Papillary thyroid carcinoma

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Abstract

Papillary thyroid carcinoma (PTC) belongs to well-differentiated thyroid cancers. It is the most common of all thyroid cancers and is among the most curable cancers. The annual incidence rate of PTC in different parts of the world varies from 0.5-10 per 100.000 populations. Clinically, PTC presents as asymptomatic thyroid nodules, it is usually single, firm, freely moveable during swallowing, and it is not distinguishable from a benign nodule. A thyroid nodule should be suspected of being a carcinoma when it is found in children or adolescents or in patients above 60 years, and when there is a history of progressive increase in size. Hoarseness, dysphagia, cough and dyspnea are suggestive of advanced stages of the disease. Histologically, PTC is an unencapsulated tumor with papillary and follicular structures. It is characterized by changes in cell nuclei: nuclear overlapping, large sized nuclei, a ground glass appearance, longitudinal nuclear grooves, and invaginations of cytoplasm into the nuclei. The tumor spreads through the lymphatic vessels within the thyroid, to the regional lymph nodes, and less frequently to the lungs. Some oncogenes are clearly involved in either patients with no history of radiation and thus irradiated (Chernobyl accident or external irradiation). The most common rearrangements concern RET gene, RAS mutations and B-RAF mutation. Treatment includes surgery, ^{131}I therapy, radiotherapy and thyroxin intake. Follow up after initial therapy is required.

Keywords

Thyroid cancers, ^{131}I therapy, radiotherapy, thyroxin, pTNM staging system

Definition

Papillary thyroid carcinoma (PTC) belongs to well-differentiated thyroid cancers, which include also follicular and Hurthle cell carcinoma. These sorts of tumors are the most common of all thyroid cancers (>70%) and are among the most curable cancers. However, some patients are at high risk of recurrence or even death. These patients can be identified at the time of diagnosis using well-established prognostic indicators. The extent of initial treatment and follow-up should therefore be individualized.

Etiology

Oncogenes

Recent advances in molecular biology have improved the understanding of the pathogenesis of thyroid carcinomas.

In papillary carcinomas occurring in patients with no history of radiation, rearrangements of the tyrosine kinase domains of the *RET* gene with the amino-terminal sequence of an unrelated gene are found in 2.5 to 33%, RAS mutations in 10%, and *B-RAF* mutation in 40-60% of cases. Thus, abnormalities in the *RET/ RAS/ B-RAF/MAP* kinase pathway are found in 80% of cases with no important overlap. In papillary carcinomas occurring after irradiation in children, either in Belarus after the Chernobyl accident or after external radiation, *RET* rearrangements are found in 60 to 85% of cases and *B-RAF* mutations are less frequent.

Thyroid irradiation

External irradiation to the neck during childhood increases the risk of papillary carcinoma. The latency period between exposure and diagnosis of thyroid carcinoma is at least 5 years. The risk is maximal at about 20 years, remains high for about 20 years and then decreases gradually. The risk is increased after a mean dose to the thyroid as low as 10 cGy. Above this dose there is a linear relationship between the dose (up to 1500 cGy) and the risk of carcinoma. Beyond this point, the risk per Gray decreases, probably due to cell killing. A major risk factor is a young age at irradiation; above age 15 or 20 years the risk is not increased. In children exposed to 1 Gy to the thyroid, the excess risk of thyroid carcinoma concerns 7.7% of the children. The risk of thyroid carcinoma is not increased in adult patients given ^{131}I for diagnosis or therapy. Conversely, a direct tumorigenic effect on the thyroid of radioactive isotopes of iodine, both ^{131}I and short-lived isotopes, has been strongly suggested by the increased incidence of papillary carcinomas in children in the Marshall Islands after atomic bomb testing, and more recently in Belarus and Ukraine after the Chernobyl accident. In Belarus and Ukraine, to date, about 1500 cases have been reported in subjects who were younger than 10 at the time of the accident.

Other Factors

In countries where iodine intake is adequate, papillary cancers represent more than 80% of all thyroid carcinomas. There is no increase in incidence of thyroid carcinomas in countries where iodine intake is low, but there is a relative increase in follicular and anaplastic carcinomas

A high incidence of papillary carcinomas has been reported in patients with adenomatous polyposis and Cowden's disease (multiple hamartoma syndrome). About 5% of cases of papillary carcinoma are familial, and several loci for predisposing genes have been identified.

Clinical description and diagnosis

Most differentiated thyroid carcinomas present as asymptomatic thyroid nodules, but occasionally the first signs of the disease are lymph node metastases and rarely lung metastases. Hoarseness, dysphagia, cough and dyspnea are suggestive of advanced stages of the disease.

At physical examination, the carcinoma, usually single, is firm, freely moveable during swallowing, and not distinguishable from a benign nodule. A thyroid nodule should be suspected of being a carcinoma when it is found in children or adolescents or in patients above 60 years, in man, when it is hard and irregular, when ipsilateral lymph nodes are enlarged or compressive symptoms are present, and when there is a history of progressive increase in size. Virtually all patients are clinically euthyroid and have normal serum thyrotropin concentrations.

Whatever the presentation, fine needle aspiration cytology is the best test for the diagnosis of papillary thyroid carcinoma, provided that an adequate specimen is obtained.

Thyroid ultrasonography is useful for assessing the size of the nodule and detecting other nodules, and to guide the fine needle biopsy of small or poorly palpable nodules.

Pathology

Papillary carcinoma is an unencapsulated tumor with papillary and follicular structures that is characterized by changes in cell nuclei: nuclear overlapping, large sized nuclei, a ground glass appearance, longitudinal nuclear grooves, and

invaginations of cytoplasm into the nuclei. Recognized histological variants are the encapsulated, the follicular, the tall cell, the columnar cell, the clear cell and the diffuse sclerosing variants. Their typical nuclear features characterize Papillary carcinomas. The tumor is multicentric in 20 to 80% of cases; it is bilateral in about one third of cases. It spreads through the lymphatic vessels within the thyroid, to the regional lymph nodes, and less frequently to the lungs.

Prognostic factors

The overall 10-year survival rates for middle-aged adults with thyroid carcinomas are about 80 to 95%. Five to 15% of patients have local or regional recurrences and 5 to 10% have distant metastases. Prognostic indicators of recurrence and of death are age at diagnosis, histologic type, and extent of the tumor.

There are many scoring systems for thyroid carcinoma, among which the Pathological tumor-node-metastasis (pTNM) staging system is the most widely accepted (Table 1). Based on this system, 80 to 85 % of patients are classified as being at low risk of cancer-specific mortality (stages I and II). Some patients have a higher risk of recurrences, even if their risk of cancer-specific mortality is low. They include young (< 16 years) and older (> 45 years) patients, those with certain histological subtypes (the tall-cell, the columnar-cell and diffuse-sclerosing variants), and those with large tumors, extension of the tumor beyond the thyroid capsule, or large and/or multiple lymph node metastases. Therefore, the extent of initial treatment and follow-up should be adapted according to these prognostic indicators.

Epidemiology

Although thyroid nodules are extremely common, differentiated thyroid carcinomas are relatively rare. Clinically detectable thyroid carcinomas constitute less than 1% of all human malignant tumors, and the annual incidence rate in different parts of the world varies from 0.5-10 per 100.000 populations. These carcinomas are rare in children and adolescents, and their incidence increases in adults with age, the median age at diagnosis being 45 to 50 years. Thyroid carcinomas are 2 to 4 times more frequent in women than in men.

Thyroid microcarcinomas, with a diameter $\leq$ 1 cm, are found in 5-36% of adults in autopsy studies, but are rare in children.

In recent years, an apparent increase has been reported in the incidence of thyroid carcinomas that is mainly related to an increased incidence of small carcinomas in adults, and this increase was attributed to an improvement in diagnostic techniques.

Initial treatment

Surgery

The goal of surgery is to remove all neoplastic tissue in the neck. Therefore, the thyroid gland and affected cervical lymph nodes should be resected.

Although some controversies still exist regarding the extent of thyroid surgery, there are strong arguments in favor of a total thyroidectomy for all patients. Total thyroidectomy reduces the recurrence rate as compared with more limited surgery because many papillary carcinomas are multifocal and bilateral. Removal of most if not all of the thyroid gland facilitates total ablation with ^{131}I. The argument against total thyroidectomy is that it increases the risk of surgical complications such as recurrent laryngeal nerve injuries and hypoparathyroidism, and yet often some thyroid tissue remains, as detected by post-operative scanning with ^{131}I. This is the reason why only skilled surgeons should operate papillary thyroid carcinomas.

In low-risk patients (those with papillary carcinomas less than 1 cm in diameter, if unifocal and intralobar), a lobectomy may be appropriate.

Surgery of lymph nodes is routinely performed. It includes dissection of the central compartment (paratracheal and tracheoesophageal areas, level VI) and may also include dissection of the supraclavicular area and the lower third of the jugulocarotid chain. A modified neck dissection is performed if there are palpable lymph node metastases in the jugulo-carotid chain. Dissection is preferable to lymph node picking. This type of lymph node dissection was proven to improve the recurrence and survival rates in several series, and several arguments support its routine use: about two thirds have lymph node metastases, more than 80% of whom have involvement of the central compartment; metastases are difficult to detect in lymph nodes located behind the vessels or in the paratracheal groove.

^{131}I therapy

^{131}*I* therapy is given post-operatively for three reasons: it destroys normal thyroid remnants, thereby increasing the sensitivity of subsequent ^{131}*I* -total body scan and the specificity of measurements of serum thyroglobulin for the

detection of persistent or recurrent disease; it may destroy occult microscopic carcinoma, thereby decreasing the long-term recurrence rate, and it permits a post-ablative ^{131}I -total body scan, a sensitive tool for persistent carcinoma.

Table 2:.Indications for ^{131}I Ablative Treatment in Patients with Thyroid Carcinoma After Initial Surgery

No indication low risk of cancer-specific mortality and lowrelapse pTNM stage I
Indication : Definite - distant metastases - incomplete tumor resection - complete tumor resection but high - risk for mortality/recurrence: - pTNM stages II-III. Probable: - age : < 16 years - histologic subtype : papillary tall-cell, columnar-cell, diffuse sclerosing; - elevated serum Tg concentrations > 3 months after surgery on L-T4.

Postoperative ^{131}I therapy should be used selectively (Table 2). In low-risk patients, the long-term prognosis after surgery alone is so favorable that ^{131}I ablation is not usually recommended. However, patients who are at high risk of recurrence are routinely treated with ^{131}I, because it decreases both recurrence and death rates.

Postoperatively, ^{131}I therapy is administered 4 to 6 weeks after surgery, during which no thyroid hormone treatment is given. A diagnostic total body scan with 2 mCi (74 MBq) ^{131}I is performed only when thyroidectomy has been partial. Another total body scan is done 4 to 7 days later, and thyroxin therapy is initiated.

Total ablation (no visible uptake on a ^{131}I total body scan performed 6 to 12 months later with 2 mCi (74 MBq) is achieved after administration of both 100 mCi (3700 MBq) and 30 mCi (1000 MBq) in almost all patients who had a total thyroidectomy. After less extensive surgery, ablation is achieved in only two-thirds of patients with 30 mCi (1000 MBq). Therefore, total thyroidectomy should be performed in all patients who have to be treated with ^{131}I. Total ablation requires a dose of at least 300 Gy is delivered to thyroid remnants, and a dosimetric study allows estimating more precisely the dose of ^{131}I that should be administrated.

External Radiotherapy

External radiotherapy to the neck and mediastinum is indicated only in patients older than 45 years in whom surgical excision is incomplete or impossible, and in whom the tumor tissue does not take up ^{131}I.

Follow up

The goals of follow-up after initial therapy are to maintain adequate thyroxin therapy and to detect persistent or recurrent thyroid carcinoma. Most recurrences occur during the first years of follow-up, but some occur later. Therefore, follow-up is necessary throughout the patient's life.

Thyroxin treatment

The growth of thyroid tumor cells is controlled by thyrotropin (TSH), and inhibition of thyrotropin secretion with thyroxin improves the recurrence and survival rates. Therefore, thyroxin is given to all patients with thyroid carcinoma, whatever the extent of thyroid surgery and other treatment. The initial dose is about 2.0 µg/kg body weight in adults; children require higher dose. The adequacy of therapy is monitored by measuring serum TSH three months after the treatment is begun, the initial goal being a serum TSH concentration of ≤ 0.1 µU/ml and a serum free triiodothyronine concentration within the normal range to avoid overdosing.

Early Detection of Recurrent Disease

Clinical and Ultrasonographic Examinations. Palpation of the thyroid bed and lymph node areas should be routinely performed but is poorly sensitive. Ultrasonography is performed in all patients. Lymph nodes that are small, thin or oval, in the posterior neck chains, and when they decrease in size after an interval of three months are considered benign. Serum thyroglobulin is undetectable in 20% of patients receiving thyroxin treatment who have isolated lymph node metastases. These false negative can be found with neck ultrasonography, with an ultrasound-guided node biopsy performed in suspicious cases for cytology and thyroglobulin measurement in the fluid aspirate.

X-Rays. Chest X-rays are no longer routinely performed in patients with undetectable serum thyroglobulin concentration. The reason is that virtually all patients with abnormal X-rays have detectable serum thyroglobulin concentrations.

Serum Thyroglobulin (Tg) Determinations. Thyroglobulin is a glycoprotein that is produced only by normal or neoplastic thyroid follicular cells. It should not be detectable in patients who have had total thyroid ablation, and its detection in them means the presence of persistent or recurrent disease.

The sensitivity of good Tg assays is 1 ng/ml or even less. The results can be artefactiously altered by serum anti-Tg antibodies, which are found in about 15% of patients with thyroid carcinoma, and these antibodies should always be sought by a radioimmunoassay or by a recovery test. In IRMA methods, interferences induce falsely reduced or falsely negative serum Tg measurements.

The production of Tg by both normal and neoplastic thyroid tissue is in part TSH-dependent. Thus, when interpreting the serum Tg value, the serum TSH value should be taken into account, as well as the presence or absence of thyroid remnants. When serum Tg is detectable during thyroxin treatment, it will increase after the treatment is discontinued.

^{131}I -*Total Body Scan.* The results of ^{131}I total body scan depend on the ability of neoplastic thyroid tissue to take up ^{131}I in the presence of high serum TSH concentrations, which are achieved by withdrawing thyroxin for 4 weeks. However, some patients poorly tolerate the resulting hypothyroidism. This can be attenuated by substituting the more rapidly metabolized triiodothyronine for thyroxin for three weeks and withdrawing it for two weeks. The serum TSH concentration should be above some arbitrary value (30 µU/ml) in patients managed in this way; if it is not, ^{131}I administration should be delayed until it is. Intra-muscular injection of recombinant human thyrotropin (rhTSH) is an alternative (0.9mg intramuscular for 2 consecutive days with ^{131}I administration on the day following the second injection and TBS and serum Tg determination 2 days later), because thyroxin treatment should be continued and side effects are minimal. Its efficiency for the detection of persistent and recurrent disease is comparable to that of thyroxin withdrawal in most patients.

When ^{131}I scanning is planned, patients should be instructed to avoid iodine-containing medications and iodine-rich foods, and urinary iodine should be measured in doubtful cases. Pregnancy must be excluded in women of childbearing age. For routine diagnostic scans, 4mCi (148 MBq) ^{131}I is given; higher doses may reduce the uptake of a subsequent therapeutic dose of ^{131}I. The scan is done and uptake, if any, is measured 72 h after the dose using a double-head gamma camera equipped with high-energy collimators. False-positive results are rare.

Post- ^{131}I *Therapy Total Body Scan.* Assuming equivalent fractional uptake after administration of a diagnostic and a therapeutic dose of ^{131}I, uptake too low to be detected with 2 to 5 mCi (74-185 MBq) may be detectable after the administration of 100 mCi (3700 MBq). Thus, a total body scan should be routinely performed 3 to 5 days after a high dose.

Follow-up strategy

If the total body scan performed after the administration of ^{131}I to destroy the thyroid remnant, no iodine uptake outside the thyroid bed is seen. Physical examination is performed and serum TSH, FT3 and Tg are measured during thyroxin treatment three months later. At 6 to 12 months later, the present protocol includes a determination of serum Tg following rhTSH stimulation and a neck ultrasonography (Fig. 1). Recent reports demonstrated that ^{131}I -TBS does not provide any useful information in these patients. If serum thyroglobulin following TSH stimulation is undetectable and neck ultrasonography is normal, the risk of recurrence is less than 0.5% at 10 years. Low-risk patients are considered cured, and the dose of thyroxin is decreased to maintain a low but detectable serum TSH concentration (around 0.5 µU/ml). In higher-risk patients, higher doses of thyroxin are given, the goal being a serum TSH concentration of $\leq$ 0.1 µU/ml. Clinical, ultrasonographic and biochemical evaluation is performed annually; any other testing is unnecessary as long as the patient's serum Tg concentration is undetectable.

If serum Tg is detectable following TSH stimulation, the attitude depends on the level of Tg: in those patients with a relatively low Tg level (<10ng/ml), another determination is obtained following rTSH stimulation 6 to 36 months later, because with longer follow up serum Tg became undetectable in 2/3 of these patients. In those with high serum Tg levels and in particular in those with increasing serum Tg at consecutive determinations, 100 mCi (3700 MBq) ^{131}I is administered with a TBS 3-5 days later. If no uptake is detected, a FDG PET scan may be performed.

In patients receiving thyroxin in whom serum Tg becomes detectable, serum Tg should be measured after TSH stimulation. If the serum Tg concentration increases above 10 ng/ml, 100 mCi ^{131}I should be given.

In low-risk patients who have had a total thyroidectomy but who were not given ^{131}I post-

operatively, the follow-up protocol is based on Tg determinations and neck ultrasonography. In low-risk patients who underwent a lobectomy, yearly follow-up consists of a neck examination and of serum Tg determination during thyroxin treatment. Ultrasonography will show abnormalities in the remaining lobe in most patients with detectable Tg concentrations. If the size is small, fine needle biopsy may be impossible, and surgery is frequently the only option.

Local or regional recurrences

Local or regional recurrences occur in 5 to 15% of patients with PTC. Some are related to incomplete initial treatment (in a thyroid remnant or in lymph nodes), and the others indicate tumor aggressiveness (in the thyroid bed after total thyroidectomy or in soft tissues).

A local or regional recurrence that is palpable or easily visualized with ultrasonography or CT scan should be excised. Total excision may be facilitated by total body scanning 4 days after administration of 100 mCi (3 700 MBq) ^{131}I, because additional tissue that should be excised may be identified. Surgery is performed one day later, preferably using an intra-operative probe. The completeness of resection is verified 1 to 2 days after surgery by another total body scan.

External radiotherapy is indicated in patients with soft tissue recurrences that cannot be completely excised and that do not take up ^{131}I.

Distant metastases

Distant metastases, mostly in the lungs and bones, occur in 5 to 10% of patients with PTC. Lung metastases are more frequent, and are almost the only site of distant spread in children. Bone metastases are more common in older patients. Other less common sites are the brain, liver and skin.

Diagnosis

Clinical symptoms of lung involvement are uncommon. The pattern of lung involvement may vary from macronodular to diffuse infiltrates. The latter, when not detected by chest X-ray, are usually diagnosed with ^{131}I total body scan and may be confirmed by CT ; enlarged mediastinal lymph nodes are often present in children. Nearly all patients with distant metastases have high serum Tg concentration, unless the metastases are not visible on X-rays, and two thirds of patients have ^{131}I uptake in the metastases.

Treatment

Patients with metastases that take up ^{131}I should be treated with 100 to 150 mCi (3700 to 5550 MBq) every 4 to 6 months. The effective radiation dose, that depends on the ratio between total uptake and the mass of thyroid tissue, is correlated to the outcome of ^{131}I therapy. Lower doses (1 mCi(37 MBq)/kg body weight) are given to children. There is no limit to the cumulative dose of ^{131}I given to patients with distant metastases, although above a cumulative dose of 500 mCi (18 500 MBq), further ^{131}I therapy has little benefit but significantly high risk of leukemia. External radiotherapy is given to bone metastases visible on X-rays. Chemotherapy is poorly effective and should be reserved to patients with progressive and non functioning metastases ; new drugs directed against specific targets are under study.

Treatment Results

Complete responses have been obtained in 45% of patients with distant metastases with ^{131}I uptake. Overall survival after the discovery of distant metastases is about 40% at 10 years. Young patients with well-differentiated tumors that take up ^{131}I and have metastases that are small when discovered have a more favorable outcome.

Complications of treatment with ^{131}I

Acute Side Effects

Acute side effects (nausea, sialadenitis) after treatment with ^{131}I are common but usually mild and resolve rapidly. Radiation thyroiditis is usually trivial, but if the thyroid remnant is large, the patient may have enough pain to warrant corticosteroid therapy for a few days. Tumor in certain locations -brain, spinal cord and paratracheal- may swell in response to TSH stimulation or after ^{131}I therapy, causing compressive symptoms that should be prevented by corticosteroid administration. Radiation fibrosis may develop in patients with diffuse lung metastases, if high doses (> 150 mCi (5 550 MBq)) are administered at short intervals (< 3 months).

^{131}I Genetic Defects and Infertility

Particular attention must be paid to avoid administration of ^{131}I in pregnant women.

After ^{131}I treatment, spermatogenesis may be transiently depressed, and women may have transient ovarian failure. Genetic damage induced by exposure to ^{131}I before conception has been a major subject of concern. However, the only

anomaly reported to date is an increased frequency of miscarriages in women treated with ^{131}I during the year preceding the conception. Therefore, it is recommended that conception be postponed for one year after treatment with ^{131}I. There is no evidence that pregnancy affects tumor growth in women receiving adequate thyroxin therapy. Thyroxin treatment should be monitored carefully (at least every 2 months with TSH measurement) during pregnancy.

Carcinogenesis and Leukemogenesis

Mild pancytopenia may occur after repeated ^{131}I therapy, especially in patients with bone metastases who are also treated with external radiotherapy. The overall relative risk of secondary carcinoma and of leukemia was found to be increased in patients treated with a high cumulative dose of ^{131}I (> 500 mCi (18,500 MBq)) or in association with external radiotherapy. Because, the dose-effect relationship is linear, any therapeutic dose of ^{131}I may increase the risk of leukemia and of solid tumors.

Conclusion

Most patients with papillary carcinomas can be cured. However, both initial treatment and follow-up should be individualized according to prognostic indicators and thereafter to any evidence of disease in order to improve their quality of life.

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Table 1. TNM Staging System for Papillary and Follicular Carcinoma of the Thyroid

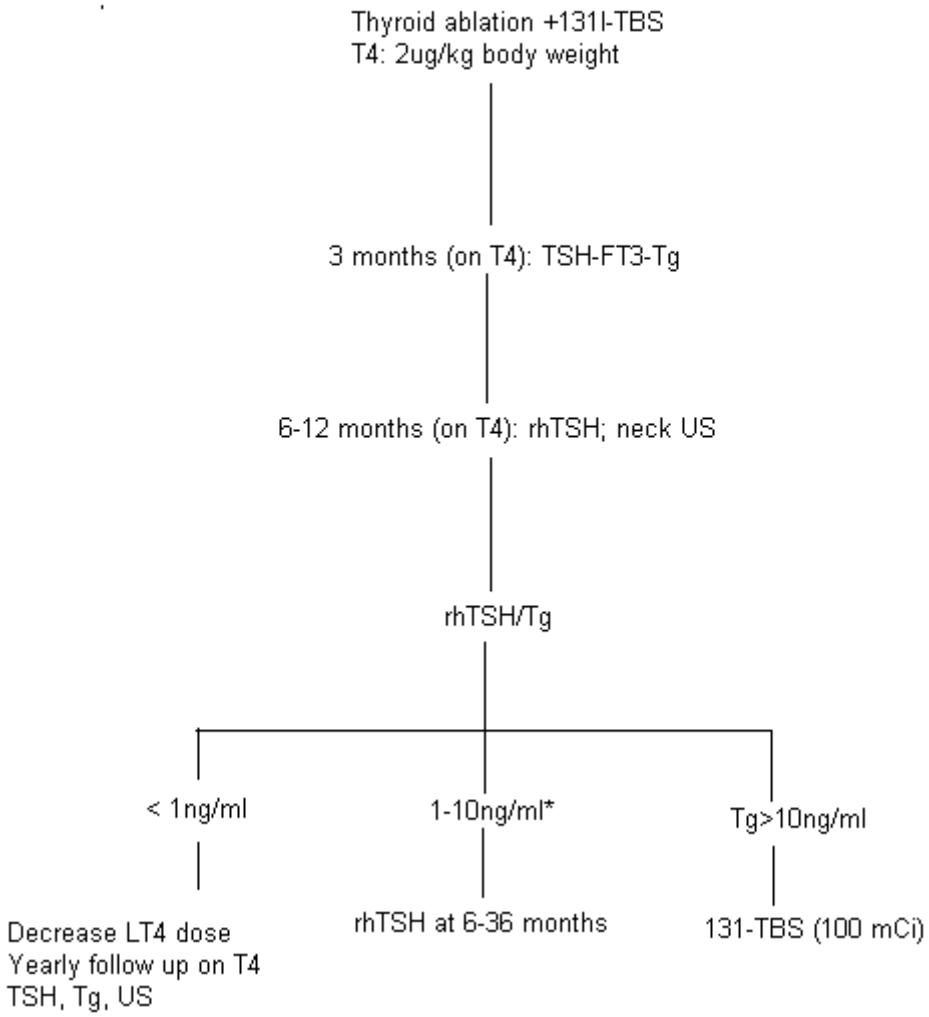
Development of the definition of TNM

1992	2002
Primary tumor (T) **T0**: No evidence of primary tumor **T1**: Tumor ≤1cm limited to the thyroid **T2**: Tumor>1-≤4cm limited to the thyroid **T3**: Tumor>4cm limited to the thyroid **T4**: Any size extending beyond the thyroid capsule T4a T4b	 No evidence of primary tumor Tumor ≤2cm limited to the thyroid Tumor>2-≤4cm limited to the thyroid Tumor>4cm limited to the thyroid or any tumor with minimal extrathyroid extension (e.g.; extension to stern thyroid muscle or perithyroid soft tissues Tumor of any size with extension beyond the thyroid capsule and invades any of the following: subcutaneous soft tissues, larynx, trachea, oesophagus, recurrent laryngeal nerve Tumor invades prevertebral fascia, mediastinal vessel encases carotid artery.
Regional Lymph Node (N): (In the 2002 system, to be classified as N0 or N1, at least 6 lymph nodes should be examined at histology. Otherwise, the tumor is classified aNx). **N0**: No regional lymph node metastasis **N1**: Regional Lymph Node metastasis **N1a** **N1b**	 No regional lymph node metastasis Regional lymph node metastasis Metastases in pretracheal and paratracheal, including prelaryngeal and delphian lymph nodes Metastases in other unilateral, bilateral or contralateral cervical or upper mediastinal lymph nodes.
Distant metastases (M) **M0**: No distant metastasis **M1**: Distant Metastasis	 No distant metastasis Distant Metastasis

TNM staging

1992	2002
Age <45 **Stage I:** Any T, any N, M0 **Stage II:** Any T, any N, M1 Stage III: none Stage IV: none	 Any T, any N, M0 Any T, any N, M1 None none
Age≥45 years **Stage I:** T1, N0, M0 **Stage II**: T2-T3, N0, M0 **Stage III:** T4,N0,M0 or any T,N1,M0 **Stage IV**: Any T, any N, M1 **Stage IVA** **Stage IVB** **Stage IVC**	 T2, N0, M0 T3, N0, M0 or any T1-3, N1a, M0 T1-3, N1b, M0 or T4a, Any N, M0 T4b, Any N, M0 Any T, Any N, M1

Figure 1: Follow-up of Patients after Total Thyroid Ablation, Based on Serum Thyroglobulin Determinations and neck ultrasonography. The decision level depends upon the assay used to measure serum Tg.



TG: serum throglobulin; TSH: thyrotropin; rh TSH: recombinant human thyrotropin, US: ultrasonography, FT3 : Free Triiodothyronine, TBS: total body scan, LTA: levothyroxine