



## Review Article

## Controversies Regarding the Management of Carcinoma of the Thyroid Gland

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### Abstract

Of all solid cancers presenting in adults, papillary thyroid cancers generally carry best long-term prognosis. However, very little is understood about the molecular pathogenesis of this neoplasm. Any patient presenting with thyroid nodule—initial work up will be fine needle aspiration cytology (FNAC). Surgical treatment depends on FNA finding, age and clinical presentation. After surgical debulking whole body diagnostic scan should be performed which will follow the need for radioactive iodine (RAI) ablation therapy. Life long assessment after ablation therapy is needed using serum thyroglobulin (Tg) estimation, whole body scan and most recent introduction of rTSH by FDA, USA.

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### Introduction

Carcinoma of thyroid gland has attracted the interest because of its broad range of phenotypes ranging from papillary carcinoma to often lethal anaplastic thyroid carcinoma. The most common are the differentiated thyroid carcinoma (DTC), which carry high, long term survival. Prevalence of thyroid carcinoma in the US of 180,000 and a incidence of 16,000 newly diagnosed cases per year<sup>1</sup>. Females are more likely to have thyroid cancer at a ratio of 3:1. In Singapore it is about 4.6% with a male female ratio 3.6:1<sup>2</sup>. Thyroid cancer occur at any age group, although most common after age 30 and prognosis is poor in elderly one. Despite the generally good prognosis for most patients, approximately 8-10% of those eventually die of their disease<sup>1</sup>. About 400 death occurs in UK due to this disease per year<sup>3</sup>.

Clinically detectable thyroid carcinoma constitute less than 1% of human cancers; yet differentiated thyroid carcinoma is most common endocrine cancer and the most curable<sup>4</sup>. The primary treatment modalities used for thyroid carcinoma (i.e.-surgery, radio iodine therapy and thyroid hormone therapy) have been used for more then 50 years, and yet little consensus prevails regarding the most appropriate choice of treatment for different group of patients<sup>3</sup>.

### Clinical Presentation

Differentiated thyroid carcinoma is usually asymptomatic for long periods and presents as a solitary thyroid nodule, giving no clue to their cause. Nodule size has a bearing on the risk of malignancy and clinical evaluation. Nodule smaller then 1cm is generally asymptomatic and diagnosed incidentally. By contrast, nodule over 4

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em is more suspicious and carries a high risk of malignancy. Although half of the nodules are asymptomatic, the probability of malignancy in a nodule rises considerably when signs or symptoms are present, eg. chance of malignancy increases about sevenfold if it is fixed to adjacent structures, associated with regional lymphadenopathy, causes vocal cord paralysis or rapidly growing – if two or more of these features are present the likelihood of thyroid carcinoma is assured<sup>5</sup>. Patient's age also has a bearing in the probability of malignancy. The mean age is 45 years. The risk is higher in patient under age 15 and over 60 years, especially in older men. A man over 60 years with thyroid nodule has about 4 times the risk of having carcinoma than a middle aged woman with a thyroid nodule<sup>6</sup>. Other factors that raises the suspicion of malignancy includes a past history of head-neck irradiation, family history of thyroid cancer, presence of certain familial syndromes associated with cancer thyroid or evidence of other disease with multiple endocrine neoplasia type 2 (MEN2)<sup>5</sup>. Radiation associated thyroid cancer involves young patient, not in orders and an increased risk for papillary carcinoma. Adequate dietary iodine is associated with an increasing proportion of papillary cancer in young patient, but not in older patient. The average age of differentiated thyroid carcinoma patients in iodine adequate areas is younger than in iodine deficient areas. The proportion of follicular carcinoma, particularly in older patient, is lower in iodine adequate than in iodine deficient areas. Most strikingly, the proportion of cases that are anaplastic has declined dramatically since dietary iodine become adequate but remains high in iodine deficient areas even today. Anaplastic thyroid cancer sometimes represents conversion of longstanding or recurrent papillary cancer by clonal overgrowth of aggressive cells<sup>7</sup>.

### Prognostic Factors

Prognostic factors are associated with an increased mortality and these are:

- Distant metastasis present at the time of diagnosis (45 fold increase in mortality)
  - Age over 45(32 fold) with mortality rate increasing in age
  - Primary lesion larger than 2cm(6 fold)
  - Local or extrathyroidal invasion (6 fold)
  - Male sex (2 fold)
- Local recurrence is associated with an increase mortality .It occurs in about 5-15% of patients and is associated with approximately 40% mortality . The incidence of local recurrence, subsequent nodal and distant mets are higher in children and age over 45y.Radio-iodine therapy has been shown to decrease local recurrence by about 50%, but has not been shown to statistically decrease mortality in thyroid cancer patients<sup>8</sup>.

### Histological Subtypes

Papillary thyroid carcinoma (>70%) – lymphatic spread to local nodal metastasis are most commonly seen. Angioinvasion is seen in only 2% and carries a worse prognosis<sup>8</sup>. Distant metastasis are seen in 3-7% of patients to lung, bone and mediastinum.

- a) Follicular thyroid carcinoma (15%) – tends to occur in slightly older age group (50 years) than papillary cancer. Capsular invasion is associated with worse prognosis. Distant metastasis are found in 25% cases in lungs, bones, brain, and regional nodes
- b) Medullary thyroid carcinoma (5-8%) – arises from parafollicular C - cells. Mean age of presentation is 60years.These tumor actively secrete calcitonin and associated with MEN Syndrome IIa, IIb - Metastasis occurs to regional lymph nodes, liver, lungs, and bones. This tumor may have 2 components: C-cells and follicular cells and occasionally concentrate radioiodine due to trapping within the follicular component.<sup>8</sup>
- c) Anaplastic / Poorly differentiated thyroid carcinoma (2-3%)- is usually seen in older patients. The tumor typically does not concentrate iodine and prognosis is poor.
- d) Primary thyroid lymphoma – is usually B-cell origin, more common in women, usually present as a rapidly enlarging tumor. This tumor does not concentrate radioiodine and treatment is XRT, and about 50% survival at 10 yrs.<sup>8</sup>

- f) Hurthle cell carcinoma is a follicular variant, composed of large oxyphilic (Hurthle) cells, which contain abundant mitochondria. Most do not accumulate radioiodine, but are capable of synthesizing thyroglobulin, tends to invade locally and recur.<sup>8</sup>

### Diagnostic Tools

Availability of the simplified biopsy techniques with fine needle aspiration of thyroid nodule or a clinically suspicious lymph node is recommended as the first diagnostic test in a clinically euthyroid patient before any imaging studies are done<sup>9</sup>. It carries a positive predictive value of 96% for malignant disease. In comparison, scintigraphy and ultrasound have a predictive value of only 20%<sup>10</sup>. Some clinicians, especially European thyroidologists<sup>11</sup> recommended obtaining serum calcitonin levels from all patients with thyroid nodules but this practice is not recommended by American Thyroid association<sup>12</sup>.

Fine needle aspiration cytology (FNAC) results are – benign, malignant, inadequate and indeterminate or suspicious<sup>5</sup>. Benign pathology on FNA can be followed by periodic clinical, ultrasound exam as well as by TSH hormone suppression and do not require repeat FNA unless nodule shows evidence of growth. Malignant FNAC mandates surgical resection with no further workup. Inadequate FNAC often results from technical errors and should be repeated. Indeterminate FNAC is usually due to inability to differentiate follicular adenoma from follicular carcinoma. Under these circumstances two clinical paradigms can be used<sup>10</sup>. Repeat FNA is generally not recommended because it will not solve the diagnostic dilemma.

Thyroid scanning using either<sup>123</sup>I or <sup>131</sup>I or <sup>99m</sup>Tc can identify patients with a hot nodule, who can be spared surgery<sup>13</sup>. Thyroid carcinoma almost invariably appears as a cold nodule on routine thyroid scanning. In general it is estimated that thyroid tumor will accumulate 0.01-0.02% of the injected dose. Of <sup>131</sup>I per gram, when contrasted with the normal thyroid which accumulate 0.5-1% of the injected dose per gram – thus it becomes obvious thyroid nodule appears cold<sup>8</sup>. An equally accepted clinical strategy is to perform a serum

TSH level. In patients in whom TSH level is normal or elevated, the clinician can reasonably assume that the nodule is hypo functioning. This implies an increased probability of malignancy and thus surgical resection can be recommended without further diagnostic work-up<sup>10</sup>. Interestingly malignant foci occur in 80% of lesions larger than 4cm<sup>13</sup>. Therefore in patients with large lesions immediate surgical intervention can be considered without diagnostic testing<sup>10</sup>. Pascal Fuschuber & his colleagues<sup>15</sup> suggest that response to TSH suppression is not a reliable predictor of a malignant potential in a solitary thyroid nodule.

Fifteen percent of patients placed on TSH suppression and followed by serial ultrasounds showed continued lesion growth, 20% demonstrated regression and 65% shows no change<sup>15</sup>. In the case of total resolution with TSH suppression, further treatment, aside from periodic surveillance is unnecessary. Thyroid ultrasound is helpful in detection of small nodule. Occult nodules less than 1 cm detected incidentally on imaging studies (ultrasound, CT Scan) can simply be followed by serial examinations<sup>10</sup>. Most thyroid nodule appears as hypo echoic (65%) or isoechoic (25%) on ultrasound. Hyperechoic thyroid lesions tend to be benign (95%). Only 2 % of thyroid cancer appears as cystic lesions. Calcification can be found in both benign and malignant disease-particularly medullary carcinoma<sup>8</sup>.

### Surgical Management

When the diagnosis of thyroid cancer is known preoperatively, most advise total or near total thyroidectomy for all patients<sup>16</sup>, because it improves disease free survival, even in children and adults with low risk tumors<sup>5, 17, 18</sup>. Some find that patient treated by lobectomy alone have a 5-10% recurrence in the opposite thyroid lobe<sup>19</sup> and an overall recurrence rate is over 30% and the highest frequency (11%) of subsequent pulmonary metastasis<sup>5</sup>. Whereas only 1% recurrence after total thyroidectomy and <sup>131</sup>I therapy<sup>20</sup>. On the other hand, most feel that lobectomy alone is adequate surgery for papillary microcarcinomas, provided the patient has not been exposed to radiation, has no other risk factors, the tumor is smaller than

1cm. unifocal and confined to thyroid without vascular invasion<sup>5,20</sup>. The same is true for minimally invasive follicular cancers smaller than 4cm.<sup>5</sup>

Ernest L. Mazzaferri and et al suggest that complete thyroidectomy should be considered for tumors that have the potentials for recurrence because large thyroid remnants are difficult to ablate with <sup>131</sup>I.<sup>20</sup> Total thyroidectomy is also recommended for patients with a prior history of irradiation, gross pathology at both lobes at the time of operation and those who present with distant metastases<sup>15</sup>. Completion thyroidectomy has a low complication rate and is appropriate to perform routinely for tumors 1cm or larger, as about half of the patients have residual cancer in the contra lateral thyroid lobe<sup>5</sup>. In another study it is mentioned that patients who underwent completion thyroidectomy within 6 months of their primary operation, developed significantly fewer lymph node and hematogenous recurrences and survived significantly longer than did those in whom the second operation is delayed for more than 6 months<sup>7</sup>. Those who are in favor of limited thyroid resection, argue that the risk of permanent hypocalcaemia and recurrent nerve damage does not justify the use of total thyroidectomy in low risk patients<sup>15,22,23</sup>. They also point out that limited thyroid resection may obviate the need for lifelong thyroid replacement<sup>15, 24</sup>.

### Post-Surgical Diagnostic Whole Body Scan

The first point to consider is whether a diagnostic whole body scan (WBS) is needed. WBS <sup>131</sup>I scan are often performed after surgery to assess the completeness of surgery and to see presence of functioning thyroid residuals. M Teresa Bajen states that some thyroid tissue usually remains after total thyroidectomy<sup>25</sup>. Several studies have shown that with high dose (5-10mCi), information obtained is more diagnostic and staging of disease should be done more accurately.

A high tracer dose, although producing a beneficial scan, seems to produce stunning effect – which can be defined as decreased radioiodine

uptake by thyroid remnants and tumor after administration of diagnostic dose of radioactive iodine (RAI), given subsequently. Stunning may also change the tumor kinetics of RAI by decreasing its efficacy<sup>25</sup>. Although 2-3mCi dose of <sup>131</sup>I have been recommended to avoid stunning, but it is less sensitive than high dose for diagnostic purpose. A few offers a solution to the problem to perform scan with <sup>123</sup>I, as it is a pure gamma emitter, it delivers low radiation dose to the thyroid and does not decrease the uptake of subsequent therapeutic dose of <sup>131</sup>I and gives same diagnostic information. But the major disadvantages are its high cost, shorter half life (13hr) – as whole body imaging require an interval of at least several hours for the thyroid metastasis to take up the iodine. So it seems to be less sensitive and less accurate. Another drawback for <sup>123</sup>I is that patients who have undergone ablation therapy with RAI, accuracy is less<sup>25</sup>. O Mera states no stunning at 5mCi of <sup>131</sup>I diagnostic dose of post treatment scan, when therapy was given shortly after the diagnostic dose. Although some recommended that diagnostic <sup>131</sup>I scan be avoided completely but others argue that diagnostic scan should be performed, because the results determine the optimal dose of <sup>131</sup>I to ablate residual thyroid tissue or cancer.<sup>5</sup> During diagnostic scanning, Dr Waxman feels that 20 min spot images of head, neck, chest, abdomen, pelvis are more desirable than total body scan with a moving camera, Dr Mike McBiles (brook Army Medical Center) feels that WBS with a table speed of 5cm/min bare comparable to spot images but this varies with detector size, given the same imaging distance from the detector<sup>20</sup>.

### Thyroid Remnant Ablation

Effective treatment of local, regional and distant metastatic disease raises the controversial issue regarding the use of adjuvant Radioactive Iodine (RAI). RAI therapy is proposed to serve 3 clinical goals:

- 1) To ablate residual thyroid tissue preventing local recurrence.

- 2) To treat distant metastatic foci.
- 3) To ablate local, regional recurrence that are not amenable to surgical extirpation.

RAI remains the mainstay of the treatment of distant metastatic foci. Distant metastases are seen more frequently in orders (>45%) both at the initial presentation and after prior surgical therapy. Before RAI therapy is given serum TSH level should be more than 30uU/ml. High serum TSH level will stimulate iodine uptake in functioning metastasis. In order to ensure adequate serum TSH elevation, T<sub>4</sub> should be discontinued for at least 4-6 wks and T<sub>3</sub> for 10-14days.<sup>26</sup> Daily dietary iodine intake is maintained below 50ug/day. Lithium suppresses the release of thyroid hormone from the thyroid gland and has been found to prolong the biologic T<sub>1/2</sub> of <sup>131</sup>I in tumors, if given 1 week prior to RAI it may increase the radiation dose delivered to functioning thyroid tissue.<sup>26</sup>

### Radioactive Iodine (Rai) Therapy

#### *Evolution of radio iodine therapy:*

On December 7, 1946, Dr Sam Seidlin and his associates at Network's Monfiore Hospital published an article in JAMA announcing that radioiodine can effectively treat metastatic thyroid cancer.<sup>27</sup> This demonstration of radioiodine's curative power stimulated the Atomic Energy Commission to fund research in the medical application. The growth of Nuclear medicine was initiated by this information.<sup>27</sup>

Iodine is an essential ingredient for the production of thyroid hormone. Certain types of thyroid cancer cell still retain this ability and trap iodine in a lower degree than a normal gland. Both normal and functioning thyroid cells can't distinguish the radioactive iodine from nonradioactive one and metabolize radioiodine in the same way. Thus the base of radioiodine therapy for functioning thyroid cancer cells arise. Radioiodine therapy is use to ablate remnant thyroid tissue following partial or total thyroidectomy (surgical debulking of the gland) and to treat iodine- avid recurrent metastatic sites of thyroid cancer. Two important determinants of success of thyroid ablation are the

mass of the remaining thyroid tissue in the neck and initial dose rates to the tissue. Dose rates below 300rad/hr and or more then 5gm of residual thyroid tissue are associated with a lower success rate for complete ablation.<sup>26</sup>

There are three approaches to RAI therapy:<sup>3</sup>

- a) Fixed <sup>131</sup>I Doses – the most widely used and simplest method is to administer a fixed dose.
  - \* Residual thyroid capsule: 150-200mCi.
  - \* Lymph node mets: 100-175mCi.
  - \* Distant mets: 200mCi.
- b) Quantitative tumor <sup>131</sup>I dosimetry– quantitative dosimetry method to estimate tumor uptake. Some favor this because radiation exposure from arbitrarily fixed doses of <sup>131</sup>I can vary considerably. If the calculated dose is less then 3500cGy, it is unlikely that the cancer will response to <sup>131</sup>I therapy. Doses that will deliver 50,000 to 60,000cGy to the residual thyroid tissue and 4000 to 5000cGy to metastatic foci are likely to be effective.
- c) Blood <sup>131</sup>I dosimetry–This method is to administer a dose calculated to deliver a maximum of 200cGy to the blood, keeping the whole body retention less then 120mCi at 48hrs and the amount in the lungs less then 80 mCi when there is diffuse pulmonary uptake. The maximum administered dose is kept at 300mCi.

Following therapy, patients must be hospitalized until retained radioactivity is less then 30mCi, or the metered exposure rate from the patient is less then 5mR/hr at one meter.<sup>26</sup>

WBS should be performed 3 – 5 days after the diagnostic dose is given to document <sup>131</sup>I uptake by the tumor, because 25% of post therapy scan can detect new lesions not detected by diagnostic scan.<sup>5</sup>

### Post Therapy Hormonal Treatment

Thyroid hormone (T<sub>4</sub>) replacement therapy is significantly reduces the recurrence rates and cancer specific mortality. The dosage needed to attain serum TSH levels in the euthyroid range is higher in patients with thyroid carcinoma

(2.1 Iug/kg/day) then in those who develop primary hypothyroidism spontaneously (1.62 ug/kg/day). A French study found that a constantly suppressed TSH (< 0.05u/mL) was associated with a longer relapse-free survival then when serum TSH levels were always 1uU/mL or higher.

### Follow-Up Post Ablation Screening

The overall recurrence of thyroid cancer is about 20%.<sup>26</sup> The risk of recurrence is related to age at diagnosis, extent of primary disease, size of primary lesion, and the presence of mets. Surveillance for recurrence for recurrence is a life long process. Following surgery and <sup>131</sup>I ablation therapy, patients should be monitored for recurrence using serum thyroglobulin level and <sup>131</sup>I WBS. Serum thyroglobulin (Tg) determination and WBS provide early detection of persistent and recurrent differentiated thyroid carcinoma of follicular cell origin after total thyroidectomy. Sensitivity is 91% and specificity is 99% for identifying patient with persistent or recurrent differentiated thyroid carcinoma.<sup>28</sup> Few study suggest that serum Tg level is reliable only in the absence of Tg antibodies. Sensitivity increases with TSH stimulation either by withdrawal of thyroxine (T<sub>4</sub>) hormone or administration of recombinant human TSH (rTSH). In some patients Tg levels are positive but <sup>131</sup>I WBS may be negative. This may be due to that the recurrent tumor is too small and below the sensitivity of the diagnostic scan. However, extensive literature has established the roles of both serum Tg level and <sup>131</sup>I WBS in the detection and subsequent treatment of metastatic DTC in high risk group.<sup>4</sup> Temporary discontinuation of the thyroid hormone therapy was previously the sole effective approach for TSH stimulated testing. Again hormone withdrawal is associated with morbidity of hypothyroidism and occasional tumor progression. The induction of recombinant human TSH (rTSH) stimulated testing offers an alternative therapy. Recent clinical trials have shown that the sensitivity of combined rTSH stimulated radioiodine scanning serum Tg measurement has equivalent sensitive to testing after thyroid hormone withdrawal. Furthermore the measurement of rTSH stimulated serum Tg measurement is a

more sensitive way to detect residual thyroid cancer or normal tissue then Tg measurement on thyroid hormone therapy.<sup>29</sup>

Medullary thyroid carcinoma (MTC) is derived from thyroid C cells with serum calcitonin is a specific and a sensitive marker. Tg measurement in conjunction with <sup>131</sup>I WBS results also provide prognostic information. Patients with elevated Tg levels and a positive scan had a lowest overall mortality (44%), while those with mets and negative Tg level and negative scan had a mortality of 71%. Patient with elevated Tg but negative scan had a mortality of 58%.<sup>26</sup> Current evidence suggest that post ablation patient that are Tg positive and WBS negative should be treated with 100mCi of <sup>131</sup>I.<sup>26</sup>

### Conclusion

Papillary thyroid cancer is the most common endocrine malignancy. Of all solid cancers presenting in adults, papillary thyroid cancers generally carries best long-term prognosis. However, very little is understood about the molecular pathogenesis of this neoplasm. Any patient presenting with thyroid nodule-initial work up will be FNAC. Surgical treatment depends on FNA finding, age and clinical presentation. After surgical debulking WB diagnostic scan should be performed which will follow the need for RAI ablation therapy. Life long assessment after ablation therapy is needed using Tg estimation, whole body scan and most recent introduction of rTSH by FDA, USA.

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