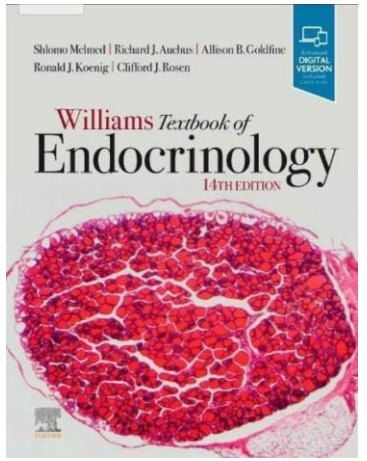
JNCCN

OFFICIAL JOURNAL OF THE NATIONAL COMPREHENSIVE CANCER NETWORK

NCCN National Comprehensive Cancer Network®

UpToDate



Differentiated Thyroid Cancer, From Active Surveillance to Advanced Therapy

frontiers in Endocrinology

Italian consensus on diagnosis and treatment of differentiated thyroid cancer (2018)

AMERICAN THYROID ASSOCIATION

ATA | Founded 1923

INTRODUCTION

The recent advances in knowledge about differentiated thyroid cancer (DTC) showed the need of a personalized management approach.

Despite the increased diagnosis of DTC, in particular small papillary thyroid cancers, cancer-related death remained stable over time.

The clinical challenge is moving toward the identification of patients with indolent tumors, who can be treated and followed with a more conservative approach, as opposed to those in which aggressive therapy and intensive follow-up should be recommended

ACTIVE SURVEILLANCE

Active surveillance has been proposed as an alternative to immediate surgery to avoid overtreatment in unifocal intrathyroidal papillary microcarcinoma (mPTC), without metastatic lymph nodes or aggressive cytological features.

Many retrospective papers showed the excellent outcome of mPTC over time likely related to the indolent behavior of mPTC, rather than the efficacy of treatments.

ACTIVE SURVEILLANCE

To date, in the Japanese series, active surveillance has the same outcome of immediate surgery. After 10-year observation, only 8 and 3.8% of 1, 235 mPTC under active surveillance showed nodule enlargement or appearance of lymph node metastases, respectively.

None of the patients who underwent surgery after disease progression showed higher rates of recurrence or mortality compared to patients who performed immediate surgery.

ACTIVE SURVEILLANCE

Neither clinical nor pathological features, like sex, familial history of thyroid cancer, and multifocality, were related to mPTC progression.

Conversely, the estimated lifetime probability of mPTC progression was related to the age at diagnosis, being 60.3% for younger (25 years) and 3.5% for older patients (75 years).

Therefore, older mPTC patients represent the best candidates for active surveillance.

However, 40% of younger patients could be safely followed up without requiring surgical treatments during lifetimes, corroborating the feasibility of active surveillance.

ACTIVE SURVEILLANCE

Active surveillance is a likely safe and feasible strategy also in pregnancy:

- only 8% of pregnant women showed mPTC progression, and the following postpartum thyroidectomy was completely curative.

ACTIVE SURVEILLANCE

It was observed that mPTC changes in volume during time, rather than in maximum diameter, represent a more sensitive tool to select those patients who could benefit from a more careful monitoring or surgical treatment.

ACTIVE SURVEILLANCE

A risk stratification of mPTC patients according to a clinical framework has been proposed:

clinical features (nodules with well-defined margins without evidence of extrathyroidal extension and cN0, cM0) and sociocultural and psychological evaluation (willing to accept this approach, aware of possible surgical treatment in the future, compliant to follow-up) are critical to identify the ideal candidate for active surveillance.

ACTIVE SURVEILLANCE

Several issues remain open, such as:

- The **ideal frequency of follow-up evaluations**, currently recommended every 6 months for the first 2 years and yearly afterwards,
- The **optimal timing for surgery** in progressive cases,
- The **availability of more precise radiologic tools** to improve the detection of minimal extrathyroidal extension,
- The identification of **molecular biomarkers**.

ACTIVE SURVEILLANCE

To date, the role of genetic mutations (e.g., BRAF, RAS, TERT, etc.) and/or rearrangements (such as RET/PTC) are not completely understood in mPTC during active surveillance. These biomarkers could be able to distinguish the more aggressive forms of mPTC.

Patient Classification	Tumor/Imaging Characteristics	Patient Characteristics	Medical Team Characteristics
Ideal	Solitary thyroid nodule confined to thyroid ≤1 cm Well-defined tumor margins by ultrasound Surrounded by ≥2 mm normal thyroid parenchyma Previous US documenting stability cN0 cM0	Medical minimalist Older patients (>60 yr) Willing to accept active surveillance Understands that future surgery may be necessary (deferred intervention) Understands that lymph node metastases may be identified during follow-up Compliant with follow-up plans Supportive significant others (including family and other members of the health care team) Life-threatening comorbidities or medical conditions requiring therapy	Experienced team Expeditious evaluation by multidisciplinary team High-quality neck US Prospective data collection Tracking/reminder program to ensure proper follow-up

Classification System to Aid in Proper Patient Selection for Active Surveillance (Willams)

Patient Classification	Tumor/Imaging Characteristics	Patient Characteristics	Medical Team Characteristics
Appropriate	Multifocal papillary microcarcinoma 1–1.5 cm maximal dimension Subcapsular location not adjacent to RLN without evidence of extrathyroidal extension Ill-defined tumor margins Background US findings that will make follow-up difficult (thyroiditis, reactive lymph nodes, multiple other benign-appearing nodules) FDG-avid papillary microcarcinomas Isolated BRAF V600E mutation	Minimalist/maximalist Patients aged 18–59 yr Strong family history of PTC Childbearing potential	Experienced endocrinologists or thyroid surgeon Neck US routinely available
Inappropriate	Aggressive cytologic features (rare) Location adjacent to RLN/trachea Evidence of extrathyroidal extension N1 or M1 disease High-risk molecular profile Demonstrated increase of 3 mm diameter or 50% increase in tumor volume over a relatively short period	Medical maximalist Young patients (<18 yr) Unlikely to be compliant with follow-up plans Not willing to accept an observation approach Severe anxiety regarding diagnosis	Reliable neck US not available Little experience with thyroid cancer management

Classification System to Aid in Proper Patient Selection for Active Surveillance (Williams)

Surgery

Accurate preoperative staging is essential to evaluate the primary tumor and the presence of lymph node metastasis to guide the extent of surgical treatment.

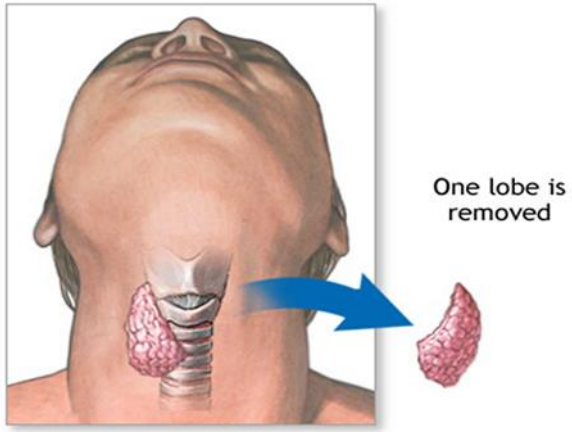
Clinical and ultrasonographic evaluation of the neck (nUS) is the cornerstone of the initial assessment.

Cross-sectional imaging (i.e., CT scan with IV contrast) might be useful in selected, locally advanced cases.

Surgery

Many changes in the extent of surgery for DTC have been recently advocated.

In the past, total thyroidectomy (TTx) was recommended for all DTC >1 cm, regardless of other pathological features, based on several studies that showed lower recurrence rates in patients treated by TTx compared to lobectomy.



Surgery

Currently, **lobectomy** is recommended for low-risk and well-differentiated unifocal thyroid cancer ⩽4 cm.

In this setting, the use of **nUS** before surgery is essential: any suspicion of extrathyroidal extension, multifocal disease, or lymph node metastasis should lead to **TTx**.

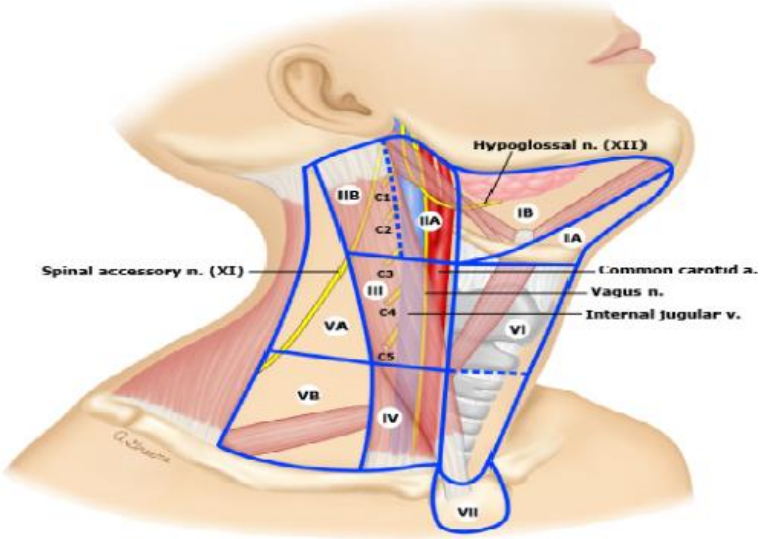
Surgery

Lobectomy can avoid postoperative hypoparathyroidism and the need of thyroid hormone replacement.

Conversely, in patients who perform **TTx**, there is no need for completion thyroidectomy, thyroglobulin (Tg) can be used as marker of recurrence, and 131I treatment can be performed, if needed.

For all DTC >4 cm, or <4 cm with aggressive features, **TTx** is usually recommended.

Surgery



In the presence of clinically evident lymph node metastasis of the central or latero-cervical compartment, an oriented therapeutic lymph node dissection is recommended because it is associated with lower recurrence and disease-specific mortality rates.

Prophylactic lymph node dissection of central compartment is still debated and, to date, not routinely recommended.

uptodate

- **Tumor <1 cm without extrathyroidal extension and no lymph nodes**

When surgery is planned for unilateral intrathyroidal differentiated thyroid cancer <1 cm, a thyroid **lobectomy** is preferred

unless there are clear indications to remove the contralateral lobe (eg, clinically evident thyroid cancer in the contralateral lobe, previous history of head and neck radiation, strong family history of thyroid cancer, or imaging abnormalities that will make follow-up difficult).

uptodate

- **Tumor 1 to 4 cm without extrathyroidal extension and no lymph nodes**

For intrathyroidal tumors between 1 and 4 cm, the initial surgical procedure can either be a **total thyroidectomy** or thyroid **lobectomy**.

Total thyroidectomy would be chosen either based on patient preference, the presence of ultrasonographic abnormalities in the contralateral lobe (nodules, thyroiditis in the contralateral lobe, or nonspecific lymphadenopathy that will make follow-up difficult), or on a decision by the treatment team that radioiodine therapy may be beneficial either as adjuvant therapy or to facilitate follow-up.

uptodate

- **Tumor ≥4 cm, extrathyroidal extension, or metastases**

Total thyroidectomy is recommended if the primary tumor is 4 cm in diameter or greater, there is extrathyroidal extension of tumor, or there are metastases to lymph nodes or distant sites.

- **Any tumor size and history of childhood head and neck radiation**

Total thyroidectomy should also be performed in all patients with thyroid cancer who have a history of exposure to ionizing radiation of the head and neck, given the high rate of tumor recurrence with lesser operations in these patients.

uptodate

- **Multifocal papillary microcarcinoma (fewer than five foci)**

Unilateral lobectomy and isthmusectomy is an appropriate procedure for patients whose pathology reports subsequently show multifocal papillary microcarcinomas with fewer than five foci.

- **Multifocal papillary microcarcinoma (more than five foci)**

When multifocal papillary cancer is appreciated preoperatively, particularly when a large number of microcarcinoma are suspected (eg, greater than five foci, especially if the foci are in the 8 to 9 mm size range), we are more likely to perform a **total thyroidectomy**.

uptodate

For patients whose initial procedure was a lobectomy and in whom pathology shows multifocal papillary microcarcinomas with more than five foci, especially if the foci are in the 8 to 9 mm range, we typically refer patients for **completion thyroidectomy**.

Patient Classification	Tumor/Imaging Characteristics	Patient Characteristics	Medical Team Characteristics
Ideal	<1 cm Intrathyroidal Thyroid US otherwise normal Clinical N0 neck	Medical minimalist Motivated patient Willing to accept possibility of small volume disease in contralateral lobe Desire to preserve normal thyroid function Desire to minimize surgical complications Open to intraoperative decision making Willing to accept a low risk of needing an immediate completion thyroidectomy based on histology findings TSH <2 mIU/L Antithyroid antibodies undetectable Anti-Tg antibodies undetectable	Experienced MDT Experienced US Shared treatment philosophy Uses RAI very selectively for ablation/adjuvant therapy and follow-up Frozen section available

Preoperative Classification System to Aid in Proper Patient Selection for Lobectomy/Isthmusectomy in Differentiated Thyroid Cancer (Williams)

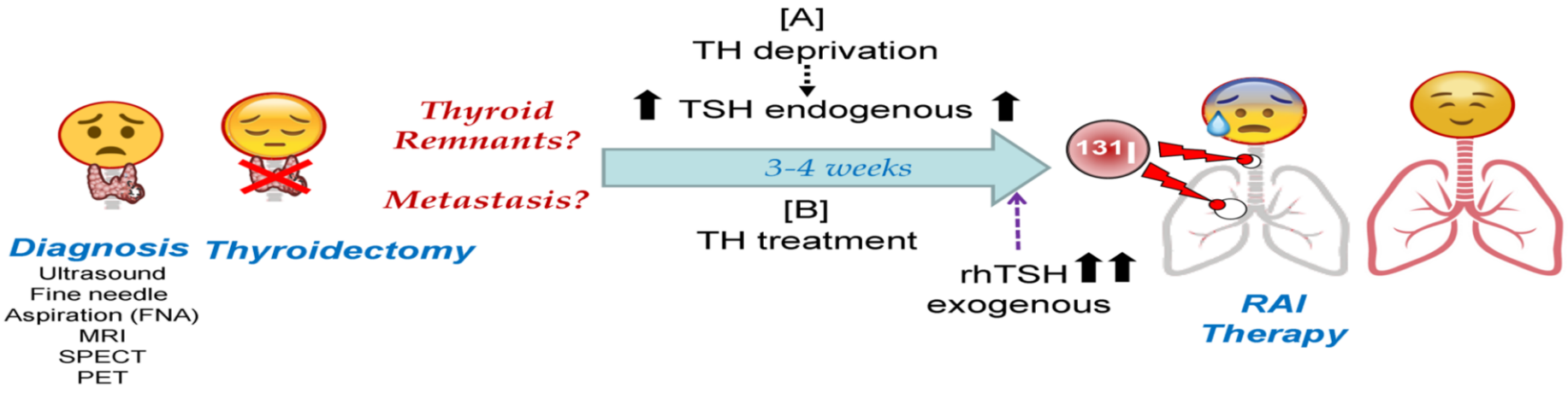
Patient Classification	Tumor/Imaging Characteristics	Patient Characteristics	Medical Team Characteristics
Appropriate	1–4 cm Benign-appearing changes on US (thyroiditis, benign nodules) Clinical N0 neck	Minimalist/maximalist Desire to keep normal thyroid (or avoidance of surgical complications) outweighs concern for disease in the contralateral lobe or the desire for RAI TSH >2 Antithyroid antibodies present Anti-Tg antibodies	Surgeon and endocrinologist agree on postoperative management plan Unlikely to include need for RAI Comfortable that follow-up US is adequate for low-risk patient
Inapropriate	Extrathyroidal extension Clinical N1 metastases Distant metastases High-risk molecular profile	Medical maximalist Patient desires total thyroidectomy and/or RAI Clinical indications for RAI for ablation/adjuvant therapy/staging	Treatment team desires RAI for ablation/adjuvant therapy/staging/follow-up

Preoperative Classification System to Aid in Proper Patient Selection for Lobectomy/Isthmusectomy in Differentiated Thyroid Cancer (Williams)

POSTOPERATIVE RADIOIODINE TREATMENT WITH ^{131}I

Radioiodine treatment with 131I (RAI) is not generally recommended after lobectomy. After TTx, RAI could be used for three different purposes:

(1) Remnant ablation: to eliminate any thyroid tissue/cells left over the surgery, making the measurement of serum Tg more specific for persistent/recurrent disease;



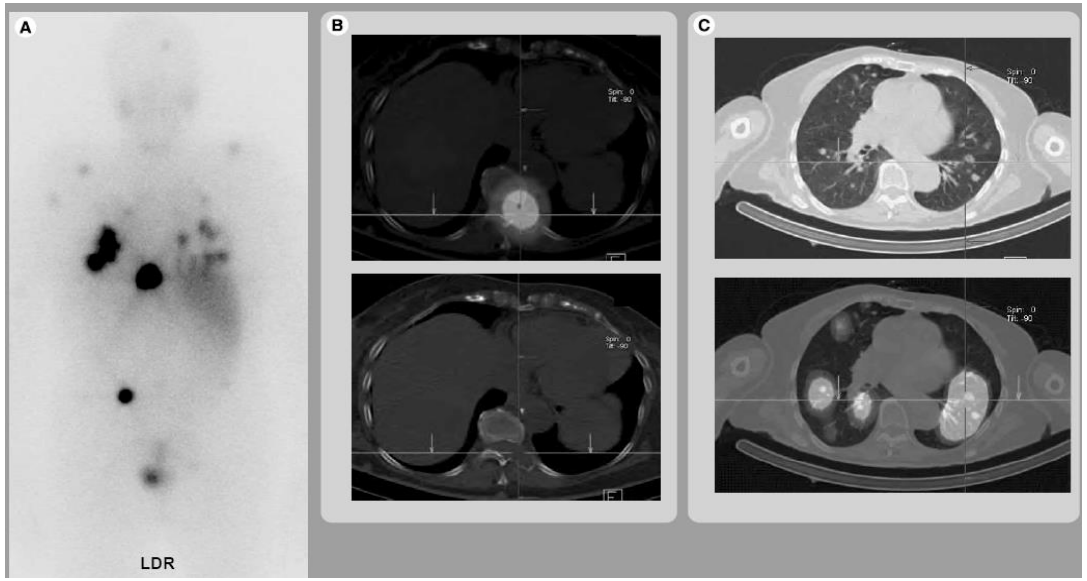
POSTOPERATIVE RADIOIODINE TREATMENT WITH ^{131}I

(2) Adjuvant treatment: to eliminate any potential foci of thyroid cancer, which might be present after surgery and to destroy small-volume microscopic lymph node metastasis;

(3) Treatment of known disease: to treat the tumor residual disease in the case of advanced stage, both at local and distant level.

POSTOPERATIVE RADIOIODINE TREATMENT WITH ^{131}I

Moreover, RAI treatment allows to perform a post therapeutic whole-body scan, with or without single-photon emission CT–CT (SPECT-CT), to evaluate the presence of radio avid local or distant metastasis, which could change the initial staging and theoretically further treatments.



POSTOPERATIVE RADIOIODINE TREATMENT WITH ^{131}I

Initial treatment of DTC consisted of TTx plus RAI for all patients until few years ago;

Nowadays, patients treated with RAI should be selected on the basis of the initial risk stratification (low, intermediate, and high).

POSTOPERATIVE RADIOIODINE TREATMENT WITH ^{131}I

To increase thyroid stimulating hormone (TSH) levels, to rise ^{131}I uptake in thyroid cells, RAI can be performed after thyroid hormone withdrawal (THW) or administration of recombinant human TSH (rhTSH).

Initial risk stratification

Low risk

Papillary thyroid cancer with all of the following present:
No local or distant metastases/ All macroscopic tumor has been resected/ No invasion of locoregional tissues/ Tumor does not have aggressive histology (aggressive histologies include tall cell, insular, columnar cell carcinoma, Hürthle cell carcinoma, follicular thyroid cancer, hobnail variant)/ No vascular invasion/ No 131I uptake outside the thyroid bed on the post-treatment scan, if done/ Clinical N0 or ≤5 pathologic N1 micrometastases (<0.2 cm in largest dimension)/ Intrathyroidal, encapsulated follicular variant of papillary thyroid cancer/ Intrathyroidal, well-differentiated follicular thyroid cancer with capsular invasion and no or minimal (<4 foci) vascular invasion/ Intrathyroidal, papillary microcarcinoma, unifocal or multifocal, including BRAF V600E mutated (if known)

Initial risk stratification

Intermediate risk

Any of the following present:

Microscopic invasion into the perithyroidal soft tissues/ Cervical lymph node metastases or 131I avid metastatic foci in the neck on the post-treatment scan done after thyroid remnant ablation/ Tumor with aggressive histology or vascular invasion (aggressive histologies include tall cell, insular, columnar cell carcinoma, Hürthle cell carcinoma, follicular thyroid cancer, hobnail variant)/ Clinical N1 or >5 pathologic N1 with all involved lymph nodes <3 cm in largest dimension/ Multifocal papillary thyroid microcarcinoma with extrathyroidal extension and BRAF V600E mutated (if known)

Initial risk stratification

High risk

Any of the following present:

Macroscopic tumor invasion/ Incomplete tumor resection with gross residual disease/ Distant metastases/ Postoperative serum thyroglobulin suggestive of distant metastases/ Pathologic N1 with any metastatic lymph node ≥3 cm in largest dimension/ Follicular thyroid cancer with extensive vascular invasion (>4 foci of vascular invasion)

POSTOPERATIVE RADIOIODINE TREATMENT WITH ^{131}I

In **high-risk** patients, routine postoperative RAI with high activities is required because it improves the specific cancer survival.

POSTOPERATIVE RADIOIODINE TREATMENT WITH ^{131}I

Activities up to 150 mCi are generally recommended when RAI is used as remnant ablation or adjuvant therapy.

In the presence of known distant metastasis, higher activities can be used.

POSTOPERATIVE RADIOIODINE TREATMENT WITH ^{131}I

In **low-** and **intermediate-risk** cases, two randomized noninferiority trials comparing low and high activities of radioiodine, each with either THW or rhTSH, demonstrated that the ablation rate was similar in the four groups. In addition, recurrence rates are similar in patients prepared with THW or rhTSH, both in low- and intermediate-risk patients.

However, the preparation with rhTSH significantly improves quality of life and reduces both whole-body irradiation and hospitalization time.

POSTOPERATIVE RADIOIODINE TREATMENT WITH ^{131}I

Selective use of RAI is advocated for patients with **intermediate** risk.

Aggressive variants have a worse prognosis than classic variant, and RAI increased cancer-specific survival rate.

The role of microscopic extrathyroidal extension (mETE) in deciding to perform RAI or not is debated; some studies demonstrated a risk of death, while others did not.

POSTOPERATIVE RADIOIODINE TREATMENT WITH ^{131}I

The presence of BRAF V600E mutation is associated with increased cancer-specific mortality and a higher risk of recurrence compared to wild-type tumors.

In intermediate-risk BRAF-positive tumors, reasonably, the associated histological features have more relevance in deciding to perform RAI, compared to the presence of mutation alone.

POSTOPERATIVE RADIOIODINE TREATMENT WITH ^{131}I

Therefore, RAI should be performed, with low or high activities (i.e., 30–150 mCi) and after rhTSH or THW, in selected **intermediate-risk** cases with advanced age, aggressive histology, and higher volume of lymph node metastasis.

In other clinical scenarios (i.e., mETE, small lymph node metastasis, and intrathyroidal PTC with BRAF mutation), postoperative evaluation should guide the decision.

POSTOPERATIVE RADIOIODINE TREATMENT WITH ^{131}I

In **low-risk** cases, including those with positive BRAF mutation and small volume metastatic lymph node involvement, ~~RAI~~ is not recommended anymore because the cancer-specific mortality and the persistent/recurrent disease is negligible and therefore not improved by RAI.

Accordingly, based on the postoperative evaluation and in selected cases, RAI should be performed with low activity (i.e., 30–50 mCi) and after rhTSH stimulation.

Uptodate

- ATA **high-risk** disease – We recommend postoperative radioiodine ablation to patients with high-risk disease, including patients with distant metastases, macroscopic tumor invasion, and/or incomplete tumor resection with gross residual disease.

Uptodate

- ATA **intermediate-risk** disease – We suggest postoperative radioiodine ablation to selected intermediate-risk patients, including those with clinically significant lymph node metastases outside of the thyroid bed; vascular invasion; or more aggressive histologic subtypes such as tall cell, columnar cell, insular, or poorly differentiated histologies.

Uptodate

- ATA **low-risk** disease – In the absence of a proven benefit on either disease-free survival or recurrence, we do not routinely administer radioiodine for remnant ablation to patients with low-risk disease, especially patients with unifocal tumors <1 cm without other high-risk features or multifocal cancer when all foci are <1 cm in the absence of other high-risk features, even in the presence of small-volume regional lymph node metastases (less than five lymph nodes measuring less than 2 mm).

Follow-Up After Initial Treatment and Dynamic Risk Stratification (DRS)

In the last few years, DTC follow-up has changed. Differently from the past, dynamic risk stratification (DRS) is widely performed at both the first postoperative and the subsequent evaluations, and it takes into account information obtained during follow-up.

After Lobectomy

DTC is often multifocal and bilateral and is inclined to spread to the loco-regional lymph nodes.

After lobectomy, all patients should undergo basal serum Tg and TgAb measurement and periodical nUS.

When patients are carefully selected to surgery, the recurrence rate is low, ranging from 1 to 7%, with no impact on overall survival.

In addition, if properly treated, most of these patients remain free of disease also after recurrences.

After Lobectomy

A predefined threshold value of Tg, to recognize those patients with an incomplete response after initial treatment or with recurrence, is difficult to obtain because of the presence of the remaining lobe. For the same reason, TgAb trend loses its meaning during follow-up.

However, it could be argued that a stable, non-stimulated value of Tg <30 ng/dl, in the absence of a suspicious nUS, could be predictor of an excellent response.

On the contrary, a rising trend of Tg may predict a structural disease.

After Lobectomy

Similarly to TTx, in patients treated by lobectomy, response to treatment can be divided into four classes:

(1) **Excellent response**: stable basal serum Tg levels related to the presence of a contralateral thyroid lobe and negative neck US;

(2) **Biochemical incomplete response**: basal serumTg not related to the presence of a contralateral thyroid lobe, or increasing basal serum Tg levels without evidence of structural disease;

After Lobectomy

(3) **Structural incomplete response**: evidence of structural disease;

(4) **Indeterminate response**: non-specific findings on neck US and doubtful trends of Tg.

After Lobectomy

TSH Targets During Short and Long-Term Follow-Up

In these patients, little evidence is available on the TSH level to be maintained during follow-up.

In **low-risk** patients treated by lobectomy:

TSH should be maintained between 0.5 and 2 mU/l

levothyroxine is generally not recommended for all patients with a TSH value ⩽2 mU/l.

In iodine-deficient areas, levothyroxine can be indicated according to patient age and comorbidities to reduce nodular hyperplasia of the remaining lobe.

After TTx With or Without RAI

Postoperative evaluation should be performed after 4–12 months from diagnosis and includes Tg, using high-sensitive Tg assay, TgAb measurement, and nUS . Additional imaging evaluations could be useful in selected cases.

After TTx With or Without RAI

Patients are re-evaluated over time according to the DRS and are classified into four groups, regardless of RAI:

(1) **Excellent response**: non-stimulated Tg <0.2 ng/ml (both for TTx and TTx + RAI) and/or stimulated Tg <1 (TTx + RAI) or <2 ng/ml (TTx alone) plus undetectable TgAb and negative imaging;

After TTx With or Without RAI

(2) **Indeterminate response**: non-stimulated Tg 0.2–1 ng/ml (TTx + RAI) or 0.2–5 ng/ml (TTx alone) and/or stimulated Tg 1–10 ng/ml (TTx + RAI) or 2–10 ng/ml (TTx alone) and TgAb levels stable or declining, in the absence of structural or functional disease or non-specific findings on imaging studies or faint uptake in thyroid bed on RAI scanning;

After TTx With or Without RAI

(3) **Biochemical incomplete response**: non-stimulated Tg ⩾1 ng/ml (TTx + RAI) or >5 ng/ml (TTx alone) and/or stimulated Tg ⩾10 ng/ml or rising TgAb levels plus negative imaging;

(4) **Structural incomplete response**: structural or functional evidence of disease regardless of Tg or TgAb levels.

After TTx With or Without RAI

The risk of recurrence depends on DRS status rather than initial risk category. The impact of DRS has likely more relevance for intermediate and high-risk patients with an excellent response during follow-up (decreased risk of recurrence up to 1-2%).

After TTx With or Without RAI

TSH Targets During Short and Long-Term Follow-Up

The appropriate degree and duration of TSH suppression remains to be established. Currently, the international guidelines suggest a degree of TSH suppression according to the risk classification after initial treatment:

(1) **High risk**: TSH ≤0.1 mU/l

(2) **Intermediate risk**: TSH 0.1–0.5 mU/l

(3) **Low risk**: TSH in the normal range (0.5–2 mU/l)

After TTx With or Without RAI

Despite an improved outcome in high-risk patients, currently, the use of TSH suppression is being reconsidered both in intermediate- and high-risk cases; no evidence of benefits has been documented in low-risk cases.

Moreover, in patients with associate comorbidities (at high risk of adverse effects by TSH suppression therapy), TSH values should be individualized, balancing risks, harms, and benefits.

After TTx With or Without RAI

TSH values should be titrated also after the restratification process during the follow-up:

(1) **Excellent response** (clinically and biochemically free of disease): TSH 0.5–2 mU/l (in patients with high-risk disease at diagnosis, TSH 0.1–0.5 mU/l during the first 5 years)

(2) **Biochemical incomplete or indeterminate response**: TSH 0.1–0.5 mU/l

(3) **Structural incomplete response**: TSH ⩽0.1 mU/l.

ADVANCED THERAPY

Despite patients with DTC usually having an excellent prognosis, a small subgroup could develop distant metastasis or become radioiodine refractory (RAI-R), with a significant impact on survival rates.

ADVANCED THERAPY

There is no fully consensus on the **definition of RAI-R disease**.

According to the American Thyroid Association guidelines, it refers to the absence of radioiodine uptake in all or some lesions, at the first posttherapeutic whole-body scan or after previous evidence of RAI-avid disease, or in the case of progression of diseas despite RAI uptake.

Furthermore, also the existence of a **maximum cumulative RAI dose** to be administered is still debated.

ADVANCED THERAPY

These patients with a structural disease should be assessed by biochemical and imaging evaluation.

Tg may give an estimate of tumor burden, and Tg doubling time <1 year is associated with a poor prognosis.

However, **imaging techniques** (US, MRI, and CT scan) provide the most precise information on tumor burden to evaluate tumor growth and define tumor progression according to the response evaluation criteria in solid tumors.

ADVANCED THERAPY

Positron emission tomography with 2-deoxy-2-fluorine-18-fluoro-D-glucose/CT (18FDG-PET/CT) may provide additional prognostic information, since 18FDG-PET positive lesions usually have a more aggressive behavior.

ADVANCED THERAPY

In general, in patients with oligometastatic, rapidly progressive, or symptomatic disease, a **local treatment** should be preferred.

Surgery is the most widely used therapeutic procedure in these scenarios.

Other techniques include thermal ablation (radiofrequency and cryoablation), ultrasound-guided percutaneous ethanol ablation, transarterial chemoembolization, cementoplasty, and external beam radiotherapy.

ADVANCED THERAPY

Thermal ablation has been used to treat metastatic lymph nodes and distant metastasis to the bone, lung, and liver. Radiofrequency thermoablation takes advantage of the heat produced by the radiofrequency generator, while cryoablation alternates cycles of freezing and thawing to destroy tumor cells.

These procedures are safe and have a high therapeutic success rate.

ADVANCED THERAPY

Ultrasound-guided percutaneous ethanol ablation has the main role for neck recurrences.

Transarterial chemoembolization is used for small and diffuse liver metastases, placing chemotherapy and embolic agents directly into the hepatic artery and permit to treat multiple metastases in the same session treatment, when surgery and local ablative therapy have a limited role.

ADVANCED THERAPY

In cases of osteolytic bone lesions, **cementoplasty** has been used to provide bone reinforcement and pain relief.

In these cases, bisphosphonates (Zoledronic acid) and monoclonal antibodies (Denosumab) may reduce skeletal related adverse events, such as pathological fractures, metastatic spinal cord compression, and malignant hypercalcemia.

ADVANCED THERAPY

Finally, **external beam radiotherapy** was widely used in the past, but its efficacy is questionable, and it may be considered only for palliative purposes in patients with locally advanced disease.

ADVANCED THERAPY

When these local treatments are not feasible or in patients with widespread metastatic disease, a **systemic therapy** should be initiated.

These patients had no effective therapeutic options, until few years ago, but their management has dramatically changed with the availability of tyrosine kinase inhibitors (TKIs).

ADVANCED THERAPY

Sorafenib and Lenvatinib, two oral multitargeted TKIs with antiproliferative and antiangiogenetic effects, were approved by the US Food and Drug Administration and European Medicines Agency after the publication of two phase 3, randomized, doubleblind, multicenter trials.

ADVANCED THERAPY

No head-to-head comparison between Sorafenib and Lenvatinib in DTC patients has been conducted so far.

In the DECISION trial, Sorafenib significantly prolonged median progression-free survival in patients with advanced DTC (10.8 vs. 5.8 months with placebo) and led to an overall response rate increase (12.2 vs. 0.5%).

ADVANCED THERAPY

Similarly, in the SELECT trial, advanced DTC patients treated with Lenvatinib showed a significant prolongation of median progression-free survival in comparison to placebo (18.3 vs. 3.6 months), with a marked improvement in the response rate (64.8 vs. 1.5%).

ADVANCED THERAPY

It must be underlined that patients treated with Sorafenib were all TKI naive; by contrast, Lenvatinib represented a second-line TKI therapy for 25% of treated patients in the trial.

No significant conclusions can be drawn on overall survival in TKI-treated patients, due to the crossover design of both studies which potentially misrepresents the real effect of the two TKIs.

ADVANCED THERAPY

Most of TKI-treated patients experienced **adverse events (AEs)** in both phase III trials. The most frequent AEs reported on Sorafenib were hand–foot syndrome, diarrhea, alopecia, and rash.

During treatment with Lenvatinib, more than half of the treated group experienced hypertension, diarrhea, fatigue, and decreased appetite.

ADVANCED THERAPY

At least for Lenvatinib, AEs seemed to be more severe in older patients.

In most cases, AE management was achieved by supportive care and by dose reduction or transient drug interruption.

Lenvatinib discontinuation might be necessary in a limited number of cases for toxicity or marked progression. For these patients, salvage therapy with a different TKI is generally recommended, but their availability is restricted to the clinical trial setting or to the “off-label” use

ADVANCED THERAPY

Recently, **immune checkpoint inhibitors** have been tested in preliminary trials for the treatment of advanced thyroid cancer.

The antitumor activity of the antiprogrammed cell death-1monoclonal antibody Pembrolizumab has been evaluated in advanced PD-L1-positive DTC with promising results.

ADVANCED THERAPY

Recommendations of the American Thyroid Association (ATA) Guidelines (2015), Italian Consensus (2018), and National Comprehensive Cancer Network (NCCN) (2019) about the management of radioiodine-refractory locally advanced/metastatic differentiated thyroid cancer (DTC) patients.

ATA 2015

Active surveillance

Serial radiographic imaging (every 3–12 months) in patients with asymptomatic, stable, or minimally progressive disease, not likely to develop rapidly progressive, clinically significant complications.

TSH-suppressive thyroid hormone therapy to be continued.

ATA 2015

Locoregional treatments

In case of symptoms and risk of local complications before systemic treatment (or during systemic therapy in case of progression of a single lesion): surgery, external beam radiotherapy (EBRT), percutaneous approach (i.e., radiofrequency, laser ablation, ethanol injection, cryoablation, cementoplasty) in selected cases.

ATA 2015

Systemic treatments

Approved kinase inhibitor (KI; i.e., lenvatinib, sorafenib) in rapidly progressive, symptomatic, and/or imminently threatening disease not otherwise controlled using other approaches.

Second-line KI therapy in case of progression or prohibitive adverse effects on first-line treatment (ideally within the context of clinical trials).

Few data and disappointing results about conventional chemotherapy; to be considered after failure of KI therapy.

Bisphosphonates (especially zoledronic acid every 3 months) or denosumab in case of diffuse and/or symptomatic bone metastases.

Italian Consensus 2018

Active surveillance

Cross-sectional imaging at regular intervals (every 3–12 months) in case of stable disease without symptoms, with a slow progression during the follow-up and without lesions at risk of life.

TSH-suppressive thyroid hormone therapy to be continued.

Italian Consensus 2018

Locoregional treatments

Strongly suggested in case of progression related to a single lesion treatable with a local and selective approach: surgery, EBRT, other local procedures (i.e., thermoablation, ethanol injection, chemoembolization).

Italian Consensus 2018

Systemic treatments

Approved KI (i.e., sorafenib, lenvatinib) for rapidly progressive, significantly symptomatic, and/or with life threatening lesions not suitable for local therapies.

In case of progressive disease during KI therapy, indication to another KI based on evidence of high probability of efficacy.

Traditional chemotherapy only in case of failure or contraindication of KI.

NCCN 2019

Active surveillance

In case of non-progressive and indolent disease, distant from critical structures.

TSH-suppressive thyroid hormone therapy to be continued.

NCCN 2019

Locoregional treatments

To be considered in case of progressive and/or symptomatic disease if feasible, depending of the site, and the number of tumoral foci: surgery, EBRT, other interventional procedures (i.e., ethanol ablation, cryoablation, radiofrequency, embolization) in selected patients.

NCCN 2019

Systemic treatments

Lenvatinib (preferred) or Sorafenib for progressive and/or symptomatic disease.

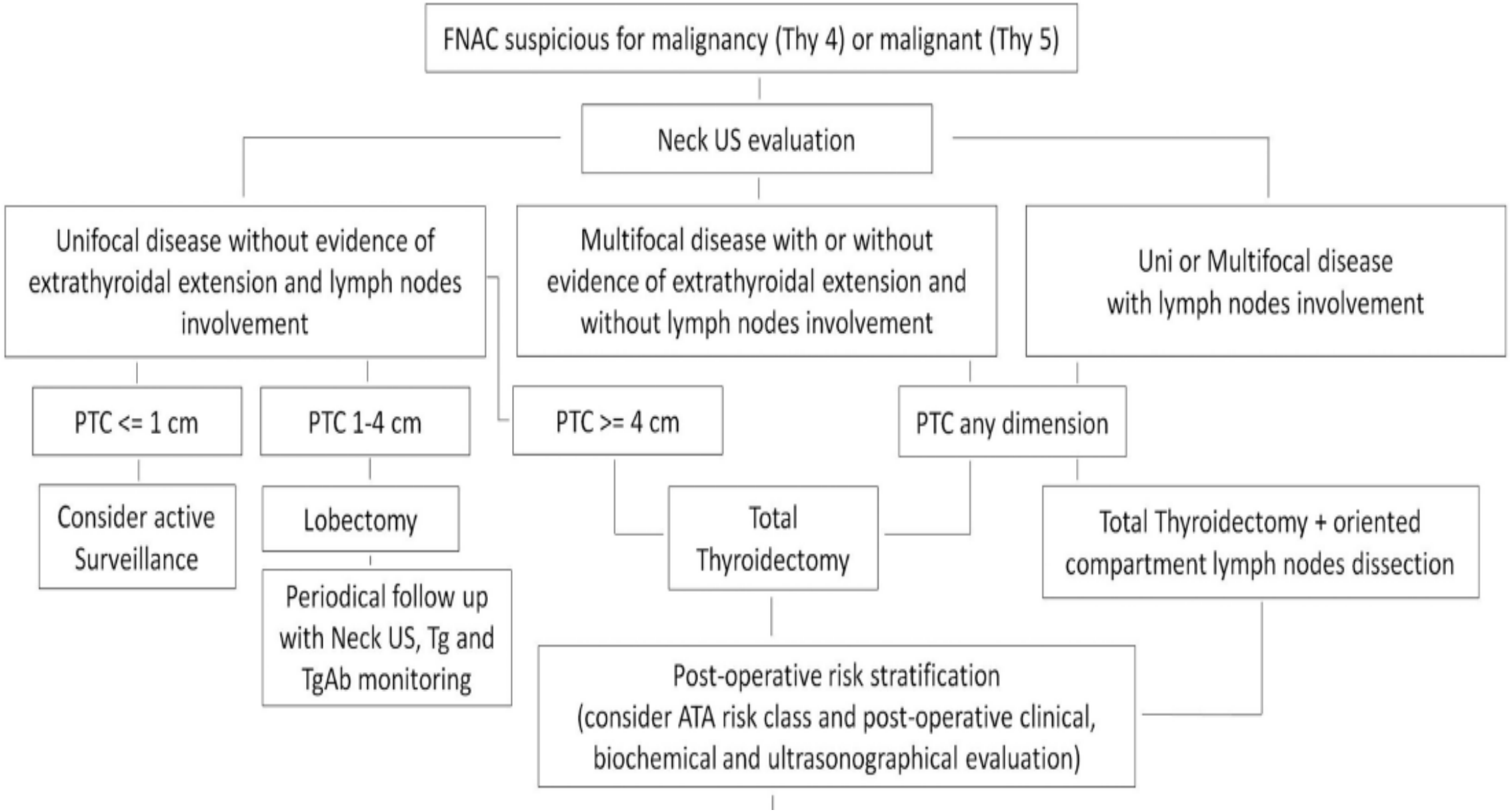
Other commercially available KI to be considered if clinical trials not available or appropriate.

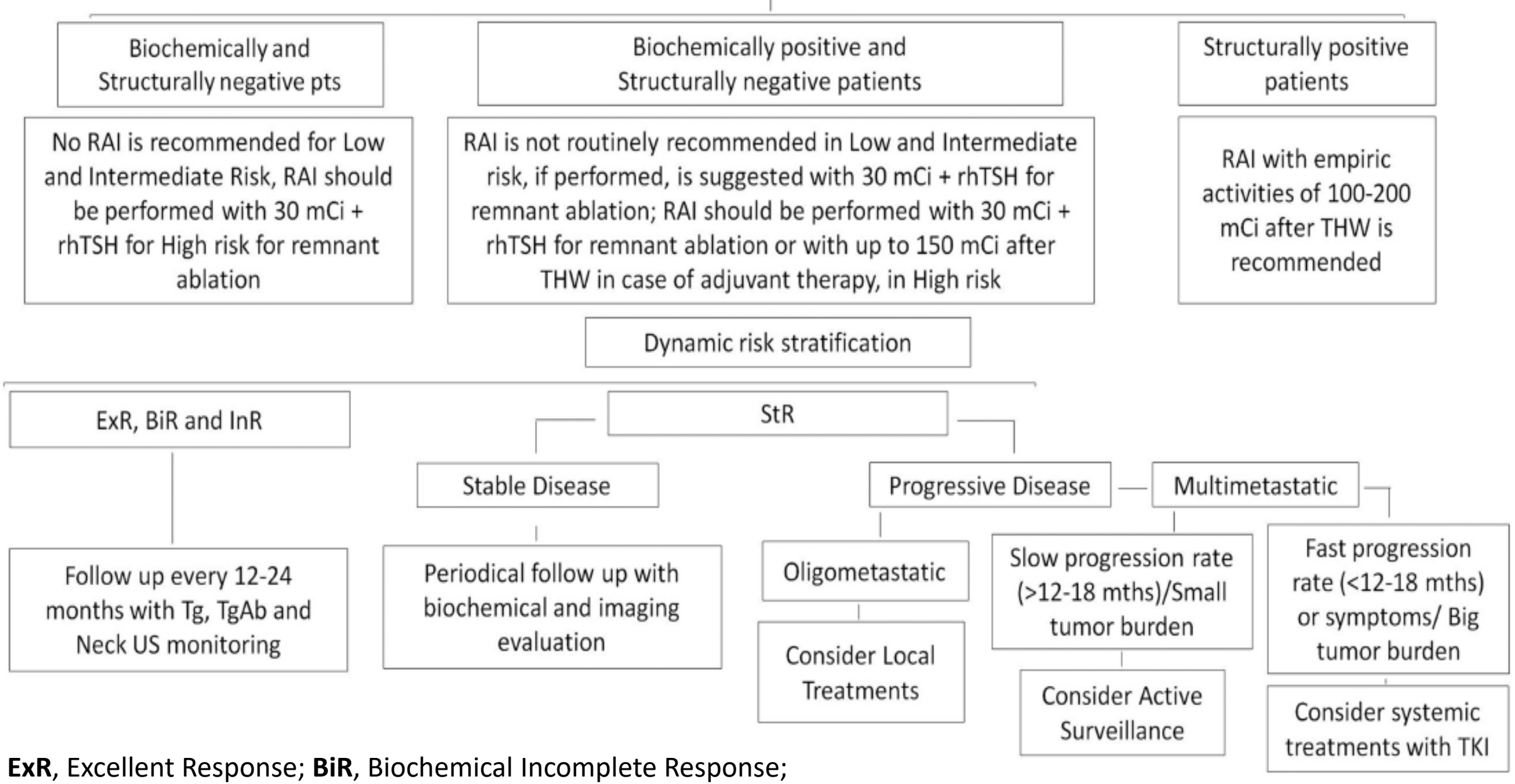
Minimal efficacy of cytotoxic chemotherapy.

Intravenous bisphosphonates or denosumab if bone metastases.

177Lu-DOTATATE

Endocrine tumours may express somatostatin receptors, and this characteristic has been used, not only for diagnosis, but also for their treatment through somatostatin analogue labelling with radioactive isotopes (**177Lu-DOTATATE**)


FNAC suspicious for malignancy (Thy 4) or malignant (Thy 5)
Neck US evaluation
Unifocal disease without evidence of extrathyroidal extension and lymph nodes involvement
Multifocal disease with or without evidence of extrathyroidal extension and without lymph nodes involvement
Uni or Multifocal disease with lymph nodes involvement
PTC <= 1 cm
PTC 1-4 cm
PTC >= 4 cm
PTC any dimension
Consider active Surveillance
Lobectomy
Periodical follow up with Neck US, Tg and TgAb monitoring
Total Thyroidectomy
Total Thyroidectomy + oriented compartment lymph nodes dissection
Post-operative risk stratification (consider ATA risk class and post-operative clinical, biochemical and ultrasonographical evaluation)



ExR, Excellent Response; **BiR**, Biochemical Incomplete Response;
InR, Indeterminate Response; **StR**, Structural Incomplete Response.