Guidelines in the Management of Thyroid Cancer

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Introduction

The main objectives
1. To obtain an overview of patterns of cancer in different parts of the country;
2. To calculate estimates of cancer incidence wherever feasible.

The overall aim of the study is to get to know the similarities and differences in patterns of cancer across the country in a relatively cost-effective way using recent advances in computer and information technology transmission. Knowing patterns of cancer across the country would provide important leads in undertaking etiological research, in targeting cancer control measures and in examining clinical outcomes.

Since 1982, under the aegis of the National Cancer Registry Programme (NRCRP), cancer registries have provided information on the pattern and magnitude of the burden of cancer in selected urban centres and few rural pockets. However, many urban centres and the majority of rural areas largely remain uncovered and, therefore, the pattern and magnitude of cancer in the entire population remains unknown. India is a vast country with diverse cultures, customs, habits, dietary practices, socioeconomic and environmental conditions. There are huge differences in the lifestyles of the urban and the rural. Data from these registries has demonstrated geographical differences in patterns of cancer. For instance, gall bladder cancer has a comparatively higher incidence in population based cancer registries (PBCRs) of Delhi and Bhopal. On the other hand, stomach cancer is most common among males of Chennai and Bangalore. Some cancers, such as female breast cancer and esophageal cancer have shown a statistically significant increase in incidence over the years in some registries while a few, such as cervical cancer and oral cancer have shown a decline. Thyroid cancer is rare and the incidence differs marginally between states. A population survey from the years 1990-1996 carried out at the Mumbai Indian cancer registry revealed that the incidence of cancers in males was 0.73% and females, it was 1.93%. The age range was from 15 to over 65 years, with peak occurrence in the 4th to the 6th decades of life. In the pediatric age group the incidence was 0.27% of all childhood cancers.

Thyroid (ICD-10 : C73) - Females

Of the PBCRs under NCRP, Bangalore PBCR has shown the highest AAR of cancer of the thyroid. The PBCR at Thiruvananthapuram has shown a high incidence of cancer of the thyroid where it was the third leading site of cancer in women in that registry (Fig. 1).

First All India Report: 2001-2002

District wise data for males was not available.

Development of the Guidelines for the Management of Thyroid Cancer

In 2002, the Royal College of Physicians published the first edition of the Guidelines for the management of thyroid cancer in adults. These guidelines were updated in 2006/7 in the light of recent evidence based medical (EBM) data in the diagnosis and management of thyroid cancer.

Several endocrine societies in USA, Britain and Europe have expert panelists to draw up guidelines at intervals as new knowledge and technologies develop. No Indian guidelines are officially available.

Aim of the guidelines

The guidelines were published with three main objectives:
- To improve survival, both long-term and disease-free, in patients with thyroid cancers.
- To improve the quality of life of thyroid cancer patients.
- To improve the management and referral pattern of thyroid cancer patients.

Differentiated Thyroid Cancer: Papillary with its Variants and Follicular with its Variants

Initial management after establishing diagnosis by FNAC/biopsy

Goals of initial therapy of differentiated thyroid cancer are:
1. To remove the primary tumor, disease that has extended

Fig. 1 : Data published in development of an atlas of cancer in India

Consultant nuclear medicine physician, Institute of functional Imaging and Research, Chembur; Indian Council for Medical Research has a project on the development of an atlas of cancer in India as a part of the activities of the National Cancer registry programme.
beyond the thyroid capsule, and involved cervical lymph nodes. Completeness of surgical resection is an important determinant of outcome. Residual metastatic lymph nodes with microscopic metastases represent the most common site of disease recurrence.

2. To minimize treatment- and disease-related morbidity. The surgeons experience as well as the extent of surgery play significant roles in minimizing surgery-related and differentiated thyroid cancer related morbidity.

3. To permit accurate staging of the disease. Accurate post-operative staging is crucial in the management of patients with differentiated thyroid cancer. This helps in determining the prognosis and in developing appropriate disease management and follow-up strategies.

4. During initial surgery of differentiated thyroid cancer, removal of all the normal thyroid tissue is preferable in patients who will undergo radio-iodine remnant ablation or radioiodine treatment of residual or metastatic disease. Near total or total thyroidectomy may also reduce the risk of recurrence of cancer in the contralateral lobe.

5. Accurate long-term surveillance for thyroid cancer recurrence is important. Near total or total thyroidectomy is required in patients who are supposed to undergo long-term monitoring by radio-iodine whole-body scanning and serum thyroglobulin measurements because these monitoring modalities are affected by normal residual thyroid tissue.

6. Adequate surgery is the most important factor influencing prognosis, risk of disease recurrence and metastasis. In some patients, radioactive iodine treatment, thyrotropin suppression and external beam radiation all play adjunctive roles.²

How is preoperative staging used in conjunction with diagnostic imaging and laboratory tests?

Imaging of the neck

All patients undergoing thyroidectomy should have neck ultrasound of the contralateral lobe and cervical (central and bilateral) lymph nodes prior to surgery. Cervical lymph nodes are involved in 20 to 50% of patients with differentiated thyroid carcinoma (particularly in papillary carcinoma). This may occur even in the presence of a small primary tumor or intrathyroidal tumor. The frequency of micrometastases may be up to 90%, depending on the sensitivity of the detection method. Suspicious cervical adenopathy can be identified by ultrasound prior to surgery in about 20 to 31% of cases and can result in altered choice of the surgical approach.

In patient with differentiated thyroid carcinoma, adequate staging is significant in determining the disease prognosis and for tailoring treatment. The presence of metastatic disease in differentiated thyroid cancer, however, does not preclude the need for surgical excision of the primary tumor unlike in many tumour of other types.

Initial treatment in metastatic disease should involve removal of the thyroid as well as the primary tumour and accessible loco-regional disease. This is because remaining metastatic disease may respond to radio-iodine therapy.

What is the appropriate operation for differentiated thyroid cancer?

The goal of thyroid surgery can include

Lobectomy -

1. provision of a diagnosis after a nondiagnostic or indeterminate biopsy,
2. A biopsy suspicious for papillary or follicular carcinoma.
3. The risk of malignancy of solitary nodules that are repeatedly non-diagnostic on biopsy is close to 5 to 10%.
4. Thyroid lobectomy alone may be sufficient treatment for small, low-risk, isolated, intrathyroidal papillary carcinomas in the absence of cervical nodal metastases

Near-total thyroidectomy (removal of all grossly visible thyroid tissue, leaving only a small amount (<1 gram) of tissue adjacent to the insertion of the recurrent laryngeal nerve into the cricothyroid muscle),

According to current recommendations, near-total or total thyroidectomy should be carried out in presence of any of the following:

1. Primary thyroid carcinoma more than 1 to 1.5 cm in size
2. Thyroid nodules on the contralateral lobe
3. Metastases, either regional or distant
4. History of radiation therapy to the head and neck
5. History of differentiated thyroid carcinoma in a first-degree relative
6. Age over 45 years, because of the higher recurrence in and above this age
7. Large tumours (4 cm) with marked atypia on biopsy
8. High-risk and low-risk patients, because extensive primary surgery may improve survival in high-risk patients and rates of recurrence are reduced even in low-risk patients

Radioactive ablation-staging and preparation

Dissection of the lymph nodes: About 20 to 90% of patients with papillary carcinoma have regional lymph node metastasis at the time of diagnosis. However, in patients with thyroid cancer of other histotypes, the incidence of lymph nodes metastasis is lower.

The risk of nodal recurrence may be diminished and survival improved with bilateral central (compartment VI) dissection. In patients with papillary thyroid carcinoma and suspected Hürthle carcinoma, routine dissection of central compartment (level VI) neck should be considered.

Near-total or total thyroidectomy without central node dissection may be appropriate for follicular cancer, and when followed by radioactive iodine therapy, may provide an alternative approach for papillary and Hürthle cell cancers.

Lymph nodes in the lateral neck (compartments II–IV) and posterior triangle (compartment V) may also be involved by thyroid cancer, most often in papillary and Hürthle cell carcinoma.

For those patients in whom nodal disease is evident

- clinically,
- on preoperative ultrasound,
- or at the time of surgery, especially when they are likely to fail radioactive iodine treatment based on lymph node size, number, or
- Other factors, such as aggressive histology of the primary tumor, surgical resection may reduce the risk of recurrence and possibly mortality.

Functional compartmental en-bloc dissection is favored over selective dissection (berry picking) with limited data suggesting improved mortality.
Completion thyroidectomy may be necessary when the diagnosis of malignancy is made
1. After lobectomy for an indeterminate or nondiagnostic biopsy.
2. Resection of multicentric disease for papillary carcinomas
3. To allow radioiodine therapy.

Near-total or total thyroidectomy and two-stage thyroidectomy

ALGORITHSM FOR REMNANT ABLATION:
Initial Follow-up in Patients with Differentiated Thyroid Carcinoma in Whom Remnant Ablation is Indicated
One to Three Months after Surgery

Final Surgery is a Total or Near-Total Thyroidectomy

Completion Thyroidectomy Prior to Ablation (R29,R30)

Known Residue Macroscopic Tumor?

Consider Pretherapy Diagnostic WBS Using rh TSH or THW\(^e\) if Expected to Change Management (R35)

Suspected\(^d\) or Known Residue Disease

Consider Pretherapy Diagnostic WBS Using rh TSH or THW\(^e\) if Expected to Change Management (R35)

rh TSH or THW\(^e\) 30-100mCi \(^{131}\)I (R32,R36)

Follow-up 6-12 Month with TSH-Stimulated DxWBS,Tg and Neck US

Uptake Only in Thyroid Bed\(^f\)

RxWBS\(^g\) 5-8 Days Post \(^{131}\)I

rhTSH or RHW 100-200 mCi \(^{131}\)I (R37)

Further Testing and/or Treatment as Indicated

Uptake Only in Thyroid Bed\(^f\)

Uptake Outside Thyroid Bed

NO

Neck US, CT scan
Serum Tg\(^c\)
Consider PET Scan Surgery if Feasible and / or Consider EBRT(R41)

Suspected\(^d\) or Known Residue Disease

Consider Pretherapy Diagnostic WBS Using rh TSH or THW\(^e\) if Expected to Change Management (R35)

rh TSH or THW\(^e\) 30-100mCi \(^{131}\)I (R32,R36)

Fig. 2: Algorithm for initial follow-up of patients with differentiated thyroid carcinoma.

EBRT, external beam radiotherapy. The usual indication of EBRT is macroscopic unresectable tumor in a patient older than 45 years; it is not usually recommended for children and adults less than age 45.

Neck ultrasonography of operated cervical compartments is often compromised for several months after surgery.

Tg, thyroglobulin with anti-thyroglobulin antibody measurement; serum Tg is usually measured by immunometric assay and may be falsely elevated for several weeks by injury from surgery or by heterophile antibodies, although a very high serum Tg level after surgery usually indicates residual disease.

Some clinicians suspect residual disease when malignant lymph nodes, or tumors with aggressive histologies (as defined in the text) have been resected, or when there is a microscopically positive margin of resection.

rh TSH is recombinant human TSH and is administered as follows:
0.9 mg rhTSH i.m. on two consecutive days, followed by \(^{131}\)I therapy on the third day.

THW is levothyroxine an/or triiodothyronine withdrawal.

See text for exceptions regarding remnant ablation. The smallest amount of \(^{131}\)I necessary to ablate normal thyroid remnant tissue should be used. DxWBS (diagnostic whole-body scintigraphy) is not usually necessary at this point, but may be performed if the outcome will change the decision to treat with radioiodine and / or the amount of administered activity.

RxWBS is posttreatment whole-body scan done 5 to 8 days after therapeutic \(^{131}\)I administration.

Uptake in the thyroid bed may indicate normal remnant tissue or residual central neck nodal metastases.

Completion thyroidectomy may be necessary when the diagnosis of malignancy is made
1. After lobectomy for an indeterminate or nondiagnostic biopsy.
2. Resection of multicentric disease for papillary carcinomas
3. To allow radioiodine therapy.

Near-total or total thyroidectomy and two-stage thyroidectomy

Fig. 3: Shows remnant thyroid, nodes and lung uptake in a post therapy scan

Fig 4: Shows there were multiple lung metastases besides bone metastases. (A) CT scan shows osteolytic lesions on both sides of iliac bones (arrows). (B) \(^{201}\)TI SPECT image shows high uptake on both sides of iliac bones (arrows), right lower lung, and left lung hilus (arrowheads). (C) \(^{18}\)F-FDG PET shows high uptake on both sides of iliac bones (arrows), right lower lung, and left lung hilus (arrowheads). (D) \(^{99m}\)Tc-HMDP bone scintigraphy shows no obvious abnormal uptake.

((Lobectomy followed by completion thyroidectomy) share similar surgical risks.

As an alternative to completion thyroidectomy, radio-iodine ablation of the remaining lobe has been found useful. However, this practice is not currently recommended.

What is the role of postoperative radioiodine remnant ablation?

Postoperative radioiodine remnant ablation is increasingly being used to eliminate the post-surgical thyroid remnant.

The goals of this treatment are
1. Radioiodine remnant ablation post-operatively is performed with the aim of destroying residual thyroid tissue. This helps
to reduce the risk of recurrence of locoregional disease and facilitates long-term surveillance of whole-body iodine and/orstimulated thyroglobulin estimation.

This is controversial as retrospective studies are for and against this premise. Studies show benefit in patients with large tumors (> 1.5 cm), or with residual disease after surgery, while low risk patients do not show evidence for benefit.

2. Radioiodine ablation is recommended for patients with
   • stages III and IV disease,
   • all patients with stage II disease <45 years and most patients with stage II disease ≥45 years, and
   • Selected patients with stage I disease, especially those with multifocal disease, nodal metastases, extrathyroidal or vascular invasion, and/or more aggressive histologies (Fig. 2).

   TSH stimulation is required for remnant ablation and subsequent monitoring for thyroid cancer recurrence/persistence using radio-iodine whole body scans (WBS) and/or thyroglobulin estimation. TSH above 30mU/L is associated with sufficient radio-iodine uptake in tumors. Single-dose exogenous TSH studies suggest that TSH levels between 51 and 82 mU/L is associated with maximal thyrocyte stimulation. Thyroid hormone withdrawal to elevate endogenous TSH levels can be achieved by using two approaches: withdrawing levothyroxine (LT4) and switching to levothyroiodothyronine (LT3) for 2 to 4 weeks followed by stopping LT3 for 2 weeks, or discontinuing of LT4 for 4 weeks.12

Radioiodine WBS (Whole body scan) provides information on the presence of iodine-avid thyroid tissue, which may represent the normal thyroid remnant, the presence of residual disease or distant metastasis.

If there is a large thyroid remnant, the sensitivity of disease detection by radio-iodine whole body scan (WBS) is reduced. This occurs because of the dominant uptake of radio-iodine within the remnant, resulting in masking of extrathyroidal disease within locoregional lymph nodes, the upper mediastinum or at distant sites. Stunning of the thyroid induced by pre-treating with a diagnostic dose is the reduced uptake of 131I therapy dose. Higher doses (5 to 10 mCi) of 131I and a larger time interval between diagnostic dose and therapy cause prominent stunning, while stunning is not visually appreciable at lower doses (1 to 3 mCi). With 123I stunning may also occur though to a lesser degree than with 131I. Determination of the thyroid bed uptake can be achieved using 10–100 μCi 123I. Successful remnant ablation is usually defined as an absence of visible radioiodine uptake on a subsequent diagnostic radioiodine scan. 131I shows similar rates of successful remnant ablation at activities between 30 and 100 mCi, with higher success rates achieved using higher doses. The minimum activity (30–100 mCi) necessary to achieve successful remnant ablation should be chosen, particularly for low-risk patients. Higher activities of 131I (100 to 200 mCi) are appropriate for suspected or documented residual microscopic disease and for a more aggressive tumour histology (such as insular, columnar, tall cell carcinoma). The efficacy of radioactive iodine depends on the radiation dose delivered to the thyroid tissue. Low-iodine diets (< 50 g/d of dietary iodine) have been recommended prior to radioiodine therapy to increase the effective radiation dose.

Post-therapy WBS is typically conducted approximately 1 week after radioactive iodine therapy to visualize metastases.

In about 10 to 26% of patients who underwent WBS scan post high-dose radio-iodine treatment, additional metastatic foci have been reported as compared to diagnostic scan. New areas of abnormal uptake were found in the neck, lungs and mediastinum (Figs 3, 4). The discovery of new disease prompted an alteration of the disease stage in 10% patients that influenced clinical management.3

What is the role of TSH suppression therapy?

TSH stimulation in differentiated thyroid cancer causes the increased expression of several thyroid-specific proteins (such as thyroglobulin, sodium iodide symporter) and augmented rates of cell growth. This occurs because of the expression of thyrotropin receptors on the cell membranes of differentiated thyroid cancerous cells. Supraphysiological doses of LT4 are frequently used to treat patients with thyroid cancer. The high dose suppresses TSH and decreased the risk of recurrence. The efficacy of TSH suppression therapy in preventing major adverse clinical events was supported by a recent meta-analysis (relative risk [RR] < 0.73; confidence interval [CI] < 0.60–0.88; p < 0.05).

TSH suppression may precipitate the well-known complications of subclinical thyrotoxicosis that include exacerbation of angina in ischemic heart disease patients, heightened risk of atrial fibrillation, and increased risk of osteoporosis in postmenopausal women. Initial thyrotropin suppression to below 0.1 mU/L is recommended for high-risk patients with thyroid cancer, while maintenance of the TSH at or slightly below the lower limit of normal (0.1–0.5 mU/L) is appropriate for low-risk patients.

Serum TSH levels should be kept below 0.1 mU/L indefinitely in patients with persistent disease if no contraindications exist.

In patients who are clinically free of disease but who presented with high risk disease, consideration should be given to maintaining TSH suppressive therapy to achieve serum TSH levels of 0.1 to 0.5 mU/L for 5–10 years. For those at low risk for recurrence, the TSH may be kept within the low normal range (0.3 to 2 mU/L).1,3

Differentiated Thyroid Cancer: Long-Term Management

What are the appropriate features of long-term management?

In patients thought to be free of disease, a major goal of long-term follow-up is accurate surveillance for possible recurrence. Patients in low, intermediate, and high-risk groups of having persistent or recurrent disease are followed-up differently from each other. Staging was developed to predict risk for death, not recurrence. For assessment of risk of recurrence, a three level stratification can be used. Low-risk patients have the following characteristics after initial surgery and remnant ablation:

• no local or distant metastases;
• all macroscopic tumor has been resected,
• there is no tumor invasion of locoregional tissues or structures,
• the tumor does not have aggressive histology (e.g., tall cell, insular, columnar cell carcinoma) or vascular invasion,
• If 131I is given, there is no 131I uptake outside the thyroid bed on the first post treatment whole body radioiodine scan (RxWBS).

Intermediate-risk patients have microscopic invasion of tumor into the perithyroidal soft tissues at initial surgery or tumor with aggressive histology or vascular invasion.
**ALGORITHMS for MANAGEMENT of DTC SIX to TWELVE MONTHS after REMNANT ABLATION**

- **Tg(4) and Neck US (R46a)** While on T4
  - US Suspicious for Lymph Nodes or_Nodule 5-8mm
  - Biopsy for Cytology and Tg Wash (R46b/c)

- **rh TSH or THW Tg Stimulation (R44b)**
  - Tg > 0.3 Tg/Ab Pos
  - Follow Tg/Ab and Neck US; Consider Tg RIA

- **Tg > 1**
  - Long-Term Follow-up (R44b and R46a)
  - Consider Diagnostic RAI WBS (R47)

- **Tg 1-2**
  - Monitor Tg, Neck US (R47)
  - Tg Rising, US Negative
  - Consider **31**I Therapy (R56,58,61,75)

- **Tg > 2**
  - Consider Neck/Chest CT, Neck MRI, Or PET/CT R44d
  - Monitor Tg, Neck US (R47)

- **Negative WBS or Stimulated Tg < 5-10**
  - Negative WBS or Stimulated Tg < 5-10
  - Assess for Cytology
  - Consider Surgery, 31I Therapy, EBRT, Clinical Trial, or Tyrosine Kinase Inhibitor Therapy (R56,78b)

- **Positive WBS**
  - Consider Neck/Chest CT, Neck MRI, Or PET/CT R44d
  - Monitor Tg, Neck US (R47)
  - Tg Rising, US Negative
  - Consider **31**I Therapy (R56,58,61,75)

- **Positive WBS**
  - Consider Neck/Chest CT, Neck MRI, Or PET/CT R44d
  - Monitor Tg, Neck US (R47)
  - Tg Rising, US Negative
  - Consider **31**I Therapy (R56,58,61,75)

**Fig. 5:** Longer term follow-up of patients with differentiated thyroid carcinoma.

- TgAb is anti-thyroglobulin antibody usually measured by immunometric assay.

The use of heterophile blocking tubes or heterophile blocking reagents have reduced, but not completely eliminated this problem. Tg that rises with TSH stimulation and falls with TSH suppression is unlikely to result from heterophile antibodies.

- Tg radioimmunoassay (RIA) may be falsely elevated or suppressed by TgAb. Tg results following TSH stimulation with rhTSH or thyroid hormone withdrawal are invalidated by TgAb in the serum even when Tg is measured by most RIA tests. TgAb levels often decline to undetectable levels over years following surgery (Chovato L, Latrofa F, Braverman LE, Pacini F, Capezzone M, Masserini L, Grasso L, Pinchera A. Disappearance of humoral thyroid autoimmunity after complete removal of thyroid antigens. Ann Intern Med 2003;139:346-351). A rising level of TgAb may be an early indication of recurrent disease (Spencer CA, Takeuchi M, Kazarosyan M, Wang CC, Guttler RB, Singer PA, Fatemi S, LoPresti JS, Nicoloff JT. Serum thyroglobulin autoantibodies: prevalence, influence on serum thyroglobulin measurement, and prognostic significance in patients with differentiated thyroid carcinoma. J Clin Endocrinol Metab 1998;83:1121-1127).

- See text for decision regarding surgery versus medical therapy, and surgical approaches to locoregional metastases. FNA confirmation of malignancy is generally advised. Preoperative chest CT is recommended as distant metastases may change management.

**High-risk patients** have
- macroscopic tumor invasion

**Criteria for absence of persistent tumor**

Disease free status (in patients who have undergone near-total or total thyroidectomy and subsequent thyroid remnant ablation) is comprised of all of the following:

- Absence of clinical evidence of tumour.
- Absence of evidence of tumour on imaging (absence of uptake of radioiodine external to the thyroid bed on initial post treatment WBS, on a recent diagnostic scan or ultrasound of the neck).
- Undetectable thyroglobulin levels for the period of TSH suppression.
- Stimulation when no interfering antibodies are present.¹³

**How does serum Thyroglobulin as a tumor marker help in management**

Measurement of serum thyroglobulin levels is an important modality to monitor patients for residual or recurrent disease. Serum thyroglobulin exhibits high degree of sensitivity and specificity in detecting thyroid cancer, particularly post total thyroidectomy and remnant ablation. The highest degree of sensitivity of serum thyroglobulin is noted post thyroid hormone withdrawal or stimulation using recombinant human thyrotropin (rhTSH).

**Drawbacks**

- Serum thyroglobulin may be undetected
- in small remnants,
- because of antithyroglobulin antibodies
- abnormal thyroglobulin
- with aggressive or poorly differentiated tumors
- small cervical node metastasis

Follow-up for low-risk patients (approximately 85% of postoperative patients) who have undergone total or near total thyroidectomy and 131I remnant ablation should be based

- Mainly on non-TSH-suppressed thyroglobulin and cervical ultrasound. A thyroglobulin cut-off level of more than 2 ng/mL after rhTSH stimulation is highly sensitive in identifying patients with persistent tumors, as shown by substantial amount of evidence.

- The presence of antithyroglobulin antibodies, which occur in approximately 25% of thyroid cancer, will falsely lower serum thyroglobulin determinations in immunometric assays. Serial serum antithyroglobulin antibody measurements can be used as a rough indicator of the presence of residual normal thyroid tissue or tumor.

Serum thyroglobulin should be measured every 6–12 months during follow-up of patients with differentiated thyroid carcinoma who have undergone total or near-total thyroidectomy and thyroid remnant ablation. With every measurement of serum thyroglobulin, quantitative estimation of thyroglobulin antibodies should be performed.

**Investigations recommended for follow-up of differentiated thyroid cancer (DTC).**

- Diagnostic whole-body radioiodine scans. (DxWBS)

There are two main issues that affect the use of (Dews) during
follow-up: stunning and accuracy.

When little or no remaining thyroid tissue exists, DxWBS is most useful for follow-up. DxWBS does not visualize disease, regardless of the $^{131}$I activity employed. However, disease may occasionally be visualized on the RxWBS images obtained after larger, therapeutic amounts of $^{131}$I.

After radioiodine ablation, subsequent DxWBS have low sensitivity and are usually not necessary in low-risk patients who are clinically free of residual tumor and have an undetectable serum thyroglobulin level during thyroid hormone suppression of serum TSH and negative cervical ultrasound.

In patients with high or intermediate risk of persistent disease, DxWBS may be of value during follow-up, 6 to 12 months after remnant ablation. However, it should be performed using low-dose $^{131}$I or $^{123}$I.

Cervical ultrasonography

Cervical ultrasonography is highly sensitive in the detection of cervical metastases in patients with differentiated thyroid cancer. Evaluation of the thyroid bed and central and lateral cervical nodal compartments by cervical ultrasound should be done between 6 and 12 months after surgery and annually thereafter for a minimum of 3 to 5 years (based on the patient’s risk of recurrent disease and thyroglobulin status).

Management of patients with metastatic disease

Persistent disease that has survived initial treatment may manifest as metastases discovered at follow-up, and is frequently incurable by additional $^{131}$I therapy.

The preferred treatment for metastatic disease is

- Surgical excision of locoregional disease. Complete ipsilateral compartmental dissection of involved compartments with persistent/recurrent disease while sparing vital structures is used. Surgery in conjunction with additional therapy such as external beam radiation or $^{131}$I is generally advised for tumors invading the upper aero-digestive tract.

There are three approaches to $^{131}$I therapy:

1. Therapy determined by the upper bound limit of blood and body dosimetry,
2. Empiric fixed amounts
3. Quantitative tumor dosimetry
   - External beam radiation
   - Observation of patients with stable asymptomatic disease
   - Experimental chemotherapy trials.
   - A small fraction of patients may benefit from radiofrequency ablation, ethanol ablation, or chemoembolization.

Treatment of pulmonary metastases

Key criteria to decide therapy for the management of patients with pulmonary metastases are as follows:

- Metastatic lesion size (chest radiography typically detects macronodular metastases; CT typically detects micronodular metastases; lesions beneath the resolution of CT).
- Avidity of radio-iodine uptake and response to prior radio-iodine therapy, if applicable.
- Metastatic lesion stability.
- Partial response rates of not more than 25% have been achieved with traditional cytotoxic chemotherapeutic agents such as doxorubicin and cisplatin, while complete remission rates are rare. In many patients with slow progression of metastatic disease, conservative management with TSH-suppressive therapy and follow-up, exhibits minimal evidence of radiographic or symptomatic progression. However, in selected patients, other treatment options such as metastasectomy, endobronchial laser ablation, or external beam radiation for palliation of symptomatic intrathoracic lesions (e.g., obstructing or bleeding endobronchial masses), and pleural or pericardial drainage for symptomatic effusions should be considered.

Non radioiodine avid pulmonary disease

Partial response rates of not more than 25% have been achieved with traditional cytotoxic chemotherapeutic agents such as doxorubicin and cisplatin, while complete remission rates are rare. In many patients with slow progression of metastatic disease, conservative management with TSH-suppressive therapy and follow-up, exhibits minimal evidence of radiographic or symptomatic progression. However, in selected patients, other treatment options such as metastasectomy, endobronchial laser ablation, or external beam radiation for palliation of symptomatic intrathoracic lesions (e.g., obstructing or bleeding endobronchial masses), and pleural or pericardial drainage for symptomatic effusions should be considered.

In the management of the patient with bone metastases

Key criteria for therapeutic decisions include

- Risk for pathologic fracture, particularly in a weight-bearing structure;
- Risk for neurologic compromise from vertebral lesions;
- Presence of pain;
- Avidity of radioiodine uptake;
- Potential significant marrow exposure from radiation arising from radioiodine-avid pelvic metastases.

Complete surgical resection of isolated symptomatic metastases has been associated with improved survival and should be considered, especially in patients less than 45 years old.

Radioiodine therapy of iodine-avid bone metastases has been associated with improved survival and should be used. Radioiodine therapy for iodine-avid bone metastases can be given empirically (150 to 300 mCi) or estimated by dosimetry.

External radiation and the concomitant use of glucocorticoids should be considered when skeletal metastatic lesions arise in locations where acute swelling may produce severe pain, fracture, or neurologic complications. This helps in minimizing potential TSH-induced and/or radiation related tumor expansion.

Unresectable painful lesions can be treated by a combination of options or individual therapy that includes:

- Radioiodine
- External beam radiotherapy
- Intra-arterial embolization
- Radiofrequency ablation
• Periodic pamidronate or zoledronate infusions (with monitoring for development of possible osteonecrosis)
• Bone-seeking radiopharmaceuticals such as strontium-89 or samarium-153

**Treatment of brain metastases**

Brain metastases typically occur in older patients with more advanced disease at presentation, and are associated with a poor prognosis. Surgical resection and external beam radiotherapy traditionally have been the mainstays of therapy. There are few data showing efficacy of radioiodine. Often much targeted approaches (such as radiosurgery) are employed to limit the radiation exposure of the surrounding brain tissue. Radioiodine can be considered for CNS metastases that concentrate radioiodine. In such settings, it is strongly recommended to make the patient undergo external beam radiotherapy and concomitant glucocorticoid therapy before radioiodine exposure. This helps in minimizing the effects of potential TSH-induced augmentation of tumor size and the subsequent inflammatory effects of radioiodine.

**Management of complications of radioiodine therapy**

While radioiodine is a reasonably safe therapy, it is associated with a cumulative dose-related low risk of early and late onset complications such as salivary gland damage, nasolacrimal duct obstruction, and secondary malignancies.

For acute transient loss of taste or change in taste and salivadenitis, some have recommended measures to prevent damage to the salivary glands including amifostine, hydration, sour candies and cholinergic agents. For chronic salivary gland complications, such as dry mouth and dental caries, cholinergic agents may increase salivary flow. Patients with xerostomia are at increased risk of dental caries and should discuss preventative strategies with their dentists.

**Second malignancies and leukemia from radioiodine therapy**

Long-term follow-up studies demonstrate a very low risk of secondary malignancies (bone and soft tissue malignancies, colorectal cancer, salivary tumors, and leukemia) in long-term survivors. The risk of secondary malignancies is dose-related. There appears to be an increased risk of breast cancer in women with thyroid cancer. It is unclear whether this is the result of screening bias, radioiodine therapy, or other factors (Fig. 5).

**Other risks to the bone marrow from radioiodine therapy**

Minimal transient effects are noted in WBC and platelet counts if administered radioiodine activities selected remain below 200 cGy, according to published reports. However, patients who have received multiple radioiodine therapies frequently have persistent mild decrements in WBC and/or platelet counts. Moreover, several other factors such as renal function may also affect bone marrow function.

**Effects of radioiodine on gonadal function and in breastfeeding women**

Gonadal tissue is exposed to radiation from radioiodine in the blood, urine and feces. In about 20 to 27% of menstruating women, temporary amenorrhea/oligomenorrhea may occur that may last for 4 to 10 months after 131I therapy for thyroid cancer. Radioiodine therapy does not seem to increase the long-term rates of infertility, miscarriage, and fetal malformation in women, although this has been studied in only a small number of patients. Ovarian damage secondary to radioiodine therapy may result in one year early menopause as compare to the general population. However, the results are not influenced by the cumulative dose administered or the age during therapy. Temporary reduction in sperm counts and elevated serum follicle-stimulating hormone (FSH) levels are some of the associated effects of radioiodine therapy on gonadal function in men. Moderate radioiodine doses (approximately 200 mCi) are not associated with fertility and risks of miscarriage or congenital abnormalities in subsequent pregnancies. However, higher cumulative doses (500–800 mCi) are associated with a heightened risk of persistent elevation of serum FSH levels in men. Permanent male infertility is unlikely with a single ablative dose of radioiodine, but theoretically there could be cumulative damage with multiple treatments.

Women receiving radioactive iodine therapy should avoid pregnancy for 6–12 months—radioactive iodine should not be given to breast-feeding women.

**How should thyroglobulin-positive patients be managed?**

If the unstimulated thyroglobulin is or becomes detectable or stimulated thyroglobulin levels rise to greater than 2 ng/mL, imaging of the neck and chest should be performed to search for metastatic disease, typically with neck ultrasound and with thin-cut (5–7 mm) helical chest CT.

**Considerations for empiric treatment with radioiodine**

Empiric radioactive iodine therapy (100–200 mCi) might be considered in patients with elevated or rising serum thyroglobulin levels in whom imaging has failed to reveal a potential tumor source. Patients, who cannot be cured by surgery, are RxWBS negative but thyroglobulin positive and whose disease is structurally evident or visualized on FDG-PET scan can be managed by:

- Thyroid hormone suppression therapy,
- External beam radiotherapy,
- Chemotherapy,
- Radiofrequency ablation,
- Chemoembolization,
- Monitoring without additional therapy if stable.
- Considering clinical trials.

On the other hand, patients who are thyroglobulin-positive, RxWBS-negative and have no structural evidence of disease can be followed:

- By serial structural imaging studies.
- Serial thyroglobulin measurements.

**What is the role of external beam radiotherapy in treatment of metastatic disease?**

External beam radiation should be used in the management of unresectable gross residual cervical disease, painful bone metastases, metastatic lesions in critical locations likely to result in fracture, neurological, or compressive symptoms that are not amenable to surgery (e.g., vertebral metastases, CNS metastases, selected mediastinal or subcarinal lymph nodes, pelvic metastases).

**What is the role of chemotherapy in the treatment of metastatic disease?**

Studies of chemotherapy for advanced, radioiodine-resistant differentiated thyroid carcinoma are limited. Doxorubicin monotherapy may be effective in up to 40% of patients (most partial response or stable disease) when dosed appropriately (60–75 mg/m2 every 3 weeks) but durable responses are uncommon.
Most studies of combination chemotherapy show no increased response over single agent doxorubicin and increased toxicity. In patients with anaplastic thyroid carcinomas, some specialists recommend the use of single agent doxorubicin or paclitaxel, or a combination of these agents, because of limited data.

One recent study evaluated the effect of combination chemotherapy (carboplatinum and epirubicin) under TSH stimulation (endogenous or rhTSH), demonstrating an overall rate of complete and partial response of 37%. These data need to be confirmed prior to consideration for general use. Patients with advanced, radiiodine-resistant thyroid cancer benefit only modestly by chemotherapy. Therefore, clinical trials should be first considered for patients with such progressive disease.

Therapies in waiting

Progressive, life-threatening growth and metastatic spread of thyroid cancer occur in a minority of patients. For these individuals, experimental treatments may be considered.

These therapies can be grouped into a number of categories:

Oncogene inhibitors

Tyrosine kinase inhibitors target the activated RET/PTC oncogene, responsible for a proportion of PTC. Inhibitors of RAS, RAF, and MEK kinase target various members of the same signaling pathway. Several of these agents are in development, with at least one clinical trial underway. Specific oncogene targeting for follicular thyroid cancer and Hürthle thyroid cancer awaits better understanding of the pathways involved in initiation of these tumor types.

Modulators of growth or apoptosis

PPAR activators target key components of growth and apoptotic pathways. Some of these agents that have been tested for thyroid cancer in clinical trials are COX2 inhibitors, retinoids (which activate PPAR_/_RXR heterodimers), Bortezomib (Velcade®, Millenium Pharmaceuticals, Cambridge, MA, which inactivates the cancer proteasome), and geldanomycin derivates (which target the hsp-90 protein).

Angiogenesis inhibitors

Inhibiting neoangiogenesis by targeting the vascular endothelial growth factor (VEGF) and other members of the signaling cascade may limit cancer growth by restricting their blood supply. These agents are currently being tested in clinical trials for both anaplastic and differentiated thyroid cancer.

Immunomodulators

Immunomodulators stimulate the immune response to cancer by enhancing the activity of antigen-presenting dendritic cells. Possible benefits of this approach have been demonstrated in phase 1 trials. However, these agents have not been studied in thyroid cancer, although, the apparent immunogenicity of thyroid cells make immunomodulators an attractive approach.

Gene therapy

Gene therapy has demonstrated efficacy in preclinical cell-line studies. Introduction of toxic genes under thyroid-specific promoter control and restoration of the p53 tumor-suppressor gene in anaplastic thyroid cancer cell lines are two approaches that have been studied. However, the clinical utility of gene therapy is limited by problems with gene delivery and therefore, these approaches are yet to enter clinical trial stages in thyroid cancer.

Redifferentiation therapy

Employing retinoic acid 1.5 mg/kg per day for five weeks has been found to induce re-differentiation of thyroid cancer cells with regain of iodide concentrating ability. Redifferentiation therapy with retinoic acid increased both iodide uptake and thyroglobulin (in 63%) in patients.
**Medullary Thyroid Carcinoma**

In patients with suspected medullary thyroid carcinoma (MTC), FNAC and plasma calcitonin measurements are carried out initially. Access to clinical genetics service and RET gene testing are required for an MDT. Genetic counseling together with RET mutation analysis should be offered to all patients with MTC regardless of evidence of family history. RET mutation testing should include exons 10, 11, 13, 14, 15 and 16; screening of exons 10 and 11 alone is an incomplete test. Out of all the patients of MTC, familial MTC (FMTC) occurs in 25% of cases. It is associated with endocrinopathies (MEN2A and 2B), for must be looked for in such patients. In new patients with MTC, measuring 24-hour urine catecholamines and metanephrines and serum calcium, should be carried out to exclude phaeochromocytoma and primary hyperparathyroidism. The minimum treatment is total thyroidectomy and level VI node dissection. Prophylactic surgery should be considered in disease-free carriers of germ line RET mutations. Surgery should be performed in MEN2A patients before the age of 5 years. Thyroid surgery should ideally be performed by age 12 in patients with aggressive MTC in MEN2B. Surgery should be postponed until after 10 years of age in children from FMTC kindred. Calcitonin monitoring as a tumor marker should be carried out as part of the essential life-long follow-up in such patients (Fig. 6).

Algorithm for medullary cancer

**Rare malignancies of the thyroid**

**Thyroid lymphoma**

Primary thyroid lymphomas occur on a background of Hashimoto’s thyroiditis in the vast majority of cases, although the Hashimoto’s thyroiditis may be undiagnosed.

- A clinical diagnosis or high index of suspicion of lymphoma may be confirmed by FNAC with the addition of molecular techniques, although usually a core biopsy is required to allow a full range of immunocytochemical studies to be performed.
- Incision biopsy is not essential for the diagnosis of lymphoma.
- Thyroidectomy is not indicated.
- The treatment of choice is chemotherapy followed by radiotherapy or radiotherapy alone. Most cases are high-grade B cell lymphomas. Some are MALT (mucosa-associated lymphoid tissue) tumours.
- Prognosis is generally excellent.
- Patients should be referred to an MDT specialising in lymphoma management.

**Anaplastic thyroid cancer**

This has a very poor prognosis.

- Where the diagnosis has not been possible on FNAC, core biopsy may assist the diagnosis.
- Surgery is rarely indicated. In a very small subgroup of cases, chemotherapy/radiotherapy and surgery may achieve a slightly longer period of survival.
- ^131^I ablation or therapy has no place.
- External beam radiotherapy is the mainstay of treatment, with or without chemotherapy.\(^1\)\(^3\)

**Conclusions**

- Management of thyroid cancer is a multidisciplinary strategy and a close coordination and cooperation is essential in diagnosis and long term follow-up.
- Surgery and the judicious use of radioactive iodine, as described in these guidelines, is sufficient treatment for the majority of patients with differentiated thyroid cancer. A rigorous and prolonged that is life-long observation should be mandatory and this should be indicated to the patients as well as family by the treating panel of doctors. Newer technologies are available for better staging and detection of metastatic disease.
- A minority of these patients experience progressive, life threatening growth and metastatic spread of the disease. For these individuals, experimental treatments may be considered. Several clinical trials are already in progress; others are at various stages of development and the number of available clinical trials is likely to grow rapidly

**References**