

Management of Goitre

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Contents

	Page
Introduction	04
Section 1 Evaluation of Thyroid Swellings	08
Section 2 Guidelines in the Management of Euthyroid Goitre	25
Section 3 Guidelines in the Evaluation and Management of Thyrotoxicosis	32
Section 4 Clinical guidelines for diagnosis, evaluation and therapy of hypothyroidism	52
Section 5 Guidelines in the management of carcinoma of the thyroid	60
Section 6 References	70

Introduction:

Goitres are the most common endocrine disorder encountered in surgical practice. The majority of goitres in Sri Lanka at present are thought to be related to deficiency or excess of iodine. Though the exact incidence of goitres in Sri Lanka is not known, an incidence of between 5% -10% has been reported in individual series (1). When dealing with goitre, a proper diagnostic evaluation will enable appropriate and effective therapy to be given.

Historical

The documentation of the presence of goitre in Sri Lanka in the colonial literature is almost non-existent, though that of other disorders of any magnitude is abundant. The conclusion drawn in the early literature was that it is comparatively a recent disease and hence was not likely to be due to iodine deficiency. (2)

Iodination

The government of Sri Lanka made it compulsory that all salt be iodized to an extent of 25-50 ppm from January 1994 (3). The national requirement of salt is approximately 200,000 metric tons (4).

Iodination of salt was handicapped by a lack of industrial capacity to do so. Salt is produced by solar evaporation of sea water and is very low in its iodine content. 135,000 metric tons are produced nationally and the remaining 65,000 metric tons are imported from India. Only one third of the local salt production is iodinated in factories equipped for this purpose. The remaining two thirds of the local salt and the entire stock imported from India is iodinated as a cottage industry leading to improper iodination. Several studies have highlighted this improper iodination of packeted household salt (4,5,6)

With the assistance of UNICEF, an attempt has been made to strengthen the capacity to produce proper iodinated salt by investing heavily in modernizing the factories in Puttlam and Hambantota. Additional iodination units were more recently established in Mannar and Kilinochchi (5).

Key points

BUYING AND COOKING WITH IODISED SALT

- Important to advise patients to buy properly processed iodized salt. E.g. Salt from salt corporation i.e. Laklunu
- The salt must be kept away from heat to prevent loss of its content of iodine.
- 50% of iodine in the salt will evaporate during cooking. Therefore it is best to cook only with 50% of the salt needed and add on the remaining 50% to the food once cooked. Another option is to add salt at the end of cooking
- Proper use of iodized salt needs emphasis and reinforcement in the community

PREVENTION OF ENDEMIC GOITRE

- Avoiding goitrogens i.e. cabbage, radish, knobkohl and manioc is probably unnecessary as they are not consumed in large quantities

- Do not ignore goitre on the basis of it being a physiological goitre. Such an entity is no longer considered in regions of endemic goitre.

Section 1 Evaluation of Thyroid Swellings

In thyroid swellings the following information is required to arrive at a proper diagnosis

- 1. Is it a swelling of the thyroid, i.e. a goitre?**
- 2. If it is a goitre, what type of goitre is it? - e.g. diffuse, multinodular solitary nodule etc**
- 3. Is the function of the thyroid affected, ie is he/she hyper or hypo thyroid?**
- 4. Is there evidence of malignancy? - e.g. rapid growth, hard nodules, cervical lymph nodes ?.**
- 5. Is there any evidence of special features such as tracheal deviation, retrosternal extension ?**

To obtain the above information

History (should include)

- Demographic data -sex, age, residence (endemic /non endemic region).
- Nature and rate of enlargement
- Age at onset, rate of growth, pain and such possible contributory factors as pregnancies, lactations, consanguinity, and a family history of goiter.

- Consumption of goitrogens, brands of salt consumed would be relevant.
- Previous investigations, diagnosis of the enlargement and treatments offered including surgery, its extent, histology, the drugs used in the follow up and details of a possible recurrence.
- It's effects, i.e. obstruction of airway (e.g. noisy breathing) and cosmetic aspects.
- It's degree of activity, toxicity or hypothyroidism and their effects?
- Possible presence of neoplasia, especially malignancy i.e. evidence of direct spread e.g. hoarseness lymphatic spread or of distant metastatic spread. (e.g. bone pain, bony swelling etc)

Examination

- Must commence with a proper inspection from the front – looking for movement with swallowing and any obvious features such as asymmetry, nodules etc (figure1)

- Land mark for palpation is the cricoid cartilage as the isthmus of the thyroid is just below this structure
- Palpation is traditionally done from behind, but this approach has been now been superseded and complemented by other methods of palpation. (Figures 2, 3 and 4)
- The gland could be examined from any position focusing more on developing a three dimensional image in the examiners mind [i.e. “a mental hologram”]. We feel the gland is best examined first from in front, complemented by palpation from behind and for the lymph nodes, palpation from behind and front as well.



Fig 1 - Inspection



Fig 2 Palpation of trachea



Fig 3 Pushing the sternomastoid laterally and palpating the surface of the gland.

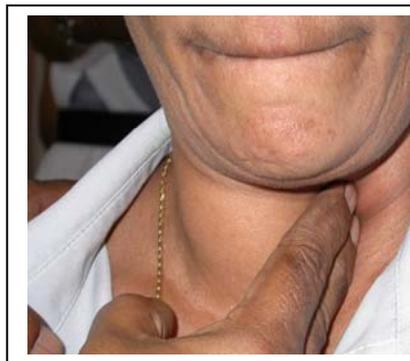


Fig 4 - Palpation of lobes

- The position of the trachea once elicited,, by following the trachea (Fig. 2) from the thyroid to cricoid cartilages and then to the manubrial notch. Will help establish the location of each lobe of the thyroid and their relative size which is assessed by insinuating a finger which pushes the sternomastoid laterally (Fig. 3) and then feeling the thyroid lobe on the firm trachea medially (Fig. 4), feeling for its surface, nature and extent. Swallowing with the finger in this position, helps to finger demarcate the lobe and it's nature better.
- A normal lobe is the size of the distal phalanx the affected patient's thumb 7

WHO GRADING OF GOITRE

Grade of goitre

- | | | |
|------------|------------|---------------------------------------|
| I | (a) | Palpable goiter |
| | (b) | Visible with the neck extended |
| II | | Visible from near |
| III | | Visible from afar |
| IV | | Giant goitre |

The dynamics of growth of the thyroid of the neck relates to the length and muscularity of neck short squat thick muscled necks encourage the ramification of the thyroid in the neck and chest.

One sided enlargement of the thyroid causes the trachea to deviate. Bilateral enlargement in a tight neck can cause compression as also can the entry into the chest.

The extent of the gland, and evidence of retrosternal or retrotracheal extension needs be elicited.

- retrosternal extension may be shown up by prominent veins in upper chest and neck or seen on elevation of upper limb – Pemberton’s sign with dullness to percussion over the manubrium and the inability to get below the lump on swallowing – (each lobe must be examined separately).

These techniques are clinically inaccurate, sometimes and will require imaging for confirmation.

- Note the position and size of nodule/nodules. e.g. superior pole of right lobe etc

Clinically solitary nodule and dominant nodule-
could be

- part of a multinodular gland
 - Thyroid adenoma
 - Thyroid carcinoma
 - Thyroid cyst
 - Focal thyroiditis
- The nature of the enlargement, simple diffuse or nodular (i.e. density differences) and texture i.e. (soft, firm or hard) will be helpful in the

diagnosis as would it's vascularity and the presence of tenderness.

- Features of toxicity, extra thyroid manifestations of Grave's disease and evidence hypothyroidism should be looked for

Some useful features and their interpretation

- Rapid enlargement – Haemorrhagic, cyst, malignancy
- Tenderness / Pain – thyroiditis, acute hemorrhage
- Firm uniform – , malignancy, thyroiditis, tense cyst
- Hard enlargement – malignancy, calcification, Reidle's thyroiditis
- Evidence of spread - often signifies malignancy

Local spread

- Recurrent laryngeal nerve- hoarseness
- Trachea – stridor, haemoptysis.
- Carotid – impalpability of common carotid pulse (**Berry's sign**)
- Oesophagus -Dysphagia – ?malignancy
- Muscles– diminished mobility on swallowing

Lymphatic spread

- Central group lymph, upper anterior deep cervical, supraclavicular and posterior triangle ? malignancy.
- Lymph node enlargement in the upper anterior deep cervical and the lower posterior deep cervical groups are specifically looked for, preferably from behind (Fig. 5).



Fig 5 Palpate the nodes also from behind.

Distant Metastases-Often to axial skeleton and lungs.

Other lumps in the front of the neck that can simulate a thyroid swelling

Differential diagnosis of a Goitre

- Mediastinal cystic hygroma
- Lymph node enlargement in the central group of neck.
- A space of Burns dermoid
- A Sebaceous cyst

Of these, only the central lymph node will move on swallowing, hence DD is not difficult.

Make a complete diagnosis

e.g. Euthyroid asymmetrical diffuse Grade 11 Goitre

Investigations

There are several investigations for thyroid swellings. They assess

- **The Function of the Thyroid**

Serum T3 T4 and TSH

of these serum TSH is done as a first line assessment as it is the most sensitive, if it is above or below the normal range serum free T3 and free T4 are done to identify sub clinical, toxicosis or hypothyroidism.

- **Size and Morphology of the gland**

- Ultrasound scan of the thyroid**

- a) can refine clinical findings – for example may show up sub-clinical nodules and their nature and dimensions
 - b) can help follow up suspicious nodules
 - c) Locate intracystic growths

- **Nature and Pathology of the swelling**

- Fine needle aspiration cytology (FNAC)**

- can identify a- papillary carcinoma

- Follicular neoplasm (cannot differentiate between adenoma and carcinoma)
 - Other thyroid carcinoma-medullary, anaplastic
 - Thyroiditis
 - Colloid (Benign enlargement)

Recommended Investigations for any goitre

- **Hormone Assay**
- **FNAC**
- **US Scan**

Special Investigations

Other investigations are required for specific indications. They are expensive and should be used judiciously in consultation with colleagues with endocrine interests.

❖ **Thyroid auto antibodies**

There are two main antibodies that are assessed

1. Microsomal Thyroid Antibody
(Thyropoxidase- TPO)
2. Anti Thyroglobulin antibody

both are useful in autoimmune disorders of the thyroid. The microsomal antibody is much more commonly elevated than the anti thyroglobulin and is cheaper to get done.

❖ **Imaging** -Examples are given below of various uses of imaging



Fig 6: Normal X ray Neck



Fig 7: Deviation and Compression of the Trachea



Fig 8: Retro tracheal Extension

- In the normal person on the lateral X ray of neck the width of the trachea, retro tracheal space and the AP width of cervical vertebrae (lateral projection) are about equal Fig. 6.
- Deviation, note, does not cause stridor but compression of trachea does. Fig 7.
- The retro tracheal space widens with such extension Fig. 8.

A CXR and a lateral chest X ray will show retrosternal extension Fig. 9.

❖ **Isotope scans**

Detect activity levels of the lobes of the thyroid. Reduction of activity is often seen over tumors but this is not specific and as a tissue diagnosis is not available – it's often not currently used for this purpose.

- It is useful to identify diffuse/focal activity in toxicosis
- retrosternal extension (Fig. 11);
- active metastatic deposits

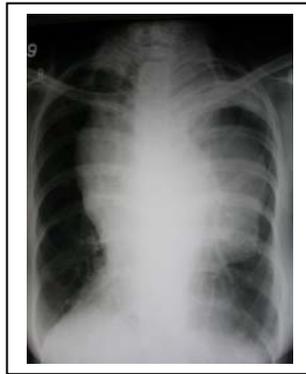


Fig 9: Plain Xray Retrosternal Extension

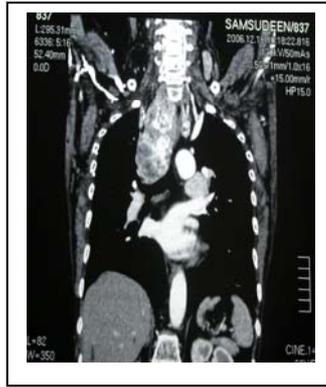


Fig 10: CT scan
Retrosternal Extension

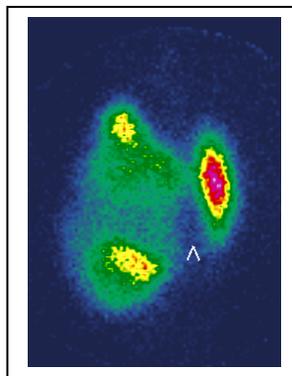


Fig 11:
¹³¹I Scan to show Retrosternal
Extension

- ❖ **CT scans and MRI scans (Fig 10)**
also helps to confirm the extent of ramification of
the thyroid in the neck and the chest.

Section 2 Guidelines in the Management of Euthyroid Goitre

Overview – Key Points

- Euthyroid simple diffuse and multinodular goitres are the commonest type of goitre found in endemic and non-endemic environments. They are clinical diagnoses made of phases in the enlargement of the thyroid and its apparent clinical function.
- Thyrocytes are heterogeneous with hereditary and acquired mechanisms to control growth. Goitrogenesis operates through these innate mechanisms.
- Superimposed iodine shortage greatly enhances the incidence of MNG and shifts its clinical appearance towards younger ages by adding one more growth factor presumably enhanced TSH secretion - to an intrinsically activated growth regulating network. The process affects the whole gland. Thyroid growth immunoglobulins are also recognized 8.
- Thyroid growth factors are responsible for the hyperplasia involution cycles of thyroid follicles. Such stimuli can precipitate not only cellular proliferation and enhancement of their activity 9 but can secondarily precipitate, haemorrhage, degeneration and calcification. The combination of all these changes results in the nodularity which is a common feature of endemic goiter.

- Gradual proliferation as per follicle of thyrocytes that were inherently autonomous, be they monoclonal or polyclonal in origin, could eventually lead to autonomy and subclinical or frank hyperthyroidism.
- Demands associated with the menstrual cycle, pregnancy and lactation are believed to account for the greater prevalence in women.
- *The suspicion of malignancy in the many goitres seen in an endemic area weighs heavy in the mind of the clinician. That malignant transformation could occur especially in the endemic setting¹¹ have many advocates but remains as yet controversial¹²*

Management Principles- Benign Euthyroid goitre

- Physiological goitre **should not** be diagnosed in an endemic environment.
- Some clinicians believe that euthyroid clinical simple diffuse goitre may often be kept without further change in size or density by TSH suppressive therapy¹³. However others feel that there is no evidence for such a conclusion¹⁴. Regression of the goitre is unusual except in the very young. It is best to undertake a hormone assay **before** commencing any hormone therapy.

- The adult dosage of levo thyroxine (Usually 100-150 µg per day) should be titrated to get TSH suppression but yet be within the normal range. TSH if tested post suppression may take time (2 months – 2 years)¹⁵ to show change, a.free T4 and T3 could in these circumstances be helpful.
- Accidental long term over suppression of TSH could risk osteopenia in the older age groups and must be watched for.
- The use of levo thyroxine in nodular goitre to suppress further nodularity is not indicated as most nodules are not responsive to TSH suppression. They may have other growth factors responsible for their development.
- If thyroxine is used it must be given in an appropriate dose with proper instructions and be monitored closely. It is best done in collaboration with a colleague with endocrine interest.

Role of Surgery

Indications for surgery are

- 1. Obstruction of airway**
- 2. Retrosternal extension**
- 3. Suspicion of malignancy**
- 4. Secondary toxicosis**
- 5. Cosmetic**
- 6. Oesophageal compression (very rare with benign disease)**

Extent of Surgery

Is guided by the difficulties and the morbidity of surgery on recurrent goitre

Recurrence is especially seen in those who have had surgery in their youth.

It is advocated that

1. Near total or total thyroidectomy should be performed on all benign goitres ¹⁶
2. To obtain low morbidity rates (recurrent laryngeal nerve, external laryngeal injury or hypo-parathyroidism) such surgeries should be performed by experienced thyroid surgeons.

3. The practice of parathyroid auto transplantation; in case of doubtful viability has made surgery much safer now¹⁷.

Appendix 1

Advise to a Primary care Physician

be alert to

- Malignancy of the thyroid
- Many elderly patients with MNG are often hypothyroid or hyperthyroid
- Goitre in the short thick muscled neck often risks obstruction
- Diagnosing physiological goiter in an endemic setting is best avoided.

Pregnancy and the euthyroid goitre

- Patient should not be hypothyroid.
- The demands on the thyroid are mostly in the third trimester and during lactation.
- A TSH assay is recommended for all patients with a goitre at the diagnosis of being pregnant.

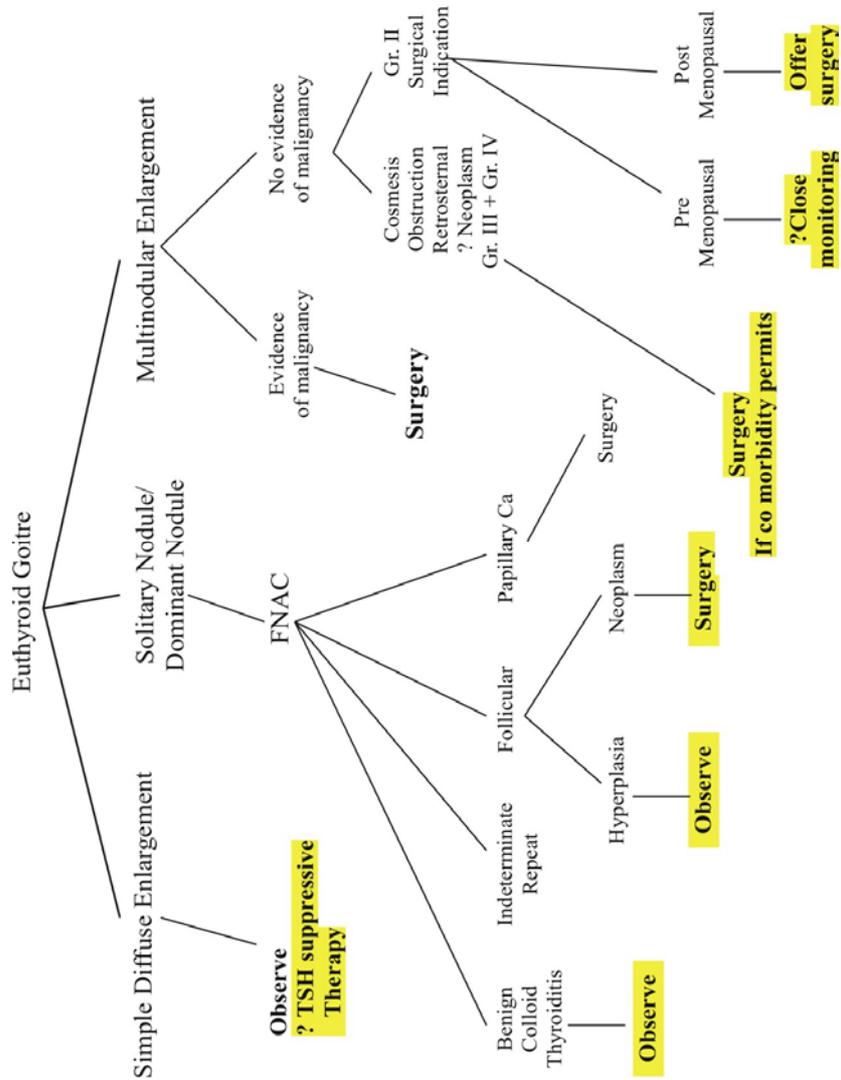
When to refer

- When in doubt about malignancy
- Any patient with an indication for surgery
- When a FNAC report is difficult to interpret or is at variance with the clinical findings.
- When the patient's request to do so.

Administration of levo thyroxine

1. Tablets available are 50 μ g and 100 μ g in content.
2. **Best kept in a cool place. Sunlight can destroy potency.**
3. **Best ingested on an empty stomach. i.e. “first thing in the morning”**
4. Doses commonly used are 50-150 μ g /day for Sri Lankans.
5. Side effects are rare and includes cramps, headache, flushing
6. Titration is done by measurement of Free T4 and T3 and TSH later.

Appendix 2 – Management Plan for Euthyroid goitres



Section 3 Guidelines in the Evaluation and Management of Thyrotoxicosis

The need to treat

Thyrotoxicosis if untreated can lead to considerable morbidity and sometimes mortality. Symptoms such as anxiety, weakness, tiredness, shortness of breath can have personal, domestic and social consequences. Cardiac dysrhythmias and heart failure risks death. Thyrotoxic women may suffer from amenorrhoea, subfertility and those pregnant, stillbirth, preterm delivery and low birth weight of their babies.

Definition

Thyrotoxicosis is the clinical syndrome associated with excessive concentration of thyroid hormones in circulation.

Hyperthyroidism is the excessive synthesis and secretion of thyroid hormones by the thyroid gland.

Non hyperthyroid thyrotoxic patients include post inflammatory release of stored hormones in thyroiditis and extrinsic sources of thyroid hormones.

DECISION 1: Has the patient got thyrotoxicosis?

Diagnosis of Thyrotoxicosis

Clinical suspicion of thyrotoxicosis is aroused by an anxious, apprehensive, patient with sweaty tremogenic hands, the pulse being rapid occasionally irregular often bounding.

Clinical differential diagnosis includes patients presenting with

- Anxiety, emotional instability
- Fear psychosis
- Loss of weight
- Chronic diarrhea
- Oligomenorrhoea or amenorrhoea
- An irregular pulse

Difficulties with diagnosis

- Thyrotoxicosis could be clinical or sub clinical.
- Sub clinical toxicosis has TSH suppression with normal levels of thyroid hormones. Sub-clinical toxicosis is more common in a community than clinical toxicosis and is also more common in the older patient.
- Initial investigations

TSH through a cost effective and highly sensitive as a stand alone investigation, it will not alone detect sub clinical thyrotoxicosis. Having used TSH as a screening test, free T4 and T3 must be assayed in those with TSH suppression as an initial baseline is then established

Biochemical confirmation includes

Low TSH with or without elevation of free T₄ and T₃

However a low TSH is also found in.

- Non thyroid illness like chronic liver and chronic renal disease
- Excess of exogenous or endogenous thyroxine
- Corticosteroids or Dopamine therapy

The establishing a firm biochemical diagnosis at the outset is ESSENTIAL

Decision 2: What is the type of thyrotoxicosis that afflicts the patient?

Causes of thyrotoxicosis % prevalence in hospital based studies.

Primary

	SL ¹⁸	UK ¹⁹
Graves' Disease	18	60-85

Secondary

Multinodular goitre	59	10-30
Hot nodule	6	2-20
Other	18	

**Other causes include
extrinsic sources of thyroid stimulation**

- Pituitary – TSH excess
- Trophoblastic Tumors
 - Hydatidiform moles
 - Choriocarcinoma
- Struma ovarii
- Excess intake of T4
- Thyroid carcinoma with metastatic disease
- Iodine induced

Hot nodule	6	2-20
Other	18	

The diagnosis of primary toxicity- Graves disease

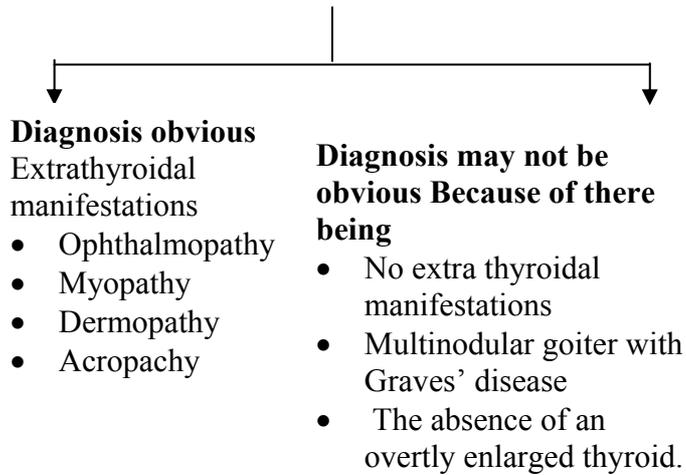
- Female predominant
- Often aged 20-40 years.
- More recent onset of a simple diffuse goiter (in goitre endemic countries Graves' disease can supervene on a MNG)
- Toxicity could be severe
- Thyroid gland could be vascular i.e. pulsatile / bruit
- Vascularity confirmed by Colour Doppler ultrasound
- TSH receptor antibody is elevated in 90% with very few false positive.
- Microsomal (Peroxidase) Thyroid antibody is elevated in (90%)

- Thyroglobulin antibody elevated (50%) but not specific.
- Associated features may be present.

Features of Graves' disease

- Often **ophthalmopathy with lid retraction, lid lag, exophthalmos** much less often external **ophthalmoplegia and chemosis**
- The other features such as **acropachy** (clubbed swollen fingers).
- **Dermopathy (e.g. Pretibial myxodoema)**
- **Myopathy** (global, proximal limb girdle and paralytic) are occasionally present.
- Very rarely features such as **vitiligo, the features of McCane Albright Syndrome** (Polyostotic fibrous dysplasia, cutaneous hyperpigmentation with hyper function of endocrine glands, e.g.: precocious puberty may be seen.)

- The diagnosis of Graves' disease in a toxic patient could however be



The following investigations may be helpful.

- T^{99} or I^{131} Isotope scan uptakes show a uniform diffuse and rapid uptakes
(Subacute thyroiditis will often show <1% uptakes)
- TSH receptor antibody needs to be done in cases of
 - a) when in doubt.
 - b) Pregnancy and Lactation when isotopes are contraindicated

The diagnosis of secondary toxicity

Brief overview of the evolution of the toxic multi nodular goitre

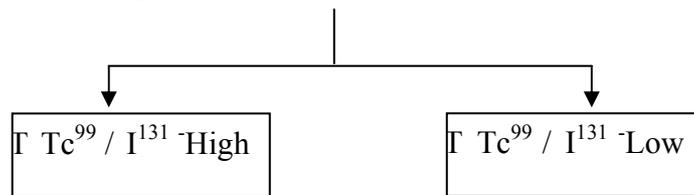
Thyrocytes are heterogeneous with hereditary and acquired mechanisms to control growth. Goitrogenesis operates through these innate mechanisms. Naturally occurring goitrogens and Iodine deficiency are responsible for an endemic goiter and other growth factors for the non endemic goiter. Both types of goiter could have areas that become autonomously active. Females with long duration goiters and elderly patients are particularly at risk.

In time thyroid follicular cells in a follicle with high intrinsic potential to proliferation will do so, and develop new follicles. The original follicles and new follicles contribute to hyperplasia and enlarge the gland. Such foci have a greater ability for hormonogenesis. These hyperplastic and hyperfunctioning cells present as locally hyperactive foci giving 'hot nodules' on uptake scans. There may be single or multiple such foci in the gland. More rarely the internodular hyperplastic region in a degenerate large nodular goiter may become

autonomous. When the thyroid hormone production by the population of such active and hyperplastic follicles exceeds the normal range of thyroid hormones, toxicity becomes manifest.

On occasion iodine deficiency keeps such autonomous glands not toxic but iodination can provide the substrates which would unmask the latent autonomicity. Such toxicosis is referred to as Jod Basedow toxicosis.

The diagnosis of the cause of secondary toxicity



- **Multinodular goiter**
- **Hashi- toxicosis**

Diagnosis of toxicosis in a multinodular goitre (Plummer's Disease)

- Females are dominantly affected.
- Patients are in the older age group.
- They usually have a goiter long duration.

- **Sub acute thyroiditis**
- **Post partum thyroiditis**
- **De Quervain's thyroiditis**
- **Other forms**

The goitre can present clinically as

1. Simple diffuse
2. Multinodular
3. Dominant nodule
4. Thyroid nodule

In Secondary toxicity due to multinodular goitre

- T3 is often the hormone elevated
- Toxicity is not often severe
- Cardiac clinical features can often be seen early in the presentation
- Eyes signs are usually absent

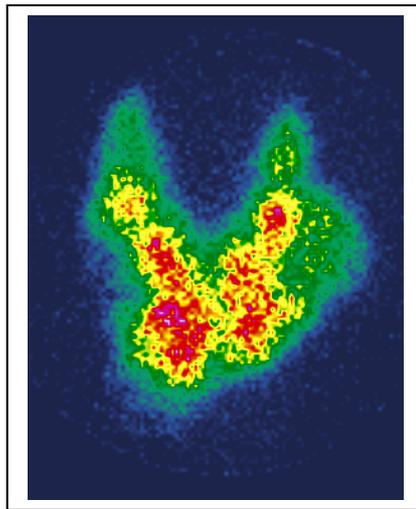


Fig. 23

- Fig 23. -Isotope scan-shows multiple foci of increased activity
- Hyperplastic nodules larger than 3cm in diameter are more likely to be show autonomous activity and a percentage will go on to toxicity.

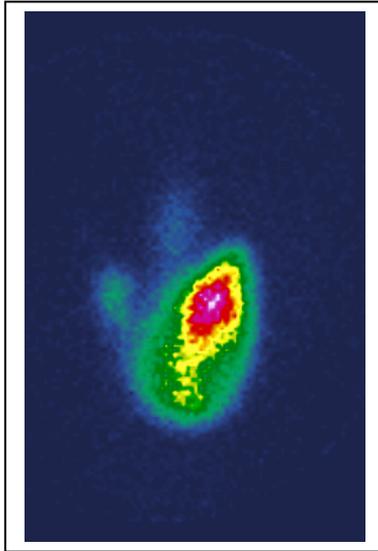


Fig. 24

- Fig 24. Isotope scan-shows a “hot nodule” i.e. increased activity with suppression of activity in the contra lateral lobe due to suppression of TSH.

Management

Principles of Management

The different aetiologies require different management strategies

- Graves' disease – control toxicosis and await a possible natural remission within 1-2 years, If there is no remission a surgical or I131 ablation of the thyroid or long term anti thyroid drugs are indicated.
- Multinodular goitre – will **never** remit, hence it must be removed by surgery or destroyed by isotopes,
- Sub acute and chronic thyroiditis are all self limiting disorders with usually mild toxicosis hence waiting till it subsides with peripheral blockage of activity using β blockers is acceptable.

Management of Primary Toxicosis – Graves' disease:

- Two considerations
 - i. Control of symptoms and toxicosis
 - ii. Regression of extra thyroid manifestations (e.g. Ophthalmopathy)

- Decisions
 - 1) which patients are unlikely to remit ?

suggestion that those with

 - severe toxicosis
 - Large goitresshould be offered early definitive therapy.

(However there is no proof that this premise is consistently correct.)

Control of Thyrotoxicosis

Drugs

- **Iodine trapping blockers**

Iodination of Tyrosines – thionamides, Carbimazole

Methimazole,

Propyl thiouracil

- **Peripheral blocker of T4 -T3 conversion –
β blocker**

Propranolol

Atenolol

Medalol

Drugs. Dose schedule of Carbimazole

- Titration Regime 10mg 8 hourly and once control has been achieved to gradually reduce the dose, with a serial monthly Free T4 assays [or T3 in T3

toxicosis] to the lowest single dose which will control the toxic state.

- Large single dose therapy - 30mg - 60mg /day single dose - (Advantages fewer clinics visits, greater compliance and early control of toxicity but could risk side effects of carbimazole in those sensitive].
- Blocking replacement regime – e.g. Carbimazole 30 -60 mg daily with thyroxine 50-100µg of T₄ is sometime used.
- Propranolol is used initially to counter the sympathomimetic effects of toxicosis till carbimazole takes effect.
- Carbimazole has, it is thought an immuno suppressive effect. Ophthalmopathy improves with its use. Regression of ophthalmopathy may become important when, corneal ulceration, visual effects due to optic neuropathy is detected. Steroids immuno suppressive drugs, diuretics, orbital radiation, or decompressive surgery may become rarely necessary. Partial tarsorrhaphy or protective eye cover is often advocated.

Before starting on carbimazole check that

- baseline TSH has been established
- the TSH suppression was not due to excess thyroxine administered to a patient with autonomous thyroid activity
- in case of side effects which include rashes, arthralgia, myalgia, fever and abnormal taste sensation, and the physician should be informed.
- Sore throat, fever that could herald agranulocytosis, the need to stop the drug and do

a WBC / DC and to inform a physician must be stressed. Note agranulocytosis occurs in 0.5% of persons and is dose related.

Other Key points

- Reactions to carbimazole including agranulocytosis occur usually within a month or two of starting therapy.
- Monitoring the results of Carbimazole is done every 4-6 weeks with free T4 and T3 assessments. TSH titers takes time to change and is best assessed 4-6 weekly to guide therapy.
- Larger doses of Carbimazole or longer duration of its use is not very useful from a remission point of view.
- Family planning advice is necessary for those likely to become pregnant.
- I ¹³¹ therapy for Graves' disease is a well accepted therapeutic option. Even in the younger female. Definite contraindications include pregnancy, lactation. Most clinician avoid using it in children and young adolescent (<18 years) in view of some claims of thyroid malignancy and gonadal damage. Such claims through have not been substantiated.
- Aggravation of ophthalmopathy is well documented and such patients can be offered an alternative therapeutic option or a course of corticosteroid offered at the time of administration of the isotope can reduce the possibility of such aggravation..

- Mild to moderately toxic patients can be controlled by beta blockage and the therapeutic I¹³¹ dose is often calculated on the basis of the size of the gland and uptakes. Severe toxicosis must be controlled before the use of isotopes to prevent a thyroid storm.
- Control with I¹³¹ therapy is slower than the correction by the surgical option. Through smaller enlargements of the thyroid regress, the larger goiters are often resistant and are best handled by surgery.
- Patient may be required to avoid non essential close contacts with family and friends for 1-2 weeks.
- Pregnancy is discouraged for at least 6 months after I¹³¹ therapy. Side effects of therapy are often minimized if antithyroid drugs have been used to control toxicosis prior to surgery. They include exacerbation of toxicity and radiation thyroiditis. The latter makes the gland painful and tender but is self limiting. Transient pain in the salivary glands post treatment is not unusual.
- Long term follow up after I¹³¹ therapy with TSH assays helps to pick up persistent toxicosis (warranting a second dose of I¹³¹) or hypothyroidism which needs replacement therapy.

Thyrotoxicosis in Pregnancy and Lactation

- Pregnancy is best avoided in thyrotoxicosis
- In pregnancy carbimazole and methimazole are best avoided as they cross the placental barrier ,they may induce a teratogenic syndrome called ‘methimazole embryopathy ‘associated with Aplasia cutis and Choanal or oesophageal atresia .These are however rare.
- Carbimazole crosses the placental barrier and can cause depression of the thyroid axis in the foetus. Hence it is important that the patient is informed of the risks of carbimazole in pregnancy.
- Propyl thiouracil is the preferred drug in pregnancy. No reported case of aplasia cutis has been reported with this drug.
- Carbimazole can depress the neonatal thyroid axis as it is transmitted in breast milk.
- Grave’s disease is often found in young females hence sorting out their toxicity early becomes mandatory. Neonatal Graves due to transmission of maternal TSH-receptor antibody is recognised.

Key points in the Management of Graves' disease

- **Control thyrotoxicosis for 1-2 years with anti thyroid drugs**
- **Stop drugs in 1-2 years time and look for a sustained remission which occurs in 40-60% of patients. If it recurs, offer surgery or isotopic destruction .After re-control, follow up with replacement T4.**
- **In those that remit recurrence can occur years later and hence such patients need monitoring.**
- **TSH must also be measured to guide therapy as prolonged low TSH can cause osteopenia.**

Management of toxic nodular goitre

Autonomous activity of the thyroid will not usually subside. The toxic thyroid gland needs ablation surgically or by isotopic methods.

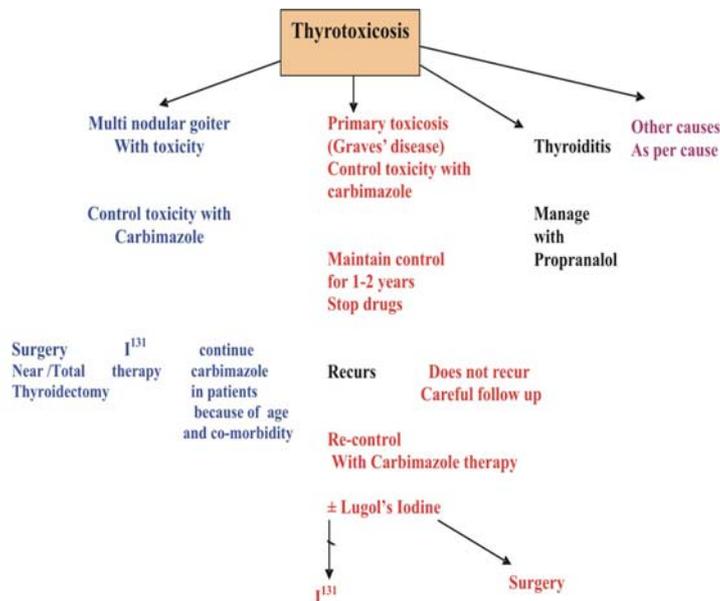
- Long term antithyroid therapy, surgery or isotopic ablation are the established modalities of therapy. Long term anti thyroid drug therapy could be the patient's choice or the physician's choice where co-morbidity precludes surgery.
- Isotopic ablation other than for children, adolescents (16-18 years) , pregnant and lactating mothers is the modality choice, though in Sri Lanka instituting these doses could be costly in the private sector.
- Premenopausal women often need the toxicity sorted out because of the risk to a foetus by I^{131} during pregnancy or lactation. Total/Near total thyroidectomy is now the operation of choice. It is best done in an endocrine surgical unit or a surgeon with special interest in endocrine surgery to minimize morbidity due recurrent or external laryngeal nerve damage or hypoparathyroidism.
- In the preparation for thyroidectomy Lugol's iodine is not usually used in this group as it could precipitate hyperthyroidism. Hence control with carbimazole is all that is required.

- Long term levo thyroxine is administered for life after surgery the dose being titrated by serial post operative adjustments.

Management of Subclinical Hyperthyroidism

Those presenting with sub clinical toxicosis require only careful monitoring. With clinical examination and serial hormonal assays. (Once in 6-12 months)

- Currently available data cannot confirm that undiagnosed sub clinical toxicity causes morbidity and mortality secondary to atrial fibrillation, embolism or osteopenia leading to fractures.



Section 4 Clinical guidelines for diagnosis, evaluation and therapy of hypothyroidism

Hypothyroidism results when production of thyroid hormones from the thyroid gland becomes deficient.

1. Causes of hypothyroidism

1.1 Patients should undergo assessment for the cause

Primary	Secondary
Chronic autoimmune thyroiditis (Hashimoto's disease)	Pituitary disease
Surgical removal of the thyroid gland	Hypothalamic disorder
Thyroid gland ablation with radioactive iodine	
External irradiation	
Biosynthetic defect in iodine organification	
Replacement of the thyroid gland by tumor (lymphoma)	
Drugs e.g. lithium or interferon	

of their hypothyroidism.

2. Diagnosis

2.1 A clinical diagnosis of hypothyroidism may be made in the presence of signs and symptoms listed below.

Symptoms	Signs
Fatigue	Dry & yellow skin
Weight gain	Coarseness or loss of hair
Cold intolerance	Hoarseness
Constipation	Reflex delay, relaxation phase
Memory and mental impairment	Ataxia
Decreased concentration	Bradycardia
Depression	Myxoedema
Irregular or heavy menses and infertility	Hypothermia
Myalgias	Goitre

2.2 The clinical features are not specific for hypothyroidism and some patients especially elderly may be asymptomatic.

2.3 Biochemical confirmation is required for diagnosis and initiation of treatment for hypothyroidism.

3. Laboratory diagnosis of hypothyroidism

3.1 The best screening test for the diagnosis of hypothyroidism is a sensitive TSH (Thyroid Stimulating Hormone) assay.

3.2 A very high TSH value even in the presence or absence of clinical features is sufficient evidence for a diagnosis of clinical hypothyroidism.

3.3 In the presence of clinical features, an elevated TSH of above 10mU/L alone will be sufficient to confirm a diagnosis of clinical hypothyroidism.

3.4 However, in the absence of clinical features a TSH greater than 10mU/L combined with a FreeT4 below the reference range indicates the presence of overt primary hypothyroidism.

3.5 A TSH level of less than 10mU/L may indicate **sub-clinical hypothyroidism** or **secondary hypothyroidism**.

- a) In sub-clinical Hypothyroidism free T4 assay is within the normal reference range in the presence of an elevated TSH.
- b) Subjects with sub-clinical hypothyroidism should have repeat TSH & Free T4 assay within 3-6 months to exclude transient causes of elevated TSH.

3.6 When a patient is ill or starving, the body tends to compensate by decreasing metabolic rates, which may result in a low free T4 or T3 estimate and a normal or low TSH level.

- a) If the TSH value is less than 10mU/L, treatment should ideally be deferred until the patient's medical condition has resolved and patient is re-assessed with repeat testing of TSH & free T4 assays.

3.7 Presence of low free T4 & low or normal TSH is likely to be due to Secondary Hypothyroidism.

- a) A combination of TSH, FT4 and FT3, may be required to differentiate secondary hypothyroidism from thyroid hormone dysfunction as a result of Non Thyroidal Illness.
- b) Very rarely a TRH test may help to establish the final diagnosis.
- c) In case of Secondary Hypothyroidism an assessment of pituitary hormone profile and pituitary imaging is required to identify disorders of hypothalamic-pituitary axis.

3.8 *The following additional tests may be indicated in the evaluation of an individual patient;*

- Radionuclide Thyroid scan, ultrasonography, or Fine Needle Aspiration Cytology (FNAC) to

evaluate suspicious structural thyroid abnormalities.

- Thyroid auto-antibodies – helps to identify autoimmune thyroiditis. Sub-clinical hypothyroid patients who are TPOAb or TgAb positive are more likely to have higher serum TSH and are more likely to develop overt hypothyroidism

3.9 All newborn babies should be screened for congenital hypothyroidism by measurement of TSH using a sample collected within 2-8 days after birth, as part of a national screening programme.

4. Treatment

4.1 Clinical Hypothyroidism

- a) Clinical Hypothyroidism is treated with levothyroxine.
- b) There is no consistent evidence to recommend the use of combined therapy with thyroxine and tri-iodothyronine in comparison to thyroxine alone.
- c) The appropriate dosage and pace of treatment for each individual patient may vary depending on the age, duration and severity of the hypothyroidism and

presence of other associated medical disorders.

- d)** The mean replacement dose of levothyroxine is 1.6 µg/kg of body weight per day.
 - The usual starting dose of levothyroxine is 25 – 50 µg per day. Thereafter, 25 – 50 µg of dose increment is recommended with repeat measurement of TSH in 8-12 week interval.
 - A minimum period of 2 months, and in some patients up to 3 months, is required to restore stability in thyroid function tests after a change in dose.

- e)** The target is TSH in the normal reference range.
 - Once the patient is clinically stabilized on thyroxine serum TSH alone may be used to monitor therapy in 6-12 month interval.

- f)** Measurement of TSH combined with FT4 is recommended in patients who have intermittent or poor compliance with their treatment.

- g)** In the rare incidence of levothyroxine resistance a much higher dose of levothyroxine will be required. (Thyroxine resistance is identified when patient continues to have symptoms despite therapy with elevation of both TSH & FT4.)

- h)** Absorption of levothyroxine is reduced in malabsorption and in the presence of certain drugs such as cholestyramine, ferrous sulfate, sucralfate, calcium, and some antacids containing aluminum hydroxide. Anticonvulsants affect thyroid hormone binding, whereas rifampin and sertraline may accelerate levothyroxine metabolism requiring a higher replacement dose.
- i)** It is recommended that the tablet be taken as the first thing in the morning on an empty stomach at least half an hour before breakfast.

4.2 Subclinical Hypothyroidism

- a)** Treatment of Subclinical Hypothyroidism is controversial.
- b)** If the serum FT4 concentration is normal but the serum TSH is more than 10mU/L, then treatment with thyroxine is recommended
- c)** If the serum FT4 concentration is normal and the TSH is elevated but less than 10mU/L then thyroxine therapy is not recommended as a routine therapy but indicated in patient with pregnancy,

subfertility, hyperlipidaemia, goitre, or a rising TSH.

4.3 Secondary Hypothyroidism

- a)** The degree of hypopituitarism must be established before commencing thyroxine replacement.
- b)** Thyroid hormone replacement should not be commenced in patients with cortisol deficiency as this could provoke an Addisonian crisis.
 - In such patients steroids should be given prior to commencing on thyroxine therapy.
- c)** Measurement of TSH cannot be used to assess the response to therapy in patients with hypopituitarism.
 - An appropriate target for adequate thyroxine replacement in patients with secondary hypothyroidism may be a FT4 concentration in the upper third of the reference range.

Section 5 Guidelines in the management of carcinoma of the thyroid

Overview

The main issue is the need to suspect the presence of a carcinoma and this can be quite worrying especially in a goitre endemic country like ours where clinicians see large number of goiters and have to make decisions on their aetiology. Minimizing mistakes in diagnosis can be quite demanding. The following clinical features could make one suspect the existence of a carcinoma in the presenting goiter.

- Hard goitres
- Solitary nodules in the extremes of age.
- Dominant and Solitary nodules.
- Rapid enlargement of a goitre.
- A family history of thyroid cancer
- Goitre in an non endemic environment
- Onset of a goitre after menopause or in the elderly
- Evidence of local spread, fixity to adjacent structures
 - diminished mobility on swallowing
 - hoarseness of voice
 - impalpable carotid pulse (Berry's Sign)
 - airway (stridor) and swallowing difficulty

- Enlargement of the draining lymph nodes
- Goitre with a metastatic deposit/s
- Goitres in Males
- Combination of above

Tissue diagnosis

Fine needle aspiration cytology is mostly relied on
(Non aspiration technique is sometimes preferred by the pathologists to minimize bleeding - FNC)

- Papillary carcinoma can be diagnosed in majority of patients .It may simulate thyroiditis in cytology
- Follicular carcinoma cannot be distinguished from a follicular adenoma as there isn't enough tissue to show whether there is capsular and /or angioinvasion
- medullary carcinoma can be diagnosed on cytology
- Anaplastic carcinoma will show lack of differentiation and bizarre cells
- Thyroid lymphoma can be diagnosed on FNC but will require a core biopsy to assist further management

Establishing the extent of the tumour

Clinical examination and imaging are used to define the extent of the tumour. Operative findings and the histopathological findings supplement this data. The aim would be to establish a TNM and hence stage the disease. Each stage there is an internationally accepted management protocol.

T N M Classification for thyroid cancer

T1	1 cm or less
T2	>1-4cms
T3	> 4cms
T4	extension through the capsule of the thyroid.
N0	nodal spread not detected
N1	nodal spread present
M0	blood stream metastases absent
M1	blood stream metastases present.

AJCC STAGING OF THYROID CANCER.

Stage	papillary / follicular		medullary	anaplastic
	<45 years	>45 years		
I	M ⁰	T1	T1	-
II	M1	T 2-3	T 2-4	-
III	-	T4 or N1	N1	-
IV	-	M1	M1	any

A **tumour marker** is available for medullary cancer i.e. **calcitonin**. Approximately twenty five percent of these tumours are familial and hence all patient's 1st and 2nd degree relatives should be screened for its presence and the clinical presence of a tumour, evidence features of MEN 2 and screened for a **phaeochromocytoma**

Decision making

The multidisciplinary team concept and the patient awareness program is advocated in all decision making.

The therapeutic options are based on the histological type of tumour

Papillary carcinoma - including its follicular, columnar, tall cell, diffuse sclerosing variants are associated with intra thyroidal lymphatic spread, a near total or a total thyroidectomy with central node excision is indicated on account. Lymph nodes detected clinically or picked up at surgery should be removed by a modified block dissection leaving behind the sternomastoid, internal jugular vein and the accessory nerve.

Follicular carcinoma- +/- {Hurthle cell carcinoma}

Divided into minimally invasive and widely invasive groups based on the presence of only capsular invasion or two to three foci of microscopic angio invasion in the minimal group. Minimal capsular with no angio invasion is not associated with a mortality at follow up. In the widely invasive group the greater the extent of invasion poorer the prognosis near total or total thyroidectomy is recommended.

Stage iv disease – Occult primary with metastatic deposit commonly a solitary in bone,

If the biopsy of the secondary is positive for thyroid cancer:

1. Consider total Thyroidectomy
2. Local RT to the lytic bone lesion
3. I¹³¹ ablative therapy.

Total Thyroidectomy is recommended in Differentiated thyroid Carcinoma for the following reasons

- Radio Iodine can be used to detect metastasis
- Serum Thyroglobulin level is more sensitive if thyroid is removed
- Up to 85% of patients have multiple foci of cancer in other lobes
- Recurrence develops in about 10% in the other lobe
- 50% with recurrences will die from the disease
- Re-operative thyroid surgery entails high risk of complications
- Recurrence is lower in patients who have undergone total thyroidectomy
- 1% risk of residual disease undergoing anaplastic change
- Total Thyroidectomy is a safe operation in experienced hands

*World J.Surg 2000; 24: 942-51*²⁰

- **Hurthle cell carcinoma are more aggressive and are less likely to take up I¹³¹**
- **Differentiated thyroid carcinoma of < than 1 cm showing minimal local spread and with no lymphadenopathy can be dealt with effectively by lobectomy. An incidental discovery of such tumours in resections for benign disease is also managed in this fashion.**

Medullary carcinoma: Surgery i.e. a total thyroidectomy with central node dissection including upper Mediastinal nodes remains the mainstay of treatment. It is best done in tertiary care centre or an endocrine surgical unit.

Anaplastic carcinoma is generally not surgically attended to except as a palliative procedure for e.g. in stridor. Radiation remains the mainstay of treatment.

Surgical procedure: - Total or near total thyroidectomy and central node dissection can lead to complications. They include recurrent laryngeal nerve damage, external laryngeal nerve damage, and transient hypo parathyroid, permanent hypoparathyroidism. **Morbidity rates will depend on the expertise of the operator. Experienced units have a lower morbidity.**

Post operative management

Replacement thyroxine is withheld till histological confirmation is obtained. The pathological TNM is then established using all the data available.

- **Serum Tg (Thyroglobulin) should be done 4-6 weeks after surgery.**

The rising TSH will stimulate the residual thyroid residues and any functional metastases and can be both detected by I¹³¹ diagnostic imaging and the residual tissue load and tumour load can then be assessed and the therapeutic I¹³¹ dose calculated.

Radioiodine therapy with I¹³¹ if started before 3-4 weeks, replacement therapy with T3 or T4 need not be initiated. However if there is a delay, the interim use of T3 (tri iodo thyronine) could be initiated at 20 µg tds and needs to be stopped two weeks prior to the radioiodine therapy *.A TSH level of >30mµ/l is recommended before I¹³¹ therapy.

- *T3 is not available as yet in Sri Lanka hence T4 is used but TSH will take longer to rise after withdrawal of T4.*

Residual thyroid tissue

Routine ablation of residual thyroid tissue with I¹³¹ is controversial if no nodal or metastatic disease is demonstrable.

- Tumours larger than 1cm should have radioiodine therapy. Pregnant and lactating mothers have to be excluded.

- **Thyroxine can be started three days after I¹³¹ therapy.**
- **Thyroxine in supra physiological (Suppressive) doses (Thyroxine around 200 µg daily) to keep the TSH at below 0.1mu/l is used.**

Prolonged TSH suppression at these levels can lead to likely to lead to osteopenia. But is considered acceptable. Such suppression needs be lifelong as the tumour has a prolonged natural history. Some evidence exists now that oestrogen and biphosphonates could mitigate osteopenia in those on prolonged TSH suppression.

Recurrent Thyroid cancer

- Evidence of recurrence is sought at clinic visits. Local, cervical and mediastinal recurrences are most common. At least annual checks are recommended, when evidence of recurrence is carefully sought
- Clinical evidence by examination
- Imaging (ultrasound, MRI, and CT), FNAC where indicated.
- Serum thyroglobulin assay
 - A post isotope ablation scan done after six months may pick up residues requiring further I¹³¹ therapy.

Recurrent disease requires a combination of surgery and I¹³¹ therapy

External beam irradiation is often offered for anaplastic and extensive tumours.

Prognosis

Several Scoring systems are available to assess prognosis.

They assess

1. Degree of differentiation, in anaplasia it is extremely poor.
2. Of differentiated tumours, the papillary cancer is best with medullary cancer and metastatic follicular the worst.
3. Age, histo:Grading, Extent, tumour Size(AGES)
4. Completeness of resection, gender (worse in males) and Metastases are also considered.

Prognostic scoring systems eg. AGES, AMES, MACIS etc. help in identifying subsets of patients for prognostication and therapy. They do not include lymph node metastases.

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