

Update on thyroid cancer management and the limitations faced by us

Kanishka de Silva¹

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Magnitude of the problem

Thyroid problems are universal with pockets of high prevalence areas around the world. In United States new thyroid nodules develop at 0.1% per year (2% per year if exposed to head and neck radiation) resulting in palpable nodules which increase with age reaching 5% prevalence at 50 years or older. The magnitude of the problem was even more when thyroid glands were examined at autopsy, surgery or by ultrasound scans with 50% of thyroid glands having nodules which were almost always benign (95%). (1).

Goiters are also very common in Sri Lanka with thyroid malignancies forming a small fraction of thyroid nodules. Unfortunately these may be missed easily in the general pool of benign thyroid enlargement, unless a special effort is made to diagnose and treat these. Missing is something that should be avoided, as most patients with differentiated thyroid cancer, if properly treated by experienced medical personnel have a potentially curable disease. In this scenario, it is always easy to miss and do too little or over react and do too much.

Initial evaluation of a thyroid nodule

Thyroid nodules are generally found by the patient or the clinician on clinical examination but at times may be detected incidentally during neck imaging for other reasons. In a patient with a thyroid nodule, a history and clinical examination must be undertaken to guide further investigations. But in a significant number of patients, the only detected abnormality is the thyroid nodule. The first recommended investigations in nodule evaluation are thyroid stimulating hormone (TSH) level and ultra sound scan (US). The clinical features, TSH measurements and US features are used to determine whether it is necessary to do a fine needle aspiration cytology (FNAC) of the nodule or whether there is a low risk for malignancy (2).

Clinical indications for FNAC

There are certain clinical features which would indicate a FNAC. These include a nodule larger than 1 cm (smaller than 1 cm or incidentalomas are typically benign and generally FNAC is not needed unless the patient

belongs to a high risk clinical category or has suspicious features on examination or ultrasonography (3)); Patients with a history such as a history of radiation exposure, past history of thyroid cancer, first degree relative with thyroid cancer, familial syndromes (Gardner's syndrome, Carney complex, Cowden's syndrome, MEN types 2A, 2B); Patients of age less than 15 years or more than 45 years; A male patient; Patients with suspicious features such as nodule which is very firm, has a fixity, show a rapid growth, is associated with enlarged cervical lymph nodes, or has associated vocal cord palsy (these features increase the likelihood of malignancy by 7 fold) are at high risk (2).

Further analysis based on TSH level

If there is a normal or an elevated TSH, a FNAC (based on clinical and US features) is indicated to exclude malignancy. In addition patients with elevated TSH must be further evaluated and treated for hypothyroidism. Patients with a low TSH would benefit by an isotope scan. Hot (autonomous) nodules are rarely associated malignancy and would require treatment for thyrotoxicosis. Cold or warm nodules require FNAC (based on clinical and US features) and management depending on the FNAC findings.

US features indicating FNAC

Certain US features create a higher degree of suspicion and thereby indicate FNAC. These include hypoechoic nodules, microcalcification, increased central vascularity, infiltrative margins, nodule taller than wide in transverse plane, a solid nodule more than 1.5 cm, a cystic and solid nodule, spongiform nodule more than 2 cm and associated suspicious cervical lymph node enlargement. FNAC is not indicated for simple cysts other than for therapeutic aspiration (4).

FNAC findings

The FNAC results could be reported using different classifications (2,5,6). Two main systems currently used are the USA based NCI / Bethesda and UK based BTA / RCP Thy 1- Thy 5 categories. These parallel system FNAC categories are as follows:

¹Consultant Oncological Surgeon, National Cancer Institute, Maharagama, Sri Lanka.

- I. Insufficient cytology or a non diagnostic smear [Thy 1 and Thy 1c (cystic lesions)].
- II. Benign – includes nodular goiter, colloid nodule, hyperplastic/adenomatoid nodule, Hashimoto's thyroiditis, granulomatous thyroiditis. [Thy 2 and Thy 2c (cystic lesions)].
- III. Atypia of undetermined significance or follicular lesions of undetermined significance (atypical follicular lesions, cellular follicular lesion, neoplasm cannot be ruled out) [Thy 3a (atypia)].
- IV. Follicular neoplasm or suspicious of follicular neoplasm and include hurthle neoplasm [Thy 3f (follicular)].
- V. Suspicious of malignancy [Thy 4].
- VI. Malignant (papillary, medullary, anaplastic, lymphoma, metastatic) [Thy 5].

Management strategies based on FNAC

Based on the FNAC finding following management strategies could be adopted (2,6):

A report of insufficient cytology or a non diagnostic smear (Thy 1 and Thy 1c) should be correlated with the ultra sonic findings. If it is a cyst with suspicious areas, US guided aspiration of these areas should be offered. If it is a solid nodule, a repeat FNAC under US guidance has shown better yields. Further management will depend on the final cytology.

A report of benign (Thy 2 and Thy 2c) carries a malignancy risk of less than 1%. These patients, if they do not have any other indication for surgery (thyrotoxicosis, pressure symptoms or unsightly appearance) can be safely observed and the US scan should be repeated at 6-12 month times. If it still remains stable, the scan should be repeated at 1-2 year intervals initially and subsequently at 3-5 years. But if serial US measurements show a nodular enlargement, a repeat FNAC or surgery should be considered.

Atypia of undetermined significance or follicular lesions of undetermined significance (Thy 3a), where the risk of malignancy is 5 - 10%, the FNA should be repeated and if still not suspicious can be observed. Surgery can be considered based on clinical grounds of growth or suspicious ultrasonographic features. Molecular diagnostics to detect individual mutations in BRAF, RET, or RAS or pattern recognition approaches using molecular classifiers could be useful in further evaluating FNA samples that are indeterminate.

Follicular neoplasm or suspicious of follicular neoplasm (Thy 3f) carries a 20 - 30% risk of malignancy. Follicular and Hurthle cell carcinomas are rarely diagnosed on FNAC, as for diagnosis, vascular and capsular invasion

is needed to differentiate from adenomas. Therefore a minimum of a lobectomy is required to resolve this problem. If the histology proves it to be malignant, a completion thyroidectomy could be offered later.

Suspicious of malignancy (Thy 4) and malignancy (Thy 5) where the risk of malignancy is respectively 50-75% and 100% should be offered surgery based on the stage of the disease.

Special investigations for medullary carcinoma

In medullary carcinoma patients basal levels of serum Calcitonin and CEA, serum calcium and genetic counselling for screening of RET proto-oncogene mutation should be considered. Patients with germ line RET mutation must be screened for pheochromocytoma (MEN 2A and B) and for hyperparathyroidism (MEN 2 A) (2).

Extent of surgery for thyroid cancers

Appropriate thyroid resection especially for lower risk papillary cancer is very controversial. Mayo clinic result analysis indicate that in low risk papillary thyroid cancer (MACIS score: 3.99 or less) there is no improvement in survival rates after surgery more extensive than lobectomy. National Comprehensive Cancer Network (NCCN) panelists analyzed large number of studies which show that lobectomy alone is adequate for unifocal papillary microcarcinoma (less than 1 cm in diameter in patients who have not been previously exposed to radiation and have no other risk factors and whose disease is confined to the thyroid and has no vascular invasion) as well as minimally invasive follicular cancers. Analysis of AMES criteria show that patients offered total thyroidectomy for low risk papillary cancer tend to have lower 20 year local recurrence and neck recurrence (2,7).

Papillary carcinoma has been shown to be multifocal in 30 - 87.5% cases. A large thyroid remnant left behind after unilateral lobectomy may leave a potentially involved lobe behind with the possibility of progression and dissemination. In addition it may complicate long term follow up with serum thyroglobulin (TG) and whole body ¹³¹I imaging, as well as ¹³¹I treatment for metastatic disease. Total thyroidectomy will also reduce the long term risk of degeneration of differentiated tumours into anaplastic cancer. The long term recurrence rates as high as over 30% have been shown in the lobectomy alone group compared with only 1% after total thyroidectomy and radio I (¹³¹I) ablation. Some studies also show better long term survival in the aggressively treated group. It has also been shown that about 50% of patients with recurrent disease in the central neck die of the disease, whereas about 50% of patients who die of thyroid cancer die of central neck recurrences (2).

Total thyroidectomy is indicated in papillary carcinoma, if age is below 15 or over 45 years, bilateral nodular enlargement, tumour over 4 cm, aggressive variant (tall cell variant, columnar cell, poorly differentiated features), extra thyroidal extension, cervical lymph node metastasis and presence of distant metastasis. In follicular and hurthle cell carcinoma if there is invasion or metastasis and in medullary carcinoma. Anaplastic carcinoma is universally fatal, but if locally resectable disease is encountered, a total or near total thyroidectomy should be offered (2).

Total thyroidectomy increases the risk of recurrent laryngeal nerves and more importantly is associated with long term hypoparathyroidism. But an experienced surgeon recognizing and carefully preserving these structures would minimize these risks. Therefore these aspects should be discussed with the patient and the patient preference must also be taken into account prior to planning the extent of thyroid surgery.

In papillary carcinoma, hurthle cell cancer and medullary carcinoma with node negative (N0) neck, a prophylactic central neck dissection (Level VI) is indicated. Follicular carcinoma with node negative (N0) neck could be spared a neck dissection as lymphatic metastasis is uncommon. If nodes are involved a selective clearance of Levels II, III, IV and V are undertaken in any of these patients (2).

Post surgical management

Patients with papillary, follicular and hurthle cell carcinoma must be post surgically evaluated (at 2 - 12 weeks post operatively) with TSH, thyroglobulin (TG) measurement and anti TG - antibody (AB). ¹³¹I Scan after adequate TSH stimulation (thyroid withdrawal / rh TSH) could be undertaken to assess for completeness of thyroidectomy and presence of residual disease. But a phenomenon described as "Stunning effect" where ¹³¹I induced follicular cell death occurs which can reduce uptake of radio iodine to the thyroid remnant and metastasis. Use of ¹²³I or a small dose of ¹³¹I followed by a short interval between scan and the treatment dose has been tried to minimize the stunning effect. However, a significant number of centres rely on fixed dose radio iodine regime without ¹³¹I scan or dosimetry to reduce the stunning effect. Thyroid remnant can be ablated by 30-100 mci while residual or metastatic tumour is treated with 100-200 mci. Radioiodine treatment could be avoided in total thyroidectomy patients if the TG level is less than 1ng/ml, negative for anti TG-AB and negative for radio iodine imaging (2).

External beam neck radiation is used in T4 papillary carcinoma and in patients over 45 years, unresectable follicular and hurthle cell carcinoma which has an inadequate iodine uptake, T4 medullary carcinoma with

positive margins after resection, anaplastic carcinoma. Local radiation also has a place in papillary, follicular and hurthle cell carcinoma metastatic deposits nonresponsive for radioiodine treatment as well as for localized metastasis of medullary carcinoma.

TSH suppression

TSH suppression using levo thyroxin is undertaken as a standard approach for papillary, follicular and hurthle cell carcinoma. But there is a lack of data to recommend a precise level of TSH suppression. If there is residual carcinoma or a high risk for recurrence, TSH should be maintained less than 0.1 mU/L. If there is low risk for recurrence, TSH should be maintained slightly below or slightly above the lower limit of the reference range. If there is low risk with biochemical but no structural evidence of recurrence (TG increased with negative imaging) TSH should be kept between 0.1-0.5 mU/L. If the patient remains disease free for several years, TSH level within normal range can be accepted as adequate. Potential toxicity of TSH suppression include arrhythmias (especially in elderly), osteopenia (especially in post menopausal women) and frank thyrotoxicosis. In patients whom TSH has to be maintained at a chronically low level, adequate calcium (1200 mg/d) and vit D (1000 u/d) supplements should be given (2).

Chemo therapy (chemo) and other treatment

Chemo has a limited role in thyroid cancer. In radioiodine non responsive metastasis of differentiated carcinoma chemo has been tried (doxorubicin, bisphosphonate for bone metastasis). Other novel treatments include kinase inhibitors (motesanib, sunitanib, axitinib, vandetanib), histone deacetylase inhibitors (vorinostat, depsipeptide), DNA methylation inhibitor (decitabine), heat shock protein 90 inhibitor (17 AAG), proteasome inhibitor (bortezomib), selective cyclooxygenase 2 inhibitor (celecoxib) and derivative of thalidomide (lenalidomide) (2).

Post treatment surveillance

Patients with papillary, follicular and hurthle cell carcinoma – physical examination, TSH, TG and anti TG-AB at 6 months, 1 year, and annually as well as periodic US scan of the neck are used if patient is disease free. TSH stimulated TG is useful in previously radioiodine treated patients (with negative TSH suppressed TG and anti TG-AB). TSH stimulated radioiodine imaging is useful for patients with advanced disease (T3-4, M1), abnormal TG (either TSH suppressed or stimulated), abnormal anti TG-AB, abnormal US in the follow up. Non radioiodine imaging (CT, MRI, PET CT) can be used if radioiodine imaging is negative with stimulated TG over 2 - 5 ng/ml.

In medullary carcinoma the recommendation is to check calcitonin and CEA at two months after surgery and thereafter annually for calcitonin, CEA, US neck, pheochromocytoma (MEN 2 A or B patients) and hyperparathyroidism (MEN 2A patients) (2,7).

Limitations faced in Sri Lanka

Majority of our patients undergo treatment for thyroid problems in non fee levying government hospitals, where TSH, TG, anti TG-AB and other serum markers are not freely available. It also takes a long time to get a report from another distant major hospital even if it is available. Long dates may be given for US scans, and also the experience of radiologists on thyroid scanning could vary. Isotopes are brought in batches and can be out of stock for varying periods of time, leading to long waiting lists. Cyto-pathologists are not available in all hospitals and the experience levels also vary on thyroid FNAC reporting. A uniform classification for thyroid FNAC reporting is not followed in Sri Lanka leading to difficulties in decision making. Most of the surgeons overcome these problems by, routinely offering a lobectomy with a follow up completion total thyroidectomy in suspected cases of cancer or by offering a subtotal thyroidectomy if they don't suspect one. Isolation facilities for radioiodine treated patients are only available at Cancer Institute, Maharagama. Patients requiring therapeutic doses need to be transferred to this institution creating a long waiting list. There could be many more problems related to patient tracking, report tracking as well as difficulties encountered in offering a rational management discussion with our

patients. Therefore decision making as described in this article, may not be possible in a large number of hospitals in Sri Lanka. International guidelines must be respected, but practical realities in our country need to be taken into account, in managing our patients.

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