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From the Desk of Director Research

Thyroid cancer is an uncommon cancer but is the most common malignancy of the endocrine system. It mainly affects younger people and is the second most frequent cancer in women below 45 years of age. In the year 2012, it was estimated that 42 million Indians are affected with thyroid cancer. In general, this is one of the least deadly cancers with very good 5 years survival.

The incidence of thyroid cancer has continuously increased in the last three decades all over the world, the most important reason for the increase being the increased diagnostic intensity. Other contributory factors are environment and lifestyle changes. The use of sensitive diagnostic measures, including ultrasound, doppler examination, imaging techniques like CT scan, MRI or PET scanning, and biochemical markers, have affected the incidence of cancers in the thyroid more than in other sites because thyroid cancer has an indolent progression and may remain unrecognized in the preclinical stage for years or decades.

The histology and clinical behavior of thyroid cancer are highly diverse but in contrast to other cancers, thyroid cancer is almost always curable with the current standard of care therapy, though a small subset of tumors with iodineresistant cancers create a great challenge to the clinicians. The most effective form of initial thyroid cancer therapy is surgery, followed by radioactive iodine ablation and thyroid hormone suppression of serum thyroid stimulating hormone. Post-operatively, radiotherapy and chemotherapy are the most popular treatment options for advanced stages of thyroid cancer.

Because of the high incidence of thyroid cancer, this field has become a focus of effort for use of new targeted therapies, especially the new class of agents that inhibit kinases involved in signaling, cellular growth, and angiogenesis, such as pazopanib, sorafenib, motesanib, sunitib and vandetanib. Numerous clinical trials have been conducted over the last 5 years to examine the effects of these targeted molecular therapies on the outcomes of patients with iodine - refractory cancers and have represented major breakthroughs. However, till date no standard criteria for patients enrollment has beeen established for targeted therapy because more data is required on toxicities of single agent, to identify specific biomarkers to be able to predict the treatment efficacy, the clinical outcome and a tailored dosage of the drugs. If approved for use in thyroid cancer patients by the US Food and Drug Administration, sorafenib (Nexavar), a kinase inhibitor would be the first effective agent for this patient population.

This issue of Cancer News profiles the complexities and advancements in the field of thyroid cancer, and includes regular articles such as "Special Feature", "Guest Article", "Watch-Out", "Perspective", "Research & Development", "New Technologies", "Clinical Trials", "Globe Scan", and "Cancer Control".

We appreciate the contribution made by Dr Ashok R. Shaha, Professor of Surgery, Head and Neck Service, Memorial Sloan-Kettering Cancer Center, New York, USA, for providing the "Guest Article"on "Surgical Management of Thyroid Cancer".

Suggestions / comments from the readers are welcome.

Dr D C Doval

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SPECIAL FEATURE

RECOMBINANT HUMAN TSH IN THE MANAGEMENT OF DIFFERENTIATED THYROID CANCER

Recombinant human thyroid stimulating hormone (rhTSH) was approved by US Food and Drug Administration (FDA) in 1998 for use in differentiated thyroid carcinomas (DTC), based on the findings of two prospective clinical trials. Initially, it was approved for the evaluation of serum thyroglobulin (Tg) and whole body iodine (WBI) scans in follow-up cases of DTC without stopping thyroxin, by this exogenous source of TSH. However, more and more studies have now demonstrated that the primary diagnostic use of rhTSH is predominantly related to the increased sensitivity of stimulated Tg (sTg) in detecting persistent or recurrent disease than to its role in diagnostic whole body radioiodine (DxWBI) scanning which itself has a low sensitivity for disease detection. Following this and accumulated evidence of literature in favor of rhTSH, European association in 2005 approved it for ablation of low risk patients with 100 mCi radioactive iodine. In 2007, US FDA also approved it for ablation without specifying radioactive iodine dose. After that, use of rhTSH started to grow in DTC to ablate remnant tissue in patients who have undergone a near total thyroidectomy (NTT) or total thyroidectomy (TT) with no evidence of distant sites of metastasis. Finally in 2009, European guidelines revised the indication for rhTSH in DTC patients and stated rhTSH to be indicated for pre-therapeutic stimulation with 100 mCi for remnant ablation without evidence of distant metastasis after NTT or TT. A recent randomized study has shown equal efficacy of 50 mCi and 100 mCi iodine dose for thyroid remnant ablation with rhTSH. So far, it has been highlighted that rhTSH has only being approved for remnant ablation both by European association and US FDA but not in distant metastatic scenario. However, many researchers have individually acclaimed promising role of rhTSH in metastatic situation with better quality of life. Similar results have been obtained in RGCI & RC, both in remnant ablation and metastatic disease with rhTSH.

It has been well established that elevated TSH stimulates DTC cells and makes them more sensitive to iodine-131 ablation or makes serum Tg and DxWBI scan more predictive during follow-up. Conventionally, endogenous TSH stimulation is done by thyroid hormone withdrawal (THW) for above process. Endogenous TSH elevation further can be achieved by two basic approaches to thyroid hormone withdrawal, stopping levo-thyroxin (LT_4) and switching to levo-tri-iodothyronine (LT_3) for 2–4 weeks followed by withdrawal of LT_3 for 2 weeks, or discontinuation of LT_4 for 3 weeks without use of LT_3. Both methods of preparation can achieve serum TSH levels > 30mU/L in > 90% of patients. These two approaches have not been directly compared for efficiency of patient preparation (efficacy of ablation, iodine uptake, Tg levels, disease detection), although a recent prospective study showed no difference in hypothyroid symptoms between these two approaches. Routinely rhTSH based preparation is well accepted for ablation in non-metastatic situation and follow-up Tg assay or DxWBI scan. To eliminate hypothyroid symptoms for better quality of life or those patients who are unable to generate an elevated endogenous TSH state (pituitary disease) or those who are associated with underlying co-morbidities and in whose case delay in radioactive iodine treatment might be deleterious, this new method of TSH stimulation by exogenous TSH (rhTSH) is advised by experts for even metastatic or recurrence cases. Conventional method of preparation with THW is associated with reduced kidney function, as such effective half life of iodine-131 will be more as compared to rhTSH method and well lead to more whole body radiation dose.

Recombinant human TSH is commercially available as thyrotropin alfa. It is a heterodimeric glycoprotein which is produced by recombinant DNA technology in a genetically modified Chinese hamster ovary cell line. Recombinant human TSH comprises two non-covalently linked subunits, an alpha subunit of 92 amino acid residues containing two N-linked glycosylation sites, and a beta subunit of 118 residues containing one N-linked glycosylation site. The amino acid sequence of thyrotropin alfa is identical to that of human pituitary TSH (pTSH), however unlike pTSH which is secreted as a mixture of sialylated and sulfated forms, thyrotropin alfa is sialylated but not sulfated. RhTSH is supplied as a sterile, non-pyrogenic and white to off-white lyophilized form for intramuscular administration after reconstitution with sterile water for injection.

For stimulated Tg and DxWBI scan in follow-up patients of DTC, a five-day protocol (Table 1) is recommended. 0.9 mg of rhTSH should be administered for initial two days 24 hours apart (day 1 and day 2) by

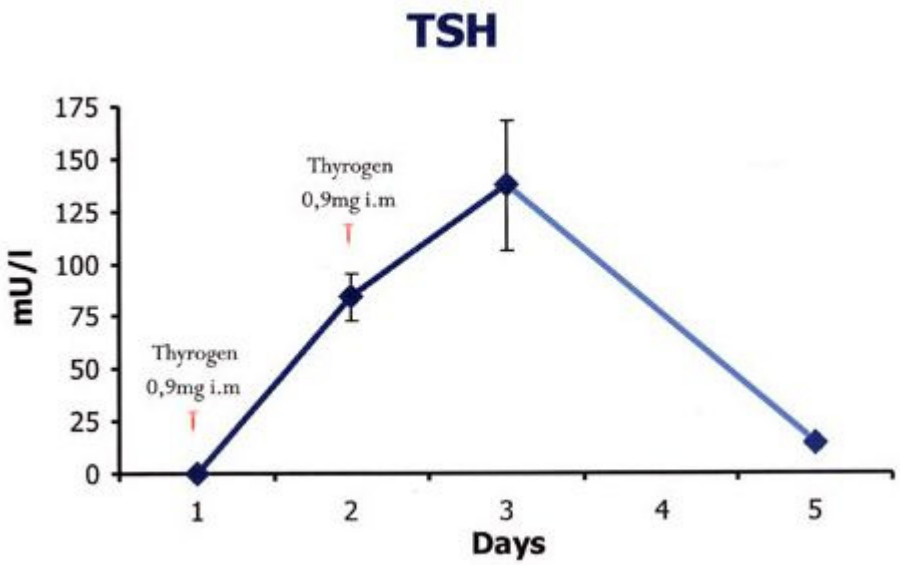

Figure 2: Serum TSH stimulation following rhTSH injection

deep intramuscular (i.m.) injection preferably in buttocks due to good blood supply. Leonidas H. Duntas has showed maximum TSH stimulation on day 3 after two rhTSH injections (Figure 2). So on day 3, serum TSH will be measured and if it is > 30 mU/L, 4 mCi radioactive iodine-131 (^{131}I) should be given orally if DxWBS is planned. On day 5 stimulated Tg and DxWBI scan should be performed.

Table 1: Five-day Protocol for Diagnostic Use of rhTSH

Diagnostic use of rhTSH (Five - day protocol)				
Day 1	Day 2	Day 3	Day 4	Day 5
0.9 mg rhTSH	0.9 mg rhTSH	Lodine-131 (if DxWBS is planned)		S Tg and DxWBI scan

For remnant ablation, same two i.m. injections of 0.9 mg rhTSH were given on day 1 and day 2. After confirming TSH value > 30 mU/L on day 3, therapeutic dose of iodine-131 is administered orally. Stimulated Tg on day 5 and post therapy whole body iodine scan may be done between day 5 to day 8 or some time even on day 10 (10 days protocol).

Recombinant human TSH is quite safe with fewer side effects. Hypersensitivity skin test is recommended. Common side effects after rhTSH administration are nausea (10.5%), headache (7.3%), asthenia (3.4%), vomiting (2.1%), dizziness (1.6%) and paraesthesia (1.6%).

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) which in turns makes 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 nearly in 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. Successful remnant ablation will be defined as no radioactive iodine uptake in follow up DxWBI scan, suggesting complete ablation (Figure 3). 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 follow-up. Those patients, who are being treated with adjuvant treatment intention, undetectable stimulated Tg during first follow-up and to reduce recurrence rate and disease specific mortality during long term follow up are the end points. A recent article by Tuttle et al has showed rhTSH for remnant ablation in intermediate and high risk group patients to be 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 show equivalent efficiency of 50mCi and 30mCi

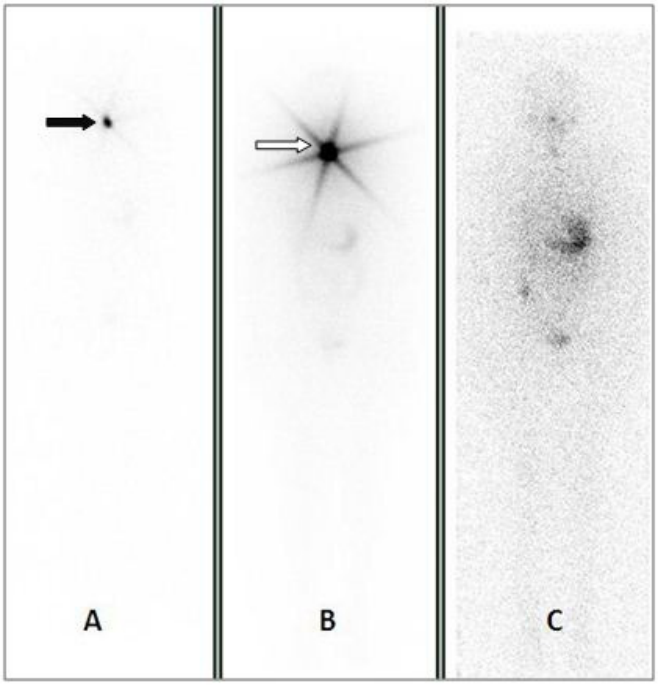

Figure 3: (A) Diagnostic whole body iodine (DxWBI) scan revealed residual thyroid tissue in thyroid bed. (B) Post ablation therapy whole body iodine scan revealed good concentration of radioactive iodine in thyroid bed with no iodine uptake outside thyroid bed. (C) Follow-up DxWBI scan revealed no radioactive iodine uptake in thyroid bed suggesting complete ablation.

ablation as well with rhTSH. So there is growing data favoring low dose (30mCi) of radioactive iodine for ablation in low risk group patients and keeping higher doses for adjuvant scenario (high risk group).

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 patients with metastasis for radioiodine treatment with rhTSH as compare 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 are available.

In conclusion, rhTSH as compare 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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(Dr Manoj Gupta & Dr PS Choudhary, Dept of Nuclear Medicine, RGCI & RC)

GUEST ARTICLE

SURGICAL MANAGEMENT OF THYROID CANCER

Thyroid cancer represents a spectrum of diseases. At one end of the spectrum there is one of the best human cancers, papillary carcinoma of the thyroid; while at the other end there is anaplastic thyroid cancer, universally fatal disease. Even though there are approximately 62,000 new patients with thyroid cancer every year in the United States, the mortality from thyroid cancer has essentially remained unchanged over the last two decades. The incidence of thyroid cancer is most rapidly increasing in the United States, especially in women. Whether this is related to true increase in the incidence of thyroid cancer or incidentalomas, is unclear. A variety of nuances have been recognized in the last decade in the management of thyroid cancer.

One of the major advances is the use of thyroglobulin. If the patient has undergone total thyroidectomy and radioactive iodine ablation, the rising thyroglobulin invariably indicates the presence of recurrent or metastatic disease. The recurrent disease in the thyroid bed can be very well documented with appropriate imaging studies, including an ultrasound and ultrasound-guided needle biopsy. The ultrasound has become an important tool in the follow-up of patients with thyroid cancer, both for identification of the local recurrence in the thyroid bed and metastatic disease in the lymph nodes. The other major nuance in the management of thyroid cancer is the availability of Recombinent TSH (Thyrogen) which can be used for radioactive iodine dosimetry and for ablation. Clearly, this has changed the quality of life of patients who are undergoing radioactive iodine treatment. The patients do not have to become hypothyroid anymore and they can be easily evaluated for radioactive iodine treatment with Thyrogen.

The fine-needle aspiration biopsy continues to be the mainstay of diagnostic evaluation of a patient presenting with a thyroid mass. A variety of immunohistochemical studies, including molecular markers, could be performed on fine-needle aspiration biopsy; however, in the future it is quite likely that we will be able to perform appropriate molecular markers on fine-needle aspiration biopsy specimen and define the nature of the primary tumor and plan treatment appropriately. BRAF has been used both to suspect malignancy and the aggressive mature. The gene expression classifier has been used recently in evaluation of follicular lesions.

There continues to be a long term battle in the management of thyroid cancer as to the routine utility of total thyroidectomy versus less than total thyroidectomy. Our understanding of thyroid cancer has improved considerably over the last two decades by recognition of the prognostic factors and risk group analysis. At Memorial Sloan-Kettering Cancer Center, we have identified the prognostic factors such as grade of the tumor, age, distant metastasis, extrathyroidal extension, and size of the tumor. Based on these prognostic factors, we are able to divide our patients into low and high risk groups. The low risk group patients generally are younger than 45 with a tumor less than 4 cm and good histology. The high risk includes patients above 45 with larger tumors, more than 4 cm or with extrathyroidal extension or high grade histology and distant metastasis. Even though many other institutions have divided their patients into low and high risk groups, we have divided our patients at Memorial Sloan-Kettering Cancer Center, including an intermediate risk group, where a young patient may have aggressive tumor or an older patient generally with a small tumor. The understanding of these risk group definitions is very crucial in the overall management and follow-up of patients with thyroid cancer. In the low risk group one, can easily treat the patient with lobectomy and the role of radioactive iodine in these patients remains unclear and undefined. However, in the high risk group, one would be quite aggressive not only doing total thyroidectomy and paratracheal clearance, but using radioactive iodine and in select cases, where the patient may have a poorly differentiated tumor, with the use of external radiation therapy. In the intermediate risk group, the decision regarding the extent of thyroidectomy and adjuvant therapy needs to be made based on the factors related to the tumor and its prognosis.

The management of neck nodes generally includes paratracheal evaluation in all patients with suspected thyroid cancer. If there are no obvious enlarged lymph nodes in the paratracheal area, this area is not dissected. However, if there are suspicious nodes, a complete paratracheal clearance is done and the jugular vein is evaluated for any obvious nodes. In patients who present with clinically palpable neck node metastasis, a modified neck dissection is usually performed. Subsequent to the surgery, the decision regarding radioactive iodine is

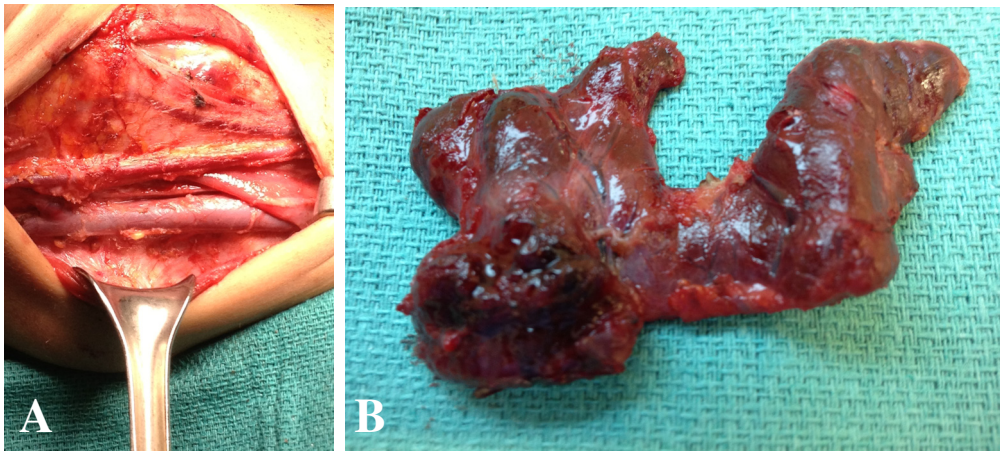

Figure: (A) Modified Neck Dissection for Papillary Thyroid. (B) Total thyroidectomy for Papillary Thyroid Cancer Cancer

made based on the prognostic factors and risk group analysis as described above. The patients are usually followed by clinical examination, occasionally ultrasound of the thyroid, and serum thyroglobulin levels. If the serum thyroglobulin continues to rise, most of the time the disease is noted in the lymph nodes in the neck and an ultrasound of the neck will identify such enlarged lymph nodes. An ultrasound-guided fine-needle aspiration biopsy will confirm the presence of metastatic disease in the neck at which time a modified neck dissection is performed. The modified neck dissection for thyroid cancer includes removal of lymph nodes at level II, III, IV, and V without removing the sternomastoid muscle, internal jugular vein and accessory nerve. The incidence of level I metastatic disease is quite rare and generally the submandibular area is not dissected to avoid injury to the lower division of the facial nerve. The metastatic disease generally progresses in a sequential fashion with paratracheal, and tracheoesophageal groove nodes involvement initially and subsequently jugular lymph nodes. There continues to be considerable debate about the extent of nodal dissection in patients presenting with lateral nodal dissection. A variety of procedures, such as selective nodal dissection, modified neck dissection, compartment oriented neck dissection, have been described. Radical neck dissection is rarely indicated in well differentiated thyroid cancer. The level IIB nodal metastasis is also quite rare and generally the accessory nerve is not dissected extensively. The major complications related to modified neck dissection include hematoma, extended chyle leak especially more common on the left side, shoulder weakness due to accessory nerve dissection and rarely Horner's syndrome.

In recent years, there has been a considerable debate and controversy about elective prophylactic central compartment node dissection. This has generated considerable debate and national symposia. The major genesis of this controversy began in 2006 when ATA published their guidelines with a recommendation of elective central compartment node dissection in patients with papillary carcinoma of the thyroid. However, the committee realized soon that routine elective central compartment dissection was generally not indicated in patients with well differentiated thyroid carcinoma and there clearly was a higher morbidity related to recurrent laryngeal nerve injury and temporary or permanent hypoparathyroidism. In 2009 guidelines, the ATA recommended selective indications for prophylactic neck dissection. The debate continues regarding prophylactic versus therapeutic central compartment dissection, unilateral or bilateral dissection, and the extent of dissection involving level VI and level VII. The general consensus remains as to consider paratracheal dissection only if there are suspicious paratracheal nodes or the frozen section is positive. In the United States, Hashimoto's disease is quite common and it is not uncommon to see enlarged paratracheal nodes. The proponents of routine prophylactic central compartment dissection recommended, based on the avoidance of future surgical procedures in the central compartment, appropriate follow-up with thyroglobulin and ultrasound on these patients with minimal morbidity in experienced hands. However, the opponents support their views based on higher incidence of complications, and overall low recurrence rate of 2% in the central compartment.

The recurrent nodal disease, either in the central compartment or in the lateral compartment, requires appropriate evaluation of the extent of the disease, identification of the location of the tumor and the size of metastatic disease. If the suspicious nodal disease is less

than 1cm, we generally monitor the patient rather than consider fine-needle aspiration biopsy. The cytologic interpretation augmented with thyroglobulin assay from the needle aspirant is helpful to make a diagnosis. However, the surgical procedure in these sub-centimeter lymph nodes may be extremely difficult and unrewarding. Appropriate TSH suppression, including close monitoring, is a good alternative. However, if the lymph node continues to increase in size, appropriate neck dissection should be undertaken. The nodal metastasis has no major impact on the survival of patients with well differentiated thyroid cancer; however it does have an impact on the recurrence and additional surgical intervention.

The understanding of the pathology of thyroid cancer is very crucial to distinguish between poorly differentiated thyroid cancer and well differentiated thyroid cancer. A variety of pathological entities have been noted in recent years, such as tall cell, insular, trabecular, scirrhous, etc. The poorly differentiated tumors generally behave much more aggressively and will require aggressive treatment.

One of the most crucial findings in the management of thyroid cancer is extrathyroidal extension. Whenever there is a tumor invading the surrounding structures, those areas need to be resected completely for gross total tumor excision which may mean removal of the strap muscles, recurrent laryngeal nerve, or the tracheal wall or esophageal musculature. If there is intraluminal disease extension into the trachea, a sleeve resection should be considered with primary end-to-end anastomosis of the trachea. We strongly feel that the extrathyroidal extension is a major prognostic factor to avoid local recurrence in the central compartment of the neck.

In recent years, there has been an enormous interest in molecular markers and molecular analysis of the thyroid tumors, wherein the comparative genomic hybridization and other technologies, such as DNA array, have been used. Based on these molecular analyses one can now develop a progression model of anaplastic thyroid cancer from a benign follicular thyroid cell.

Thyroid cancer continues to generate considerable debate and controversy. The controversy revolves mainly around the diagnostic evaluation and the therapeutic approaches related to extent of thyroidectomy. However, the recent understanding of the prognostic factors and risk groups should direct appropriate management of well differentiated thyroid cancer.

(Dr Ashok R. Shaha, Professor of Surgery, Head and Neck Service, Memorial Sloan-Kettering Cancer Center, New York, USA)

WATCH-OUT

Biomarkers for Follicular Thyroid Carcinoma

Hunsucker, et al of the University of Colorado, USA have been awarded US patents No. 8,455,208 on 4th June 2013 for their invention "Biomarkers for follicular thyroid carcinoma and methods of use". The present invention provides protein biomarkers for determining whether a thyroid nodule is malignant or benign and methods for using the same. It relates to methods for analyzing a thyroid nodule comprising determining a protein level in follicular thyroid nodules. Thyroid cancer is one of the most common endocrine malignancies with the most common clinical presentation being a thyroid nodule. Currently, the fine-needle aspiration biopsy (FNAB) is used in the initial work-up of a patient with a thyroid nodule to determine whether the thyroid nodule is malignant or benign. It is particularly challenging to distinguish between thyroid neoplasms of the follicular type, i.e., benign follicular thyroid adenoma (FTA), malignant follicular thyroid carcinoma (FTC), and follicular variant of papillary carcinoma, based on cytologic examination alone. These tumors have similar cytologic features and surgery is usually required to obtain a definitive tissue sample.

(USPTO, Sep 28, 2013)

Novel ERK Inhibitors

An application No. WO2013063214 (A1) has been published by the European Patent office on 2nd May 2013. LIM JONGWON et al of Merck Sharp & Dohme Corp., USA, are the inventors. This invention provides compounds that inhibit the activity of of ERK2. The processes involved in tumor growth, progression, and metastasis are mediated by signaling pathways that are activated in cancer cells. The ERK pathway plays a central role in regulating mammalian cell growth by relaying extracellular signals from ligand-bound cell surface tyrosine kinase receptors, such as erbB family, PDGF, FGF, and VEGF receptor tyrosine kinase. Activation of the ERK pathway is via a cascade of phosphorylation events that begin with activation of Ras. Therefore, a welcome contribution to the art would be small-molecules (i.e, compounds) that inhibit ERK activity (ERK2 activity), which small-molecules would be useful for treating a broad spectrum of cancers, for example, melanoma, pancreatic cancer, thryroid cancer, colorectal cancer, lung cancer, breast cancer, and ovarian cancer.

(Espace.net, Sep 30, 2013)

PERSPECTIVE

TARGETED THERAPY IN THYROID CANCER

The treatment of most patients with differentiated thyroid carcinoma (both papillary [PTC] and follicular [FTC] histologies) includes surgery, radioactive iodine, and thyroid hormone therapy. When metastatic disease occurs, radioactive iodine and TSH suppressive thyroid hormone therapy can be used with some success. Traditionally, chemotherapeutic agents have not been found to be successful in the treatment of thyroid cancer. However targeted therapies are fast emerging as effective treatment for advanced and metastatic thyroid cancer.

Tyrosine Kinase Inhibitors

Thyroid cancers frequently carry gene mutations and rearrangements that lead to activation of the mitogen activated protein kinase (MAPK) that promotes cell division. Rearrangements of RET and NTRK1 tyrosine kinases, activating mutations of BRAF, and activating mutations of RAS are sequential components leading to activation of MAPK. In the last decade, many small molecule TKIs have been developed that block some of these pathways. Some of the TKIs which have been investigated in differentiated Thyroid cancer are enumerated below:

1) Sorafenib is an oral, small molecule TKI targeting VEGF receptors 2 and 3, common RET/PTC subtypes, and BRAF. It has been tried in various phase II trials. In a trial, of 32 patients with progressive, radioiodine-negative DTC treated with sorafenib for 26 weeks, eight (25 percent) patients had a partial response, 11 had stable disease (34 percent), seven had progressive disease (22 percent), and six were non-evaluable [12]. Median PFS was 14.5 months, although patients with bone metastases had significantly worse median PFS than those without (47 weeks compared with 69 weeks).
2) Sunitinib is an oral, small molecule kinase inhibitor of all three VEGF receptors and RET/PTC subtypes 1 and 3. It has also been evaluated in small Phase II trials and has shown to have a response rate of approx 13%. The side effect profile of both Sunitinb & Sorafenib include mucositis, Gastro intestinal disturbances, stomatitis, hypertension , neutropenia & Hand Foot syndrome.
3) Vandetanib is an oral inhibitor that targets VEGF receptor, RET, and the epidermal growth factor receptor (EGFR). In a randomized trial, 145 patients with locally advanced or metastatic differentiated thyroid cancer unresponsive to radioactive iodine were randomly assigned to vandetanib (300 mg once daily) or placebo. After a median follow-up of approximately 19 months, fewer patients treated with vandetanib had disease progression [72 versus 84 percent]). Median progression-free survival was 11.1 and 5.9 months in the vandetanib and placebo groups, respectively. There was no difference in objective partial response or overall survival. The most common adverse events resulting in discontinuation of vandetanib were prolongation of the QT interval and diarrhea.

MEK Inhibition

Papillary thyroid cancers frequently carry gene mutations and rearrangements that lead to activation of the mitogen activated protein kinase (MAPK), which promotes cell division and inhibits the sodium-iodide symporter (which usually facilitates iodine uptake) and thyroid peroxidase (facilitates organification).

Selumetinib is an investigational drug that selectively inhibits MEK 1 and MEK 2. In a study of 20 patients with radioiodine-refractory papillary thyroid cancer, 12 patients (60 percent) had new and/or increased radioiodine uptake after treatment with selumetinib (75 mg orally twice daily for four weeks). In eight patients (40 percent), the absorbed radiation dose in the lesion was sufficient enough to continue selumetinib and receive a therapeutic dose of radioiodine. During six months of follow-up, there were partial responses in five patients and stable disease in three. Selumetinib was most effective in patients with NRAS-mutant thyroid cancers.

These drugs remain investigational for the treatment of refractory metastatic DTC. For most patients with metastatic DTC, a clinical trial is preferred.

Medullary Thyroid Cancer

Medullary thyroid cancers (MTCs) are neuroendocrine tumors of thyroid parafollicular cells that do not concentrate iodine. They occur both as sporadic tumors and as components of multiple endocrine neoplasia (MEN) type 2. They secrete calcitonin and carcinoembryonic antigen (CEA), both of which can serve as tumor markers.

The primary treatment for MTC is extensive and meticulous surgical resection. There is a limited role for external-beam radiotherapy. Because the neuroendocrine-derived MTC is not responsive to either radioiodine or TSH-suppression, these options are not available for treatment of progressive metastatic MTC.

Patients with progressive or symptomatic metastatic disease who cannot be treated by surgery or radiotherapy should be considered candidates for systemic therapy

At present, 2 Oral TKIs have been approved by FDA in the treatment of advanced medullary thyroid cancer.

1) Vandenatib: An international randomized phase III trial of vandetanib (300 mg daily) was performed in over 300 patients with unresectable locally advanced or metastatic sporadic or hereditary MTC. After a median follow-up of 24 months, progression-free survival was significantly prolonged for patients randomly assigned to vandetanib versus placebo. The median progression-free survival had not yet been reached for the vandetanib group but was predicted to be 30.5 months compared with 19.3 months in the placebo group. The objective response rate was significantly higher in the vandetanib group (45 versus 13 percent). The presence of a somatic RET M918T mutation predicted an improved progression-free survival.

2) Cabozantinib(XL184) is also approved by the US Food and Drug Administration for the treatment of progressive, metastatic medullary thyroid cancer. Cabozantinib is an oral, small molecule TKI that targets VEGFRs 1 and 2, c-MET, and RET . In a randomized trial, 330 patients with progressive, metastatic or unresectable locally advanced medullary thyroid cancer were randomly assigned to receive either cabozanitinib (140 mg) or placebo once daily A significant prolongation in progression free survival was observed for cabozantinib treatment compared with placebo (11.2 versus 4.0 months. The most common side effects, occurring in e"25 percent of patients, were diarrhea, stomatitis, palmar-plantar erythrodysesthesia syndrome, hypertension, and abdominal pain.

Other agents that have been tried in medullary thyroid cancer are Sunitib, Sorafenib, Pazopanib etc. However, they are not as yet approved by FDA in treatment of Medullary thyroid cancer.

Investigational Therapy

Tumor Vaccines: A novel approach to targeted immunotherapy is the use of tumor vaccines. Dendritic cells, which are derived from bone marrow antigen-presenting cells, are capable of presenting tumor-associated antigens, thereby generating cytotoxic T-cells targeting tumor cells. In preliminary studies in patients with metastatic MTC, treatment with stimulated dendritic cells has been promising with minimal toxicities including low grade fever & transient development of autoantibodies. Further studies are underway to define the role of tumor vaccines in the treatment of thyroid cancer

Radioimmuno Therapy: The expression of CEA on MTC cells led to the exploitation of radiolabeled anti-CEA monoclonal antibodies for radioimmunotherapy. In the initial trials, antitumor effects were noted using anti-CEA/anti-diethylenetriamine pentaacetic acid (DTPA)-indium recombinant bispecific antibody (BsMAb), followed four days later by a 131I-labeled bivalent hapten. In a subsequent nonrandomized trial in patients with progressive metastatic MTC (defined as a calcitonin doubling time less than two years), median overall survival after administration of this therapy was 110 months. This compared favorably with a contemporaneous untreated cohort's median survival of only 60 months.

Significant toxicities included grade 4 neutropenia and thrombocytopenia, lasting up to three weeks, and one patient (who had received previous radiotherapies) developed myelodysplasia.

Radiolabeled Octreotide: In a phase II trial in 31 patients with progressive metastatic MTC, treatment with radiolabeled octreotide, (90)Yttrium-1,4,7,10-tetra-azacyclododecane N,N',N'',N'''-tetraacetic acid [(90)Y-DOTA]-Tyr(3)-octreotide (TOC) resulted in decreases in calcitonin levels in nine patients (29 percent) . Responders had a significantly longer median survival (109 months from time of diagnosis compared with 80 months in nonresponders). Hematologic and renal toxicities occurred in four and seven patients, respectively

The availability of tyrosine kinase inhibitors that can stabilize progressive metastatic disease is changing the standard approach to treating metastatic MTC. These are exciting times in the treatment of thyroid cancer. With ongoing trials, next decade will hopefully usher in a new era in the treatment of thyroid cancer.

(Dr Ullas Batra, Consultant, Dept of Medical Oncology, RGCI & RC)

RESEARCH & DEVELOPMENT

Expression Based Signatures

A group of researchers in Canada have utilized whole-transcriptome profiling to develop and validate a genomic classifier that significantly improves the accuracy of preoperative thyroid cancer diagnosis. Nucleic acids were extracted and amplified for microarray expression analysis from formalin fixed and paraffin embedded (FFPE) thyroid tumor tissue cores. A training group of 60 thyroidectomy specimens (30 cancers and 30 benign lesions) were utilized to assess differential expression and for subsequent generation of a genomic classifier. The classifier was validated in a blinded fashion on a group of 31 FFPE thyroid fine-needle aspiration biopsy (FNAB) specimens. Expression profiles for the 57 thyroidectomy training and 31 FNAB validation specimens were analyzed. A genomic classifier composed of 249 probe sets that corresponded with 154 genes, had an overall validated accuracy of 90.0% in 31 patient FNAB specimens. Whole-transcriptome profiling of thyroid nodule surgical specimens may help in improving accuracy of pre-operative thyroid cancer FNAB diagnosis.

(J Clin Endocrinol Metab, Aug 8, 2013)

Novel Dendritic Nanocarrier

To improve safety and efficiency of small interfering RNA (siRNA) delivery, a triblock dendritic nanocarrier, polyamidoamine-polyethylene glycol-cyclic RGD (PAMAM-PEG-cRGD) was developed and studied as an siRNA vector targeting the human ether-à-go-go-related gene (hERG) in human anaplastic thyroid carcinoma cells. Structure characterization, particle size, zeta potential, and gel retardation assay confirmed that complete triblock components were successfully synthesized with effective binding capacity of siRNA in this triblock nanocarrier. Cytotoxicity data indicated that conjugation of PEG significantly alleviated cytotoxicity when compared with unmodified PAMAM. Gene silencing was evaluated by reverse transcription polymerase chain reaction and PAMAM-PEG-cRGD-siRNA complex downregulated the expression of hERG to 26.3% of the control value. Furthermore, gene knockdown of hERG elicited growth suppression as well as activated apoptosis by means of abolishing vascular endothelial growth factor secretion and triggering caspase-3 cascade in anaplastic thyroid carcinoma cells. This study demonstrates that this novel triblock polymer, PAMAM-PEG-cRGD, exhibits negligible cytotoxicity, effective transfection, "smart" cancer targeting, and therefore is a promising siRNA nanocarrier.

(Int J Nanomedicine, Aug 2013)

Potential New Marker of Thyroid Malignancy

The immunohistochemical expression of galectin-3 is currently considered to be the most accurate stand-alone marker for thyroid cancer diagnosis. A new study conducted in Italy has established whether the methylation state of the galectin-3 gene is a candidate molecular marker for thyroid malignancy. Thyroid specimens from 50 patients were analyzed, including 5 normal thyroid, 3goiters, 39 papillary and 3 anaplastic thyroid carcinoma cases. High-resolution methylation analyses was performed to investigate the methylation state of a large genomic region (from -89 to +408) encompassing the galectin-3 transcriptional start site. Within this region, 5 CpG sites were observed to be differentially methylated among the samples and were further analyzed by the quantitative pyrosequencing technique. The average methylation state of the 5 CpG sites clearly distinguished cancer from the non-neoplastic thyroid tissues.

(Oncol Lett, Jul 2013)

Thyroid Ultrasound Imaging Characteristics

Researchers have quantified the risk of thyroid cancer associated with thyroid nodules based on ultrasound imaging characteristics. A retrospective case-control study of 8806 patients who underwent 11618 thyroid ultrasound imaging was conducted. Thyroid nodules were common in patients diagnosed as having cancer (96.9%) and patients not diagnosed as having thyroid cancer (56.4%). Three ultrasound nodule characteristics, including microcalcifications, size greater than 2 cm, and an entirely solid composition, were the only findings associated with the risk of thyroid cancer. Compared with performing biopsy of all thyroid nodules larger than 5 mm, adoption of this more stringent rule requiring 2 abnormal nodule characteristics to prompt biopsy would reduce unnecessary biopsies by 90% while maintaining a low risk of cancer (5 per 1000 patients for whom biopsy is deferred). Thyroid ultrasound imaging could be used to identify patients who have a low risk of cancer for whom biopsy could be deferred.

(JAMA Intern Med, Aug 26, 2013)

NEW TECHNOLOGIES

New Diagnostic Test

Roche, a leading biopharmaceutical company, has announced the global launch of a new laboratory test, Elecsys Calcitonin, for the diagnosis and lifelong monitoring of medullary thyroid cancer patients after thyroid surgery. The Elecsys Calcitonin works by calculating levels of amino acid calcitonin in blood, the increased levels of which are associated with onset of thyroid cancer. This test would be available worldwide with exception of United States. The new tool is designed for use on Roche's Elecsys Calcitonin cobas modular analyser platform, i.e., an in vitro diagnostics laboratory system. The new test is an important part of medical evaluation, especially when the patient's symptoms are not specific. When the Calcitonin test was performed along with further examinations, it supported final clinical clearance. The survival rate for thyroid cancer is relatively high, although recurrence after treatment is common with about one-third of patients relapsing. Delay of diagnosis of relapse can be a significant factor in a patient's chances of survival, and a delay in diagnosis of more than one year increases mortality rate significantly. Elecsys Calcitonin offers an integrated solution for accurate diagnosis and reliable patient monitoring, significantly improving medical decision-making and treatment planning. The development of new laboratory tests for cancer management supports the healthcare professionals with clear, actionable information and can thus contribute to increasing patient survival.

(www.roche.com, Apr 4, 2013)

New Drug Stalls Cancer Progression

The U S Food and Drug Administration (FDA) has granted priority review designation to the supplemental new drug application for oral multi-kinase inhibitor Nexavar® (sorafenib, Bayer/ Onyx Pharmaceuticals) tablets for the treatment of locally advanced or metastatic radioactive iodine (RAI)-refractory differentiated thyroid cancer. The priority review is based upon the findings of a new study which illustrated that targeted agent Nexavar® could become the first new drug for metastatic thyroid cancer. A total of 417 patients with locally advanced or metastatic, RAI refractory, differentiated thyroid cancer (papillary, follicular, Hurthle cell and poorly differentiated) were included in the study. All of them had received no prior chemotherapy, tyrosine kinase inhibitors and monoclonal antibodies. These patients were no longer responding to radioactive iodine or surgical treatments. A significant improvement in median progression-free survival (PFS) of 10.8 months in the Nexavar® group compared with 5.8 months in the placebo arm was observed. This demonstrated that sorafenib almost doubled the PFS. The drug is already approved for use in the treatment of kidney and liver cancers. If approved by FDA, this new drug may open up new field in medical oncology and provide hope to metastatic thyroid cancer patients worldwide.

(FiercePharma, Aug 27, 2013)

Trans-Oral Video-Assisted Neck Surgery

Clinicians at Kagoshima University, Japan, have developed trans-oral video-assisted neck surgery (TOVANS), an innovative gasless trans-oral technique for endoscopic thyroidectomy, a well eastablished technique. The video-assisted neck surgery (VANS) with a gasless anterior neck skin lifting method using an approach from the chest wall is utilized for endoscopic thyroidectomy. Recently, the natural orifice translumenal endoscopic surgery (NOTES) has been developed as a surgical technique for potentially scar-free surgery. The newly developed trans-oral technique of completely scarless endoscopic thyroidectomy incorporate the concept of NOTES in a VANS-technique with gasless anterior neck skin lifting by mechanical retraction. This method without CO_2 insufflation created an effective working space and provided an excellent cranio-caudal view which helped in performing thyroidectomy and central node dissection safely. A total of eight such procedures were performed with the clinical application of TOVANS. Three of eight patients had papillary microcarcinoma and they received central node dissection. All patients began oral intake 1 day after the surgery. The sensory disorder around chin persisted for more than 6 months after surgery in all patients. The recurrent laryngeal nerve palsy was revealed in one patient. No patient had mental nerve palsy, and no infection found to be developed with the use of preventive antibacterial tablets for 3 days. This new method is novel and progressive and has not only a cosmetic advantage but also provides easy access to the central node compartment for dissection in endoscopic thyroid cancer surgery.

(Surg Endosc, Apr 27, 2013)

CLINICAL TRIALS

Fosbretabulin for Anaplastic Thyroid Cancer

Researchers at Duke University conducted largest prospective , open-label, randomized safety and efficacy study of doublet carboplatin/paclitaxel (cp) with or without fosbretabulin in patients with anaplastic thyroid cancer. A Total of eighty patients were recruited and randomly assigned in 2:1 ratio. The first group received 6 cycles of paclitaxel 200 mg/m^2 followed by carboplatin auc 6 on day 1 every 3 weeks (cp) and another group of patients given these drugs on day 2 after fosbretabulin 60 mg/m^2 (cp/fosbretabulin) on days 1, 8 and 15. The primary endpoint was overall survival (OS). Results showed that median OS was 5.2 months for CP/fosbretabulin arm (n=55), and 4.0 months for CP arm (n=25). One-year survival for CP/fosbretabulin vs CP was 26% vs 9%, respectively, but the study did not show any significant diffrence in progression free survival. The study reveals that addition of fosbretabulin to the drugs does not show any statistical significant improvement in OS. However, the regimen was well-tolerated in the patients.

(Thyroid, May 2013)

Human Thyroid Stimulating Hormone

The treatment for differentiated thyroid cancer consists of thyroidectomy followed by radio ablation therapy (RAT), usually after 4-6 weeks. However, scientists have come up with an approach that could reduce to the to one week by by using recombinant human thyroid stimulating hormone (rhTSH) to replace hypothyroidism. To observe the consequences of the approach, a prospective randomized trial was done in 44 patients. Twenty-four patients were prospectively randomized for stimulation by rhTSH and 20 patients for thyroidectomy and radio ablation separated by four weeks of L-T4 withdrawal. Overall results showed that rate of recurrence was very less in patients who had received radio ablation in euthyroidism after one week of thyroidectomy and they also had significantly advantageous quality-of-life ($P < 0.001$), sick-leave time ($P < 0.001$), and job performance ($P = 0.002$). Results showed that after thyroidectomy, rhTSH could be the standard procedure in the initial treatment and could be used safely and with good efficacy.

(Int J Endocrinol., July 2013)

Oral PPAR-Gamma Agonist, Efatutazone

According to the results of the multicenter Phase I trial, combination of therapies may prove to be a better option for the treatment of anaplastic thyroid cancer. Present trial was done to establish the safety, potential effectiveness, and maximal tolerated dose and recommended dose of efatutazone and paclitaxel in anaplastic thyroid cancer. Efatutazone works by activating transcriptional factor PPAR-gamma that further activates two tumor suppressor gene expressions which normally stop in anaplastic thyroid cancer. Fifteen patients had participated in the trial, of them 10 were women. Seven patiets received 0.15 mg of efatutazone, six received 0.3mg and two patients were given 0.5mg. One patient had partial response, and 7 attained short-term stable disease. The study found that mdian time to progression was increased from 48 days to 68 days by doubling the dose of drug from 0.15 mg to 0.3mg. The adverse events related to efatutazone were anemia and edema. Overall results showed that maximal tolertaed dose was not achieved for efatutazone in the study but it was found to be safe, well tolerated in combination with paclitaxel and had also shown biologic activity.

(J Clin Endocrinol Metab, Jun 2013)

Vandetanib for Medullary Thyroid Cancer

Mutations in the RET (REarranged during Transfection) proto-oncogene is responsible for multiple endocrine neoplasia type 2 (MEN2) syndromes, which may cause Medullary thyroid cancer (MTC). A Phase I/II trial was conducted to define a recommended dose and assess antitumor activity of vandetanib, a VEGF and EGF receptor inhibitor, that blocks RET tyrosine kinase activity. Sixteen patients, children (5-12 years) and adolescents (13-18 years) with locally advanced or metastatic MTC were enrolled in the trial. Vandetinib was given with dose of 100 mg/m(2) orally, once daily, continuously for 28-day treatment cycles. The dose could be increased to 150 mg/m(2)/d after two cycles. In subjects with M918T RET germline mutations (n = 15), the confirmed objective partial response rate was 47%. Biomarker response was measured by comparing post treatment serum calcitonin and carcinoembryonic antigen levels to the basline. Diarrhea was the primary dose-limiting toxicity. Study concluded that vandetanib 100 mg/m(2)/d is a well-tolerated and highly active new treatment for children and adolescents with MEN2B and locally advanced or metastatic MTC.

(Clin Cancer Res, Aug 2013)

GLOBE SCAN

Factors Influencing Radioiodine Uptake

Total thyroidectomy followed by radioactive iodine (RAI) ablation is indicated for most patients with differentiated thyroid cancer. There have been no quantitative studies testing factors that affect uptake on post-ablation whole body scan. Medical records and whole body scan images of thyroid cancer patients were reviewed. Thyroid uptake, as percentage of Iodine-131 dose, was calculated for each scan. RAI uptake was compared to procedure type, central lymph node dissection (CLND), extrathyroidal invasion, presence of thyroiditis and pre-operative diagnosis. One hundred six patients who underwent total thyroidectomy and RAI ablation for differentiated thyroid cancer were included. RAI uptake appeared higher in two-stage thyroidectomy than one-stage thyroidectomy. This difference may be attributed to CLND being performed more often in one-stage thyroidectomy. These results add to the discussion about the role of CLND in surgery for differentiated thyroid cancer.

(Australia: ANZ J Surj, Aug 2013)

Chernobyl Follow-Up Study

More than a quarter of a century after the Chernobyl nuclear disaster, many children and teenagers who developed thyroid cancer due to radiation, are in complete or near remission, according to a recent study. Following the April 26, 1986 explosion and fire at the Chernobyl nuclear plant in the former Soviet Union, the number of children and teenagers diagnosed with differentiated thyroid cancer spiked in Ukraine, Belarus and western areas of Russia. Most of the patients developed the papillary subtype of differentiated thyroid cancer. Although this cancer tends to be more aggressive in children than adults, nearly all of the patients tracked in the study responded favorably to treatment. The observational study followed the treatment and outcomes of 229 Belarusian children and adolescents who underwent surgery in Belarus and radioiodine therapy in Germany. Despite the risk, 64 percent of the patients are in complete remission and 30 percent nearly complete remission of their cancer. Hence, Chernobyl has taught us how important it is to have screened at-risk children and adolescents for thyroid cancer to catch any cases in their early stages.

(Germany: J Clin Endocrin & Metabol, Apr 24, 2013)

Circulating Cell-Free DNA

Recently high levels of circulating cell-free DNA (cf-DNA) have been found to be associated with cancer diagnosis and progression, and cf-DNA has become a potential candidate as biomarker for tumor detection. cf-DNA has been investigated in plasma or serum of many tumor patients affected by different malignancies, but not yet in thyroid cancer (TC). cf-DNA was measured by quantitative real-time PCR in nine cases of anaplastic thyroid cancer (ATC), 58 medullary thyroid cancers (MTC), five of synchronous medullary and follicular thyroid cancers (SMFC), 23 follicular adenomas (FA), and 86 papillary thyroid cancers (PTC). A control group of 19 healthy subjects was taken. cf-DNA showed a high ability to discriminate healthy individuals from cancer patients. Its possible implication in clinical setting remains to be elucidated.

(Italy: Biomed Pharmacother, Jul 5, 2013)

Thyroid Cancer Biopsy Guidelines

A team led by UC San Francisco researchers has called for simplified guidelines on when to biopsy thyroid nodules for cancer, which they say would result in fewer unnecessary biopsies. Compared with other existing guidelines, many of which are complicated to apply, following these simple, evidence-based guidelines would substantially decrease the number of unnecessary thyroid biopsies in the United States. The research team analyzed the medical records of 8,806 patients who underwent 11,618 thyroid ultrasound examinations at a UCSF inpatient or outpatient facility from January 2000 through March 2005. The patients did not have a diagnosis of thyroid cancer at the time of the ultrasound, but were referred to ultrasound for a variety of reasons, such as a physician's suspicion that a patient had a nodule, an abnormal thyroid function test or a CT or MRI examination that revealed the presence of at least one nodule. The authors found that while 97 percent of the cancer patients had at least one nodule, 56 percent of patients without cancer had nodules as well. Ultimately, the researchers identified only three significant ultrasound imaging findings that indicated an increased chance of thyroid cancer: microcalcification, a nodule diameter greater than two centimeters, and a nodule that was solid rather than cyst-like. The time has come to start doing diagnostic tests and procedures more selectively and prudently, as there are harms to doing unnecessary tests and procedures.

(USA: JAMA Int Med, Aug 26, 2013)

CANCER CONTROL

Hyperthyroidism and Thyroid Cancer Risk

Researchers form the Chi Mei Medical Center, Taiwan, have evaluated the risk of thyroid cancer with hyperthyroidism. The study included one million individuals from Taiwan's National Health Insurance database. It was found that 17033 patients had newly diagnosed hyperthyroidism between 2000 and 2005. These patients were recruited along with a match cohort of 34 066 patients without hyperthyroidism. Starting from index date, all patients were followed up for 4 years to identify those who developed cancer. During the 4-year follow-up, cancer was diagnosed in 1.23% of patients with hyperthyroidism and 1.02% of the members of the comparison cohort. Regression analysis showed that patients with hyperthyroidism were at greater risk of cancer incidence, especially thyroid cancer, than the comparison cohort (HR: 1.213; 95% CI: 1.022-1.440; $p<0.05$ and HR: 7.355; 95% CI: 3.885-13.92; $p<0.05$, respectively). After adjusting for age, gender, diabetes mellitus, hypertension, hyperlipidemia, gout, geographic region, and income, patients with hyperthyroidism remained at increased risk of thyroid cancer (adjusted HR: 1.206; 95% CI: 1.015-1.433 and 6.803; 95% CI: 3.584-12.91, respectively) (both $p<0.05$). The longer the duration of hyperthyroidism, the greater the risk of thyroid cancer. This study suggests that patients with hyperthyroidism are at increased risk of cancer, especially thyroid cancer.

(Exp Clin Endocrinol Diabetes, Jul 2013)

Thyroid Cancer and Relatives of Patients

The familial risk of medullary thyroid carcinoma (MTC alone or as part of multiple endocrine neoplasms, MEN2A/MEN2B) is supposed to be high. The scientists from German Cancer Research Center, Germany and Center for Primary Health Care Research, Lund University, Sweden, conducted a study to answer open questions about the lifetime cumulative risk of thyroid cancer (LCRTC at 0-79 years) among relatives of MTC patients by age and sex. In this study, a cohort of 3217 first-/second-degree relatives (FDRs/SDRs) of 389 MTC patients diagnosed in 1958-2010 in the Swedish Family-Cancer Database was followed for the incidence of thyroid cancer. The LCRTC in female relatives of patients with early-onset MEN2B (diagnosis age < 25 years) was 44-57%, representing 140-520 times increase over the risk in their peers without a family history of endocrine tumors (men: LCRTC = 22-52%, 320-750 times) depending on the number of affected FDRs/SDRs. The LCRTC in female relatives of patients with late-onset MEN2B (diagnosis age >= 25 years) was about 15-43% (men = 24%). The LCRTC among relatives of early-onset MTC-alone patients was 3-20%. The LCRTC among relatives of late-onset MTC-alone patients was 5-26%. The LCRTC in female relatives of MEN2A patients was 16-63% (men = 52%). The relatives of patients with early-onset MTC exhibited a high tendency to develop early-onset thyroid cancer. Simply available data on the number of FDRs and even SDRs affected with MTC and their age at diagnosis were quite informative for the estimation of the risk of thyroid cancer in probands. In settings where genetic testing is not available or affordable for all, evidence-based cumulative risks reported in this nationwide study may help physicians to identify very high-risk individuals.

(Endocr Relat Cancer Sep 3, 2013)

Zealous Imaging and Low Risk Thyroid Cancer

New technologies, such as ultrasound, CT and MRI scanning, can detect thyroid nodules as small as 2mm, and many of these small nodules are papillary thyroid cancers. These imaging techniques are fuelling an epidemic in diagnosis and treatment of thyroid cancers that are unlikely to ever progress to cause symptoms or death. This expanding gap between incidence of thyroid cancer and deaths suggests that low risk cancers are being overdiagnosed and overtreated. Scientist, consider that unnecessary thyroidectomy (the surgical removal of all or part of the thyroid gland) is costly and carries a risk of complications, such as low calcium levels and nerve injury. Using radioactive iodine in patients with low risk thyroid cancer has also increased from one in 300 patients to two in five patients between 1973 and 2006 in the US, despite recommendations against using it. They suggest a term that conveys favorable prognosis for low risk thyroid cancers (microPapillary Lesions of Indolent Course or microPLIC) and makes it easier to give patients the choice of active surveillance over immediate and often intensive treatment. And they call for research to identify the appropriate care for these patients.

(Science Daily, Aug 27, 2013)

IN FOCUS

MOLECULAR DIAGNOSIS OF THYROID CANCERS

Thyroid cancer is the leading endocrine malignancy globally with ASR of 3.1 per 10^6/ year and mortality rate of 0.5 per 10^6/ year. 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 commonly present as solitary nodule diagnosed clinically or incidentally on imaging for some other purpose. The work up begins with evaluation of clinical history, physical examination, followed by TSH and FT4 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 FNAC 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 gamut of molecular markers have been identified in thyroid carcinoma in the recent past. Table 1 lists the genetic signatures which can be searched to establish diagnosis and draw important information about prognosis, thus helping optimize treatment in terms of extent of surgery and use of radioiodine ablation.

Table 1: PTC: Papillary Thyroid Carcinoma, FTC: Follicular Thyroid Carcinoma, FTA: Follicular Thyroid Adenoma

S. No.	Molecular marker	Incidence - histological type	Characteristic imparted to the tumor	Utility
1.	BRAF	45% - PTC	1. Tall & columnar cell mrphology 2. ETE common 3. High stage at presentation 4. Higher rate of tumor recurrence 5. Proclivity towardes dedifferentiation	1. BRAF mutation diagnostic of PTC 2. Detectable on FNAC material 3. Indicates worse outcomes - consider enhanced extent to 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 FNAC material 3. Consider more conservative approach
3.	RAS	15% - PTC 05% - FTA 25% - FTC	1. The PTC harboring RAS mutations 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 FNAC material 2. Some believe that detection in FNAC material shall result in treatment for cancer as the FTA with RAS mutation have proclivity for progression to FTC 3. FVPTC more akin to FTC may show vascular metastasis. All FVPTC must be examined by pathologist for extensive vascular embolization as this group amongst FVPTC can have bad prognosis.
4.	PAX8 - γ PPAR	35% - FTA 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 invasion - reduce false negative diagnosis of FTC.

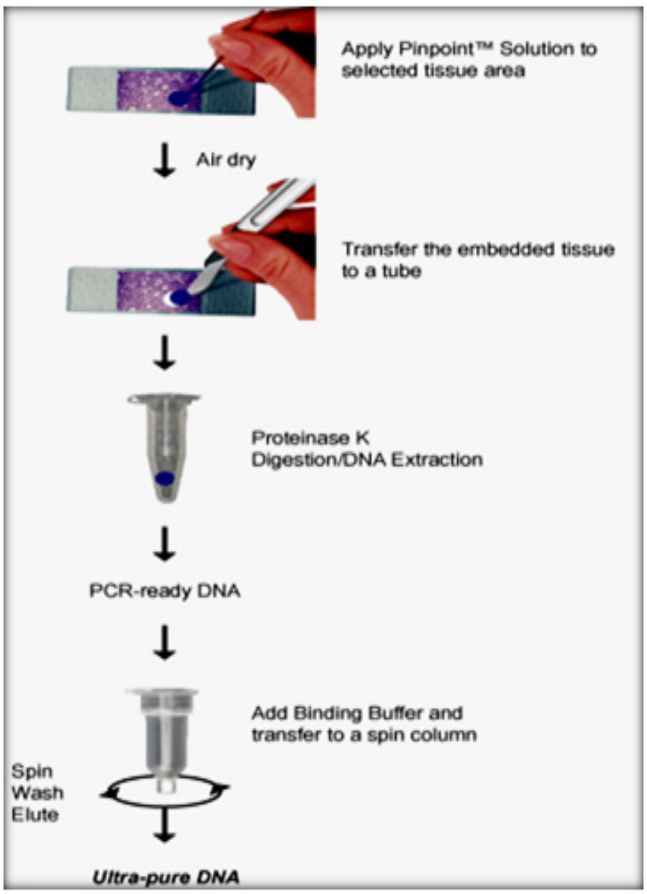

Fig1: DNA Extraction method using Pinpoint DNA extraction Kit

BRAF mutation is the most important of these and is noted in 40-45% of PTC. Of many BRAF mutations, the one that affects the PTC is caused by replacement of thymidylate by adenylate at 1799(T1799A) position, resulting in translation to glutamic acid instead of valine at 600th amino acid (V600E). This 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 FNAC smears for ultrapure DNA extraction is shown in Fig1 above.

Detection of BRAF mutation in FNAC 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 radioiodine ablation.

It is also exciting to note that presence of BRAF mutation may provide the opportunity of using targeted molecules in advanced PTC. Several inhibitors of BRAF have been developed, including sorafenib, PLX4032, RAF265, PLX4720, and XL281 with different selectivity. Indeed, encouraging results with the BRAF inhibitors sorafenib and PLX4032 were recently reported in clinical trials with malignant melanoma which has a high prevalence of BRAF mutations. These drugs showed marked inhibition of cell proliferation, survival, motility, and invasion in vivo and in vitro. PLX4032, a compound that selectively targets BRAF V600E, can effectively inhibit the proliferation of PTC cell lines bearing BRAF mutation.

Several of the kinase inhibitors of RAS-RAF pathway have now been tested in Phase II and Phase III trials, with modestly encouraging results. Additional Phase III trials will be needed to conclusively show that treatment benefit exceeds risk.

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 or medullary carcinomas. Of various PTC histological variants; RET/PTC1 rearrangement is most frequently seen in PTC with classic morphology. It is rare in the follicular variant of PTC. RET/PTC1 has 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/PTC1 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.

RET-PTC rearrangement 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 RT-PCR. 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.

ZD 6474 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 with RET/PTC rearrangements.

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 RAS mutations are noted in follicular adenomas, the value of determining RAS mutation to make a diagnosis of cancer on FNAC material is limited. It is, however, observed that FTA with RAS mutation has a chance of progression and deserves 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 / PPAR γ

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 and shows a negligible presence in FTA, and has not been reported in papillary thyroid carcinoma. As a biomarker, a PAX8 / PPARγ rearrangement is a strong indicator that the tumor is a follicular carcinoma with an early propensity for vascular invasion. Besides RT PCR as a molecular method of detection, PPARγ 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. C634A and M918T are the two common mutations seen in most cases of MEN2A and MEN2B respectively. 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.

Conclusion

Finding the above alluded mutations in a thyroid nodule provide 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.

Many of these molecular markers will also be the targets for precision medicine in advanced cases with radioiodine refractoriness.

(Dr Anurag Mehta, Director Laboratory Services; RGCI & RC, Dr Neha Seth, Resident, Pathology; RGCI & RC)

ACTIVITIES OF RGCI&RC

Thyroid Cancer Symposium

A symposium on 'Differentiated Thyroid Cancer: Beyond Primary and Conventional Management' was organized by RGCI&RC on 31st August 2013 at Hotel Crowne Plaza, Rohini, Delhi. Dr PS Choudhury, Director Nuclear Medicine was the Organizing Secretary. The half-day symposium mainly focused on recurrent thyroid cancer and consisted of plenary lectures, debates and a panel discussion.

The lectures deliberated upon the nuances of surgery in a recurrent setting, the complications expected and current concepts of lymph node dissection in this disease followed by the utility of radioactive iodine and importance of long term follow-up as practiced in RGCI&RC and compared it with the international data. Discussions were very interesting and interactive that it brought out

(Scientific Proceedings at Thyroid Cancer Symposium)

where and when to attempt revision thyroidectomy or ablation of an intact lobe with radioactive iodine post thyroidectomy and the optimum method of patient preparation with recombinant TSH (rH-TSH). Quality of life issues which are pertinent to any form of treatment were discussed in conjunction with rH-TSH. The last most interactive session consisted of panel discussion on a few challenging cases in recurrent thyroid cancer which was well appreciated by the audience. In addition to the faculty from the Institutie, specialists from other major institutions in the city took active part in the proceedings.

(Dr PS Choudhury, Director Nuclear Medicine, RGCI&RC)

Breast Cancer Symposium

A symposium on "Current Trends in Breast Imaging" was organized on Saturday, 21st September, 2013 by Rajiv Gandhi Cancer Institute and Research Centre (RGCI & RC) at Hotel Crown Plaza, Rohini, Delhi.

(L to R: Mr DS Negi, CEO, RGCI&RC; Mr Rakesh Chopra, Chairman, RGCI&RC; Dr AK Chaturvedi, Director, Radiology & Organizing Chairman, Breast Imaging, RGCI&RC; Dr AK Dewan, Medical Director, RGCI&RC; Dr DC Doval, Director, Medical Oncology & Research, RGCI&RC)

The meeting started with the traditional lamp lighting and welcome address by Mr DS Negi, Chief Executive Officer, RGCI&RC. The 'Keynote address' was delivered by Dr DC Doval, Director Medical Oncology, RGCI&RC. Dr AK Chaturvedi, Chairman of the Organizing Committee introduced the content and purpose of the meeting to the audience. Diverse topics related to breast imaging were discussed in depth. However, the highlight of the meeting was digital breast tomosynthesis or three dimensional imaging which is being considered a game changer. This new technology is very promising in detecting breast cancer, even in dense breasts. It is already available at RGCI&RC and involves obtaining multiple images of each breast, similar to a CT scan. Slice by slice interpretation of breast tissue helps in a more accurate diagnosis. Instead of one image for each breast, there are multiple sliced images of each breast which are analyzed on a monitor resulting in a much higher sensitivity and specificity. It is the new standard for breast cancer screening.

Other topics of interest were a discussion on future of screen film technology and relevance of screening mammography in India. A panel discussion involving the breast surgeons, oncologists, pathologists and radiologists was moderated by Dr A K Chaturvedi, Director Radiology, with intense audience participation. Overall, the meeting was a grand success and highlighted the continuum of academic activities undertaken by RGCI & RC.

(Dr AK Chaturvedi, Director Radiology, RGCI&RC)

Rajiv Gandhi Cancer Institute and Research Centre

A Unit of Indraprastha Cancer Society
Registered under "Societies Registration Act 1860"

THE PINK RIBBON MEET

-An RGCI & RC Initiative

Event :
Annual Symposium for Breast Cancer Survivors

Venue :
Crystal Ballroom, Hotel Crowne Plaza, Rohini, Delhi

Schedule :
Saturday, 14th December 2013

Timing :
1:00 p.m. - 5:30 p.m.
(Meeting will be preceded by Lunch)

Team :

Dr. Kapil Kumar
Dr. Sandeep Mehta
Dr. Ashish Goel
Dr. S. Veda Padma Priya
Dr. D. C. Doval
Dr. Ullas Batra
Dr. Kumardeep Dutta
Dr. S. K. Sharma
Dr. Anjali Kakria

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Caring Beyond Cure...
Living Beyond Survival ...

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