

Carcinoma Thyroid—Have Turned Around the Corner?

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Thyroid surgery was revolutionized by **Theodore Kocher** and his work earned him the Nobel Prize in 1909. The techniques laid down by him hold good even today, even in thyroid cancer surgery. William Halstead, Charles Mayo, George Crile, Frank Lahey and Thomas Dunhill also made significant contributions in vastly improving the outcome of surgery of Thyroid disease. **FNAC**, a technique first performed by Greig and Gray in 1904 to aspirate trypanosomes from the lymph nodes of patients with sleeping sickness, is the best modality for work up of thyroid nodules and has eclipsed Radio Active Iodine Uptake study. After the widespread use of FNAC in thyroid disease since 1970s a pre operative tissue diagnosis was possible in most thyroid nodules. The role of FNAC is further enhanced by combining Immuno Histo chemistry and nuclear DNA analysis (*Petra Werga et al, Karolinska hospital, Sweden, 2000*). Yield is highest when done by persons well versed with this technique. The only distinct failure of FNAC is its inability to distinguish between follicular adenoma and carcinoma. But even this has been overcome with the advent of techniques like the following. **Two dimensional proton Magnetic Resonance Spectroscopic analysis** has now enabled one to effectively identify malignancy as well as to differentiate between Follicular adenoma and carcinoma and is based increased cell surface fucosylation (*Wanda. B Mackinnon et al, NSW, Australia*). **Molecular genetics** in relation to thyroid disease especially in carcinoma thyroid had exploded many myths and realities. The relationship between RET-PTC oncogene and MTC is established beyond doubt and signaled the induction of “**prophylactic thyroid-ectomy**” in the realm of surgeons. Prophylactic thyroidectomy is ideally done in RET-PTC positive individuals at six years of age.

Central compartment lymph node dissection is added if there is a raised serum calcium or if the patient is older than 10 years. Bilateral lymph node dissection is done in patents

older than 15 with elevated serum calcitonin (*Henning Dralle et al, Germany 1998*). An Association between TSHR and Gs mutation with toxic adenosis has also been proven. P 53 mutation plays a dominant role in the development of anaplastic carcinoma (*Diana Learoyd et al, NSW, Australia, 2000*). **Familial Papillary Thyroid Carcinoma [FPTC] and MNG** has also been recognized as a distinct entity apart from other familial syndromes like Gardener's syndrome and Cowden's disease. Primary criteria for susceptibility to FPTC include PTC in two first degree relatives, MNG in three first or second degree relatives, patients younger than 33 years with multi focal, bilateral or metastatic PTC (*Thomas.Musholt et al, Hannover, Germany 2000*). **Surgical techniques** are opted based on various scoring systems like **AMES, MACIS, AGES**. These systems help prognosticate thyroid cancer based on age, size of tumor, extra thyroidal spread, metastasis and completeness of thyroidectomy. **Sentinel lymph node mapping was first** with isosulfan blue dye is safe and sentinel nodes even if present in the lateral cervical compartments and mediastinum are detected (*Elijah Dixon et al, Alberta, Canada 2000*). **Microdissection** with central compartment lymph nodal clearance has been shown to positively influence survival and decrease local recurrence in patients with PTC (*Lars-Erik Tissel et al, Goteberg, Sweden 1996*). **Complications** of surgery like permanent Recurrent laryngeal nerve palsy [1%] and hypo parathyroidism [2%] have been reduced and recurrence scaled down significantly because of well established endocrine centers and training of young surgeons (Tom Reeve, NSW Australia, 2000). Complications are higher in **re operative thyroid surgeries with RLN palsy** as high as 2% and hypoparathyroidism seen in almost 5% of the cases (*Puzzolo et al, Italy 1997*). (**Korean J Endocrine Surg 2002;2:5-9**)

Key Word: Thyroid cancer

Thyroid surgery came of age in the 20th century. Theodore Kocher refined techniques and laid down principles, which holds good even today. Other great stalwarts include the William Halsted, Charles Mayo, George Crile, and Frank Lahey. There was a drastic reduction in complication rates owing to the techniques laid down by the above people and one can say that all recent development and those in future will merely be building blocks over the foundation laid down by these illustrious surgeons.

Role of FNAC in Thyroid Pathology (1)

Fine needle aspiration cytology is now considered the investigation of choice in work up for thyroid nodules, since the need for reliable preoperative diagnosis is absolutely essential in planning out appropriate treatment strategies.

The use of FNA to procure tissue for microscopic diagnosis is almost 100 years old. In 1905 Greig and Gray reported that trypanosome organisms could be detected in needle aspiration material from lymph nodes in a patient with sleeping sickness. It was in 1934 that Martin and Ellis reported a large review of tumours diagnosed by FNA. FNAC was popularised by pioneers such as Soderstrom and Franzen, who proved FNA to be a highly accurate and cost effective procedure, with low morbidity.

During 1970's FNAC became a standard procedure in Sweden to diagnose thyroid nodules. However, only during mid and late 70's, FNAC received worldwide recognition as the investigation of choice for thyroid nodules.

FNAC technique can be used to diagnose a wide spectrum of disorders of thyroid gland with nodules that are either non-palpable or normal size, differently enlarged, multi nodular (or) solitary. Nodule located deep in the neck can be aspirated with ultrasound guidance. The draw back of FNAC is that is cannot distinguish between a follicular adenoma and carcinoma. The reason is that diagnosing a follicular carcinoma is based on histopathologic criteria such as capsular (or) vascular invasion, where cytology does not contribute.

Frozen section is of limited value as it may require several sections and excellent morphology. Immunostaining with HBME-1 monoclonal antibody may be of value for differentiation in the future in detecting follicular carcinoma.

FNAC and Immuno Cytochemistry

Immuno cytochemistry techniques have been used mainly to aid cytomorphology in the characterisation of poorly differentiated epithelial tumours and lymphoid infiltrates in the thyroid. It is best

performed in cytospin preparations from aspirated cells.

Antibodies of thyroglobulin, cytokeratins, and calcification can be analysed. This is useful in differential diagnosis between a primary thyroid neoplasm and a metastatic deposit in the thyroid. Immunocytochemistry is used to sub classify lymphoma into high grade T, B (or) anaplastic large cell, Ki-67 positive neoplasm, which is of prognostic and therapeutic importance.

Immunohistochemistry also aids in prognostication of thyroid cancer by analysing fraction of tumour cells in growth phase by using a monoclonal antibody to Ki-67 antigen. High proliferation rate in thyroid cancer indicates a bad prognosis.

Role of Proton Magnetic Resonance Spectroscopy (H-MRS) (2)

One dimensional proton magnetic resonance spectroscopy can distinguish normal thyroid tissue from thyroid carcinoma. Two-dimensional H-MRS allows identification of specific molecules that have overlapping peaks in MR spectrum. A single cross peak attributable to cholesterol / choletryl ester was commonly seen in carcinomas attributable to cell surface fucosylation. This contracts two unassigned cross peaks unique to thyroid that are more prevalent in benign lesions. This MRS has been used to study tumour development and progression by monitoring alterations in cellular chemistry, thus allowing more specific tissue characterisation of thyroid neoplasms. The sensitivity and specificity of one-dimensional MRS in distinguishing benign from malignant lesions with tissue from biopsy FNAC is 100%.

Molecular genetics of thyroid tumours (3)

Molecular genetics has helped us in understanding tumour pathogenesis, prediction of tumour behaviour and in management decisions. The relevance of surgeon is to help weed out families at risk and plan appropriate screening and to cater treatment according to behaviour of tumours.

Oncogenes

1) Ret proto oncogenes

Ret Proto-oncogene has important role in the pathogenesis of both papillary and medullary thyroid cancer. RET, located on chromosome 10 is a tyrosine kinase receptor. Somatic rearrangement of RET has been identified in PTC. RET/PTC's are generated by fusion of the tyrosine kinase (TK) domain of RET to the 5' terminal sequence of another gene such as gene H4 in RET/PTC.

Five types RET/PTC have been identified in young age. Radiation exposure is a risk factors for the presence of RET/PTC. Although RET-PTC is associated with early lymph node spread and low potential for distant metastatic spread, this is not yet conclusively proven.

It is well established that radiation predisposes to thyroid tumour formation. This is seen as a fall out from the Chernobyl nuclear accident in 1986. A high incidence of thyroid cancer has been found in children, with increased prevalence of RET/PTC 3 oncogene. These radiation induced PTC tumours are less well differentiated than denovo PTC. RET/PTC has been associated with radiation exposure in France.

RET in Medullary Carcinoma Thyroid

1) Familial MTC

The most important pathogenic role for RET is in the autosomal dominant MEN-II syndrome. Germ line mutations have been found in the cysteine encoding codon 609, 611, 618, 620 of 634 in MEN-IIA. MEN IIB has been associated with mutation in codon 918.

The RET-Proto oncogene initiation screening has largely replaced the traditional biochemical screening tests such as the Pentagastrin (PG) stimulation test in MEN-II families.

Prophylactic Thyroidectomy (7)

The concept of prophylactic thyroidectomy was introduced after association between RET-PTC and MTC were proven conclusively.

1) The indications are as follows

1. Total thyroidectomy if patient >6 yrs with normal serum calcitonin levels.
2. 1+central compartment lymph node if age >10 yrs (or) with increased Serum Calcitonin.
3. 2+central lymph node dissection and bilateral lymph node dissect if patient >15 yrs age including elevated Serum Calcitonin.

Sporadic MTC

Somatic RET mutations are common in the sporadic MTC. Mutations occur in codon 918 ATG substitutions. This is associated with poor prognosis.

Familial non-MTC

There are now several reports of autosomal dominant inheritance of PTC. No RET oncogene has been implicated in their pathogenesis. Susceptibility link for familial multinodular goitre and familial PTC has been described. Familial cases of papillary thyroid cancer (or) follicular thyroid cancer are seen in associated with familial cancer syndrome such as Gardner's and Cowden's syndrome.

Criteria for Diagnosis of PTC and MNG (4)

An increasing number of case reports, epidemiologic analysis and retrospective clinical studies support the existence of a distinct clinical entity of familial PTC with a strong association with multi nodular goitre. An autosomal dominant trait of hereditary predisposition with variable penetrance has been postulated for this PTC/MNG synthesis. A diagnosis of this condition is made based on the following criteria.

Primary Criteria for Suceptibility

- 1) PTC in two (or) more first degree relatives
- 2) MNG in at least three first (or) second-degree relatives of a PTC patient.

Secondary Criteria

- i. Patient younger than 33 years
- ii. Multi focal (or) bilateral PTC
- iii. Organ exceeding tumour growth (T₄)
- iv. Metastasis (N₁, M₁)
- v. Familial accumulation of adolescent onset thyroid disease.

A hereditary predisposition to PTC is considered if both primary criteria (or) one primary and three secondary criteria are present.

Surgery for thyroid carcinomas (5)

Various scoring system have been proposed to identify bad prognostic factors in carcinoma thyroid. High risk criteria includes age above 45 yrs, presence of metastasis extra thyroid spread, size of tumour 1>cm, completeness of surgery, and grade of the tumour such as the AMES (Age, Metastasis, extra thyroid tumour size of tumour) AGES (Age, grade, extra thyroid spread, size. MACIS (Metastasis, age, completion of thyroidectomy, invasion, size) systems differentiated thyroid cancer.

There is a general consensus that total thyroidectomy is the optimal treatment for patient with high-risk differentiated thyroid cancer. But the optimal extent of thyroidectomy in patients with low risk DTC continues to be controversial. Prospective studies have shown that patients viewed DTC recurrence as less desirable than thyroidectomy complications are ideal for lobectomy.

Surgeons who advocate lobectomy for patients with low risk DTC cite the following reasons:

- a. About half of all DTC recurrences can be treated by reoperation, and fewer than 5% of DTC recurrences are found in thyroid bed.
- b. Total thyroidectomy may be associated with a higher complication rate than lesser procedures.
- c. Tumour multicentricity in papillary thyroid cancer has little clinical significance.
- d. Most patients with low risk DTC enjoy an excellent prognosis regardless of the extent of initial thyroidectomy.

Surgeons who perform total thyroidectomy cite the following in their favour.

- a. Radioiodine screening for treatment for detecting (or) ablating remnant thyroid tissue or for local and distant metastasis is more effective after all thyroid tissue is removed.
- b. Postoperative serum thyroglobulin level is accurate in detecting recurrence and persistent carcinoma, which is of use only after total thyroidectomy.
- c. Since up to 80% of papillary carcinomas are multicentric, possibility of recurrence is contra lateral lobe is eliminated.
- d. Thyroid reoperation is associated with a higher complications risk.

Sentinel Lymph Node Mapping in Thyroid Neoplasms

About 50~90% of people with differentiated thyroid carcinoma have occult lymph nodal deposits. This is associated with increased local recurrence, which is reduced with loco regional radioactive iodine therapy. Hence sentinel lymph node biopsy can be used to detect those cases, which will be benefited by post op RT. The disadvantage is that lymph node metastasis is not associated with decreased survival and hence this practice may not result in significant improvement in outcome.

Elijah Dixon et al between Aug 1997-Apr conducted a study 1999 at Alberta, Canada. Isosulfan Blue drug was injected after minimal dissection, and the identified lymph node sent for frozen section analysis. This process had no complications. Parathyroid staining occurred, making their identification prior to dye injection

mandatory. Variable lymphatic drainage patterns were observed and nodes in the lateral compartment look up staining in certain cases, suggestive of skip metastasis. This technique needs further study before coming to a definite conclusion.

Surgical Microdissection

Controversy exists about the treatment of papillary thyroid cancer especially about how radical the surgical treatment should be. The strategy adopted was to perform total thyroidectomy and a careful central neck dissection between internal jugular veins, from the hyoid bone to innominate vessels. The trachea and the recurrent laryngeal nerves were freed from all lymph nodes and fibro fatty tissue.

A lateral neck dissection was performed if macroscopic lateral lymph node metastasis was found. Good lighting, magnifying glasses, small instruments and patience are pre requisites of micro dissection. Long-term follow up is needed to evaluate the outcome of this procedure.

Complications of thyroid surgery (6)

Permanent recurrent laryngeal palsy, hypo parathyroidism, local recurrence of the disease is complications higher in reoperative thyroid surgery.

Future in Thyroid Cancer Surgery

Molecular genetics helps in predicting tumours behaviour and planning appropriate treatment modality (e.g.) prophylactic thyroidectomy. Magnetic resonance spectroscopic analysis of tissue typing helps in diagnosis, especially in differentiating between follicular adenoma and carcinoma. Refinement of surgical techniques and introduction of concepts like micro dissection are sentinel lymph node mapping have also evolved as newer modalities in treatment for cancer thyroid. The day is not far ahead, where accurate prediction of tumour behaviour will help in individualising treatment and catering to specific needs.

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