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Thyroid Cancer Surgery Guidelines in an Era of De-Escalation

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Abstract

Well-differentiated thyroid carcinoma has seen a tremendous rise in global incidence over the past three decades, largely owing to widespread screening and identification of small, incidentally detected tumors. With this increased incidence has emerged a movement questioning whether all cases of thyroid cancer merit a treatment approach focused on oncologic completeness. Such trends towards thoughtful, evidence-based treatment de-escalation paradigms reflect better risk stratification of thyroid cancers, and recognition that not all detected disease poses a threat to health or survival. Thus, national and professional guidelines are evolving to incorporate higher thresholds for surgery, acceptance of less than total thyroidectomy in specific circumstances, higher thresholds for adjuvant therapy, and introducing the role of active surveillance for selected cases of low risk disease. Despite these common themes, there are significant differences among guidelines. This lack of consensus in guidelines persists due to variation in clinical practice patterns, differences in consideration and interpretation of existing evidence, cultural and geographical considerations, and resources available for both diagnosis and treatment.

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Keywords

Well-differentiated thyroid carcinoma; de-escalation; thyroidectomy; American Thyroid Association; guidelines

Introduction

Thyroid cancer is the most common endocrine malignancy. While there has been no appreciable increase in the observed mortality of well-differentiated thyroid cancer, there has been an overall rise in its incidence over the last few decades worldwide, with a current global age-standardized rate of 4.0 per 100,000^{1–3}. As rates of thyroid nodule detection have skyrocketed, the question of how to manage well-differentiated thyroid carcinoma (DTC) has become a subject of great interest.

The rise in incidence of thyroid cancer appears attributable to increases in health care utilization and imaging practices that identify small asymptomatic nodules that would otherwise go undiscovered^{4–6}. The term “overdiagnosis” defines such instances when a condition that would not otherwise go on to cause symptoms or death is diagnosed, and possibly treated⁷. The landmark study by Harach et al. found occult PTC in 36% of autopsy specimens and concluded that the true prevalence of histologically verifiable PTC was likely much higher, perhaps even existing as a “normal variant” and thus representing a silent and clinically insignificant disease reservoir⁸. Other similar examples of overdiagnosis notably include prostate cancer (prostate specific antigen screening), lung cancer (CT imaging), skin cancers (annual surveillance), and breast cancer (mammogram). Even though these disease entities are traditionally associated with higher mortality rates, emerging data suggest that a subset of these malignancies similarly demonstrate indolent biology and may not require treatment. An increasing incidence due to widespread, high-sensitivity screening practices (largely ultrasound) without associated increases in mortality supports that well-differentiated thyroid cancer is in fact being overdiagnosed^{7,9,10}.

South Korea provides a dramatic example, where introduction of ultrasound as an inexpensive and routine screening modality yielded a 15-fold increase in thyroid cancer incidence without corresponding changes in disease-specific mortality over the same period of time¹¹. Similar trends are seen in the United States and elsewhere^{4,5}. Thus, it is not surprising that many recently published professional guidelines for management of differentiated thyroid cancer have included recommendations addressing both when to image and when to biopsy based upon imaging characteristics and associated risk stratification.

Papillary thyroid microcarcinomas (PTMC), defined as papillary thyroid carcinomas (PTC) measuring 1cm or less, are reported to have extremely low locoregional recurrence rates (2–6%), and even lower disease-specific mortality (<1%)¹². As the majority of newly diagnosed cancers are attributable to PTMC, there is mounting pressure to stratify risk and minimize potential harm from overtreatment of low-risk thyroid disease^{1,2}. However, PTMC is not the only situation in which DTC demonstrates innocuous biological behavior. Thus, providers are reconsidering the risk-benefit tradeoffs of management options. In addition, the de-

escalation of indications for radioactive iodine has directly influenced the completeness of thyroidectomy in selected cases. One challenge thereof reflects the difficulty in predicting at the time of presentation which of these seemingly low-risk tumors may harbor the behavior of a “bad actor.”

Where, historically, total thyroidectomy and postoperative radioactive iodine ablation was a nearly universal paradigm for well-differentiated thyroid cancer, the professional ethos is trending towards a more conservative and individualized treatment philosophy. Physicians have become more aware that indolent disease is being over-treated, and this is reflected in updates to clinical practice guidelines over the past decade. Professional guidelines proposed by many influential stakeholders to guide treatment of papillary thyroid carcinoma address the “epidemic of papillary thyroid microcarcinoma” with a trend toward de-escalation of treatment¹³. Herein, we consider the role of guidelines in the modern-day surgical treatment of DTC; specifically, the evolution of these guidelines over time and comparisons between evolving recommendations from different organizations.

The Role of Guidelines

Clinical practice guidelines are intended to improve healthcare outcomes by promoting optimal practices supported by evidence, provide access to medical knowledge, and promote cost-effective strategies¹⁴. Common aims of thyroid cancer guidelines are to improve referral patterns and management, improve overall and disease-free survival, reduce complications, and enhance quality of life of patients with thyroid cancer. Guidelines are intended to *guide* care rather than serve as the written standard of medical care or to replace clinical judgment, and rarely do they include (or claim to dictate) all acceptable methods of care. Importantly, these documents represent the state of the field at the time of publication, and thus the date of publication and more recent evidence must be considered when making clinical decisions in real-time. Thus, some degree of variation among groups is expected and justified.

Thyroid cancer is a disease that is routinely treated by specialists in multiple fields of medicine, including endocrinology, internal medicine, nuclear medicine, medical oncology, radiation oncology, general/endocrine surgery, and otolaryngology. Given the high incidence of thyroid nodules in the general population, primary practitioners will also benefit from guidelines that delineate and outline management strategies. Thus, there is remarkable diversity among the stakeholders who are both formulating, and influenced by such guidelines. Incidence and presentation of disease will of course vary in different practice settings, regions and countries, reflecting distinct environments and risk factors, as well as differing epidemiology, public awareness, screening, and infrastructure, which may rightfully explain some differences between international guidelines. Despite differences in individual recommendations, common trends among the updates to international guidelines include a focus on multidisciplinary care, treatment based upon risk stratification, avoidance of overtreatment, and shared decision-making.

Data Sources

A literature search was performed using the InterTASC Information Specialists' Sub-Group Search (ISSG) Filter Resource, using filters to identify guidelines (University of Texas School of Public Health)¹⁵. The search identified published professional guidelines for differentiated thyroid cancer from 2006 to present. Databases included Ovid, Medline (including Medline In-Process), EMBASE, and Scopus. Additional relevant search terms were added. Using this tool, 1087 articles were retrieved and reviewed. In this context of de-escalation of treatment, we choose to focus on surgical treatment for adults with well-differentiated thyroid carcinoma. Articles addressing management that did not include surveillance or surgical treatment of well-differentiated thyroid cancer (i.e., diagnosis, adjuvant therapies or radioactive iodine ablation alone; pediatric populations; and/or other histologies/disease sites) were not included. Articles not available with English translation (about 6 national guideline documents) were excluded. The authors selected 25 of the most relevant and recent publications to inform this manuscript.

Discussion

Variation in Guidelines

Interestingly, failure to adhere to guideline driven care has itself been associated with worse outcomes¹⁶. In the United States, a minority of patients receive surgery for DTC that is not aligned with either the American Thyroid Association (ATA) or National Comprehensive Cancer Network (NCCN) Guidelines. Despite differences on recommendations between the 2009 iterations of each guideline, Adam et al. demonstrated that nonadherence to either guideline, though rare, resulted in worse overall survival, and discordance in recommendations between guidelines decreased overall adherence^{16,17}. Previous studies have also found that adherence to the ATA guidelines was imperfect¹⁸. An earlier multicenter study by Schwab et al in 2005 suggested that the German guidelines for surgical management were not followed in over 50% of cases¹⁹. Furthermore, variation in care is prevalent despite existing guidelines, with tendency toward more aggressive treatment than what guidelines recommend for both surgical extent and radioactive iodine use²⁰.

Evolution in American guidelines

In the United States, both the ATA and NCCN have published and revised clinical practice guidelines for DTC in the past decade^{21–25}. Other groups, including the American Society of Head and Neck Surgery (AHNS), American Association of Clinical Endocrinologists (AACE), and American Association of Endocrine Surgeons (AAES) have presented consensus statements, though all ultimately endorsed the most recent iteration of guidelines from the ATA²⁶.

The ATA guidelines task force includes representation from fields of endocrinology, surgery, nuclear medicine, radiology, pathology, oncology, molecular diagnostics, and epidemiology, and at least one third of the task force is replaced during each iteration to include fresh perspective²⁴. The 2015 guidelines include a medical oncologist in the task force for the first time, owing to the advanced medical/molecular treatments that are now available for

differentiated thyroid cancer, including kinase inhibitors sorafenib and levatinib, which are now approved in the United States. Regarding I-131, the 2015 ATA guidelines delineate the role of radioactive iodine ablation as part of initial treatment with thyroidectomy, adjuvant therapy and therapy²⁴. The ATA guidelines are heavily endorsed, including consensus with the following groups: American Association of Clinical Endocrinologists; American Association of Endocrine Surgeons; American Head and Neck Society; Asia Oceania Thyroid Association (AOTA); British Society of Nuclear Medicine; Canadian Association of Otolaryngology Head and Neck Surgery; The Endocrine Society; Endocrine Society of Australia; European Thyroid Association; International Association of Endocrine Surgeons; International Federation of Head and Neck Oncologic Societies; Japanese Thyroid Association; Latin American Thyroid Society; Society of Oncology; Ukrainian Association of Endocrine Surgeons.

The ATA has published three iterations of its guidelines, starting in 2006, with subsequent updates in 2009 and 2015^{23–25}. The most recent update, “*2015 American Thyroid Association Management Guidelines for Adult Patients with Thyroid Nodules and Differentiated Thyroid Cancer*” includes a comprehensive review of evidence that reflects the contemporary advances in treatment and includes significant changes from the 2009 version, with the goal of providing more individualized patient care. It offers far more recommendations (101) and references (1078) than its predecessors and other national/international counterparts. The 2015 iteration responds to the notion that early detection and treatment of “endemic” PTMC may not result in any clear overall benefit, combating a trend of overdiagnosis and overtreatment of indolent cancers.

The overall focus of the new guidelines is best stated by the authors: “*A major goal of these guidelines is to minimize potential harm from overtreatment in a majority of patients at low risk for disease-specific mortality and morbidity, while appropriately treating and monitoring those patients at higher risk*”²⁴. With regard to both biopsy threshold and extent of surgery (hemi versus total thyroidectomy), the 2015 guidelines have shifted toward a more conservative philosophy. The consideration of lobectomy as the initial surgical approach for well-differentiated thyroid cancers is fundamentally different: The 2015 guidelines consider lobectomy or total thyroidectomy to be reasonable approaches for T1-2N0M0 DTC measuring 1–4 cm, whereas the 2009 guidelines recommended clinicians should consider total thyroidectomy for all DTC nodules >1cm.

Previous retrospective data suggested that better outcomes were seen with total thyroidectomy in nearly all DTC, which influenced the recommendation of the 2009 guidelines.^{27–29} In contrast, the 2015 update supports a significant de-escalation in treatment and reflects more incremental data indicating similar clinical outcomes following lobectomy versus total thyroidectomy in properly selected patients^{30–34}. The task force concludes that “*in properly selected low to intermediate risk patients (patients with unifocal tumors <4cm, and no evidence of extrathyroidal extension of lymph node metastases by examination of imaging), initial [extent of] thyroid surgery probably has little impact on disease specific survival*”²⁴. This relies on the idea that salvage surgery is an effective treatment option in the few patients where persistent or recurrent disease is identified, making the small risk of locoregional recurrence in these patients an acceptable choice

mitigated by the incremental risk of more aggressive surgery. Moreover, this evolution reflects the changing indications for RAI, as total thyroidectomy is not predicated upon the need to facilitate adjuvant RAI in nearly as many cases³⁵. Importantly, the 2015 ATA guidelines acknowledge that active surveillance can be considered in a carefully selected patient population (Table 1), though an explicit recommendation for active surveillance is not included.

Furthermore, the 2015 ATA guidelines use a threshold of 1.5cm (previously 1.0cm) for biopsy and cytologic evaluation of some thyroid nodules, effectively broadening the group of individuals considered “low risk”²⁴. Further surgical recommendations include the following: Total thyroidectomy is recommended for DTC >4cm, gross extrathyroidal extension, or clinically apparent nodal or distant disease (clinical N1 or M1)²⁴. In contrast to the 2009 ATA guidelines, the 2015 update more clearly articulates the indications for therapeutic central and lateral neck dissections, which are recommended when the respective basins are clinically involved. Prophylactic central neck dissection can be considered in cN0 disease with advanced primary tumors (T3 or T4), clinical lateral neck disease (cN1b) or for staging and treatment planning purposes²⁴. This point of clarification is crucial, as the 2009 guidelines stated that routine CND “*should be considered*” for patient undergoing total thyroidectomy for PTC, and this wording was interpreted by many as a decisive recommendation for surgery that led to controversy. Finally, completion thyroidectomy is offered in cases where pathology would otherwise warrant total thyroidectomy with or without nodal dissection; and RAI ablation in lieu of completion thyroidectomy is not routinely recommended in the updated ATA guidelines²⁴.

The National Comprehensive Cancer Network publishes updates to its guidelines on a frequent basis, with the most recent update occurring in 2016²². Previously, differences existed between the 2009 ATA and NCCN surgical recommendations for low-risk papillary thyroid carcinoma, microcarcinoma, and minimally invasive follicular thyroid carcinoma: The NCCN guidelines had considered lobectomy for PTC measuring 1.1–4.0 cm where the ATA had recommended total thyroidectomy in all cases, total thyroidectomy for follicular microcarcinomas (<1.0 cm) where the ATA had recommended lobectomy, and either lobectomy or total thyroidectomy for minimally invasive follicular thyroid carcinoma where the ATA had recommended total thyroidectomy in all cases^{21,25}. The updated NCCN guidelines demonstrate considerably more agreement with the 2015 ATA guidelines with regard to surveillance, indications for surgery, and extent of surgery (Table 1).

Overview of European Guidelines

A comparison and summary of the ATA, British Thyroid Association (BTA), the European Consensus Statement Conference and German Society of General Surgery guidelines has been reviewed previously by Furst et al³⁶. There is generally broad consensus that total thyroidectomy is indicated for patients presenting with a DTC > 4 cm or a high-risk carcinoma of any size. For a low-risk DTC < 1 cm, lobectomy is sufficient, though active surveillance strategies have not yet been widely adopted. DTCs of 1–4 cm offer more variation in recommendation and practice. There is international consensus that therapeutic lymph node dissection is necessary with clinically positive nodal (N1) disease in the central

or lateral neck compartment; however, discrepancies exist in consideration of prophylactic lymph node dissection. No guidelines actively recommend routine prophylactic lateral neck dissection, though some previous retrospective studies have recommended it^{37,38}.

The BTA 2014 guideline represents the United Kingdom (UK) consensus opinion and is the most recent update to the first edition of guidelines from the Royal College of Physicians in 2002 and interval update in 2006/7^{39,40}. Like many of the more recent guidelines, there is a strong emphasis on multidisciplinary care, personalized decision-making, and risk stratification in the BTA guideline. Similarly, the authors have de-escalated the BTA 2006/7 recommendation to perform total thyroidectomy for all DTC >1cm and now recommend lobectomy alone for PTMC without other risk factors, and total thyroidectomy for tumors >4 cm (as well as multifocality, bilaterality, extra-thyroidal spread, familial disease, clinically involved nodal disease or distant metastasis). Personalized decision-making is employed in cases of DTC between 1–4cm. Prophylactic central neck dissection is not recommended in low risk patients, and individual choice is again invoked for those deemed high risk (adverse histological subtype, age >45, multifocality, tumor size >4cm, extrathyroidal extension), and unilateral central neck dissection is not recommended³⁹. Notably, active surveillance is not included in the 2014 BTA guidelines. As described above, the United Kingdom holds a stance that falls between the United States and continental European philosophies.

The American Association of Clinical Endocrinologists (AACE), American College of Endocrinology (ACE), and Associazione Medici Endocrinologi (AME) clinical practice guidelines for thyroid nodules was first published in 2006, and was subsequently updated in 2010 and 2016⁴¹. These guidelines cover diagnostic and therapeutic aspects of thyroid nodular disease but not thyroid cancer management, and the newest iteration notably includes task force members from the European Thyroid Association (ETA). The ATA, BTA, and AACE/ACE/AME also have all included separate, yet similar, thyroid nodule classifications systems to aid in risk stratification for early management and cytologic evaluation of thyroid nodules⁴¹.

A European consensus statement for management of patients with DTC was released in 2006 recommends that DTC <1 cm with no concerning features is the only DTC that may be suitable for less than total thyroidectomy. However, these authors have since published on the utility of de-escalation, including active surveillance, and two (Pacini, Schlumberger) are included in authorship of the 2015 ATA guidelines^{24,42}.

The German Association of Endocrine Surgeons practice guideline released in 2013 is generally in accordance with the ATA; however, they do take a notably different approach to PTMC and PTC measuring 1–4cm⁴³. The authors state that PTMC, defined by size criteria alone, in fact represents a continuum of disease that that may require greater than lobectomy alone, and that an interdisciplinary board should be consulted regarding need for total/completion thyroidectomy or RAI in select, non-classic cases⁴³. The guidelines recommend more definitively that total thyroidectomy is warranted for PTC >10mm and metastatic or grossly invasive PTC of any size⁴³. The authors cite high rate of tumor multifocality, the risk of intraglandular and extraglandular dissemination, and facilitation of radioiodine therapy and diagnostic nuclear scans on follow-up as arguments for this practice.

Indeed, existence of iodine deficient regions across Europe increase the rate of bilateral thyroid nodularity/multinodular goiter, and may contribute to the lower threshold for total thyroidectomy in these guidelines. Prophylactic neck dissection is considered after weighing risks and benefits, with a strong recommendation to be performed by an experienced surgeon.

The Spanish Society for Medical Oncology released clinical guidelines in 2014 which recommend near total or total thyroidectomy for PTC > 1cm, with consideration of lobectomy for PTMC, and no robust consideration of active surveillance⁴⁴. The European Society of Medical Oncology released a clinical practice guideline in 2012 recommending near-total or total thyroidectomy as an initial treatment for DTC with less extensive surgical procedure (lobectomy) reserved for unifocal DTC diagnosed incidentally during surgery or benign disease⁴⁵. The absence of recommendations regarding observation and lobectomy for PTMC are likely due to the fact that these were not updated in recent years.

Asian Perspectives

The Japanese guidelines for treatment of DTC were published in 2010 as a joint effort between the Japanese Society of Thyroid Surgeons (JSTS) and the Japanese Association of Endocrine Surgeons (JAES)⁴⁶. In many ways, the Japanese have been the leaders in the global movement towards treatment de-escalation since their landmark publications describing surveillance practices^{47,48}. At the time these guidelines were published, endocrine surgeons in Japan preferred lobectomy or subtotal thyroidectomy with adjuvant therapies rather than total thyroidectomy with radioactive iodine for the majority of patients with PTC. This was based on the presumption that total thyroidectomy would not improve survival in low risk patients, small contralateral lesions would be diagnosed by ultrasound and/or otherwise be deemed not clinically significant, neck recurrences could be cured by reoperation, and total thyroidectomy has higher complication rate^{49,50}. The Japanese guidelines were updated in 2014 to address six clinical questions in the context of the continuously evolving evidence⁴⁶. As the title of the Takami et al. update suggests, there has been “*A Gradual Move Towards Consensus Between Japanese and Western Practice in the Management of Thyroid Carcinoma*”. Current treatment in Japan continues to be less-invasive (narrower indications for escalated surgical treatment) than most Western guidelines: The updated guidelines introduce an observation guide for low-risk papillary microcarcinoma^{30,51,52}, including a recommendation of observation by ultrasonography without immediate surgery (active surveillance) as the best choice for patients with low-risk papillary microcarcinoma⁵³. Their indications for total thyroidectomy in PTC patients includes tumors >4cm, clinical node metastasis, distant metastasis, or extrathyroid extension to the trachea or esophagus, in agreement with their own 2010 JSTS/JAES guidelines. Several studies have shown a relationship between surgeon volume and patient outcome, with lower risks of complication seen in high volume surgeons^{54–58}, and the Japanese group does state explicitly in their guidelines that these were not established for experts in thyroid surgery, and therefore they suggest careful consideration of risks and benefits of total thyroidectomy or central neck dissection in light of the risks of surgical complication⁴⁶.

As an example where legal restrictions have influenced medical care, radioactive iodine therapy is strictly regulated in Japan and requires hospitalization. Japanese history including the atomic bombings in Hiroshima and Nagasaki in 1945, as well as the Great East Japan Disaster in Fukushima in 2011, have contributed to strong cultural feelings of “radiophobia” in Japan⁵⁹. Still, prognoses of patients treated surgically for DTC without RAIA are similarly excellent despite this restriction⁴⁶. With these restrictions in place, a treatment strategy including RAIA of remnant thyroid lobe rather than completion thyroidectomy in cases of follicular thyroid carcinoma is impertinent in Japan. Foregoing RAI is common in Japan due to the aforementioned cultural stigma, but a recent international surge in individualized treatment planning has demonstrated that fewer patients may benefit from RAI therapy³⁵. Patient specific treatment paradigms are therefore being employed in Japan as well as many additional countries to identify increasing numbers of patients who would not benefit from post-operative RAI therapy^{35,46}. Identifying patients who would not benefit from RAI therapy removes the motivation to potentiate this adjuvant modality via total thyroidectomy.

The Korean Thyroid Association (KTA) is expected to publish an updated guideline for DTC management in 2017, and author Ka Hee Yi very recently offered a review of major changes endorsed by the KTA related to ultrasound screening and FNA criteria, surveillance for PTC, and extent of surgery⁶⁰. This specifically addresses whether the changes to the 2015 ATA guidelines would be accepted with the following conclusion: The KTA will ‘flexibly’ and ‘selectively’ adopt the 2015 ATA guideline recommendations relating to active surveillance and surgical extents for DTCs sized 1 to 4cm; however, FNA criteria according to ultrasound features will continue to be guided by the Korean Thyroid Imaging Reporting and Data System (K-TIRADS)⁶⁰. The paucity of accurate markers indicating progressiveness of indolence of disease is acknowledged by the authors, and a cautious acceptance of the ATA surveillance strategy is noted⁶⁰. The K-TIRADS has a lower biopsy threshold than the corresponding ATA guideline and recommends selective FNA for ultrasound high suspicion nodules >0.5cm and 1cm^{24,60}. The Korean recommendation considers that unnecessary long-term follow up of high suspicious pattern nodules can be avoided, a small percentage of patients with PTC have clinically significant regional or distant metastases, and active surveillance is a viable option even for cytological proven PTMC^{60,61}. In contrast, from 2009 to 2015 guidelines, the ATA effectively increased biopsy threshold from similar nodules from 0.5cm to 1.0cm (in favor of surveillance) due to evidence of low disease specific mortality, locoregional recurrence, and distant recurrence rates associated with PTMC¹².

South Korea provides a striking example of how national screening and diagnostic practices contribute to the aforementioned trend in overdiagnosis. Here, a 15-fold increase in diagnosis of thyroid cancer between 1993 and 2011 when neck ultrasonography was offered at a low cost to a battery of other organized screening programs for five other cancers¹¹. In response, the “Physician Coalition for Prevention of Overdiagnosis of Thyroid Cancer”, initiated national public educational and discouragement of ultrasound screening in healthy patients⁶. A relative stabilization of thyroid cancer incidence and a 35% reduction in thyroid surgery resulted from 2013 to 2015, attributable to less screening and diagnosis rather than more conservative surgical practices⁶. In 2015, The Korean Committee for National Cancer

Screening Guidelines concluded that “thyroid ultrasonography is not routinely recommended for healthy subjects”⁶². The Korean experience offers a unique example of how large-scale introduction and incorporation of screening practices can lead to overdiagnosis, and how this trend can be combatted by both national organizational initiative, patient education, and change of screening practices.

Even when overdiagnosis is recognized, physicians face a challenge to weigh the risks and benefits of early detection for individual patients. While overdiagnosis can be readily apparent within a population, it is more difficult to recognize in an individual, and informed decision-making is considerably complex, as patients in the same clinical situation may make different choices. Challenges persist as we attempt to identify markers of aggressive disease and exclude treatment of cancers that will either not progress, or progress slowly enough as to never become symptomatic in the patient’s lifetime.

The View from Elsewhere

An updated 2013 Brazilian consensus statement recommends total thyroidectomy DTC, with consideration of lobectomy for PTMC, and no robust consideration of active surveillance⁶³. The Endocrine Society of India released a consensus statement in 2011 recommending total thyroidectomy in most cases of confirmed thyroid cancer, though noting that the ATA guidelines may be observed for PTMC⁶⁴. The Latin American Thyroid Society released recommendations in 2009, but currently endorses the American Thyroid Association Guidelines⁶⁵.

Emerging Data

The challenge to identify aggressive versus indolent disease, and how to effectively manage this uncertainty, sparks controversy. A recent Japanese prospective study by Oda et al, published after most recent guidelines, included a prolonged surveillance group and showed that oncologic outcomes of both immediate surgery and active surveillance are similarly excellent; however, the immediate surgery group experienced significantly higher rates of surgical complications and adverse events⁵³. The same author showed that immediate surgery incurred a cost over four times greater than active surveillance at their institution⁶⁶. Though active surveillance is taking a greater role in the management of small PTC, there is still a scarcity of reliable and measurable features to predict who will definitively benefit from active surveillance compared to surgical treatment. Moreover, robust prospective data has not yet been published outside of the Japanese experience.

When active surveillance of DTC primary tumors is chosen, there is not an accepted strategy to manage issues such as frequency of ultrasound evaluations, TSH goals, role of thyroglobulin, and indications for surgical intervention. Use of molecular markers and identification of driving tumor mutations are expected to play a major role in cancer prognostication, potentially identifying tumors with high risk of rapid progression, recurrence, or cancer-related mortality²⁴. The identification of new therapeutic targets and personalized treatment strategies also has potential to change the paradigm of surgical treatment significantly. Active surveillance brings up ethical concerns as well, with divergent views on whether this should be considered an option within the limits of standard of care,

or reserved for the clinical research setting^{67,68}. Further studies are required to examine physician and patient informed decision-making as it relates to the novel active surveillance approach.

Finally, we consider the newly described entity of “noninvasive follicular neoplasm with papillary-like nuclear features” (NIFTP), an indolent tumor formerly known as encapsulated follicular variant of papillary thyroid carcinoma (EFVPTC). In an international multi-institutional, retrospective trial, Nikiforov et al. described a series of 109 patients with NIFTP/EFVPTC pathology (67 treated with lobectomy, none treated with radioactive iodine ablation), none of which had evidence of progressive disease or adverse outcomes⁶⁹. The authors suggest the name change from EFVPTC to NIFTP to better reflect this very low risk pathology, notably dropping the term “carcinoma”. Like PTMC, EFVPTC has increased by an incidence of about 2–3 fold over the past 3 decades⁷⁰. Thus, the authors propose a standardized pathologic/diagnostic criteria for EFVPTC and simultaneously recommend de-escalation in clinical management as these patients are unlikely to benefit from immediate completion thyroidectomy or radioactive iodine ablation⁶⁹. This change is expected to potentially impact over 45,000 patients worldwide each year and significantly decrease over-treatment, surgical complications, and health care costs⁶⁹. How these observations might be integrated within new guidelines remains to be seen.

Conclusion

There is a clear trend in the evolution of guidelines addressing surgical management of differentiated thyroid cancer toward de-escalation, with recommendations recognizing the role of active surveillance of low-risk disease, higher thresholds for surgery, and acceptance of less than total thyroidectomy when surgery is recommended. As the rise in incidence of DTC is largely due to greater identification of small, low-risk tumors, risk stratification becomes an integral part of workup and diagnosis. Treating physicians face a challenge to avoid overtreatment by balancing de-escalated treatment including active surveillance in patients with low risk disease, with identifying which patients will benefit from surgical treatment (and to what extent). Lack of consensus in guidelines persists due to differences in clinical practice patterns, differences in consideration and critical appraisal of existing evidence, cultural and geographical differences (iodine deficiency), and resources available for both diagnosis and treatment. Recommendations are likely to continue evolving with the advent of more evidence. Ultimately, agreement among guidelines across nations and professional organizations may provide better adherence to guideline-driven, evidence-based quality care for the increasing number of patients diagnosed with well-differentiated thyroid carcinoma.

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Abbreviations

AACE	American Association of Clinical Endocrinologists
AAES	American Association of Endocrine Surgeons
ACE	American College of Endocrinology
AHNS	American Society of Head and Neck Surgery
AME	Associazione Medici Endocrinologi
ATA	American Thyroid Association
BTA	British Thyroid Association
DTC	Differentiated Thyroid Carcinoma
EFVPTC	Encapsulated follicular variant of papillary thyroid carcinoma
ETA	European Thyroid Association
ISSG	InterTASC Information Specialists' Sub-Group
JAES	Japanese Association of Endocrine Surgeons
JSTS	Japanese Society of Thyroid Surgeons
K-TIRADS	Korean Thyroid Imaging Reporting and Data System PTMC
KTA	Korean Thyroid Association Papillary Thyroid Microcarcinoma
NCCN	National Comprehensive Cancer Network
NIFTP	Noninvasive follicular neoplasm with papillary-like nuclear features
PTC	Papillary Thyroid Carcinoma
UK	United Kingdom

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Table 1

Selected National Guidelines: Summary of Surgical Treatment

	United States of America ATA (2015)	United States of America NCCN (2016)	Great Britain BTA (2014)	Germany GAES (2013)	Japan JSTS/JAES (2010, with 2014 update)
Active Surveillance (with DTC diagnosis)	Consider for: Low risk tumors (PTMC), without clinically evident metastases or local invasion, and no convincing cytologic evidence of aggressive disease High surgical risk Comorbidities limiting lifespan	No recommendation	No recommendation	No recommendation	Low risk PTMC, N0, M0, Ex(-)
Hemi-thyroidectomy	T < 4cm, Ex (-), RT (-), FHx (-), Unifocal, cN0 Completion: Need for total thyroidectomy based on final pathology. (Strong recommendation, Moderate-quality evidence)	T<4cm, RT(-), Ex(-), N0, M0 (2B) Completion: T>4cm, Ex(+), M1, N1 Bilateral, Poor Differentiation, Margins (+), Multifocal Vascular Invasion (2A) RT(+) (2B)	T<4cm, Age<45, Ex(-), N0 + M0 (4, D) Based on personalized decision making.	PTMC, Ex(-), N0, unifocal, classical subtype FTC without Vascular Invasion	T<4cm, Age <45, N0, M0, Ex(-)
Total or Near Thyroidectomy	T>4cm, or any of following, Ex(+), N1, M1 (Strong recommendation, Moderate-quality evidence)	T>4cm, or any of following: Ex(+), M1, N1, Bilateral, Poor Differentiation (2A) RT(+) (2B)	T>4cm, or any of the following: multifocal, bilateral, Ex(+), FHx(+), N1, M1 (2-, D)	T>1cm Any PTC with one of the following: N1, M1 or Ex(+) FTC without vascular invasion Widely invasive FTC	T>4 cm, or any of the following: N1, M1 Ex(+) to trachea or esophagus Widely invasive FTC
Central Neck Dissection	N1 in Central Neck (Strong recommendation, Moderate-quality evidence) Prophylactic: T3-4, cN1b, Further staging considerations (Weak recommendation, Low-quality evidence)	Clinically apparent central compartment disease (2A) Prophylactic: Consider with T3-4 and lateral disease (2B)	N1, Unclassical Histological Variant, Age>45, Multifocal, 4cm, Ex(+) (1-, C) Prophylactic: Based on personalized decision making (4, D)	cN1 PTC + Surgical expertise to avoid potential sequela	Clinically apparent central compartment disease Prophylactic: Consider based on merits and demerits of the intervention.
Lateral Neck Dissection	Clinically apparent lateral compartment disease (Strong recommendation, Moderate-quality evidence)	Clinically apparent lateral compartment disease (2A)	Clinically apparent lateral compartment disease	Clinically apparent lateral compartment disease	Clinically apparent lateral compartment disease

Ex(+), extrathyroidal extension; T, tumor stage; N, nodal stage; M, metastasis stage.

Strength of Recommendation provided when available (boldface)