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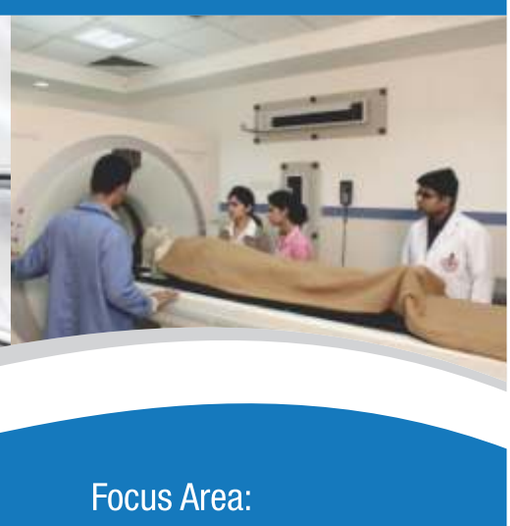

Focus Area:

THYROID CANCER

Rajiv Gandhi Cancer Institute and Research Centre
A Unit of Indraprastha Cancer Society
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From the Desk of Director Research

Thyroid cancer is a disease in which malignant cells form in the tissues of the thyroid gland. Thyroid cancers account for about 14,000 new cases in India and 52,126 in the United States each year. Thyroid malignancies are divided into papillary carcinomas (80%), follicular carcinomas (10%), medullary thyroid carcinomas (5-10%), anaplastic carcinomas (1-2%), primary thyroid lymphomas (rare) and primary thyroid sarcomas (rare).

Thyroid carcinoma most commonly manifests as a painless, palpable and solitary thyroid nodule. Factors that may increase the risk of thyroid cancer include female sex, age, exposure to high levels of radiation and certain inherited genetic syndromes etc. Females are more likely to have thyroid cancer at a ratio of 3:1. This malignancy can occur in any age group, although it is most common after the age of 30 and its aggressiveness increases significantly in older patients. Being exposed to radiation to the head and neck as a child increases the risk of thyroid cancer. Having certain genetic conditions such as familial medullary thyroid cancer, multiple endocrine neoplasia type 2A syndrome, and multiple endocrine neoplasia type 2B syndrome can also increase the risk of thyroid cancer. The discovery of the genetic causes of familial medullary thyroid cancer now makes it possible to identify family members carrying the abnormal *RET* gene and to remove the thyroid to prevent cancer from developing there. The only certain way to diagnose thyroid cancer is by examining the thyroid tissue obtained through a needle or surgery for biopsy. Other investigations such as CEA blood test, physical exam and imaging tests may be used to establish a definitive diagnosis and determine staging.

Most thyroid cancers may be cured, especially if those have not metastasized to distant parts of the body. The standard treatments for thyroid cancer include surgery, radiation therapy, including radioactive iodine therapy (RAI), and targeted therapy. The primary management for most patients with thyroid cancer is surgical removal of the entire thyroid gland. The patients with cancers likely to recur may be helped by giving RAI after surgery. Recent studies have shown that patients with very low thyroglobulin levels 3 months after surgery have a very low risk of recurrence even without RAI. Researchers are looking for the ways to make RAI effective against more thyroid cancers, e.g. the cells have changes in the *BRAF* gene, which may make them less likely to respond to RAI therapy. In general, thyroid cancers do not respond well to chemotherapy. But exciting data are emerging about some newer targeted drugs. Targeted drugs, such as kinase inhibitors, anti-angiogenesis drugs and other targeted drugs may work in some cases when standard chemotherapy drugs do not, and they have less severe side effects.

The chance of being diagnosed with thyroid cancer has risen in recent years. Much of this rise appears to be the result of the increased use of thyroid ultrasound, which can detect small thyroid nodules that might not otherwise have been found in the past. Recent international studies have suggested that some of these newly found, very small thyroid cancers (known as micro-papillary thyroid cancers) may not need to be treated right away but can be safely observed. The ongoing clinical trials in are now looking to confirm the results of these international studies.

The present issue of the Cancer News highlights the newer advances in the field of thyroid cancer and features the regular articles, such as Special Feature, Guest Article, Perspective and In Focus. We are grateful to Dr Alok Thakar, Professor of Otorhinolaryngology & Head - Neck Surgery; Dr Anup Singh, Senior Resident, Dept of Otolaryngology & Head-Neck Surgery, AIIMS, New Delhi for the "Guest Article" and Prof T K Thusoo, Chairperson, Dept of General & Minimal Invasive Surgery, Artemis Hospital, Gurgaon for Outlook.

Suggestions/comments from the readers are welcome.

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SPECIAL FEATURE

ROLE OF rhTSH IN DIFFERENTIATED THYROID CANCER

Thyroid cancer is the most common endocrine cancer with nearly 3.8 % of total newly diagnosed cancer cases in 2016 and estimated 0.3% of all cancer deaths[1].

Well-differentiated thyroid cancer is generally managed by near-total or total thyroidectomy. Post-thyroidectomy residual (remnant) thyroid tissue needs to be ablated with radioactive 131-iodine to facilitate followup. It has also been shown that ablation of remnant tissues reduces the frequency of recurrence and may reduce mortality.

High levels of thyroid stimulating hormone (TSH) is essential for effective ablation of remnant tissue as it stimulates iodine uptake by thyroid cells. Traditionally this high level has been achieved by with holding thyroxine therapy for 4-6 weeks after thyroidectomy, causing endogenous TSH to rise. However, since the patient becomes hypothyroid there can be a severe negative impact on the patient's quality of life[2].

A highly purified, recombinant form of the naturally occurring human protein TSH, rhTSH, has been developed and used as an alternative to withholding thyroxine as pre-treatment for radioiodine ablation[3, 4].

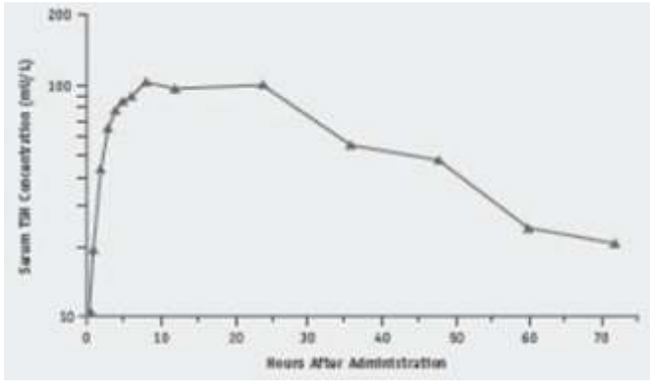
Description of rhTSH (Thyrogen)

Thyrogen is produced by recombinant DNA technology. It is comprised of two non-covalently linked subunits. The amino acid sequence of rhTSH is identical to that of human pituitary TSH.

Following graph shows the mean serum TSH concentration level vs. time on a logarithmic scale of a single 0.9 mg intramuscular (I.M.) injection of rhTSH.

Following a single 0.9 mg dose of Thyrogen administered I.M., the mean peak rhTSH concentration is reached in approximately 13±8 hours. The mean elimination half-life is 22±9 hours. The major elimination route of Thyrogen is believed to be renal and to a lesser extent hepatic[5, 6].

When Thyrogen 0.9 mg is given I.M. on two consecutive days, within 72 hours following the second injection serum TSH level will be well below 25 or 30 mIU/mL



Uses

1) In ablation

Binding of Thyrogen to TSH receptors on normal thyroid epithelial cells or on well-differentiated thyroid cancer tissue stimulates iodine uptake and synthesis and secretion of Tg and thyroid hormones.

In operated patients with low-intermediate risk DTC without extensive lymph node involvement (i.e., T1–T3, N0/Nx/N1a, M0), RAI remnant ablation or adjuvant therapy can be planned with rhTSH stimulation for achieving remnant ablation as it provides better shortterm quality of life, comparable ablation efficacy, and no significant difference in long-term outcomes.

Long term follow-up has confirmed that patients prepared for ablation with Thyrogen and 100 mCi have comparable rates of tumor recurrence and persistence to thyroid hormone withdrawal[7].

Thyrogen is currently approved by FDA for use in preparation for RAI remnant ablation in patients who have undergone a near-total or total thyroidectomy for well-differentiated thyroid cancer. Data from an observational study suggest that rhTSH raises serum TSH measurements in patients who are unable to mount an endogenous TSH rise and appears to reduce the risk of hypothyroid-related complications in patients with significant medical or psychiatric comorbidity[8]. Some of the complications that were reported to be avoided by use of rhTSH included worsening of psychiatric illness, respiratory compromise, central nervous system (CNS) compromise, aggravation of congestive heart failure, and aggravation of coronary artery disease[8]. Multiple RCTs have focused on short-term remnant ablation outcomes in low and intermediate risk DTC with lower risk features, using rhTSH compared to thyroid hormone withdrawal and found no difference after rhTSH preparation compared to thyroid hormone withdrawal, using ^{131}I dose activities ranging from 30 to 100 mCi[10-14].

In summary, the use of rhTSH for preparation for remnant ablation is associated with superior short-term quality of life and similar rates of successful remnant ablation compared to traditional thyroid hormone withdrawal.

Use in Diagnostic Follow-Up

Four primary goals of first dose of iodine-131 therapy after adequate surgery have been defined. First goal is to destroy all residual thyroid tissue after recommended surgery (remnant ablation), in turns make serum Tg and DxWBI scan test more sensitive for disease detection during follow up. Second goal is to facilitate initial staging by providing a post therapy scan that can detect unknown local or distant metastatic sites in approx. 10% of cases. Third goal is to reduce the risk of recurrence and disease specific mortality by destroying suspected but unproven micro metastasis (adjuvant therapy). Fourth goal is to treat known local of distant metastatic sites (radioactive iodine therapy). These goals are interrelated so a clear understanding of specific indication for iodine treatment is important to select correct ^{131}I dose and to define prognostication of individual patient. Clinical endpoints of each goal will be different.

After thyroidectomy and ^{131}I ablation of residual thyroid tissue, follow-up for patients with well differentiated thyroid cancer has traditionally consisted of periodic radioiodine whole body scanning (WBS) and serum thyroglobulin (Tg) testing. Both WBS and Tg tests are performed after an adequate period of thyroid hormone therapy. This is achieved by therapy with thyroxine (T4), sometimes in combination with triiodothyronine (T3). In most patients, thyroid hormone withdrawal will result in an increase of endogenous thyroid-stimulating hormone (TSH) and increased functional activity (i.e., Tg synthesis and ^{131}I uptake) of any residual, as well as metastatic thyroid tissue. Thyroid hormone must be withdrawn for 2 to 6 weeks in order to raise TSH levels.

Withdrawing thyroid hormone induces hypothyroidism. Over 90% of patients experience symptoms, which can be severely debilitating. These symptoms may result in a major disruption of the patient's family, social and work life. The signs and symptoms of hypothyroidism may persist for up to 10 weeks between initial withdrawal and restoration of normal thyroid ormone levels[9, 15].

In addition, prolonged elevation of serum TSH levels may stimulate the growth of metastases. For these reasons, many clinicians measure serum Tg levels on thyroid hormone therapy for the detection of tumor recurrence in patients during long-term follow-up. However, measuring Tg while remaining on thyroid hormone therapy is less sensitive than by withdrawal of thyroid hormone therapy and false-negative Tg tests are frequent. When Tg testing is positive, thyroid hormone therapy is withdrawn for WBS. Tg testing is repeated and followed by radioiodine treatment if required.

When used as an alternative to thyroid hormone withdrawal (THW), the combination of WBS and Tg testing after Thyrogen administration is highly sensitive for detection of thyroid remnants or cancer. The combination of Thyrogen WBS and Thyrogen Tg testing (using a cut off of <2.0 ng/ml) is not statistically significantly different from the results obtained following THW[3].

The combination of Thyrogen WBS and Thyrogen Tg testing (using a cut off of <2.0 ng/ml) detected 100% of metastatic disease in a controlled clinical trial[6]. Thyrogen significantly increases the sensitivity of on-suppression serum Tg testing. In addition, Thyrogen simplifies test scheduling and allows WBS and Tg tests to be performed over a 5-day period.

Follow-up testing for residual thyroid cancer by use of Thyrogen is diagnostically equivalent to thyroid hormone withdrawal[16-18].

Thyrogen preserves the quality of life of patients undergoing diagnostic testing for thyroid cancer recurrence and avoids the debilitating signs and symptoms of hypothyroidism that are associated with THW[19-22].

Thyrogen is well tolerated in the majority of patients. In six pivotal prospective clinical trials, and from adverse events reported to Genzyme during the post-marketing period, the most common reported adverse events were nausea and headache, occurring in approximately 12% and 7% of patients, respectively[23, 3].

Very rare cases of hyperthyroidism or atrial fibrillation have been observed. Manifestations of hypersensitivity, or other types of adverse events, have been reported uncommonly in clinical trials and the post-marketing setting, consisting of urticaria, rash, pruritis, enlargement of residual thyroid tissue or metastases, stroke, development of antibodies and respiratory signs and symptoms[23, 3].

Revised American Thyroid Association (ATA) Management Guidelines for Patients with Thyroid Nodules and Differentiated Thyroid Cancer cover all aspects of the diagnosis, assessment and management of patients with thyroid nodules and differentiated thyroid cancer. In relation to recommendations on the use of

Thyrogen, the guidelines confirm that Thyrogen is an alternative to THST withdrawal as preparation for ablation. The guidelines recommend that follow-up is determined by results from the RxWBS 5-8 days following ablation:

- If there is uptake in the thyroid bed, further follow-up is required 6-12 months later and should include neck ultrasound, TSH-stimulated DxWBS and Tg measurement.
- If there is uptake outside the thyroid bed, further testing and/or treatment may be required[24].

Successful remnant ablation will be defined as no radioactive iodine uptake in follow up DxWBI scan, suggest complete ablation (Figure 1). Because ablation is given for those patients who have low risk of recurrence (low risk group), so we expect serum Tg should be undetectable during followup. For those patients, who are being treated with adjuvant treatment intention, undetectable stimulated Tg during first follow-up and reduced recurrence rate and disease specific mortality during long term follow-up are the endpoints. A recent article by Tuttle et al showed that rhTSH for remnant ablation in intermediate and high risk group patients is associated with slight but statistically significant improvement in an initial response to therapy but similar final clinical outcomes. 85-90% of effectiveness of rhTSH preparation with 100 mCi for destroying normal thyroid remnant has been reported. More recent studies have show equivalent efficiency of 50mCi and 30mCi ablation as well with rhTSH. So there is growing data of favoring low dose (30mCi) of radioactive iodine for ablation in low risk group patients and keeping higher doses for adjuvant scenario (high risk group).

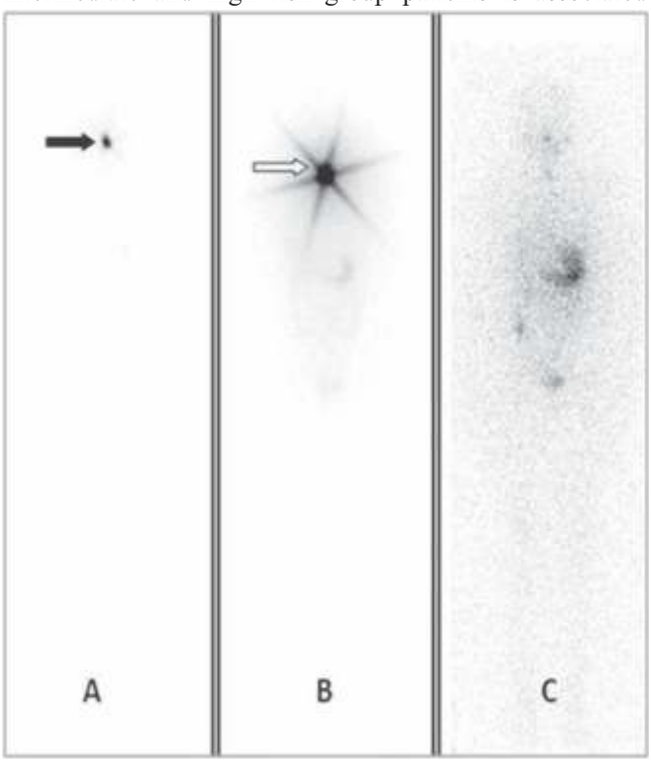


Fig. 1: *(A) Diagnostic whole body iodine (DxWBI) scan revealed residual thyroid tissue in thyroid bed. (B) Post ablation therapy, whole body iodine scan revealed good concentration of radioactive iodine in thyroid bed with no iodine uptake outside thyroid bed. (C) Follow-up DxWBIscan revealed no radioactive iodine uptake in thyroid bed suggested complete ablation.*

rhTSH-based preparation has not been accepted for those patients who have distant metastasis across the board. Studies are available suggesting better tolerability of radioactive iodine therapy with rhTSH rather than THW in metastasis patients. Due to long period of hypothyroidism with THW, tumor tends to grow and patients may become more symptomatic and general condition may further deteriorate. In our experience we have seen better quality of life and acceptance by patient with metastasis for radioiodine treatment with rhTSH as compared to THW. In recurrence, role of rhTSH has not been accepted so far by various associations. However, promising results for improved quality of life and equal efficacy of radioactive iodine treatment is available.

In conclusion, rhTSH as compared to THW for preparation of remnant ablation in non metastatic DTC patients, has been well accepted by both American Thyroid Association and European Thyroid Association. Judicious use of rhTSH has been recommended by experts in other situations, however growing literature of morbidity reduction and similar efficacy in most scenarios is available.

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OUTLOOK

SURGICAL MANAGEMENT OF WELL DIFFERENTIATED THYROID CANCER – HAS THE SCENARIO CHANGED?

Introduction

The term Differentiated Thyroid Cancer (DTC) is used for the tumors arising from the cells lining the thyroid follicles which includes papillary (PTC), follicular (FTC) and Hurthle cell carcinoma (HCC) and generally excludes the tumors arising from para follicular cells. Well differentiated thyroid cancers are the commonest type of thyroid malignancy. In the recent years the incidence of these tumors seems to be increasing (1). While surgical resection has remained the gold standard for their treatment, controversies still exist regarding the extent of surgery because of indolent nature of majority of these tumors. There has also been many changes in the surgical approach to thyroidectomy as a result of instrument innovations, such as harmonic scalpel, Liga Sure, intraoperative nerve monitoring, application of minimally invasive surgery such as use of video assisted thyroidectomy and advent of robotic surgery.

Surgical Management

The extent of surgical resection recommended for treatment of DTC includes thyroid lobectomy/ hemithyroidectomy, near total or total thyroidectomy with or without prophylactic central node dissection. The study of various prognostic factors has enabled the endocrine surgeons to develop a risk stratification system in order to arrive at some consensus regarding the extent of thyroidectomy. These include age at diagnosis, tumor size, grade of tumor, extra thyroidal extension, completeness of resection, lymph node involvement, multi centricity and presence of distant metastasis. Based of these, Tuttle et al (5) classified risk of death from thyroid cancer into four categories viz. very low risk, low risk, intermediate risk and high risk groups. Total or near total thyroidectomy is considered as the procedure of choice for most of the DTCs. Though some studies have shown comparable long term results between thyroid lobectomy/ hemithyroidectomy and total thyroidectomy in low-risk and intermediate-risk (24), majority have shown that lobectomy alone resulted in significantly higher risk of recurrence and death in tumors of > 1 cm, when compared to total or near total thyroidectomy (6,7,8). High rate of occult cancer (35 to 60%) in the contralateral lobe, especially in papillary cancers, and 6-10% rate of recurrence in the contralateral lobe further strengthens the need for total/ near total thyroidectomy in management of DTC. Another major advantage of total thyroidectomy is that it facilitates detection of metastatic disease by radio isotope scan, use of radioactive iodine as adjuvant therapy whenever necessary and disease surveillance by estimation of serum thyroglobulin levels during follow-up. Thyroid lobectomy/ hemi-thyroidectomy should be reserved for very small tumors < 1 cm, confined to one lobe with a favourable histology such as no micro vascular invasion, absence of worrisome histology in papillary cancer such as tall cell variant, columnar variant, insular variant and poor cell differentiation. This could save these patients from potential risk of contralateral recurrent laryngeal nerve and parathyroid injury. The long term survival in such case a does not seem to get affected (24) though recurrence rate may be marginally higher(6).

Lymph Node Dissection: Prophylactic or Therapeutic?

Papillary cancers have propensity to spread to lymph nodes, the rate of central node involvement being quoted from 20-90%. The unanticipated microscopic metastasis in central node has been reported to be 38-45 % of patients undergoing prophylactic central node dissection (CND). American Thyroid Association (ATA) recommends prophylactic CND in patients with PTC, and locally advanced primary tumors (T3 & T4). However, in their recent guidelines no prophylactic lymph node dissection has been advocated for small T1 & T2, non-invasive, clinically node negative PTC and most FTC, as such patients have lower risk of lymph node metastasis and are less likely to benefit from additional surgery. The European Thyroid Cancer Taskforce recommends prophylactic CND only in patients with suspected and/or intra-operatively proven lymph node metastasis (47). Conflicting reports are available regarding increased risk of recurrent laryngeal nerve and parathyroid injury after CND (15,19,49). Therefore, role of prophylactic CND is still a topic of considerable debate and larger prospective trials are needed to evaluate benefit of CND in DTC.

Therapeutic lymph node dissection is recommended as and when there is clinical and /or cytological evidence of lymph node metastasis. Apart from central lymph nodes, nodes in lateral compartment viz. level III & IV and less

commonly Level II & V may be involved as per clinical assessment, or ultrasound detected and confirmed cytological (pre-operative or per-operative FNAC) findings. A modified radical neck dissection is recommended in node positive cases to avoid the morbidity of classical neck dissection as lymph node metastasis particularly in young patient with a favourable histology, does not alter the overall survival. A targeted compartmental lymph node dissection, aided by preoperative assessment, rather than "berry-picking" or isolated lymphadenectomy is well accepted.

Technical Advancement

A) ***Endoscopic Thyroid Surgery:*** Endoscopic thyroid surgery was first described in 1997 by Huscher et al(27). Over the years the technique has been refined and with the availability of high definition video endoscopic instruments, it has been found to be safe and effective approach in the hands of trained surgeons and in selected patient populations. Three main endoscopic approaches have been described for the thyroid gland: the cervical (29), the axillary (30), and the breast/ lateral approach (31) with better cosmetic results and faster recovery (10-14).

B) Robotic Thyroid Surgery: Robotic surgery was introduced with the aim of overcoming the limitations of conventional endoscopic surgeries. Robotic thyroid surgery was initially described by Kang et al (33). However, its major drawbacks are long learning curve (34), longer operative time and above all increased cost of the robot.

Future Perspectives/Conclusions

DTC is the commonest of thyroid malignancies and its incidence is ever increasing. Surgical resection is the main stay of treatment. Total / near total thyroidectomy is the treatment of choice for most of the DTCs. Thyroid lobectomy/ hemi-thyroidectomy should be reserved only for small < 1cm tumors localised to a single lobe, noninvasive and favourable histology, particularly in young patients to avoid potential risk to contra lateral recurrent laryngeal nerve and parathyroid glands. The role of prophylactic CND is debatable and warrants randomised prospective studies to further refine the indications for the same. Therapeutic node dissection is indicated in all node positive patients, preferably targeting lymph node compartments and not by" berry picking" which needs to be discouraged. Endoscopic thyroidectomy is an oncological feasibility with better cosmesis and early recovery but only possible in selected patient populations.

Robotic Thyroid surgery does overcome the limitations of endoscopic surgery but is not cost effective and more time consuming.

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RESEARCH & DEVELOPMENT

Glutamine Metabolism and Thyroid Cancer

Researchers in South Korea studied the expression of glutamine metabolism-related protein in tumor and stromal compartments among the his to logic subtypes of 557 thyroid cancer cases [papillary thyroid carcinoma (PTC): 344, follicular carcinoma (FC): 112, medullary carcinoma (MC): 70, poorly differentiated carcinoma (PDC): 23, anaplastic carcinoma (AC): 8 & 152 follicular adenoma (FA)] by tissue microarray analysis. Glutaminolysis-related proteins [glutaminase 1 (GLS1), glutamate dehydrogenase (GDH) & amino acid transporter-2 (ASCT-2)] were proceeded for immunohistochemical staining. AC subgroup showed the highest levels of GLS1 & GDH expression in tumor and stromal compartments in comparison to the other subtypes. Tumoral ASCT2 expression was higher in MC but lower in FC ($p<0.001$). Tumoral GLS1 & GDH expressions were higher in the conventional type than in the follicular variant ($p = 0.043$ and 0.001, respectively), and in PTC with BRAF V600E mutation than in PTC without BRAF V600E mutation ($p<0.001$) in the PTC subgroup. The researchers concluded that glutamine metabolism-related protein expression differed among the histologic subtypes of thyroid cancer.

(Oncotarget, July 18, 2016)

Lymph Node Recurrence in Thyroid Cancer

Regional lymph node recurrence (RLNR) is common in patients with thyroid cancer, however, clinic opatho logical predictors are not well defined. Scientists at Shariati Hospital, Iran clarified these predictors and identified patients who would benefit from prophylactic lymph node dissection. A retrospective analysis was done involving 343 patients who underwent total thyroidectomy between 2007 and 2013. T3 ($p<0.001$;odds ratio=156.41, 95% CI [55.72-439.1]) and ICL ($p<0.001$; odds ratio=77.79, 95% CI [31.55-191.81]) were the strongest predictors of RLNR. The study concluded that patients with specific clinico-pathological features like male gender, age >45 years, larger tumor size, and extrathyroidal extension may be considered as prophylactic lymphadenectomy candidates.

(J Thyroid Res, 2016)

GUEST ARTICLE

MEDULLARY THYROID CANCER

Medullary thyroid carcinomas (MTC) are rare neuroendocrine tumors arising from parafollicular / C (-calcitonin) cells of thyroid which are embryologically derived from the ultimobranchial bodies. These tumors account for ~3-5% of neoplasms of thyroid origin and around 20-25% present as part of hereditary spectrum, the remaining 75-80% presenting in sporadic fashion[1].

The hereditary tumors are transmitted as a part of MEN2 syndrome either alone (FMTC) or as a part of combination spectrum of MEN 2A/MEN 2B2. The overall female predominance (1:1.3)3 does not apply to hereditary tumors because of autosomal dominant pattern of inheritance. The prevalence of MTC in nodular thyroid disease has been reported to be 0.4-1.8%[4].

RET (Rearranged during Transfection) is a protooncogene located on locus 10q11.2 and it's the gain in function mutations associated with this gene, transmitted in an autosomal dominant fashion, which give rise to various phenotypes of hereditary MTC related to MEN2 syndrome. The locus comprises of 21 exons, out of which exon 5,8,10,11 and 13-16 account for majority of here ditary MTC and are hence included in clinical genetic testing[6]. Rest of the loci are tested only when testing for above codons turns out to be negative in a case with strong suspicion for hereditary MTC.

The specific mutations impart a phenotype and prognostic significance[7] with MEN 2B (Exon 16, codon M918T in >95%) bearing the most aggressive phenotype followed by MEN 2A (exon 11, codon 634 in >85 %) which in turn is higher risk than FMTC. The later bears almost same prognostic significance as the sporadic FMTC. Patients with FMTC harbor mutations in a more diverse and heterogeneous fashion with mostly involving exon 13 (codon 768, 790 and 791) and 14(codon 804 and 844) but in rare cases also exon 10 (codon 618 and 620).

The patients with sporadic MTC tend to have tumor cells harboring somatic mutation involving codon 918 in 23-60% of the cases and 883 in some[8]. However, its unlike the germline mutations in hereditary cases and mutation positive and negative cell populations coexist in same tumor mass. The proportion of mutation positive cells increases with tumor mass as does the aggressiveness of sporadic tumor. 18-80% of the sporadic tumors lacking somatic *RET* mutations have mutations involving *KRAS*, *HRAS* and rarely *NRAS*[9]. On genetic testing 1-7% of the patients thought to be sporadic are found to harbor germline mutations and hence genetic testing for germline mutations involving *RET* proto oncogene is advocated for every case of MTC and in 1st degree relatives of individuals harboring *RET* mutation[10].

Table 1. MTC Classification

Variety of MTC	Incidence	Age at clinical diagnos is	Associated features	RET codon (germline mutation)
Sporadic MTC	75	5th decade	None	None
Hereditary MTC	25			
-MEN 2A	~23	3rd decade	1) Classical MEN 2A(Phaeochromocytoma, Parathyroid adenoma)	exon 11 (634) (85% of MEN 2A) exon 10 (609, 611, 618, and 620)
			2) MEN 2A with CLA (Cutaneouslichen amyloidosis)	exon 11 (634) exon 14 (804)
			3) MEN 2A with HD (Hirschprung disease)	exon 10(60 9, 618, and 620) exon 13 (791)
			4) FMTC	exon 13 (768, 790, 791) exon 14 (804, 844) exon 10 (609, 611, 618, 620) exon 15 (891) exon 16 (912) exon 8 (532, 533) exon 11 (630)
-MEN 2B	~2	1st decade	Typica l facies, Marfanoid body habitus, Thickened promin entcorneal nerves (Crying with out tears), Intestinal ganglioneuromatosis	exon 16 (918) (95% of MEN 2B) exon 15 (883) exon 14 (804, 806)

(MTC-medullary thyroid carcinoma, MEN-multiple endocrine neoplasia, CLA-cutaneous lichen amyloidosis, HD Hirschprung disease, FMTC- familial medullary thyroid carcinoma. Ref 5,12)

Table 2. Risk Groups of the RET Mutations and Management Recommendations Based on Age at Manifestation and the Aggressiveness of Medullary Thyroid Carcinoma (MTC)

MTC risk group	Mutated RET codon	Recommended age (years) for testing	Recommended age (years) for surgery	Recommended age for screening PHEO and HPTH
Highest risk	M918T	Soon after birth/ as soon as possible (genetic testing)	First year of life, possibly first month	11 years (HPTH) screening not needed)
High risk	634,883	3 years (physical examination, serum calcitonin, neck ultrasound)-6 monthly for 1 year and then annually	5 years or earlier based on serum calcitonin levels	11 years
Moderate risk	533, 609, 611, 618, 620, 790, 804, 891	5 years (physical examination, serum calcitonin, neck ultrasound)-6 monthly for 1 year and then annually	5 years or later based on serum calcitonin levels and parental concern for long term follow up.	16 years

(PHEO-Phaeochromocytoma, HPTH-Hyperparathyroidism ref -7,12)

Phenotype of the patient in terms of age of onset, aggressiveness of the disease with nodal and systemic spread is directly correlated with the inherited genotype of mutated *RET* proto oncogene. The mutations have been stratified into 3 risk groups based on penetrance and aggressiveness of resulting phenotype of MTC[7].The most aggressive mutations involving codon 918 (exon16) translating into MEN 2B are categorized in the highest risk group for development of MTC and microscopic MTC has been reported in a M918T carrier at 9 weeks of age[11].

Presentation and Evaluation

Most patients presenting sporadically come to clinical attention with a palpable thyroid mass. It is important to identify signs and symptoms pertaining to local spread with features of pressure and invasion of surrounding aerodigestive tract which is a real possibility given the origin of tumor from posterior part of upper thyroid gland. 35-50% of patients will present with regional lymphadenopathy and around 10-15% will have distant metastases at the time of presentation[13]. MTC is associated with a high rate of occult lymph node metastasis, and in palpable tumors, central and ipsilateral lateral compartment disease has been shown to present in up to 81% of cases[21,22]. Also, unlike differentiated thyroid cancers, the presence of lymph node metastasis is a poor prognostic factor, with increasing number of neck nodes imparting an increasing risk for distant metastases[26].

A subset of patients can also present with symptoms related to tumor functionality owing to secretion of various neuroendocrine hormone, principally calcitonin. These patients can have severe diarrhea, more so in advanced cases with hormonally active metastasis. Occasionally flushing can occur and rarely ACTH secretion leading to Cushing syndrome has also been described[14].

Cytological examination of palpable nodule using fine needle aspiration remains mainstay of tissue diagnosis with a sensitivity of 50-80%. The sensitivity can be improved in suspicious cases by using immunohistochemical staining for Calcitonin, CEA and chromogranin A. Even more sensitive technique is calcitonin measurement of FNAC washout fluid[13].

Cytology shows tumor cells with variable morphology arranged in nests or sheets in a stroma of amyloid (found in up to 80% of cases) which itself is calcitonin aggregates. The follicular cells and thyroglobulin staining is absent.

After cytological diagnosis of MTC, both serum calcitonin and CEA measurements, along with genetic *RET* mutation testing, are recommended by American Thyroid Association. The presence of phaeochromocytoma and hyperparathyroidism should be excluded in cases of hereditary MTC[7].

USG remains the main imaging modality and can be used for following objectives:

1) Characterization of primary tumor

2) Localization of additional intrathyroidal nodules

3) Obtaining a guided biopsy

4) Localizing occult cervical lymph nodes

However, USG remains highly operator dependent and can not be reliably used for retrosternal extension of tumor or to look for lymph nodes behind the thyroid or in upper mediastinum.

In patients with signs and symptoms of extensive neck disease or distant mets and in all patients with serum calcitonin level of > 500pg/ml, American Thyroid Association in their 2015 revised guidelines recommend contrast enhanced CT of neck and chest, 3-phase CE MDCT liver or CEMRI of liver, and axial MRI and bone scintigraphy. Neither FDG-PET/CT nor F-DOPA-PET/CT is recommended to detect distant mets specially for primary cases[7].

Biochemical Evaluation of MTC

The primary secretary product of the 'C' cells is calcitonin which can be detected in tumor mass and measured in serum. Normative value of calcitonin is considered to be <10pg/ml but is age, gender and assay dependent[15]. 95th percentile for serum calcitonin in males is 11.7pg/ml while in females it is 5.2pg/ml. Also the levels of calcitonin are physiologically higher in pediatric age group, the value of up to 40pg/ml being considered normal till 6 months of age and up to 15pg/ml till 3 years' age[15]. Even though measurement of serum calcitonin is a routine in MTC patients, the current ATA guidelines do not specify reference ranges and emphasize on individual laboratories setting up their own range based on type of assay being used.

Measurement of calcitonin carries both diagnostic as well as prognostic values and helps defining timing of surgical intervention. The calcitonin measurement can be done as basal level and stimulated levels using calcium or pentagastrin stimulation tests. Basal calcitonin levels correlate well with not only tumor mass and locoregional and distant spread but also with the tumor differentiation. However, basal levels can be falsely elevated in certain physiologic conditions like post prandial, early childhood, high BMI and pregnancy as well as pathologically in cigarrete smokers and alcoholics, with the use of PPIs, glucocorticoids, inautoimmunethyroiditis, hypercalcemia, hyperparathyroidism, hypergastrinemia, chronic renal failure and in certain malignancies like lung cancers, prostate cancers, various enteric and pulmonary neuroendocrine tumors and mastocytosis[16]. It may be noted that in non MTC tumors, the calcitonin produced per gram of tissue is less compared to MTC, and also, the stimulation tests do not lead to increase in calcitonin levels and hence true positives can be identified.

With the availability of improved two site immunochemiluminescence assays, the basal and stimulated levels have almost similar accuracy and hence the relevance of stimulated calcitonin has declined in the recent times[17].

The basal calcitonin levels of 20-50, 50-100 and >100pg/ml have been shown to have positive predictive values of 8.3%, 25% and 100% respectively, for detection of MTC. Sex specific cutoff values have been proposed for females as basal calcitonin of >20pg/ml and pentagastrin stimulated value of >250, and for males, basal calcitonin of >80 and stimulated calcitonin of >500 pg/ml. The values had a positive predictive value of 88%[18].

It has been seen that level of calcitonin correlates with extent of lymph node metastases from virtually no risk for <20pg/ml to progressive nodal involvement of ipsilateral central and lateral, contralateral central, contralateral lateral and upper mediastinal nodal involvement with values of more than 20, 50, 200 and 500pg/ml respectively[19]. The doubling time of calcitonin appears to be the most powerful prognostic indicator, with a <6months vs >10yrs doubling time imparting a 10-year survival of 8% and 100% respectively[20].

Carcinoembryonic antigen (CEA) is another biomarker produced by neoplastic C cells. It is not useful in making initial diagnosis of disease. However, its can be used to risk stratify known cases of MTC and can be used for post op follow up of MTC patients. A level of >30pg/ml is associated with ipsilateral central and lateral compartment while >100pg/ml is associated with contralateral nodal and metastatic spread of the tumor[23].

Rarely non-secretary MTC have been reported with a prevalence of 0.83%, and diagnosis in such cases can be confirmed with characteristic histopathology and staining of tumor cells for the various MTC biomarkers[24]. Some patients with progressively increasing CEA levels have stable or declining calcitonin levels. This situation signals poorly differentiated MTC and carries a bad prognosis[25].

Surgical Treatment

Surgical treatment is the only definitive treatment for MTC since the tumor cells do not concentrate radioactive iodine. Surgical treatment involves total thyroidectomy and cervical neck node compartment dissection directed by preop USG neck and serum calcitonin levels. The patients must have phaeochromocytoma excluded before surgery regardless of age and clinical symptomatology[7].

Patients with MTC with normal USG and no evidence of metastases should be treated with total thyroidectomy and bilateral central neck node dissection[22] while lateral neck dissection may be considered in such cases based on serum calcitonin(>20pg/ml) levels. When ipsilateral lateral neck node clearance is needed for apparent nodes, the decision to carry out contralateral lateral neck dissection should be made with serum calcitonin levels of >200pg/ml[7]. The metastasis in contralateral neck, however, heralds incurability[7].

In the unusual situation wherein a patient with a presurgically undetected Medullary Thyroid Cancer has a unilateral hemi-thyroidectomy revealing MTC, a completion thyroidectomy is warranted in[7]:

1) *RET* mutation positive cases

2) Raised post op calcitonin levels

3) Imaging studies showing residual MTC

If the patient has had an incomplete lymphadenectomy, repeat compartment oriented neck dissection is worth while with a curative intent only if pre op basal calcitonin was <1000pg/ml and 5 or fewer lymph nodes were dissected in previous surgery[7].

In cases with extensive locoregional or metastatic disease, limited surgery in central and lateral neck is recommended, albeit not with a curative intent but to prevent further locoregional extension of disease, to palliate the systemic effects of hormonally active tumors and improve the quality of life[7,27].

For hereditary MTC, the appropriate age of screening and intervention is given in Table 2. For MEN 2B, prophylactic total thyroidectomy with central compartment dissection is recommended. Of note, identification of parathyroids is very difficult in infants[7] and can have implications for intraoperative decision making for central neck dissection, especially for MEN 2B cases. For MEN 2A cases, with serum calcitonin values below 40pg/ml, prophylactic central compartment clearance is not needed[7,28].

Iodine is not concentrated by metastatic MTC and there is therefore no role of postop RAI therapy for pure MTC[29]. Role of postop External Beam Radiotherapy is limited to patients with high risk of recurrence (including extrathyroidal extension and extensive lymph nodal metastases), risk for airway obstruction and as palliative option for selected mets[7,30,31].

Management of Persistent/Recurrent Hypercalcitonemia

Post surgery the patients should receive replacement thyroxin +/- Ca and calcitriol supplementation as needed and a periodic calcitonin and CEA measurement should be undertaken starting after 3 months[32], thereafter every 6 months for a year and then yearly[7].

It has been seen that in patients presenting with a palpable MTC, despite total thyroidectomy and recommended neck dissection, up to 50% will develop recurrent disease[33]. Most of the recurrences occur within first 5 years[34].

1) Persistently elevated calcitonin should prompt search for locoregional/distant metastasis evaluation. Radiological search for mets often non revealing with calcitonin<250[35].

2) If calcitonin levels are <150, it should be repeated 6 monthly to see the doubling time.

3) If the levels are >150, systemic imaging should be undertaken to look for the disease focus. If imaging comes out to be negative, serial calcitonin measurement to look for doubling time should be done.

4) If no mets and only locoregional disease, look for extent of previous surgery and level of calcitonin; if calcitonin>1000 or previously > 5 metastatic neck nodes had been dissected, biochemical cure is rare for reoperation and intent of surgery shifts to improvement in quality of life by debulking to prevent locoregional complications arising out of disease progression[36].

After appropriate reoperation for locoregional disease, serum calcitonin normalization will not be achieved in up to 40% of node –ve and up to 90% of node +ve patients. Yet many patients achieve 5 and 10-yr survival rate of ~60-90%[37].

Methods to Localize the Source of Persistent Hypercalcitonemia

The best way to localize the source of raised postop calcitonin remains a high resolution USG neck, CECT chest, liver MRI, bone scintigraphy and axial skeleton MRI[38].

Hepatic angiography and selective venous sampling for calcitonin gradients along with laparoscopy can help resolve confusion in cases not detectable with conventional imaging. These techniques, however, are invasive and can be avoided by nuclear imaging scans, including octreoscan

(which will also identify patients suitable for targeted radionuclide analogue therapy),[18]FFDG PET or even more sensitive, but less readily available, [18]F- DOPA PET scan[39].

Prognosis and Prognostic Factors

Overall MTC carries a good prognosis and published survival rates at 5 and 10 yrs are cited to be 69-97% and 56-96% respectively, and that for Micro MTC is reported to be 94% at 10 yrs[40]. Biochemical cure post surgery is reported to confer a survival of 97.7% at 10 yrs[41]. The success or failure to achieve biochemical cure can be predicted by preop levels od serum calcitonin (<50 or >500pg/ml respectively)[42,43].

Certain histologic features impart a good prognosis, including presence of amyloid[44], absence of desmoplastic stromal reaction[45], somatostatin expression in tumor cells[46] and presence of DNA euploidy[44].

Systemic Chemotherapy

Cytotoxic chemotherapeutic combinations (most commonly based on doxorubicin) have a short lasting and low response rate and use of radioisotope bases treatment should be considered only in the context of a clinical trial.

Targeted Therapy with Tyrosine Kinase Inhibitors (TKIs) and Future Perspectives

Currently only two orally administered TKIs, vandetanib (2011) and carbozantinib (2012) have been approved by US Food and Drug Association (FDA) and European Medicines Agency(EMA) for treatment of advanced progressive MTC and for such cases can be used as first line systemic agents. Both the drugs have the potential to provide significant and durable response in terms of improvement of progression free survival, however, because of significant short term toxicity, dose reduction and withdrawal remains a problem as does the virtually universal development of resistance to drugs in long run.

Vandetanib[46,48] is a combined *VEGFR, RET* and *EGFR* inhibitor recommended to be started at a dose of 300 mg/d orally, but in patients with moderate (creatinine clearance 30-50ml/min) and severe(<30ml/min) renal impairment, starting dose of 200mg/d is advocated. Regular monitoring with ECG, TSH and serum levels of potassium, calcium and magnesium is recommended.

Cabozantinib[47,48] acts on *VEGFR*1 and 2, *c-MET* and *RET*. The starting dose is 140mg/d with dose reductions adjusted to tolerability.

Other TKIs, though not FDA approved but with therapeutic potential against MTC, are sorefanib, sunitinib, pazopanib and lenvatininb.

Other investigational approaches for MTC, yet in infancy, include[49]:

1. Immunotherapy: with tumor vaccines using dendritic cells.
2. Radio immunotherapy: using radiolabelled anti CEA monoclonal antibodies.
3. Radiolabelled octreotide: using [90]Yttriumor [177]lutetium labelled DOTA TOC.

In addition, inhibition of certain signal transduction pathway[13] contributing to growth and signaling in MTC cells, including PI3-Akt pathway, Notch-1—HES-1-ASCL-1 pathway, Raf-1–Mitogen-Activated Extracellular Protein Kinase–ERK Pathway, and the Glycogen synthase kinase(GSK-3) pathway (using lithium) are being investigated for their potential therapeutic application in advanced MTCs.

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NEW TECHNOLOGIES

Potential Application for Diagnosis

Due to the limitations of conventional cytopathologic analysis, several molecular analyses have been assessed and reported to have some potential as adjuncts to cytopathologic analysis in the diagnosis of thyroid cancer. A study was conducted to evaluate the potential of nuclear magnetic resonance (NMR) analysis of percutaneous fine-needle aspiration (FNA) specimens for preoperative diagnosis of thyroid cancer. In this study, the metabolome of FNA samples of papillary thyroid carcinoma (n=35) and benign follicular nodule (n=69) were analyzed using a proton NMR spectrometer. The metabolomic profiles showed a considerable discrimination between benign and malignant nodules. The receiver operating characteristic (ROC) curve analysis indicated that 7 metabolites could serve as discriminators (area under ROC curve value, 0.64–0.85). The findings of the study demonstrated that NMR analysis of percutaneous FNA specimens of thyroid nodules can be potentially useful in the accurate and rapid preoperative diagnosis of thyroid cancer.

(Scientific Reports, July, 2016)

Vemurafenib in Metastatic Thyroid Cancer

A team of researchers from Penn Medicine and other institutions had found that treating metastatic thyroid cancer patients harboring a BRAF mutation with targeted therapy, vemurafenib showed promising anti-tumor activity in patients. The phase II clinical study included the results from 51 patients with progressive radioactive iodine-refractory papillary thyroid cancer and having a BRAF mutation. A number of 26 patients in cohort 1 had not been previously treated with multi-targeted kinase inhibitors (MKIs), while 25 patients in cohort 2 were treated with MKIs. The results in cohort 1 revealed partial response in 10, stable disease in 9 patients for at least six months to vemurafenib. The median progression free survival was found to be 18.2 months. However, cohort 2 which had heavily pretreated patients, 6 achieved partial response and six showed stable disease for at least six months. The median progression free survival was 8.9 months. The researchers concluded that vemurafenib is the first non-VEGFR inhibitor to show activity in such patient population and an addition to the treatment options for these patients.

(Lancet Oncology, July, 2016)

PERSPECTIVE

TREATMENT OF IODINE REFRACTORY THYROID CANCER: CURRENT CONCEPT

Thyroid cancer is the most common endocrine malignancy and its incidence has continuously increased worldwide over the past three decades. Differentiated thyroid cancer (DTC), classified as papillary (PTC), follicular (FTC), or Hürthle cell, accounts for >90% of thyroid cancers[1]. DTC is highly treatable and frequently curable with surgery, post operative radioactive iodine (RAI) treatment in some cases, and thyroid-stimulating hormone (TSH) suppression[2].

Despite best care 10 to 20% of patients will experience disease recurrence within 5 to 15 years after primary therapy[3.4]. When tumors recur, surgery, RAI treatment, and sometimes external beam radiation therapy (EBRT), are used to decrease tumor burden and curtail growth. However, for patients whose tumors are non-resectable and/or RAI nonresponsive, systemic therapy may be indicated, which in many instances shifts the responsibility of care from the endocrinologist to a medical oncologist. Identifying tumors that are no longer likely to respond to RAI treatment and pinpointing the most appropriate time to transition patients from localized to systemic therapy are critical for optimal patient care.

Systemic Therapy in Thyroid Cancer

Systemic therapies represent an important treatment option for differentiated thyroid tumors that are nonresectable, not responsive to RAI, and not amenable to EBRT. Based on a study of 30 patients published in 1974, doxorubicin became the only US Food and Drug Administration approved agent for patients with metastatic DTC and was thus considered the standard of care. Subsequent studies using doxorubicin have demonstrated disappointing response data and considerable toxicity.

Understanding the Molecular Pathways and Advent of Tyrosine Kinase Inhibitors

Inhibition of angiogenesis is an effective tool since thyroid tumors are highly vascularized and depend on vascularization for provision of nutrients and oxygen for their growth. Vascular endothelial growth factor (VEGF) is a major driver of tumor vascularization and has been associated with larger tumor size and poorer prognosis in DTC. Platelet-derived growth factor (PDGF) is another growth factor whose activity complements that of VEGF in vessel formation (reviewed by Homsi and colleagues). Many of the targeted therapies are multikinase inhibitors that inhibit VEGF or PDGF (often along with other targets) and act, at least in part, through deprivation of the tumor vascular supply.

The mitogen-activated protein kinase (MAPK)/ERK and phosphoinositide 3 kinase/AKT pathways are also key regulators of cell proliferation and survival. Mutations in and abnormal activation of genes encoding constituents of these pathways are prevalent in DTC. A variety of targeted therapies inhibit the active mechanisms driving these paths, or they inhibit their upstream activation.

Definitions of RAI-refractory DTC (6-8)

Type of evidence	Criteria for RAI-refractory DTC
Clinical presentation	Disease progression, by RECIST criteria, after any of the following: • Cumulative RAI dose of >600 mCi • A single RAI treatment = 10 0 mCi with in the previous 16 months[a] • More than 1 RAI treatment (the last > 16 months ago) with disease progression occurring after each of 2 RAI treatments = 100 mCi administered within 16 months of each other[a]
Imaging studies	Any of the following: • Lack of I-131 up take in 1 or more tumor lesions, as determined by whole-body scan following diagnostic or the rapeutic dosing of RAI • Progression of lesions, as determined by CT, MRI, or bone scan following the rapeutic dosing of RAI • Lesions detected by FDG-PET imaging/progressive in crease in metaboic activity (SUV)[a]
Supportive but not definitive evidence	• In creased levels of tumor markers (e.g., Tg) following the rapeutic RAI dosing[a,b]

Sorafenib is the first targeted systemic agent to demonstrate benefit in RAI-refractory thyroid cancer and was approved for the treatment of locally recurrent or metastatic, progressive, differentiated thyroid carcinoma refractory to RAI treatment [US Food and Drug Administration, 2013]. The safety and efficacy of sorafenib in metastatic, RAI-refractory DTC are supported by multiple phase II trials including over 150 patients and a recent trial DECISION (Study of Sorafenib in Locally Advanced or Metastatic Patients with RAI Refractory Thyroid Cancer), completed in 2013[8].

Lenvatinib has also demonstrated promising activity for patients with RAI-refractory DTC. In a phase II trial, 50% of patients had an objective PR, with a median PFS of 12.6 months reported. Grade 3 adverse events occurring in over 5% of patients included diarrhea, fatigue, and proteinuria. Nine percent of patients experienced grade 4 adverse events. In a recent multicenter phase III trial[9], median PFS (95% CI) was 18.7 (16.4-NR) months in lenvatinib-treated patients vs 3.6 (2.1-5.3) months in placebo-treated patients.

The Decision of Whether and When to Treat with Targeted Inhibitors

Once a tumor has been established to be RAI refractory, the decision whether to start a TKI should be based on clinical presentation of the patient, as well as imaging studies. Because most patients are asymptomatic even with metastatic disease and at present there is no evidence to suggest that earlier treatment with kinase inhibitors confers a clinical advantage over later treatment, systemic therapy should be used in patients with advanced symptomatic disease, relatively large tumor burden, and demonstrable disease progression. 6 A multidisciplinary, multiregional panel of experts recently recommended that progressive disease should be defined by growth of lesions using RECIST rather than relying solely on an increase in tumor markers (e.g., thyroglobulin [Tg]).[6] Shared decision making with patients regarding treatment initiation is of critical importance.

Supportive Care and Management of Side Effects in Patients Receiving Targeted Systemic Therapy

Targeted systemic agents may have significant side effects. To avoid premature or unnecessary withdrawal from treatment, thus depriving patients of the potential for life-prolonging benefits, side effects should be proactively and aggressively managed. In phase II trial of lenvatinib, 35% of patients required a dose reduction for management of toxicity, and 23% were withdrawn from therapy due to adverse events. In DECISION, 14% of sorafenib-treated patients discontinued due to drug-related adverse events compared with 1% in the placebo group.

One of the most common side effects of TKI is Hand and Foot Syndrome (HFSR), which usually occurs within the first 45 days of therapy. Recommendations to prevent and reduce HFSR signs and symptoms include avoiding exposure to hot water and excessive friction on the skin or pressure on the feet. Calluses should be controlled by avoiding pressure points and using well-padded footwear and insole cushions. Foot soaks with tepid water and Epsom salts may also be useful. Regular use of topical agents is recommended. Urea based and corticosteroid have been found to be helpful. Wearing cotton gloves and socks at night may prevent further injury and help retain moisture .For pain control, clinicians may consider topical analgesics, like 2% lidocaine or oral codeine, pregabalin, or an antiinflammatory such as ibuprofen Temporary dose reductions, and even interruptions, may be considered for moderate or severe cases. In the DECISION trial, initial dose reductions from 400 mg twice daily to 600 mg once daily were used to manage toxicities.

Other common side effects include diarrhea, fatigue, anorexia/loss of appetite with weight loss, and hypertension. The best empirically supported intervention for cancer-related fatigue is exercise, particularly aerobic exercise such as walking and cycling. Sorafenib-related fatigue is likely to resolve after approximately 6 months of treatment without additional intervention or dose adjustment. Frequent monitoring of blood pressure is important, particularly in the first 6 weeks of treatment. In the DECISION trial, hypertension usually occurred early in the course of sorafenib treatment and was managed with standard antihypertensive therapy.

Tyrosine kinase inhibitors may interfere with exogenous thyroid suppression; in DECISION, elevation of TSH level above 0.5 mU/liter was observed in 41% of

patients treated with sorafenib compared with 16% of those on placebo. Monthly TSH monitoring should continue while patients are being treated with sorafenib for thyroid cancer, and thyroid replacement medication should be adjusted as needed.

For patients with metastases to bone, bisphosphonate may reduce bone pain, improve performance status and have a beneficial impact on quality of life. One published work recommends treatment of patients with thyroid cancer without pathological fracture twice yearly with 4 mg doses of zoledronic acid ad infinitum[10]. It was also recommended that, for those who suffer an acute fracture, 4 mg zoledronic acid be administered every 3 months for the first year and then twice yearly thereafter. This regimen differs from what is typically used in other solid tumors, because patients with DTC may live many years, and represents a compromise between the potential advantages of intravenous bisphosphonate and potential adverse effects, such as atypical femoral shaft fractures and osteonecrosis of the jaw.

Conclusion

The advent of targeted systemic therapies represents a major advance for patients with RAI refractory DTC, a disease for which there were previously few treatment options. The recent approval of sorafenib and lenvatinib in these patients foretell the possibility of more widespread use of these agents in the community. Patients with large tumors or multiple tumors with rapid progression are considered for treatment with a targeted systemic agent. For patients with smaller tumors that are progressing rapidly or those who have large tumors that are progressing slowly. Tumor location, the presence of symptoms, and the patient's performance status are additional factors that must be considered and discussed with the patient prior to initiating therapy. Diligent management of side effects is essential to avoid premature or unnecessary withdrawal from treatment. Most adverse events occur early in the course of treatment and can be easily and effectively managed. As new systemic agents become available, it will be important to maintain an awareness of the differences in response and adverse effect profiles of each agent. As a consequence, patient management may differ, at least to some extent, for each targeted agent.

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OVERVIEW

MOLECULAR BASIS FOR DIAGNOSIS AND EXPANDING TREATMENT OPTIONS OF THYROID CANCERS

Thyroid cancer is the most common endocrine malignancy, the incidence of which has steadily increased for the past three decades to reach "Annual Standardized Rate" of 3.1 per 10^6 / year and mortality rate of 0.5 per 10^6/ year, globally. Thyroid carcinoma can be broadly classified as:

- Well Differentiated Thyroid Cancers (WDTC) - ~90%
- Poorly Differentiated Thyroid Carcinoma (PDTC) ~1-2%
- Anaplastic Thyroid Carcinoma (ATC) - ~1%
- Medullary Thyroid carcinoma (MTC) - ~5-9%

Well Differentiated Thyroid Cancers (WDTC), are highly treatable and usually curable but recurrences are common (20-30%) and sometimes these recurrences are seen even in the low risk group. Poorly Differentiated Thyroid Carcinoma (PDTC) and Anaplastic Thyroid Carcinoma (ATC) are far less common, more aggressive, metastasize early and are radioiodine refractory. Some WDTC also exhibit radioiodine refractoriness and poor outcome in metastatic disease.

Cases of thyroid carcinoma present as solitary nodule diagnosed clinically or incidentally. The work up begins with evaluation of clinical history, physical examination, followed by TSH, T4 & T3 measurement. Patients with high TSH and low T4 are assessed by anti TPO Ab estimation and those with low TSH and high T4 are checked out for "Autonomous Functioning Thyroid Nodule" / Toxic goiter. Patients with normal TSH levels and those with low TSH but with toxic nodular goiter undergo USG examination to identify suspicious nodule (s) which are subjected to FNAC.

Although FNA renders a conclusive diagnosis in approximately 60 % of cases, a large indeterminate and non-diagnostic group remains without a working diagnosis resulting in suboptimal planning and treatment. **Is it possible to improve the diagnosis in this group by using molecular markers on the aspirated material? Moreover, is it possible to exploit molecular signatures to prognosticate, identify radioiodine refractoriness and use as target for precision therapy?**

A mélange of molecular markers has been identified in thyroid carcinoma in the recent past. Thyroid cancers harbor multiple gene mutations or rearrangements which are mutually exclusive. Affected genes include RET, BRAF, PAX8, and RAS (Fig1). Table 1, given underneath lists the genetic alterations which can be searched to establish diagnosis, define prognosis and utilize these towards targeted therapy.

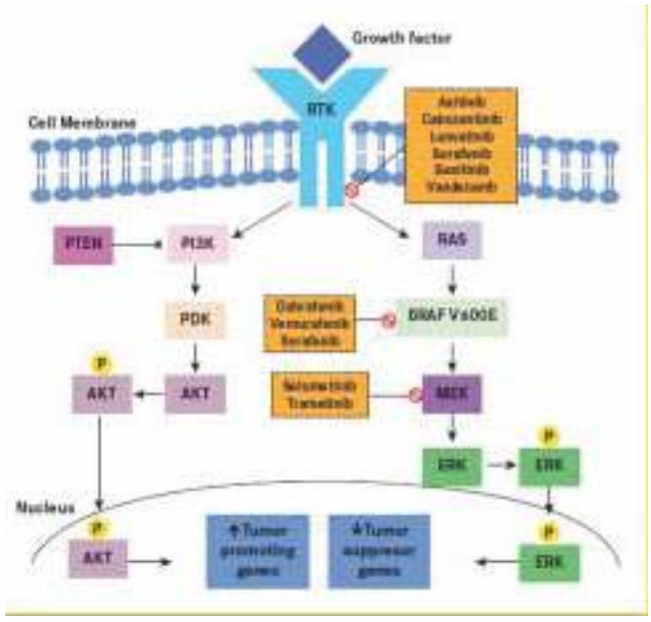
Let's discuss these alterations individually to define the rationale for their clinical usage.

BRAF mutations are the most important of the somatic mutations and are observed in 40-50% of PTC. Of many BRAF mutations, two that affects the PTC are

i) The'V600E' caused by replacement of nucleotide 'T' by 'A' at 1799(T1799A) position resulting in translation to glutamic acid instead of valine at 600th amino acid. This point mutation is common in PTC and accord the tumor aggressive behavior as shown in Table 1. An important attribute of this mutation is that it is exclusively present in PTC and is not seen in FTC and FVPTC

ii) The 'AKAP9-BRAF' rearrangement is another mechanism of BRAF activation in thyroid cancers. This translocation, which fuses the first 8 exons of the A-kinase anchor protein 9 (AKAP9) gene with the C terminal region (exons 9–18) of BRAF, is found in up to 11% of tumors associated with radiation exposure but in less than 1% of all sporadic tumors.

Fig. 1: Important signal pathways affected in thyroid carcinoma and TKI with possible benefit

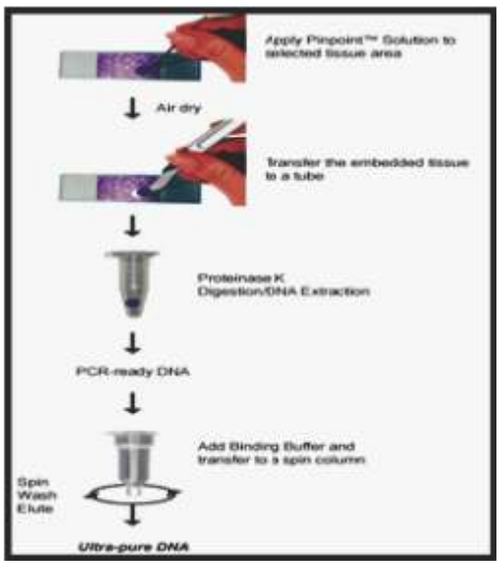


S. No	Molecular marker	Incidence histological type	Characteristics imparted to the tumor	Utility
1	BRAF	45%-PTC	1. Tall & columnar cell Morphology 2. ETE common 3. High stage at presentation 4. Higher rate of tumor recurrence 5. Proclivity towards dedifferentiation	1. BRAF mutation diagnostic of PTC 2. Detectable on FN material 3. Indicates worse outcomes- consider enhanced extent of surgery and RIA upfront
2	RET-PTC	20%-PTC	1. Younger age at presentation 2. Classic histology 3. Relation with radiation exposure 4. Ln involvement common	1. Diagnostic of PTC 2. Detectable on FN material 3. Consider more conservative approach
3	RAS	15% - PTC 5%- FTA 25% - FTC	1. The PTC harboring RAS mutation are always FVPTC 2. Nuclear features of these PTC are less distinct. 3. Presence of RAS mutation cannot distinguish FTA from FTC 4. ?? will FTA with RAS mutation only progress to FTC	1. No definite utility on FNA material 2. Some believe that detection in FNA material shall result in treatment for cancer a s the FTA with RAS mutation have proclivity for progression to FTC 3. FVPTC more akin to FTC and may show vascular metastasis. All FVPTC must be examined by pathologist for extensive vascular embolization as this group amongst FVPTC can have ba d prognosis
4	PAX8-PPARϒ	35%-FTC Rare - FTA	1. Younger age at presentation 2. Smaller tumor size 3. Solid/nested growth pattern 4. More frequent vascular invasion	1. Reasonable marker for FTC 2. Surgical specimen shall be examined with more sections in positive cases for determination of capsular / vascular invasionreduce false negative diagnosis of FTC
5	RET mutations	MTC	1. 75% sporadic 2. 25% inherited. MEN 2a and MEN 2b syndrome	1. Responds to vendatinib and cabozanitinib

(PTC: Papillary Thyroid Carcinoma, FTC: Follicular Thyroid Carcinoma, FTA: Follicular Thyroid Carcinoma. MTC: Medullary Thyroid Carcinoma)

The 'V600E' mutation is easy to identify and FNAC material / needle wash can be employed for this purpose. Even Romanowsky stained smears can be used with advantage of identifying the cell rich areas and extracting the DNA from only such region(s) using Pinpoint DNA extraction Kit (Zyme, CA, USA). This technique of using FN smears for ultrapure DNA extraction is shown in Fig2.

Fig. 2: DNA Extraction method using Pinpoint DNA extraction kit



Detection of BRAF mutation in FN material shall confirm the diagnosis of PTC and allow definitive surgery where diagnosis could not be accomplished by morphological evaluation alone. Moreover, BRAF mutation being a prognostic marker of aggressive behavior, it will be reasonable to perform total thyroidectomy even when a lobectomy is considered adequate. Same argument can also be stretched to RAI ablation.

It is also exciting to note that presence of BRAF mutation may provide the opportunity of targeted molecule in advanced PTC. Several inhibitors of BRAF have been developed eg. vemurafenib and dabrafenib. Many ongoing clinical trials in different phases are studying the benefits of these specific Tyrosine Kinase Inhibitors (TKIs). In one study (NCT01286753, No25530) vemurafenib was associated with antitumor activity in treatment-naive and TKI-pretreated patients with RAI refractory, progressive, BRAFV600E-mutated papillary thyroid cancer. The results, especially the tolerability of treatment and median PFS of 15.6 months in TKI treatment-naive patients showed vemurafenib to be

an encouraging novel treatment for papillary thyroid cancer that warrants further evaluation. Several single agent and combination TKIs are being studied in phase 3 trials. Likewise, dabrafenib has also been found useful in phase I trial.

One interesting part of treatment with specific 'V600E' TKIs is the redifferentiation of tumor with increase uptake of radioiodine. This phenomenon has been exploited in a pilot study to induce redifferentiation and attempted radioablation with ^{131}I with some success. This strategy seems to hold enormous potential.

RET-PTC rearrangements: This rearrangement constitutively activates receptor tyrosine kinase of RET type in follicular cell, thus activating the MAPK pathway and an uncontrolled proliferation. At least 13 different RET/PTC rearrangements have been described but the two frequent ones are RET/PTC1 and RET/PTC3. These rearrangements have so far been identified only in thyroid cancer and almost exclusively in PTC. No study so far has demonstrated RET/PTC rearrangements in benign follicular adenomas, follicular and Medullary carcinomas. Of various PTC histological variants RET/PTCs rearrangement is most frequently seen in PTC with classic architecture. It is rare in the follicular variant of PTC. RET/PTCs have been reported in the cribriform variant, which is typically associated with familial adenomatous polyposis, in the Hurthle-cell variant, and in hyalinizing trabecular adenoma, a rare tumor that can be morphologically similar to PTC. Controversial data have been reported on the relationship between RET/PTC rearrangements and the PTC prognosis. RET/PTC3 is usually associated with a more aggressive phenotype and in particular with a greater tumor size, the solid variant, and a more advanced stage at diagnosis which are all poor prognostic factors. In contrast, RET/PTC1 rearrangement does not correlate with any clinical pathological characteristics of PTC.

RET-PTC rearrangement, therefore, is highly specific for PTC and is seen in up to 25% of these tumors. The methodology for detecting RET-PTC is difficult and requires mRNA for RTPCR. In a suspected case the needle wash or a fraction of the aspirate has to be immediately processed to obtain mRNA. Difficulties of technique, heterogeneity of cells with this rearrangement and variable expression of mRNA are problems that still confront this test and therefore despite being of immense usefulness in confirming the diagnosis of indeterminate aspirate it has not become a popular test.

ZD6474 has shown promising activity in preclinical models against RET kinase, and its contemporary inhibition of vascular endothelial growth factor and epidermal growth factor pathways renders it a very attractive drug for clinical trials in thyroid cancer. Small molecule tyrosine kinase inhibitors, including sorafenib, sunitinib, motesanib and vandetanib, which have already shown efficacy against other neoplastic diseases, are being evaluated in clinical trials for treatment of thyroid carcinomas.

RAS Mutation

Among the RAS oncogene mutations, a higher rate of RAS mutations is seen in malignant rather than benign thyroid tumors. The activating mutations in RAS oncogene are related to chromosomal and genetic instability thus predisposing follicular cells to the accumulation of molecular abnormalities. RAS mutations are seen in approximately 25% of follicular carcinomas and also in 5% of follicular adenomas. RAS mutations are also observed in Follicular variant of papillary carcinoma. Since the RAS mutations are noted in follicular adenomas, the value of determining RAS mutation to make a diagnosis of cancer on FNAC is limited. It is however observed that FA with RAS mutation has a chance of progression and deserve more aggressive treatment.

While no targeted therapy is available specifically for RAS mutant tumors a variety of MAP kinase pathway inhibitors are being studied in phase II and III trials.

PAX8/PPARγ

This fusion event causes expression of a paired box-8/ peroxisome proliferator-activated receptor-gamma fusion protein (PPFP). This chimeric protein appears non-functional and the loss of wild PPARγ enhances proliferation, inhibits apoptosis and induces anchorage. *PAX8/PPARγ* fusion oncogene is detected in up to 70% of FTC cases & shows a negligible presence in FA, and has not been reported in papillary thyroid carcinoma. PAX8/PPAR fusion gene represents a potentially useful biomarker involved in progression of follicular adenoma to follicular carcinoma. As a biomarker, a PAX8/PPAR rearrangement is a strong indicator that a tumor is a follicular carcinoma with an early propensity for vascular invasion. Besides RT PCR as molecular method of

detection, PPAR antibodies are available for immunocytochemistry and have been tried in many research studies. There use in near future on cytological preparation for confirmation of diagnosis of follicular carcinoma is envisaged.

As of now PAX8/PPARγ is not amenable to any form of targeted therapy.

RET Point Mutations in Medullary Carcinomas

The RET proto-oncogene, located on chromosome sub band 10q11.2, encodes a receptor tyrosine kinase expressed in tissues and tumors derived from neural crest. Germline (present in every cell of the body) mutations in RET cause multiple endocrine neoplasia type 2a and 2b (MEN 2), an inherited cancer syndrome characterized by Medullary thyroid carcinoma (MTC) with other syndromic effects. This knowledge has allowed molecular diagnosis and presymptomatic DNA based testing to become possible. RET testing is considered the standard of care in MEN 2 families because clinical decisions are made based on the results of such gene testing. Somatic (in the tumor only) RET mutations have been found in a proportion of sporadic MTCs and PCs. Whether the presence of somatic RET mutation is associated with a poor prognosis is currently being investigated as another tool for molecular medicine.

Conclusion

Finding the above alluded mutations in a thyroid nodule provides strong indication for malignancy and helps to refine clinical management for a significant proportion of patients with indeterminate cytology. The literature from the last five years has emphasized these new aspects and is altering the trends in the approach to the diagnosis of thyroid nodules. Several new mutations have been identified and discussed in "The Cancer Genome Atlas". Some amongst them are point mutation like EIFA5 and others are fusion like NTRK1 fusion with several partner genes. Today, it is possible to find driver mutation in 96% of the cases of thyroid carcinoma. This will open up new vistas for diagnosis and precise treatment even further. The ability to cause redifferentiation in radioiodine refractory tumor through use of targeted medicine is a revelation that can help through short term exposure to a TKI followed by radio ablation.

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GLOBE SCAN

Incidental versus Non-Incidental Thyroid Carcinoma

The objective of this study was to assess the differences in clinical signs, surgical management, and course between incidental and clinically diagnosed thyroid tumors. A retrospective study was conducted on patients operated on for benign or malignant thyroid disease from January 2000 to March 2014. Among the 1415 patients who underwent any thyroid surgery, 264 neoplasms were found, of which 170 were incidental. Incidental carcinomas were in earlier stages and required less aggressive surgery. There were no differences in surgical complications between incidental and clinical tumors, but mortality and relapses were markedly higher in non-incidental cancers (4.4% vs 0% and 13.2% vs 4.8% respectively). So, it may be concluded that early stage thyroid cancer has better survival and prognosis after surgical treatment.

(Spain: Endocrinol Nutr, 11 Jul, 2016)

National Trends in Medullary Thyroid Cancer

In 2009, the American Thyroid Association (ATA) published guidelines with evidence-based recommendations for the treatment of Medullary Thyroid Cancer (MTC). This study aimed to determine national adherence rates of the treatment according to the ATA guidelines specific for MTC. Patients diagnosed with MTC from 2004 to 2013 were identified from the National Cancer Database. Guideline adherence rates for the treatment of MTC before and after the publication of ATA guidelines were analyzed and compared to determine patient and clinical variables that affected treatment. A total of 3693 patients diagnosed with MTC were identified. We found 60.3 % of the patients had localized MTC and 39.7 % had regional metastases. Factors such as older age, African American race, localized disease at diagnosis, lower estimated median zip code, household income, and being treated in a community versus an academic hospital, were associated with a lower likelihood of receiving care in accordance with the guidelines. Hence, adherence rates to the ATA recommendations for the treatment of MTC increased modestly following the publication of guidelines in 2009 with the largest increase seen in community hospitals.

(USA: World J Surg, 22 Jul 2016)

IN FOCUS

THYROID CARCINOMA IN CHILDREN

Epidemiology

Thyroid nodules are rare in children, found in 1% to 2% of the pediatric population as against the prevalence of approximately 30% in adults. However, the incidence of malignancy (25%) in pediatric thyroid nodules is much higher compared to that in adults (10-15%)[1, 2]. Thyroid cancer is the most common pediatric endocrine cancer[3], constituting 0.5%–3% of all childhood malignancies[4]. Thyroid carcinomas in childhood are almost always differentiated thyroid carcinoma (DTC) (i.e. papillary, follicular and medullary) with papillary thyroid carcinoma (PTC) representing 70% or more of cases[5,6]. Anaplastic thyroid carcinomas are exceedingly rare in childhood. Risk factors for developing thyroid nodules in children include head and neck irradiation, female gender, iodine deficiency, age of puberty, and family or personal history of thyroid disease and certain genetic syndromes (MEN syndromes, cowden's, carney's complex, familial adenomatous polyposis)[7].

Clinical Features

The majority of pediatric patients with thyroid carcinoma present with asymptomatic neck mass. It can be discovered by a physician during a routine physical examination or observed incidentally during imaging of the neck.Unlike adults, young patients with thyroid nodules often do not report pain, tenderness, compression of the respiratory tract or problems with swallowing. On examination in patients with thyroid nodules, features suggesting malignancy are size >1cm, soft consistency, fixation to surrounding tissues and lymphadenopathy. One should look for features of associated genetic syndromes also. Extensive regional node involvement is present in the vast majority of patients (27% to 83%) at diagnosis [8]. Disseminated disease is more common in children with pulmonary metastasis identified in 20%. Other sites of metastasis (liver, bone and brain) are rare[9]. Papillary and follicular carcinomas (FTC) behave differently as PTC is more likely to disseminate via lymphatic channels unlike follicular by hematogenous route. PTC is more likely to be multifocal and bilateral in contrast to FTC which is usually unifocal. Medullary thyroid carcinoma (MTC), although rare (< 5% of carcinoma cases), almost always arises as part of a dominantly inherited genetic syndrome (MEN1, MEN2A/2B). Thus, it is important to take the family history of pheochromocytoma or hyperparathyroidism in family members. Mucosal neuromas may be evident on examination in MEN2B patients. Hereditary MTC is typically bilateral, multifocal and located at the junction of upper one-third and lower two-third of thyroid lobes. Approximately20% of patients with MTC have familial cancer associated with a germline RET (Ret protooncogene) mutation. Although MTC patients usually present with thyroid nodules, few may present with diarrhoea and flushing due to increased calcitonin levels.

Diagnostic Workup

The main modalities for diagnosis of DTC are high quality ultrasound of neck with assessment of thyroid nodules as well as lymph nodes; and FNAB of suspicious lymph nodes.

USG characteristics associated with a higher risk of malignancy include solitary solid lesion, multifocal lesions within an otherwise clinically solitary nodule, nodule with hypoechogenic echostructure, subcapsular localization, increased intranodularvascularity (high intranodular flow by Doppler), irregular infiltrative margins, microcalcifications, and suspicious regional lymph nodes accompanying nodule[10-12]. American thyroid association (ATA) has formulated guidelines for diagnosis and management of pediatric thyroid nodules and DTC facilitating evidence based management of children with thyroid cancer.[13] Based on the higher proportion of malignant nodules in children and the potential difficulty in obtaining repeat samples from children, this task force recommends that all FNA in children should be performed with US guidance. Cytopathology findings on FNA are categorized according to The Bethesda System for Reporting Thyroid Cytopathology[14]. In this six-tier system, FNA results are reported as (a) nondiagnostic or unsatisfactory, (b) benign, (c) atypia or follicular lesion of undetermined significance (AUS/FLUS), (d) follicular/Hurthle neoplasm or suspicious for follicular/hurthle neoplasm, (e) suggestive of malignancy, or (f) malignant.

Molecular mutational analysis serves as an adjunct for diagnosis in cases with indeterminate cytology. In recent pediatric studies, the presence of a genetic mutation for RAS, BRAF, RET/PTC, PAX8/PPARg found on indeterminate cytology was correlated with malignancy in all cases[15,16]. Although current molecular diagnostics might improve the diagnostic acumen for indeterminate cytopathology in children, additional studies are required before a formal recommendation can be proffered.

After establishment of diagnosis of thyroid carcinoma, baseline thyroglobulin (TG) levels should be done. It serves as a biochemical marker for postoperative surveillance in DTC patients. TG level should not be measured until at least 14 days after FNAB to prevent an artificial level elevation from the needle instrumentation[17]. Routine chest CT is not recommended for patients with minimal neck disease. A non-contrast CT chest should be considered at diagnosis for ruling out pulmonary metastasis in patients with widespread regional metastasis. Local anatomic imaging by MRI or CT with contrast should be considered in patients with large or fixed thyroid masses, vocal cord paralysis, or bulky metastatic lymphadenopathy in order to optimize surgical planning as superior mediastinal or subclavicular involvement is not visualised well on ultrasound.

Calcitonin and carcinoembryonic antigen are excellent tumor markers for MTC. Genetic testing for RET gene mutation also plays an important role in its diagnosis. Obtain genetic testing at birth in children at risk for MEN2B and no later than age one year in children at risk for MEN2A[18]. Thyroid function tests are usually normal in carcinoma patients. Nuclear imaging studies are not helpful in the initial evaluation as radioactive iodine (RAI) scan findings are not concordant with malignancy. It should only be pursued if the patient presents with a suppressed TSH. Decreased uptake on thyroid scintigraphy is nonspecific for thyroid malignancy.

Staging and Prognosis of Thyroid Carcinoma

The pathological TNM staging system was adopted as the international staging system for thyroid cancer. However, by definition, in patients younger than 45 years, highest TNM stage is II, distinguished from stage I only by the presence of distant metastasis.Based on TNM staging, ATA classifies patients in 3 risk groups:

1. ATA Pediatric Low-Risk: Disease grossly confined to the thyroid with N0 or NX disease or patients with incidental N1a metastasis in which “incidental” is defined as the presence of microscopic metastasis to a small number of central necklymph nodes. These patients appear to be at lowest risk for distant metastasis but may still be at risk for residual cervical disease, especially if the initial surgerydid not include a central neck dissection (CND).

2. ATA Pediatric Intermediate-Risk: Extensive N1a or minimal N1b disease. These patients appear to be at low risk for distant metastasis but are at an increased risk for incomplete lymph node resectionand persistent cervical disease.

3. ATA Pediatric High-Risk: Regionally extensive disease (extensive N1b) or locallyinvasive disease (T4 tumors), with or without distantmetastasis. Patients in this group are at the highest riskfor incomplete resection, persistent disease, and distantmetastasis.

Despite high incidence of metastatic disease, DTC in children has excellent prognosis, unlike adults. In metastatic disease, micronodular lung metastasis and iodine-avid disease confer good prognosis. Children less than 10 years of age are more likely to have recurrent disease. 5-year survival rates for MTC (85-95%) are below that of PTC. MEN2B patients have the most aggressive presentation of MTC and clinical course.

Treatment

Surgery: For DTC, surgery is the mainstay of therapy and the initial procedure of choice is total thyroidectomy. In this procedure, the left and right thyroid lobes, the pyramidal lobe (when present), and the isthmus are resected. Alternatively, in patients with a small unilateral tumor confined to the thyroid gland, a near-TT, whereby a small amount of thyroid tissue (<1%-2%) is left in place at the entry point of the recurrent laryngeal nerve and/or superior parathyroid glands, might be considered in an effort to decrease the risk of permanent damage to these structures. Recurrence risks are significantly greater in children treated with lobectomy when compared with children treated with total thyroidectomy[19]. Also, total thyroidectomy facilitates the use of RAI to ablate the remaining normal thyroid tissue. Comprehensive and compartment focused lymph node resection also constitutes an important part of surgery. ATA recommends CND for children with malignant cytology and clinical evidence of gross extrathyroidal invasion and/or locoregional metastasis on preoperative staging or intraoperative findings. This approach may be associated with a decreased need for second surgical procedures and increased DFS. Central compartment is defined superiorly by the hyoid bone, inferiorly by the substernal notch, laterally by the median portion of the carotid sheath, and dorsal by the prevertebral fascia. Cytological confirmation of metastatic disease to lymph nodes in the lateral neck is recommended prior to surgery. Routine prophylactic lateral neck dissection (levels III, IV, anterior V, and II) is not recommended. Parathyroid glands should be left insitu or if devascularised, autotransplanted. Postoperative staging

is usually performed within 12 weeks after surgery and allows for stratification of patients who may or may not benefit from further therapy, to include additional surgery or ^{131}I therapy. All patients with MTC should undergo biochemical screening for pheochromocytoma prior to surgery. Children with MTC, whatever the size of the nodule, should have a total thyroidectomy and prophylactic bilateral central neck dissection[20].

RAI Ablation: The rationale of routine RAI treatment was to ablate the normal thyroid remnant so that any recurrence can be detected with increased sensitivity using thyroglobulin and to treat the iodine-avid metastatic disease. However, as per ATA 2015 guidelines, it is not recommended routinely in all patients now owing to its toxicities in pediatric population, lack of data showing conclusive benefit from routine I^{131} therapy, a possible increase in the risk of secondary malignancies, and studies showing that Tg can remain useful and become undetectable in patients post TT despite not having received I^{131}. It is indicated for treatment of iodine-avid persistent locoregional or nodal disease that cannot be resected as well as known or presumed iodine-avid distant metastases. If I^{131} is prescribed, the TSH should be above 30 mIU/L to facilitate uptake. The majority of children will achieve this level of TSH by 14 days of Levothyroxine withdrawal. Iodine intake is restricted 2 weeks before the procedure so as to facilitate the uptake of iodine by thryoid remneant. Regular bowel evacuation is also important, so stool softeners or laxatives may be considered. Nausea and/or vomiting are common following I^{131} therapy. A pretherapy scan using I^{131} may be obtained to identify the sites of metastasis and thus

Table 1. American Thyroid Association Pediatric Thyroid Cancer Risk Levels and Postoperative Management in Children with Papillary Thyroid Carcinoma

ATA pediatric risk level[a]	*Definition*	*Initial postoperative staging*[b]	*TSH goal*[c]	*Surveillance of patients with no evidence of disease*[d]
Low	Disease grossly confined to the thyroid with N0/Nx disease or patients with incidental N1a disease (microscopic metastasis to a small number of central neck lymph nodes)	Tg[e]	0.5–1.0 mIU/L	US at 6 months postoperatively and then annually × 5 years Tg[e] on LT_4 every 3–6 months for 2 years and then annually
Intermediate	Extensive N1a or minimal N1b disease	TSH-stimulated Tg[e] and diagnostic ^{123}I scan in most patients (see Fig. 2)	0.1–0.5 mIU/L	US at 6 months postoperatively, every 6–12 months for 5 years, and then less frequently Tg[e] on LT_4 every 3–6 months for 3 years and then annually Consider TSH-stimulated Tg[e] ± diagnostic ^{123}I scan in 1–2 years in patients treated with ^{131}I
High	Regionally extensive disease (extensive N1b) or locally invasive disease (T4 tumors), with or without distant metastasis	TSH-stimulated Tg[e] and diagnostic ^{123}I scan in all patients (see Fig. 2)	<0.1 mIU/L	US at 6 months postoperatively, every 6–12 months for 5 years, and then less frequently Tg[e] on LT_4 every 3–6 months for 3 years and then annually TSH-stimulated Tg[e] ± diagnostic ^{123}I scan in 1–2 years in patients treated with ^{131}I

"Risk" is defined as the likelihood of having persistent cervical disease and/or distant metastases after initial total thyroidectomy – lymph node dissection by a high volume thyroid surgeon and is not the risk for mortality, which is extremely low in the pediatric population. B Initial postoperative staging that is done within 12 weeks after surgery.

C These are initial targets for TSH suppression and should be adapted to the patient's known or suspected disease status; in ATA Pediatric Intermediate- and High-risk patients who have no evidence of disease after 3–5 years of follow-up, the TSH can be allowed to rise to the low normal range.

D Postoperative surveillance implies studies done at 6 months after the initial surgery and beyond in patients who are believed to be disease free; the intensity of follow-up and extent of diagnostic studies are determined by initial postoperative staging, current disease status, and whether or not 131I was given; may not necessarily apply to patients with known or suspected residual disease or FTC.

E Assumes a negative TgAb ; in TgAb-positive patients, consideration can be given (except in patients with T4 or M1 disease) to deferred postoperative staging to allow time for TgAb clearance.

ATA, American Thyroid Association; LT4, levothyroxine; TgAb, thyroglobulin antibody; US, ultrasound

decide the dose of RAI. There is no agreement in the literature regarding RAI dosing for children; rather, ranges have been provided. As per Rivkees et al. [21], for physically maturechildren, RAI should range from 100 to 200m Ciand may be corrected for body weight ranging from 1.35 to 2.7 mCi/kg in younger children. Significant research is needed to determine minimal effective dosages applicable to children. A post therapy thyroid scan should be done after 5-8 days to identify other sites of disease. MTC does not trap iodine, therefore should not be treated with RAI. There is no role of external beam radiotherapy to treat residual microscopic disease except in rare cases of pathologically unfavourable thyroid carcinoma with known residual disease and in palliation of distant metastasis.

TSH Suppression: As DTC can grow in response to the trophic effects of TSH, patients are treated with pharmacologic suppression of TSH to decrease the disease recurrence and progression.The initial TSH goal should be tied to ATA Pediatric Risk level and current disease status (Table 1). In MTC patients, thyroid hormone is given to replace thyroxine, not to suppress TSH.

Chemotherapy: Systemic therapy is warranted only in patients with progressive life-threatening disease not amenable to surgery and not responsive to RAI. Most commonly used agent has been doxorubicin, as a single agent or in combination with cispaltin or interferon-alfa. Targeted therapy has shown promise in the treatment of thyroid carcinoma in the form of TKIs, namely sorafenib, axitinib, motesanib and sunitinib.

Follow-Up: As children with thyroid carcinoma are known to have delayed recurrences, lifelong surveillance is required. Long-term management includes periodic assessment of TG and TG antibody levels, routine neck US and diagnostic RAI scans with frequency of followup depending on risk stratification (Table 1).

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