7 years after thyroidectomy, the serum thyroglobulin on levothyroxine was <1 ng/dL in 95% of patients and was <0.1 in 80% of a subset of these patients whose thyroglobulin was measured on an assay with even lower functional sensitivity [161]. For patients with persistently high thyroglobulin or rising thyroglobulin, remnant ablation can be considered; there is no evidence that delayed administration of RAI results in poorer outcomes [13].

A separate study of 80 patients with very-low-risk PTC who underwent TT without radioiodine therapy demonstrated that rhTSH-stimulated thyroglobulin did not provide any meaningful clinical advantage over thyroglobulin measured on suppression. Approximately half of the patients had a rise in thyroglobulin to >1 ng/mL after rhTSH stimulation, with the highest up to 25 ng/mL, but the rise in thyroglobulin did not correlate to risk of recurrent or residual disease. Rather, the rise in thyroglobulin after rhTSH was simply proportional to the size of the thyroid remnant. Diagnostic WBS similarly did not show pathologic uptake (i.e., uptake outside the thyroid bed) in any of the patients and thus was not reliable for disease detection. The few recurrences that did occur in this study were detected with cervical ultrasound [6].

In the first long-term prospective evaluation of serial stimulated and unstimulated thyroglobulin levels in patients who underwent TT without RAI, both unstimulated and stimulated thyroglobulin levels remained stable over a median follow-up of 6.5 years. The study followed 121 low- and intermediate-risk patients, the majority of whom were older than 45 years and included a

significant percent with stage 3 and stage 4 disease according to AJCC staging guidelines. No patients in this cohort manifested any clinical or imaging evidence of recurrence during the follow-up period. Because unstimulated and stimulated Tg measurements were generally found to correlate over time, the authors concluded that unstimulated Tg was sufficient for long-term surveillance of low-/intermediate-risk PTC patient who undergo TT without RAI, assuming that the corresponding stimulated value(s) were <1 ng/mL in the first 1–2 years. For patients whose stimulated Tg measure 1–5 ng/mL, additional surveillance with stimulated Tg and neck ultrasound was recommended [162].

Taken together, these three studies suggest that thyroglobulin on suppression as measured by an assay with good functional sensitivity (≤0.2) and cervical ultrasound should serve as the main surveillance methods for DTC patients who undergo TT without radioiodine. Stimulated thyroglobulin measurements in the first 1–2 years after treatment can be considered in select patients for additional reassurance, for example, older patients or those with intermediate risk of recurrence. The frequency with which to perform unstimulated thyroglobulin and cervical ultrasound after the first year should be guided by patient risk factors, initial thyroglobulin levels and trends, and ultrasound findings, with emphasis on decreasing the intensity of surveillance over time for patients who remain disease-free.

Patients who undergo LTT (lobectomy or lobectomy/isthmusectomy) alone should be followed with clinical exams and ultrasound. The range for thyroglobulin is very wide in these patients, especially as many do not require exogenous levothyroxine to maintain a euthyroid state, so routine measurement of thyroglobulin levels is not useful to predict recurrence [163]. The frequency of ultrasound follow-up should be individually determined based on the presence or absence or contralateral nodules, patient risk factors, and histology of the primary tumor. Recurrence in the contralateral lobe has been shown to occur in 20–30% of patients followed for up to 20 years after treatment [164, 165]. Patient with multifocal disease in the initial resected lobe appear to be at higher risk for recurrence in the contralateral lobe. Size of the primary tumor does not seem to predict recurrence, however [164]. Triggers for completion surgery include progressive growth of nodules in the contralateral lobe, suspicious sonographic features of these nodules or suspicious/indeterminate fine-needle aspiration, or patient preference.

Summary

Over the last two decades, the landscape of differentiated thyroid cancer surveillance has been transformed by the development of increasingly sensitive detection methods and by the availability of recombinant human TSH to facilitate stimulated testing. Serum thyroglobulin and neck ultrasound have become the cornerstones of monitoring for DTC recurrence, supplemented by diagnostic whole-body iodine scans and other imaging modalities when indicated per the estimated risk of recurrence and the individual patient's clinical situation.

The greatest challenge at present in the surveillance of DTC is avoiding unnecessary testing. The harms associated with overaggressive surveillance—including the psychological and financial burdens on patients as well as the costs to society—have been quantitatively assessed in recent years and have made it clear that more tailored surveillance strategies are needed. Already very-low-risk groups who may not require ongoing periodic ultrasound monitoring or stimulated testing have been identified. Hopefully, longer-term data from major databases (and ideally data from prospective clinical trials) will illuminate which patients in the "higher end" of the low-risk category and which patients in the intermediate-risk category would have excellent outcomes even with more limited surveillance. Biomarkers may prove useful in this regard.

An additional challenge lies in following patients with proven residual or recurrent disease. While treatment is generally indicated for macroscopic structural disease, the optimal

approach to the growing number of patients with isolated biochemical or small-volume structural disease (e.g., abnormal small cervical lymph nodes) is not as clear. Often a "wait-and-see" approach is adopted over empiric radioiodine treatment or repeat surgical dissection, but guidance is needed regarding the frequency and intensity of follow-up in these patients as well as the threshold for intervention. Moreover, since less aggressive surgical and radioiodine practices are now recommended for many low-risk and some intermediate-risk patients, it is likely that the pool of patients with detectable thyroglobulin or indeterminate findings on neck ultrasound will increase. This potential shift in management approaches underscores the urgency of identifying features that predict worse outcomes in patients with minor elevations in thyroglobulin and/or indeterminate findings on neck ultrasound. Finally, because current surveillance recommendations rely heavily on serum thyroglobulin concentration, it is critical that assays that are unaffected by circulating thyroglobulin antibodies yet retain excellent functional sensitivity become available.

In the meantime, providers who care for patients with differentiated thyroid cancer over the long term can use initial risk category and subsequent response to therapy as a guide to individualizing the surveillance regimen. The regimen should be adjusted based on findings on surveillance studies, including less aggressive surveillance if there are no positive findings and no clinical suspicion or evidence of disease. This dynamic approach to surveillance should include communication between the patient's primary thyroid cancer provider(s), e.g., endocrinologist or surgeon; and with colleagues in pathology, laboratory medicine, and radiology, particularly when unexpected findings occur. The patient should remain at the center of the decision-making process and receive counseling about available strategies along with a discussion of their advantages and shortcomings, particularly in cases where findings are ambiguous or where treatment or aggressive surveillance has the potential for significant harm.

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