Differentiated and anaplastic thyroid carcinoma: Major changes in the American Joint Committee on Cancer eighth edition cancer staging manual.

Perrier ND¹, Brierley JD², Tuttle RM³.

Abstract

Answer questions and earn CME/CNE This is a review of the major changes in the American Joint Committee on Cancer staging manual, eighth edition, for differentiated and anaplastic thyroid carcinoma. All patients younger than 55 years have stage I disease unless they have distant metastases, in which case, their disease is stage II. In patients aged 55 years or older, the presence of distant metastases confers stage IVB, while cases without distant metastases are further categorized based on the presence/absence of gross extrathyroidal extension, tumor size, and lymph node status. Patients aged 55 years or older whose tumor measures 4 cm or smaller (T1-T2) and is confined to the thyroid (N0, NX) have stage I disease, and those whose tumor measures greater than 4 cm and is confined to the thyroid (T3a) have stage II disease regardless of lymph node status. Patients aged 55 years or older whose tumor is confined to the thyroid and measures 4 cm or smaller (T1-T2) with any lymph node metastases present (N1a or N1b) have stage II disease. In patients who demonstrate gross extrathyroidal extension, the disease is considered stage II if only the strap muscles are grossly invaded (T3b); stage III if there is gross invasion of the subcutaneous tissue, larynx, trachea, esophagus, or recurrent laryngeal nerve (T4a); or stage IVA if there is gross invasion of the prevertebral fascia or tumor encasing the carotid artery or internal jugular vein (T4b). The same T definitions will be used for both differentiated and anaplastic thyroid cancer, but the basic premise of the anatomic stage groups will remain the same. CA Cancer J Clin 2017. © 2017 American Cancer Society.

Updated guidelines on the preoperative staging of thyroid cancer.

Kim HJ¹.

Abstract

Recent studies have provided prognostic information and recommendations for staging thyroid cancers that have changed the staging and management guidelines for the disease. Consequently, minimal extrathyroidal extension (ETE) was removed from the T3 stage classification in the eighth edition of the TNM staging system by the American Joint Committee on Cancer. New T categories have been subsequently added, including T3a, defined as a tumor.
>4 cm in its greatest dimension, limited to the thyroid gland, and T3b, defined as a tumor of any size with gross ETE invading only the strap muscles. In this article, the author reviews the changes in the TNM staging system for thyroid cancer, with an emphasis on ultrasonography in preoperative staging.


ROS1 Rearrangement in Thyroid Cancer.


**Abstract**

**BACKGROUND:**

Aberrations involving the ROS1 gene have not been reported in thyroid cancer. Here, a case of ROS1-associated thyroid cancer with unique and aggressive characteristics is presented.

**PATIENT FINDINGS:**

A 24-year-old athlete presented with a 3.5 cm left paramedian upper neck mass. Open biopsy demonstrated a papillary thyroid carcinoma arising in the pyramidal lobe. Additional imaging revealed involvement of her cricothyroid membrane, thyroid laryngeal cartilage, and left vocal cord. Complete en bloc surgical resection of the thyroid with cricothyroid membrane and endolarynx was performed with negative surgical margins. Microscopically, the tumor was largely solid with microfollicular architecture with focal cytoplasmic clearing and nodular invasion with rare true papillae, extending posteriorly through the cricothyroid membrane into the deep soft tissue of the left anterior vocal cord (pT4a). Metastases were present in 5/11 lateral neck and pretracheal lymph nodes with a size up to 0.4 cm (pN1b) with perinodal lymphatic involvement. She was staged according to her age (<45 years) as stage I. The solid-variant histology and locally aggressive behavior triggered oncologic genotyping, which was performed using massive parallel sequencing and anchored multiplexed next-generation sequencing for gene fusion detection on formalin-fixed paraffin embedded tissue. Targeted genotyping did not reveal a panel-specific point mutation. However, gene fusion assessment demonstrated a gene fusion involving ROS1. Mapping of the fusion and sequence analysis identified CCDC30 as the ROS1 fusion partner. Sequence-based prediction of the fusion product revealed the coiled-coil domain 30 (CCDC30) gene fused to the N-terminal ROS1 kinase domain, with CCDC30 as the postulated driver of ROS1-kinase constitutive activation. ROS1 rearrangement was confirmed using fluorescent in situ hybridization as an orthogonal method. A review of all currently reported ROS1 fusions in >7000 samples (The Cancer Genome Atlas) showed no prior report of ROS1-CCDC30, ROS1 fusions, or presence of ROS1 aberrations in thyroid cancer.
SUMMARY:

Herein, the first case of a ROS1 rearrangement in a papillary thyroid carcinoma with a locally aggressive presentation is reported.

CONCLUSION:

A review of additional patients with solid-variant papillary thyroid carcinoma and similar clinical characteristics with undetermined tumor genetics is needed, especially in light of the availability of ROS1-targeted therapeutics.


BRAF(V600E) Is Correlated with Recurrence of Papillary Thyroid Microcarcinoma: A Systematic Review, Multi-Institutional Primary Data Analysis, and Meta-Analysis.

Chen Y¹, Sadow PM², Suh H³, Lee KE⁴, Choi JY⁴, Suh YJ⁴, Wang TS⁵, Lubitz CC¹,6.

Abstract

BACKGROUND:

Given the increasing incidence of papillary thyroid carcinoma despite stable disease-specific mortality rates, the potential for the disease to reoccur is a key outcome to predict. The BRAF(V600E) mutation has been associated with recurrent disease in larger tumors. However, its correlation in papillary thyroid microcarcinoma (PTMC) is not clear in individual series.

METHODS:

The MEDLINE, EMBASE, Web of Science, and Cochrane databases were searched for studies including patients with PTMC undergoing initial surgical treatment. Studies with at least two years of follow-up, BRAF genotyping (the comparator), and recurrence as an outcome were included, as were unpublished primary data on 485 patients from two institutions. The metameter analyzed was odds ratio (OR) for recurrence between patients with BRAF(V600E) versus BRAF wild type (BRAFwt).

RESULTS:

The initial search identified 431 references. After screening of the abstracts for inclusion, 44 manuscripts were reviewed in full by two independent reviewers. Four published studies and primary data from two institutional cohorts were included in the final analysis. A meta-analysis of 2247 PTMC patients revealed that patients with a BRAF(V600E) mutation had a higher likelihood for recurrence (odds ratio 2.09 [confidence interval 1.31-3.33], p = 0.002).
CONCLUSIONS:

This meta-analysis shows that BRAF mutational status correlates with recurrence of PTMCs, highlighting the potential utility of genotyping in preoperative and postoperative planning. BRAF mutation may be helpful in risk-stratifying patients with PTMC for surgical management versus observation.


RAS proto-oncogene in medullary thyroid carcinoma.

Moura MM¹, Cavaco BM², Leite V³.

Abstract

Medullary thyroid carcinoma (MTC) is a rare malignancy originating from the calcitonin-secreting parafollicular thyroid C cells. Approximately 75% of cases are sporadic. Rearranged during transfection (RET) proto-oncogene plays a crucial role in MTC development. Besides RET, other oncogenes commonly involved in the pathogenesis of human cancers have also been investigated in MTC. The family of human RAS genes includes the highly homologous HRAS, KRAS, and NRAS genes that encode three distinct proteins. Activating mutations in specific hotspots of the RAS genes are found in about 30% of all human cancers. In thyroid neoplasias, RAS gene point mutations, mainly in NRAS, are detected in benign and malignant tumors arising from the follicular epithelium. However, recent reports have also described RAS mutations in MTC, namely in HRAS and KRAS. Overall, the prevalence of RAS mutations in sporadic MTC varies between 0-43.3%, occurring usually in tumors with WT RET and rarely in those harboring a RET mutation, suggesting that activation of these proto-oncogenes represents alternative genetic events in sporadic MTC tumorigenesis. Thus, the assessment of RAS mutation status can be useful to define therapeutic strategies in RET WT MTC. MTC patients with RAS mutations have an intermediate risk for aggressive cancer, between those with RET mutations in exons 15 and 16, which are associated with the worst prognosis, and cases with other RET mutations, which have the most indolent course of the disease. Recent results from exome sequencing indicate that, besides mutations in RET, HRAS, and KRAS, no other recurrent driver mutations are present in MTC.


Genetics of medullary thyroid cancer: An overview.
Abstract

Medullary thyroid carcinoma (MTC) represents 3-5% of thyroid cancers. 75% is sporadic and 25% is the dominant component of the hereditary multiple endocrine neoplasia (MEN) type 2 syndromes. Three different subtypes of MEN2, such as MEN2A, MEN2B, and Familial MTC (FMTC) have been defined, based on presence or absence of hyperparathyroidism, pheochromocytoma and characteristic clinical features. Mutations of the RET proto-oncogene are implicated in the pathogenesis of MTC, but there are many other mutational patterns involved. In MEN2A, Codon 634 in exon 11 (Cys634Arg), corresponding to a cysteine in the extracellular cysteine-rich domain, is the most commonly altered codon. Many other mutations include codons 611, 618, 620. In the genetical testing of RET mutations in MTCs, Next-Generation Sequencing (NGS) is taking an increasingly important role. One of the most important benefit is the comprehensive analysis of molecular alterations in MTC, which allows rapidly to select patients with different risk levels. There is a difference in miRNA expression pathway between sporadic and hereditary MTCs. Among sporadic cases, expression of miR-127 was significantly lower in those who harbor somatic RET mutations than those with wild-type RET. CDKN1B mutations are associated with many clinical pictures of cancers, such as MEN4. V109G polymorphism is associated with sporadic MTCs negative for RET mutations, and might influence the clinical course of the patients affected by MTC. Although surgery (i.e. total thyroidectomy with neck lymph node dissection) is the elective treatment for MTCs, about 80% of patients have distant metastases at diagnosis and in this cases surgery is not enough and an additional treatment is needed. Interesting results come from two large phase III clinical trials with two targeted tyrosine kinase inhibitors (TKIs), vandetanib and cabozantinib.

CONCLUSIONS:

New genetical testings and therapeutical approaches open new perspectives in MTC management.


MicroRNA-146b: A Novel Biomarker and Therapeutic Target for Human Papillary Thyroid Cancer.

Chou CK1,2, Liu RT3, Kang HY4,5.
Abstract

Papillary thyroid cancer (PTC) is the most common tumor subtype of thyroid cancer. However, not all PTCs are responsive to current surgical and radioiodine treatment. The well-established clinical prognostic factors include tumor size, lymph node/distal metastasis, and extrathyroidal invasion. The RET/PTC-RAS-BRAF linear molecular signaling cascade is known to mediate PTC pathogenesis. However, whether presence of BRAF mutation, the most common genetic alteration in PTC, can affect PTC behavior and prognosis is controversial. MicroRNAs (miRNAs) have been labeled as promising molecular prognostic markers in several tumor types. Our recent studies demonstrated that microRNA-146b (miR-146b) deregulation is associated with PTC aggressiveness and prognosis. Here we summarize the current knowledge related to the functional roles, regulated target genes, and clinical applications of miR-146b in PTC and discuss how these studies provide insights into the key role of miR-146b as an oncogenic regulator promoting cellular transformation as well as a prognosis marker for tumor recurrence in PTC. In conjunction with the current perspectives on miRNAs in a wide variety of human cancers, this review will hopefully translate these updated findings on miR-146b into more comprehensive diagnostic or prognostic information regarding treatment in PTC patients before surgical intervention and follow up strategies.


MicroRNAs in the thyroid.

Boufraqech M1, Klubo-Gwiezdzinska J2, Kebebew E3.

Abstract

MicroRNAs (miRNAs) are small non-coding RNA comprising approximately 19-25 nucleotides. miRNAs can act as tumour suppressors or oncogenes, and aberrant expression of miRNAs has been reported in several human cancers and has been associated with cancer initiation and progression. Recent evidence suggests that miRNAs play a major role in thyroid carcinogenesis. In this review, we summarize the role of miRNAs in thyroid cancer and describe the oncogenic or tumour suppressor function of miRNAs as well as their clinical utility as prognostic or diagnostic markers in thyroid cancer.
The RET oncogene in papillary thyroid carcinoma.

Prescott JD¹, Zeiger MA¹.

Abstract

Papillary thyroid carcinoma (PTC) is the most common form of thyroid cancer, accounting for greater than 80% of cases. Surgical resection, with or without postoperative radioiodine therapy, remains the standard of care for patients with PTC, and the prognosis is generally excellent with appropriate treatment. Despite this, significant numbers of patients will not respond to maximal surgical and medical therapy and ultimately will die from the disease. This mortality reflects an incomplete understanding of the oncogenic mechanisms that initiate, drive, and promote PTC. Nonetheless, significant insights into the pathologic subcellular events underlying PTC have been discovered over the last 2 decades, and this remains an area of significant research interest. Chromosomal rearrangements resulting in the expression of fusion proteins that involve the rearranged during transfection (RET) proto-oncogene were the first oncogenic events to be identified in PTC. Members of this fusion protein family (the RET/PTC family) appear to play an oncogenic role in approximately 20% of PTCs. Herein, the authors review the current understanding of the clinicopathologic role of RET/PTC fusion proteins in PTC development and progression and the molecular mechanisms by which RET/PTCs exert their oncogenic effects on the thyroid epithelium.

Surgical management of medullary thyroid carcinoma.

Konstantinidis A¹, Stang M¹, Roman SA¹, Sosa JA².

Abstract

Medullary thyroid cancer (MTC) is a malignant tumor of the parafollicular C cells of the thyroid and comprises only 1-2% of all thyroid cancer cases. Unlike most differentiated thyroid cancer, MTC is associated with a mean survival of 8.6 years and accounts for a disproportionate 8.6% of thyroid cancer deaths. Surgery is the mainstay of treatment for loco-regional disease and the only current means of cure for MTC. The relatively low incidence of MTC has made the comprehensive study of this disease difficult and most research to date has been based largely on single institution, retrospective, and/or non-randomized studies. Despite various professional organizations such as the American Thyroid Association establishing guidelines for the diagnosis and treatment of patients with MTC, there is still significant variation in actual practice patterns with regard to the extent of surgery, as well as the management of persistent or recurrent disease. The purpose of this review is to discuss the latest updates in the surgical treatment of MTC, as well as the management of locally advanced,
recurrent, and metastatic disease based on the most recent data and expert consensus guidelines.


Screening for Thyroid Cancer: Updated Evidence Report and Systematic Review for the US Preventive Services Task Force.

Lin JS¹, Bowles EJA², Williams SB¹, Morrison CC².

Abstract

Importance:

The incidence of detected thyroid cancer cases has been increasing in the United States since 1975. The majority of thyroid cancers are differentiated cancers with excellent prognosis and long-term survival.

Objective:

To systematically review the benefits and harms associated with thyroid cancer screening and treatment of early thyroid cancer in asymptomatic adults to inform the US Preventive Services Task Force.

Data Sources:

Searches of MEDLINE, PubMed, and the Cochrane Central Register of Controlled Trials for relevant studies published from January 1966 through January 2016, with active surveillance through December 2016.

Study Selection:

English-language studies conducted in asymptomatic adult populations.

Data Extraction and Synthesis:

Two reviewers independently appraised the articles and extracted relevant study data from fair- or good-quality studies. Random-effects meta-analyses were conducted to pool surgical harms.

Main Outcomes and Measures:

Thyroid cancer morbidity and mortality, test accuracy to detect thyroid nodules or thyroid cancer, and harms resulting from screening (including overdiagnosis) or treatment of thyroid cancer.

Results:
Of 10,424 abstracts, 707 full-text articles were reviewed, and 67 studies were included for this review. No fair- to good-quality studies directly examined the benefit of thyroid cancer screening. In 2 studies (n = 354), neck palpation was not sensitive to detect thyroid nodules. In 2 methodologically limited studies (n = 243), a combination of selected high-risk sonographic features was specific for thyroid malignancy. Three studies (n = 5894) directly addressed the harms of thyroid cancer screening, none of which suggested any serious harms from screening or ultrasound-guided fine-needle aspiration. No screening studies directly examined the risk of overdiagnosis. Two observational studies (n = 39,211) included cohorts of persons treated for well-differentiated thyroid cancer and persons with no surgery or surveillance; however, these studies did not adjust for confounders and therefore were not designed to determine if earlier or immediate treatment vs delayed or no surgical treatment improves patient outcomes. Based on 36 studies (n = 43,295), the 95% CI for the rate of surgical harm was 2.12 to 5.93 cases of permanent hypoparathyroidism per 100 thyroidectomies and 0.99 to 2.13 cases of recurrent laryngeal nerve palsy per 100 operations. Based on 16 studies (n = 291,796), treatment of differentiated thyroid cancer with radioactive iodine is associated with a small increase in risk of second primary malignancies and with increased risk of permanent adverse effects on the salivary gland, such as dry mouth.

Conclusions and Relevance:

Although ultrasonography of the neck using high-risk sonographic characteristics plus follow-up cytology from fine-needle aspiration can identify thyroid cancers, it is unclear if population-based or targeted screening can decrease mortality rates or improve important patient health outcomes. Screening that results in the identification of indolent thyroid cancers, and treatment of these overdiagnosed cancers, may increase the risk of patient harms.


Genetics of medullary thyroid cancer: An overview.

Accardo G¹, Conzo G², Esposito D¹, Gambardella C², Mazzella M¹, Castaldo F¹, Di Donna C¹, Polistena A³, Avenio N³, Colantuoni V⁴, Giugliano D¹, Pasquali D⁵.

Abstract

Medullary thyroid carcinoma (MTC) represents 3-5% of thyroid cancers. 75% is sporadic and 25% is the dominant component of the hereditary multiple
endocrine neoplasia (MEN) type 2 syndromes. Three different subtypes of MEN2, such as MEN2A, MEN2B, and Familial MTC (FMTC) have been defined, based on presence or absence of hyperparathyroidism, pheochromocytoma and characteristic clinical features. Mutations of the RET proto-oncogene are implicated in the pathogenesis of MTC, but there are many other mutational patterns involved. In MEN2A, Codon 634 in exon 11 (Cys634Arg), corresponding to a cysteine in the extracellular cysteine-rich domain, is the most commonly altered codon. Many other mutations include codons 611, 618, 620. In the genetical testing of RET mutations in MTCs, Next-Generation Sequencing (NGS) is taking an increasingly important role. One of the most important benefit is the comprehensive analysis of molecular alterations in MTC, which allows rapidly to select patients with different risk levels. There is a difference in miRNA expression pathway between sporadic and hereditary MTCs. Among sporadic cases, expression of miR-127 was significantly lower in those who harbor somatic RET mutations than those with wild-type RET. CDKN1B mutations are associated with many clinical pictures of cancers, such as MEN4. V109G polymorphism is associated with sporadic MTCs negative for RET mutations, and might influence the clinical course of the patients affected by MTC. Although surgery (i.e. total thyroidectomy with neck lymph node dissection) is the elective treatment for MTCs, about 80% of patients have distant metastases at diagnosis and in this cases surgery is not enough and an additional treatment is needed. Interesting results come from two large phase III clinical trials with two targeted tyrosine kinase inhibitors (TKIs), vandetanib and cabozantinib.

CONCLUSIONS:

New genetical testings and therapeutical approaches open new perspectives in MTC management.


Differentiated and Medullary Thyroid Cancer: Surgical Management of Cervical Lymph Nodes.

Asimakopoulos P¹, Nixon IJ², Shaha AR³.

Abstract

Thyroid cancer metastasises to the central and lateral compartments of the neck frequently and early. The impact of nodal metastases on outcome is affected by the histological subtype of the primary tumour and the patient's age, as well as the size, number and location of those metastases. The impact of extranodal extension has recently been highlighted as an important prognosticating factor. Although clinically evident nodal disease in the lateral neck compartments has a
significant impact on both survival and recurrence, microscopic metastases to the central or the lateral neck in well-differentiated thyroid cancer do not significantly affect outcome. Here we discuss the surgical management of neck metastases in well-differentiated and medullary thyroid carcinoma.


Revised American Thyroid Association guidelines for the management of medullary thyroid carcinoma.

Wells SA Jr1, Asa SL2, Dralle H3, Elisei R4, Evans DB5, Gagel RF6, Lee N7, Machens A8, Moley JF8, Pacini F9, Raue F10, Frank-Raue K10, Robinson B11, Rosenthal MS12, Santoro M13, Schlumberger M14, Shah M15, Waguespack SG6; American Thyroid Association Guidelines Task Force on Medullary Thyroid Carcinoma.

Abstract

INTRODUCTION:

The American Thyroid Association appointed a Task Force of experts to revise the original Medullary Thyroid Carcinoma: Management Guidelines of the American Thyroid Association.

METHODS:

The Task Force identified relevant articles using a systematic PubMed search, supplemented with additional published materials, and then created evidence-based recommendations, which were set in categories using criteria adapted from the United States Preventive Services Task Force Agency for Healthcare Research and Quality. The original guidelines provided abundant source material and an excellent organizational structure that served as the basis for the current revised document.

RESULTS:

The revised guidelines are focused primarily on the diagnosis and treatment of patients with sporadic medullary thyroid carcinoma (MTC) and hereditary MTC.

CONCLUSIONS:

The Task Force developed 67 evidence-based recommendations to assist clinicians in the care of patients with MTC. The Task Force considers the recommendations to represent current, rational, and optimal medical practice.
Management of hereditary medullary thyroid carcinoma.

Pappa T¹,², Alevizaki M³.

Abstract

Hereditary medullary thyroid carcinoma (MTC) represents up to one-third of MTC cases and includes multiple endocrine neoplasia syndrome type 2A (and its variant familial MTC) and 2B. The aim of this paper is to provide an overview of the disease focusing on the management of hereditary MTC patients, who have already developed tumor, as well as discuss the recommended approach for asymptomatic family members carrying the same mutation. A PubMed search was performed to review recent literature on diagnosis, genetic testing, and surgical and medical management of hereditary MTC. The wide use of genetic testing for RET mutations has markedly influenced the course of hereditary MTC. Prophylactic thyroidectomy of RET carriers at an early age eliminates the risk of developing MTC later in life. Pre-operative staging is a strong prognostic factor in patients, who have developed MTC. The use of recently approved tyrosine kinase inhibitors (vandetanib, cabozantinib) holds promising results for the treatment of unresectable, locally advanced, and progressive metastatic MTC. Genetic testing of the RET gene is a powerful tool in the diagnosis and prognosis of MTC. Ongoing research is expected to add novel treatment options for patients with advanced, progressive disease.
clinical management and aims to guide physicians towards a rationale for the use of imaging prior to prophylactic thyroidectomy, initial surgery and reoperations for persistent/recurrent disease. This review also concludes that, in the near future, it is expected that these patients will indeed benefit from newly developed positron emission tomography approaches which will target peptide receptors and protein kinases. Identification of MEN2-specific radiopharmaceuticals will also soon arise from molecular profiling studies. Furthermore, subtotal (cortical-sparing) adrenalectomy, which is a valid option in MEN2 for avoiding long-term steroid replacement, will benefit from an accurate estimation through imaging of differential adrenocortical function.