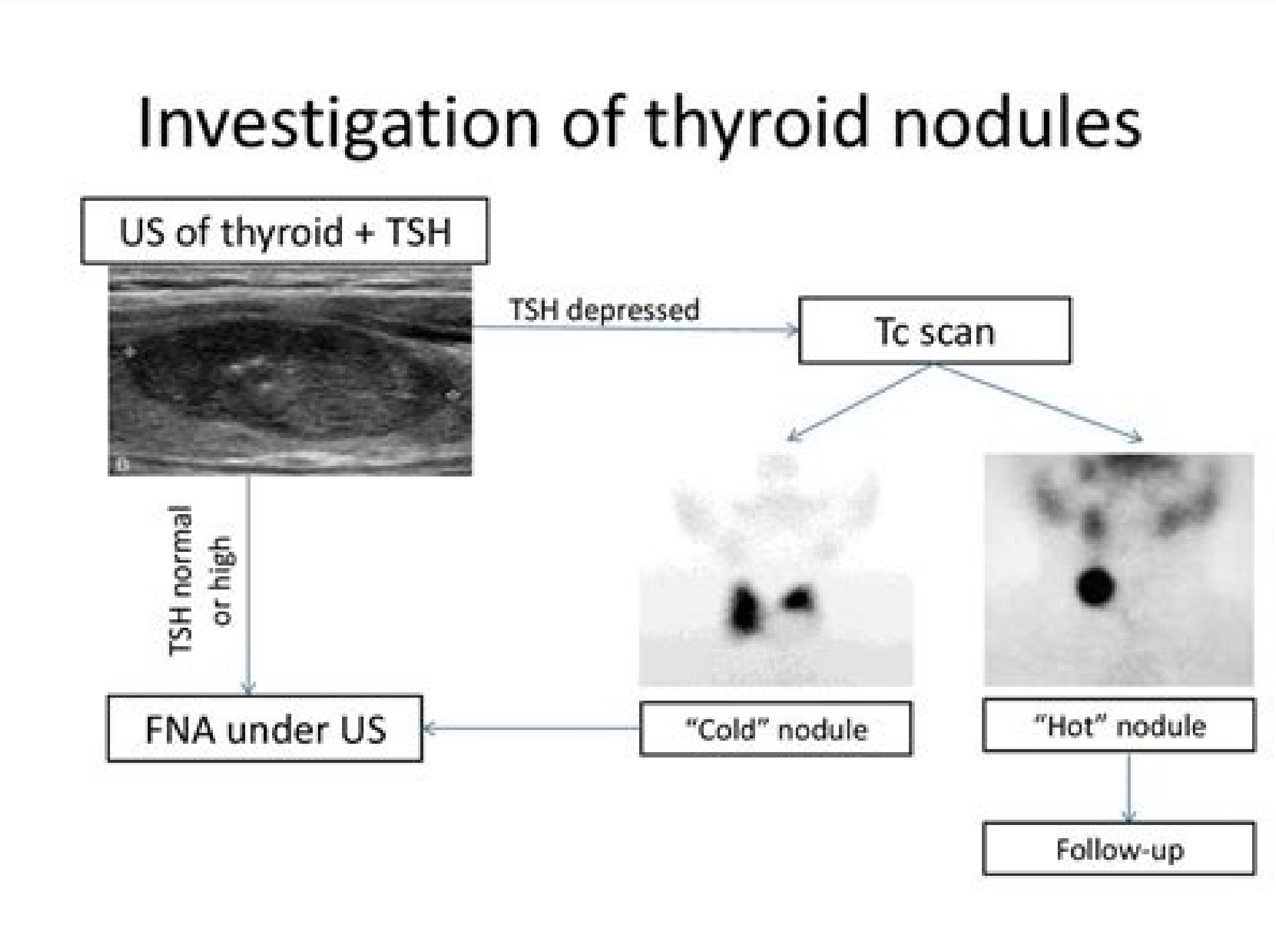
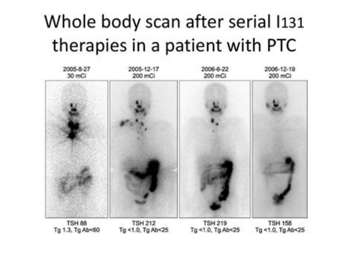
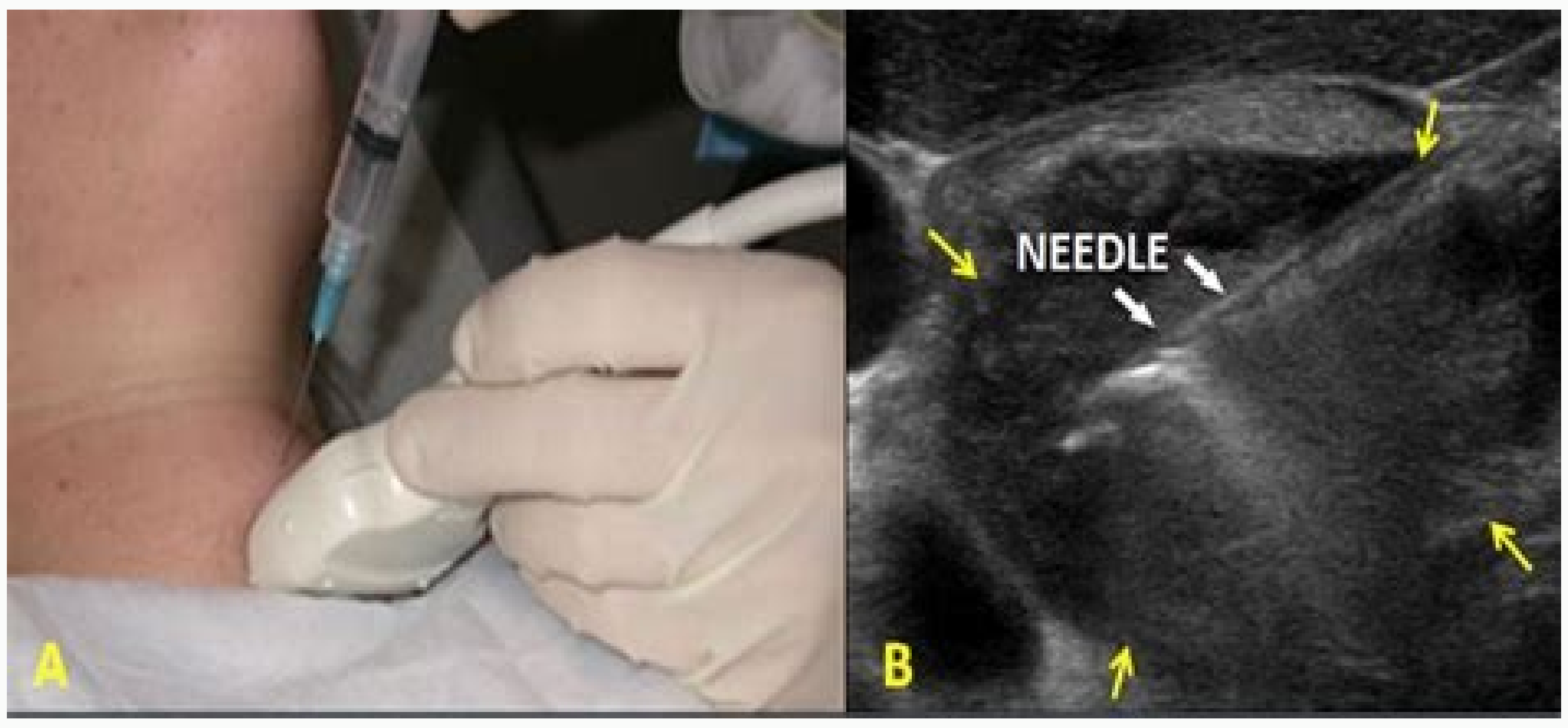
Thyroid nodules and differentiated thyroid cancer guidelines







New Rochelle, NY, October 14, 2015—New, evidence-based recommendations from the American Thyroid Association (ATA) will help guide clinicians in managing patients with thyroid nodules, a common disorder that requires evaluation to distinguish benign nodules from malignancy, interpret biopsy results and molecular marker studies, and initiate risk assessment and cancer screening. The new ATA guidelines, which also focus on the diagnosis and management of differentiated thyroid cancer (DTC), an increasingly prevalent form of cancer, are published in Thyroid, a peer-reviewed journal from Mary Ann Liebert, Inc., publishers and the official journal of the ATA. The guidelines are available free on the Thyroid website. The "2015 American Thyroid Association Management Guidelines for Adult Patients with Thyroid Nodules and Differentiated Thyroid Cancer" are coauthored by the ATA Guidelines Taskforce on Thyroid Nodules and DTC, led by Chair Bryan Haugen, MD, University of Colorado School of Medicine, Aurora. Significant scientific advances in this field since the previous guidelines were released in 2009 have led to revised recommendations regarding the initial evaluation, biopsy criteria and interpretation of biopsy results, use of molecular markers, and management of benign thyroid nodules. The new guidelines for initial management of thyroid cancer focus on screening, staging, and risk assessment; surgical approaches; radioiodine therapy; and thyroid stimulating hormone (TSH) suppression using levothyroxine. For long-term management of DTC, the recommendations include guidance on surveillance for recurrent disease using imaging and serum thyroglobulin, thyroid hormone therapy, management of recurrent and metastatic disease, when to consider participation in clinical trials or use of targeted/personalized therapies, and directions for future research. "The updated guidelines integrate an impressive amount of new information and significant advances which impact the management of patients presenting with thyroid nodules and thyroid cancer. They provide a superb framework for the evaluation, treatment, and surveillance of these patients. Importantly, the guidelines also highlight areas in need of further investigation. The task force members are to be acknowledged for their enormous efforts in compiling this complex yet balanced document," says Peter A. Kopp, MD, Editor-in-Chief of Thyroid and Associate Professor of Medicine, Division of Endocrinology, Metabolism, and Molecular Medicine, Northwestern University Feinberg School of Medicine, Chicago. "Dr. Haugen and his colleagues on the DTC Guidelines Task Force are to be congratulated on their monumental task of reviewing a vast literature," says Robert C. Smallridge, MD, President of the ATA, Professor of Medicine and former Chair, Endocrinology Division, Mayo Clinic, Jacksonville, Florida. "The field is changing rapidly, from the potential role of molecular markers to approaches to surgery, the most effective imaging, the role of 131-Iodine, risk assessment over time, and treatment of radioiodine refractory metastatic disease. The authors have provided a balanced list of 101 Recommendations that should assist practitioners in applying this information to the daily care of their patients." About the Journal Thyroid, the official journal of the American Thyroid Association, is an authoritative peer-reviewed journal published monthly online with open access options and in print. The Journal publishes original articles and timely reviews that reflect the rapidly advancing changes in our understanding of thyroid physiology and pathology, from the molecular biology of the cell to clinical management of thyroid disorders. The complete Thyroid Journal Program also includes the highly valued abstract and commentary publication Clinical Thyroidology, led by Editor-in-Chief Jerome M. Hershman, MD, and published monthly, and the groundbreaking videojournal companion VideoEndocrinology, led by Editor Gerard Doherty, MD, and published quarterly. Complete tables of content and sample issues may be viewed on the Thyroid website. About the Society The American Thyroid Association (ATA) is the leading worldwide organization dedicated to the advancement, understanding, prevention, diagnosis, and treatment of thyroid disorders and thyroid cancer. ATA is an international membership medical society with over 1,700 members from 43 countries around the world. Celebrating its 92nd anniversary, the ATA delivers its mission—of being devoted to thyroid biology and to the prevention and treatment of thyroid disease through excellence in research, clinical care, education, and public health—through several key endeavors: the publication of highly regarded professional journals, Thyroid, Clinical Thyroidology, and VideoEndocrinology; annual scientific meetings; biennial clinical and research symposia; research grant programs for young investigators, support of online professional, public and patient educational programs; and the development of guidelines for clinical management of thyroid disease and thyroid cancer. The ATA promotes thyroid awareness and information through its online Clinical Thyroidology for the Public (distributed free of charge to over 11,000 patients and public subscribers) and extensive, authoritative explanations of thyroid disease and thyroid cancer in both English and Spanish. The ATA website serves as the clinical resource for patients and the public who look for reliable information on the Internet. About the Publisher Mary Ann Liebert, Inc., publishers is a privately held, fully integrated media company known for establishing authoritative peer-reviewed journals in many promising areas of science and biomedical research, including Diabetes Technology & Therapeutics, Journal of Women's Health, and Metabolic Syndrome and Related Disorders. Its biotechnology trade magazine, Genetic Engineering & Biotechnology News (GEN), was the first in its field and is today the industry's most widely read publication worldwide. A complete list of the firm's more than 80 journals, books, and newsmagazines is available on the Mary Ann Liebert, Inc., publishers website. • • copy Thyroid nodules are frequent findings, especially when sensitive imaging methods are used. Although thyroid cancer is relatively rare, its incidence is increasing, particularly in terms of small tumors, which have an uncertain clinical relevance. Most patients with differentiated thyroid cancer exhibit satisfactory clinical outcomes when treatment is appropriate, and their mortality rate is similar to that of the overall population. However, relapse occurs in a considerable fraction of these patients, and some patients stop responding to conventional treatment and eventually die from their disease. Therefore, the challenge is how to identify the individuals who require more aggressive disease management while sparing the majority of patients from unnecessary treatments and procedures. We have updated the Brazilian Consensus that was published in 2007, emphasizing the diagnostic and therapeutic advances that the participants, representing several Brazilian university centers, consider most relevant in clinical practice. The formulation of the present guidelines was based on the participants' experience and a review of the relevant literature. Thyroid nodules; thyroid cancer; Brazilian consensus; update Nódulos tireoidianos são muito frequentes, sobretudo quando se empregam métodos sensíveis de imagem. Embora o câncer seja proporcionalmente raro, sua incidência vem aumentando, especialmente de tumores pequenos, cuja evolução clínica é incerta. A maioria dos pacientes com carcinoma diferenciado de tireoide evolui bem quando adequadamente tratada, com índices de mortalidade similares à população geral. Por outro lado, um percentual não desprezível apresenta recidivas e alguns eventualmente não respondem às terapias convencionais, evoluindo para óbito. Assim, o desafio é distinguir os pacientes merecedores de condutas mais agressivas e, ao mesmo tempo e não menos importante, poupar a maioria de tratamentos e procedimentos desnecessários. Atualizamos o Consenso Brasileiro publicado em 2007, ressaltando os avanços diagnósticos e terapêuticos que os participantes, de diferentes Centros Universitários do Brasil, consideram mais relevantes para prática clínica. A elaboração dessas diretrizes foi baseada na experiência dos participantes e revisão da literatura pertinente. Nódulo de tireoide; câncer de tireoide; consenso brasileiro; atualização CONSENSUS Thyroid nodules and differentiated thyroid cancer: update on the Brazilian consensus Pedro Weslley RosárioI; Laura S. WardII; Gisah A. CarvalhoIII; Hans GrafIII; Rui M. B. MacielIV; Léa Maria Z. MacielV; Ana Luiza MaiaVI; Mário VaismanVII IServiço de Endocrinologia e Instituto de Ensino e Pesquisa, Santa Casa de Belo Horizonte, Belo Horizonte, MG, Brazil IILaboratório de Genética Molecular do Câncer e Endocrinologia, Departamento de Clínica Médica, Faculdade de Ciências Médicas, Universidade Estadual de Campinas (FCM/Unicamp), Campinas, SP, Brazil IIIServiço de Endocrinologia e Metabologia, Universidade Federal do Paraná (SEMPR/UFPR), Curitiba, PR, Brazil IVDisciplina de Endocrinologia, Departamento de Medicina, Escola Paulista de Medicina, Universidade Federal de São Paulo (EPM/Unifesp), São Paulo, SP, Brazil VDivisão de Endocrinologia, Departamento de Clínica Médica, Faculdade de Medicina de Ribeirão Preto, Universidade de São Paulo (FMRP-USP), Ribeirão Preto, SP, Brazil VISetor de Tireoide, Serviço de Endocrinologia, Hospital de Clínicas de Porto Alegre, Universidade Federal do Rio Grande do Sul (HC-UFRGS), Porto Alegre, RS, Brazil VIIServiço de Endocrinologia, Hospital Universitário Clementino Fraga Filho, Faculdade de Medicina, Universidade Federal do Rio de Janeiro (HUCFF/UFRJ), Rio de Janeiro, RJ, Brazil Correspondence ABSTRACT Thyroid nodules are frequent findings, especially when sensitive imaging methods are used. Although thyroid cancer is relatively rare, its incidence is increasing, particularly in terms of small tumors, which have an uncertain clinical relevance. Most patients with differentiated thyroid cancer exhibit satisfactory clinical outcomes when treatment is appropriate, and their mortality rate is similar to that of the overall population. However, relapse occurs in a considerable fraction of these patients, and some patients stop responding to conventional treatment and eventually die from their disease. Therefore, the challenge is how to identify the individuals who require more aggressive disease management while sparing the majority of patients from unnecessary treatments and procedures. We have updated the Brazilian Consensus that was published in 2007, emphasizing the diagnostic and therapeutic advances that the participants, representing several Brazilian university centers, consider most relevant in clinical practice. The formulation of the present guidelines was based on the participants' experience and a review of the relevant literature. Keywords: Thyroid nodules; thyroid cancer; Brazilian consensus; update INTRODUCTION Several thyroid diseases may present as nodules. According to population-based studies conducted with adults in iodine sufficient areas, approximately 4 to 7% of women and 1% of men exhibit palpable thyroid nodules (1,2). However, the prevalence of nodules indicated by ultrasound exams (US) is substantially higher, reaching up to 68% of the population (3,4); such high frequencies are usually found among older women (5). Although most thyroid nodules are benign, the possibility of a malignancy must be ruled out; 95% of malignant tumors are well-differentiated carcinomas (6,7). Although the current incidence of thyroid cancer is not higher than 24 cases per 100,000 people (7), the incidence has been increasing in recent years (7) to become the fourth most common type of malignant tumor among Brazilian women (8). This increased incidence is mostly associated with a greater number of small papillary carcinomas (6). The recommendations described here were prepared according to the model provided by Project Guidelines (Projeto Diretrizes) by the Brazilian Medical Association (Associação Médica Brasileira - AMB) and Federal Council of Medicine (Conselho Federal de Medicina - CFM) (9), which is a nationwide initiative already known to the Brazilian medical and academic communities. Consistently, the recommendation levels or the strength of evidence degrees employed by that model were used, as described in Table 1 (9). Table 1. Recommendations according to the level of evidence (9) Following the selection of participants with established academic activity and clinical experience related to the thyroid, the clinical questions that grounded the recommendations were elaborated upon. The corresponding literature was located in the MedLine-PubMed, EMBASE, and SciELO-LILACS databases. APPROACH TO PATIENTS WITH THYROID NODULES What clinical information must be collected? With regard to patients with thyroid nodules, a thorough clinical interview and physical examination must be performed. Although these methods are most often neither sensitive nor specific, some of the data they provide are indicative of a higher risk of malignancy (5,10-14) (Table 2). Table 2. Data from the clinical history and physical examination that suggest a greater risk of malignancy in thyroid nodules ª Confirmation of these data as being suspicious of malignancy requires comparison with the results of imaging exams. As will be subsequently shown, nodules that are large or are considered suspicious upon a US exam must be subjected to fine needle aspiration (FNA) biopsy, regardless of the patient's clinical history. Conversely, nodules that are small and are not considered suspicious upon US require further investigation only in patients with high clinical risk of malignancy, in which case the personal and family history become significantly relevant. Recommendation 1 Individuals with a personal or family history of thyroid cancer, a history of exposure to radiation in childhood or adolescence, or nodules incidentally discovered on fluorodeoxyglucose positron emission tomography (FDG-PET; focal uptake) are considered to be at high risk for thyroid malignancy (Recommendation B). What are the recommended laboratory tests? Serum thyroid-stimulating hormone (TSH) As clinical assessment is not always indicative of thyroid dysfunction, TSH levels must be measured. Whenever hyperfunction is detected, even when it is subclinical, thyroid scintigraphy, preferably with radioactive iodine (RAI), is indicated to establish whether the nodule has high or low uptake. In approximately 10% of the patients with solitary nodules, TSH is suppressed and the nodule has high uptake. In such cases, FNA is unnecessary because this type of nodule is exceptionally malignant (5,15). When TSH levels are elevated, the levels of anti-thyroid peroxidase (anti-TPO) antibodies may be measured to confirm a diagnosis of autoimmune thyroiditis. When the US shows a well-defined nodule, the criteria to indicate an FNA are the same in patients with and without Hashimoto's thyroiditis (16). Although some studies have shown a direct correlation between serum TSH levels and risk of malignancy in thyroid nodules and even with initial staging (17,18), the currently available data do not support the indication of any particular approach of patients with thyroid nodules and normal-to-high or high TSH levels. Serum calcitonin and thyroglobulin levels Several studies have assessed the utility of serum (basal and stimulated) calcitonin for early diagnosis of sporadic medullary thyroid carcinoma (MTC) in patients with thyroid nodules (19-22). However, the interpretation of calcitonin (basal and stimulated) results and the cost-benefit ratio are controversial and may be more interesting in patients who have small nodules and are over 40 years of age (21). The sensitivity and specificity of the serum thyroglobulin (Tg) levels are relatively low for the diagnosis of thyroid cancer (23). Recommendation 2 Serum TSH levels must be measured at the initial assessment, primarily to eliminate the possibility of autonomous or hyperfunctioning nodules (Recommendation A). Recommendation 3 Except for patients with clinical suspicion or family history of MTC or multiple endocrine neoplasia type 2 (MEN II), measurement of serum calcitonin is not necessary (Recommendation C). Recommendation 4 Serum Tg levels are not recommended to distinguish between benign and malignant thyroid nodules (Recommendation B). What is the role of the imaging methods? Neck ultrasound US is an excellent method for the detection of thyroid nodules, with a sensitivity of approximately 95% (24), which is higher than other sophisticated methods such as computed tomography (CT) and magnetic resonance imaging (MRI) and often results in modifications of decisions exclusively based on the findings upon palpation (25). US allows for the assessment of the nodule size, composition, and characteristics. In addition, US might detect suspicious lymph nodes in the neck and eventually the compression or invasion of thyroid adjacent structures (26). US is also used in diagnostic (e.g., directed FNA) and therapeutic (e.g., cyst aspiration, ethanol injection, laser therapy) procedures and to monitor nodule growth. Some US findings are associated with increased risk of malignancy. Such findings include hypoechogenicity (especially if there is marked hypoechogenicity); micro-calcifications; irregular margins; predominantly or exclusively central vascularization detected by Doppler; larger anteroposterior diameter compared with the transverse diameter (27-31); and, more specifically, the detection of lymph nodes of the neck with suspicious characteristics. Nevertheless, US findings alone do not allow for absolute differentiation between benign and malignant lesions (24). Assessment of the nodule elasticity (elastography) demonstrates greater rigidity in malignant tumors. Although elastography cannot replace conventional US, when performed together (elastography plus US), the sensitivity and specificity of the assessment improve (32). In addition, the instances in which elastography might be clinically decisive when combined with US must still be established as well as its limitations and potential means of minimizing these limitations (33). Recommendation 5 Neck US must be performed in all patients with thyroid nodules (Recommendation A). Computed tomography, magnetic resonance imaging, and positron emission tomography Neither CT nor MRI can differentiate between benign and malignant lesions as well as US; therefore, these methods are seldom indicated for the assessment of thyroid nodules. However, these imaging modalities are useful in the assessment of substernal goiter and the compression or invasion of adjacent structures, such as the trachea (34). Although 18FDG-PET is useful in the differentiation between benign and malignant lesions (35), this technique is still not readily accessible and is quite expensive. In addition, this sophisticated technique does not allow for the dismissal of FNA and might be more useful for the cases with undetermined cytology (35). Recommendation 6 CT, MRI, and FDG-PET are seldom necessary for the assessment of thyroid nodules (Recommendation B). Isotope scintigraphy Scintigraphy with radionuclides is important to determine whether nodules are hyperfunctioning. Hyperfunctioning nodules with or without extra-nodular suppression are exceptionally malignant (5,15). Scintigraphy may be performed with 131I or 123I or 99mTc pertechnetate. The iodine radioisotopes are absorbed and organified by the thyroid and are the preferred isotypes because 3 to 8% of nodules that are hyperfunctioning when mapped with 99mTc scans are hypofunctioning with iodine (36). Scintigraphy is also indicated for nodules with cytology, which is suggestive of follicular tumor in patients with normal low or low TSH, if it was not performed earlier (37). Recommendation 7 Thyroid scintigraphy is indicated when a functioning nodule is suspected (subnormal TSH) (Recommendation A) or cytology is suggestive of follicular tumor (Recommendation B). When is a fine needle aspiration biopsy indicated? FNA is the best available method to distinguish between benign and malignant lesions (5), even in the case of nodules smaller than 1 cm (3) or larger than 4 cm (38). In addition, FNA is an easy and low-cost outpatient procedure that is virtually devoid of serious complications. Nevertheless, we emphasize the importance of having an experienced physician perform this procedure as well as the necessity of an experienced cytopathologist who can accurately analyze the biopsy material. Thyroid nodules smaller than 1 cm represent microcarcinomas in a considerable percentage of cases (3). Nevertheless, the high frequency of microcarcinomas found only in autopsies (39), their low rate of progression even when untreated (40,41), and the fact that the probability of a cure is not affected when treatment is delayed until the tumor exhibits growth (40) minimize the concerns associated with the detection of microcarcinomas. Consistently, the investigation focuses on the diagnosis of carcinomas larger than 1 cm. Recommendation 8 When hyperfunctioning or purely cystic nodules have been ruled out, the indication for FNA is based on the patient's clinical history, nodule size, and US findings (Recommendation B). These indications are summarized in table 3. Table 3. Indications for FNA in patients with thyroid nodules (except for hyperfunctioning or purely cystic nodules) ª In nodules < 10 mm without apparent invasion or suspicious lymph nodes, monitoring with US, with FNA when the nodule exceeds 10 mm is considered acceptable. b Even without suspicious US findings. What approaches follow from cytology? The National Cancer Institute (NCI, USA) held a multidisciplinary conference, which established that the cytopathology results must reflect the cytopathologist's diagnostic impression in a succinct and clear manner without leaving room for interpretative misunderstandings. The classification system suggested for that purpose, known as Bethesda System (42), is described in table 4. The approach of patients based on the cytology results is depicted below (Figure 1). Figure 1. Suggested approach in patients with thyroid nodules. Table 4. Bethesda system of thyroid cytopathology reports Recommendation 9 Surgery is recommended when cytology results indicate a suspicious malignancy (Bethesda category V) or confirmed malignancy (Bethesda category VI) (Recommendation A). Recommendation 10 When the cytology results are indicative of a follicular tumor (Bethesda category IV), scintigraphy is useful for decision making. Removal of hyperfunctioning nodules is not mandatory; however, hypofunctioning nodules remain an indication for surgery (Recommendation B). Recommendation 11 When cytology indicates follicular lesion or atypia with undetermined significance (Bethesda category III), it is recommended to repeat the FNA 3 to 6 months later. When the results persist, surgery is indicated for patients with high clinical or ultrasonographic suspicion of malignancy or nodules larger than 2 cm. Patients with nodules < 2 cm and low clinical and ultrasonographic suspicion of cancer should be monitored (Recommendation C). Recommendation 12 When the biopsy sample is unsatisfactory for cytological analysis (Bethesda category I), it is recommended to repeat the US-directed FNA 3 to 6 months later (Recommendation B). When the results persist, surgery is indicated for patients with high clinical or ultrasonographic suspicion of malignancy or nodules larger than 2 cm. Patients with nodules < 2 cm and low clinical and ultrasonographic suspicion of cancer should be monitored (Recommendation C). Some studies (43-45) have shown that when cytology is benign but the nodule exhibit a combination of US findings compatible with malignancy, repetition of the FNA can be useful, regardless of the nodule growth, as the rate of malignancy in such discordant cases is substantially higher than the traditional false-negative rate of FNA, which varies from 1 to 3% (42). 18FDG-PET helps rule out malignancy in thyroid nodules with undetermined cytology (35); however, as it is expensive and not readily accessible, 18FDG-PET is not recommended as a routine procedure in this context. What is the utility of molecular markers? Several molecular markers have been assessed, especially with regard to thyroid nodules with undetermined cytology. Markers such as HBME, galectin, and CK19, among others, can be measured by any laboratory that performs routine immunohistochemical tests. Such markers are helpful in the identification of malignant tumors, particularly papillary carcinomas (46). Although their sensitivity reaches 0.85 to 0.93, their specificity varies from 0.43 to 0.71 at most (47). Mutations in specific genes (such as BRAF V600E and RAS) or gene rearrangements (such as RET/PTC and PAX8-PPARy) can also contribute to the identification of malignancy (48). Unfortunately, a panel with these four markers (BRAF, RAS, and rearrangements RET/PTC and PAX8/PPARy) fails to identify 36% of malignant cases (sensitivity of 64%) in clinical practice (49). Other markers, such as microRNAs, are being investigated (50). Recently, a novel test designed to rule out malignancy exhibited a high negative predictive value (95%) in nodules with undetermined cytology (51). Recommendation 13 Molecular markers are helpful in defining the nature of thyroid nodules, especially those with undetermined cytology (Bethesda category III or IV) (Recommendation A). Consistently, the surgical recommendations above (especially R10 and R11) may be modified when molecular markers are used. What should the extent of the surgery be when malignancy is undetermined? Recommendation 14 A total thyroidectomy is recommended under the following conditions: (i) when a nodular disease is bilateral; (ii) when a nodular disease is associated with radiation; (iii) when the cytology is indicative of a suspicious malignancy; and (iv) when the cytology is undetermined and the nodule is > 4 cm or < 4 cm but is associated with high clinical or US suspicion of cancer (Recommendation B). Recommendation 15 Lobectomy is considered sufficient in unilateral and sporadic nodular disease when (i) the nodule < 4 cm, cytology is undetermined, and the clinical and ultrasonographic suspicion of malignancy is low or (ii) cytology is unsatisfactory (Recommendation B). As the pre-test malignancy risk is modified when molecular markers or FDG-PET scans are used, the extent of surgery described above may be modified based on their results. What is the approach in children and adolescents? Recommendation 16 The recommendations described above also apply in the case of thyroid nodules in childhood and adolescence (Recommendation B). In pregnant women, scintigraphy with isotopes is contraindicated. Surgery increases the risk of miscarriage in the first trimester and of premature birth in the third trimester; therefore, surgery is safest when performed in the second trimester (52). In addition, delay of the onset of treatment of differentiated carcinoma diagnosed in pregnancy does not appear to be associated with disease progression or interference with the probability of a cure (53). Based on those premises, the recommendations in nodules detected during pregnancy are as follows: Recommendation 17 Pregnant women with large nodules, apparent invasion, or suspicious lymph nodes on US must be subjected to FNA (Recommendation A). In the remainder of cases, when TSH levels are spontaneously suppressed, follow up with US is recommended (Recommendation B). When TSH levels are normal or high, FNA is indicated as described in table 3; however, monitoring with US (without FNA) is also acceptable (Recommendation B). Recommendation 18 When FNA is not performed in the initial assessment, it must be performed when the nodule exhibits significant growth in the course of pregnancy (Recommendation B). Recommendation 19 In case of undetermined cytology, surgery may be indicated in the second trimester if there is significant nodule growth (Recommendation B). Surgery can also be performed in the second trimester when the cytology indicates a suspicious malignancy or malignancy and the tumor exhibits significant growth or the disease is in an advanced stage (Recommendation B). TSH levels must be kept low (< 0.5 mIU/L) in patients with malignant cytology until surgery (Recommendation C). Recommendation 20 Following delivery, patient management should be reassessed according to the usual recommendations (Recommendation A). When indicated, what are the non-surgical therapeutic options for benign nodular disease? Several studies have suggested that the use of levothyroxine (T4) with consequent reduction of TSH levels suppresses nodule growth (54-56). However, the adverse effects of hormone therapy on the cardiovascular system and bone metabolism (57,58) limit its use. Focal destruction by means of sclerotherapy with ethanol or laser photocoagulation can be considered in patients with benign solitary nodules (59,60). When the main problem is thyroid hyperfunction caused by an autonomous nodule, long-term anti-thyroid drug treatment is an interesting option in elderly patients (60). In several patients with multinodular goiter, iodine uptake is not homogeneous and is relatively low due to the presence of inactive nodules (i.e., "hypofunctioning" on scintigraphy) or suppression of the paranodular tissue. As such areas concentrate 131I very weakly, the efficacy of this treatment is compromised. The use of low doses of recombinant TSH significantly increases 131I uptake in such patients and allows even low activities to efficiently reduce the goiter size by 30 to 50% in one year (60-62). Recommendation 21 Suppressive treatment with T4 is not recommended for thyroid benign nodular disease (Recommendation B). Recommendation 22 Sclerotherapy with alcohol can be considered for cystic or predominantly cystic nodules (Recommendation B). Recommendation 23 Treatment of a nontoxic multinodular goiter with 131I can be optimized through previous administration of low doses of recombinant TSH (Recommendation B). How should the patients not subjected to surgery be monitored? Although the malignancy risk of nodules without indication for FNA (63) or surgery is low [benign cytology (5,42), small nodules with unsatisfactory cytology (64,65) or undetermined follicular lesions/atypia, and non-suspicious clinical history and US], monitoring with US is recommended to detect eventual nodule growth, although its low specificity for a malignancy diagnosis is an acknowledged fact (44,66). The interval between the US tests varies from 6 to 24 months and is defined depending on the number of previous assessments and changes in the nodule size in relation to previous US(s). Recommendation 24 When an FNA is not performed in the initial assessment, it must be performed when the nodules meet the criteria listed in Table 3 (Recommendation B). Recommendation 25 In cases of benign cytology, FNA must be repeated when the nodules exhibit significant growth (> 50% compared with the initial volume; Recommendation C). Recommendation 26 Surgery must be considered for nodules that progress over time and whose initial cytology was undetermined or unsatisfactory (Recommendation B). MANAGEMENT OF DIFFERENTIATED THYROID CARCINOMA In Brazil and worldwide, sensitive imaging methods such as US are becoming increasingly accessible to an aging population, thus increasing the number of individuals diagnosed with small nodules that, even when confirmed as malignant, exhibit uncertain progression. The high frequency of carcinomas that are only found during autopsies (39) and prospective studies conducted with Japanese patients with microcarcinomas not subjected to surgery (40,41) suggest that a large number of these tumors never exhibit clinical progression, which appears to account for the low mortality rate of differentiated thyroid carcinomas (DTCs) in spite of its increased incidence (6,7). Most patients with DTC exhibit good outcomes when they are appropriately treated. However, relapse occurs in a significant percentage of cases, and some of these cases stop responding to conventional treatment and eventually die from their disease. The challenge, therefore, is to identify the individuals who require more aggressive management, while at the same time, and equally importantly, sparing the majority of patients from unnecessary treatments and procedures. Therefore, for the purpose of therapeutic planning and the definition of the best follow-up approach for patients with DTC, assessment of the risk of disease recurrence and progression is crucial. When must initial surgery be performed? Thyroidectomy is indicated together with a DTC diagnosis. Nevertheless, patients with a low life expectancy due to an associated severe disease might be spared thyroidectomy and given palliative treatment in case of advanced or progressive disease. Similarly, when surgery represents a risk due to patient condition, but the patient is expected to improve, thyroidectomy might be delayed for some months, provided the tumor is not progressing or growing (67). The same applies to women diagnosed at the beginning of pregnancy, who should also be subjected to monitoring with US. Surgery may be indicated in the second trimester if the tumor is growing (see Recommendation 19) or after labor if the tumor is stable (53). In the absence of contraindications, TSH levels must be suppressed (< 0.5 mIU/L) in patients who will not undergo surgery or must wait some months before the surgery is performed. Except for exceptional circumstances, any delay between DTC diagnosis and thyroidectomy is unjustified. What preoperative assessment is recommended? Preoperative US must be performed to identify the tumor multicentrality, which is supportive of the choice of total thyroidectomy as initial treatment, as well as to look for non-palpable lymph node metastases (26,68) because their presence requires modified neck dissection. Although it is not indicated for this purpose, US results may also suggest tracheal and/or esophageal invasion by the tumor (26). Any suspicious lymph nodes must be assessed by FNA. CT, MRI, esophagoscopy, or laryngotracheoscopy are not routinely recommended and are only indicated in case of clinical or ultrasonographic suspicion of invasion of adjacent structures (69,70). The use of iodinated contrast should be avoided; however, when iodinated contrast is necessary to better assess the extent of disease, the therapy with 131I, when indicated, must be deferred for at least one month (71). As permanent recurrent laryngeal nerve injury is uncommon when a thyroidectomy is performed by experienced surgeons, and seldom occurs asymptomatically before surgery, we do not recommend a routine performance of preoperative video-laparoscopy. The same applies to the measurement of the serum calcium levels with regard to hypoparathyroidism. Recommendation 27 Preoperative neck US is recommended, even in asymptomatic patients without palpable lymph nodes, to assess the tumor multicentrality, the presence of lymph node metastases, and the extrathyroidal invasion (Recommendation B). No other study is routinely recommended (Recommendation B). What must the extent of the thyroidectomy be? Total thyroidectomy is the most recommended surgical procedure in patients with DTC. Lobectomy may be indicated in patients with classic, unifocal, sporadic papillary carcinoma < 1 cm and without apparent lymphadenopathy or extrathyroidal invasion (67,72-75). In patients initially subjected to partial thyroidectomy, surgical complementation may be avoided in cases of papillary carcinoma presenting with the characteristics described above as well as in cases of minimally invasive follicular carcinoma and the capsulated follicular variant of papillary carcinoma (without vascular invasion) measuring up to 2 cm. Recommendation 28 Total thyroidectomy is the surgical procedure of choice in patients with a preoperative diagnosis of papillary carcinoma (Recommendation A). Recommendation 29 The indication for surgical complementation in patients initially subjected to partial thyroidectomy must take into account the anatomical-pathological data in particular and the individual risk posed by the novel intervention (Recommendation A). What is the surgical management of lymph nodes? Lymph node metastases are frequent findings by the time the diagnosis of papillary cancer is established (76). As neck palpation does not produce abnormal findings in most cases (77), a preoperative US and careful perioperative assessment by the surgeon are needed. Whenever metastases are suspected based on US or during surgery, the patient should be subjected to a total thyroidectomy and therapeutic lymph node dissection, even in the case of tumors < 1 cm, because full tumor resection improves prognosis (78). Even when preoperative US and perioperative assessment are negative, many patients with papillary carcinoma exhibit lymph node micrometastases in the central compartment (79). Nevertheless, there are no consistent data showing that elective dissection of those lymph nodes reduces the risk of relapse. Adjuvant therapy with 131I and TSH suppression may help control the progression of eventual non-resected micrometastases (80). However, such progression likely does not occur naturally in most cases (81). Although some studies have reported low morbidity associated with central compartment lymph node elective dissection (79,82), other authors found a higher risk of transient and permanent hypoparathyroidism (83), even when the procedure is performed by experienced surgeons. The lymph nodes in the lateral compartments (II to IV) and the posterior triangle may also be affected by papillary thyroid cancer metastases (76). However, removal of those lymph nodes appears to exert significant impact only on patients with clinically or US-detected metastases (68). Recommendation 30 When affection of the central compartment lymph nodes is suspected, therapeutic dissection of this compartment is indicated (Recommendation A). When the presence of metastasis is confirmed in the pre- or perioperative period, dissection must include the lymph nodes in the ipsilateral compartment (Recommendation B). Recommendation 31 When affection of the lymph nodes in the lateral compartments is suspected, therapeutic dissection of these compartments is indicated (Recommendation A). When the presence of metastases is confirmed in the pre- or perioperative period, dissection must include the central compartment lymph nodes (Recommendation B). Recommendation 32 In patients without suspected metastases on preoperative US and the surgeon's perioperative assessment, elective dissection of the central compartment lymph nodes may be considered when the tumors are > 4 cm or there is apparent extrathyroidal invasion (Recommendation C). Although the BRAF gene mutation is associated with greater initial aggressiveness of papillary carcinoma, including higher frequency of lymph node metastases, the available data are not sufficient to rule out or indicate elective dissection of the central compartment lymph nodes on the grounds of the absence or presence of this mutation, respectively (84,85). How must staging be performed after surgery? The aims of postoperative staging are as follows: 1) to estimate the mortality risk; 2) to establish the risk of relapse; 3) to assess the quality of surgery; 4) to define the initial individualized treatment; and 5) to make the terms uniform and facilitate the communication among the multidisciplinary staff that participates in patient treatment and follow up. The staging system formulated by the American Joint Committee on Cancer/International Union against Cancer (AJCC/UICC) based on the tumor size, extrathyroidal invasion, lymph node and distant metastases (TNM), and age is recommended for all tumor types including thyroid tumors as an attempt to standardize the description of tumor extent. As that system does not consider other factors known to influence the progression and prognosis of DTC patients, its ability to predict the persistence and relapse of these tumors is limited, whereas it is more useful in the estimation of the mortality rate associated with the disease. In any case, the tumor size, presence and extent of extrathyroidal invasion and lymph node and distant metastases are relevant parameters in the choice of the initial treatment. Some histological variants such as tall and columnar cells, extensively invasive follicular carcinoma, and poorly differentiated carcinoma exhibit more aggressive behavior (72,78). Other signs of a poor prognosis include considerable nuclear atypia, tumor necrosis, and vascular invasion, all of which suggest lower grades of tumor differentiation (86). The impact of lymph node compromise on the prognosis is controversial. According to prevailing opinions, lymph node metastases that are macroscopic, present in large numbers or characterized by extracapsular extension increase the risk of relapse and mortality in patients older than 45 years old (87,88). Therefore, we describe four categories of risk of persistent or recurrent disease in table 5. Table 5. Stratification of the risk of recurrence LN: lymph nodes; ECE: LN: extracapsular extent; WBS: whole body scan. a Detected on clinical or radiological assessment or post therapy WBS; b Based on the surgeon's description and postoperative assessment; c cN0: without metastases on pre- US and perioperative assessment, with (pN0) or without (pNx) elective dissection; d Only when 131I ablation is indicated. We excluded children and adolescents from that stratification, as the classification of risk should be particularized in those cases because, despite the high frequency of cases of disease not restricted to the thyroid, their long-term prognosis is excellent (67,72). Recommendation 33 The initial staging of patients must be performed according to the TNM system. However, the stratification of risk must also consider other anatomical-pathological data (histological subtype, vascular invasion, free or affected margins) as well as the postoperative assessment to achieve better estimates of the risk of recurrence (Recommendation B). How are the tissues remaining after surgery quantified? Even when thyroidectomy is reported to be total, quantification of the remaining thyroid tissue is recommended, especially when surgery is performed by a surgeon with little or unknown experience. For that purpose, neck US is superior to scintigraphy and also provides information on the persistence of lymph node metastases (89,90). For this purpose, a 3-month interval is required between surgery and ultrasonographic assessment (90). The analysis of vascularization using Doppler can be helpful in the differential diagnosis of lesions in the thyroid bed and in determining whether the lymph nodes are benign or metastatic. Recommendation 34 Measurement of thyroid remnants and postoperative assessment of the neck must be preferentially performed using a Doppler US (Recommendation B). Recommendation 35 Surgical reinterventions should be considered when the US shows large thyroid remnants or lymph node metastases (Recommendation B). When is 131I ablation/therapy indicated after total thyroidectomy? Treatment with 131I is indicated for patients with incomplete tumor resection or apparent metastases after thyroidectomy and who are not candidates for surgical reintervention. In patients with apparently complete tumor resection but high or intermediate risk of persistent disease (87,91), adjuvant 131I therapy impacts prognosis (92) and is thus recommended. 131I ablation is not indicated for very low-risk patients (67,72,73,75,93-95). In the remainder of patients, i.e., those with a low risk of persistent/recurrent disease, ablation is controversial (67,96). In such cases, administration of 131I may confer additional benefits such as improvement of the serum Tg specificity and the early detection of metastasis on a whole body scan (WBS). Nevertheless, in patients with stimulated Tg levels < 1 ng/ml and no abnormalities on an US a few months after thyroidectomy, the specificity of that marker is not affected by the remaining tissue; it is known that a WBS after 131I administration does not detect metastases (97,98); and the risk of relapse is low, even when 131I is not administered (90,99,100). For those reasons, this criterion suggests to dismiss ablation in the low-risk group (90,97-100). Indication for 131I must also consider the cost of treatment as well as its potential adverse effects such as transient alterations of the gonadal function (101-103), acute sialadenitis (103), early menopause (104), and persistent xerostomia and xerophthalmia (105) in addition to a higher risk of second cancers (106). Recommendation 36 131I is indicated for patients subjected to total thyroidectomy and with known tumor persistence or high or intermediate risk of relapse (Recommendation B). With regard to low-risk patients, ablation should be dismissed when stimulated Tg levels are < 1 ng/ml after surgery (Recommendation B). Ablation is not indicated in cases with a very low risk of relapse (Recommendation B). How should TSH stimulation be performed before 131I ablation/therapy? Human recombinant TSH is the pre-treatment procedure indicated for patients with conditions potentially aggravated by hypothyroidism [such as heart, lung, or atherosclerotic disease, kidney failure, severe depression, old age, and weakening diseases (107)] or with an inability to raise endogenous TSH to satisfactory levels (as in hypopituitarism). Even when none such condition is present, recombinant TSH is preferable when it is available in patients with complete tumor resection and no apparent metastasis after thyroidectomy because it is known to be efficacious in such cases (108-112). Furthermore, recombinant TSH exhibits advantages over discontinuation of T4: the quality of life of the patients is not affected; it eliminates the symptoms and eventual risk of hypothyroidism; and it is associated with shorter leaves of absence, less extrathyroidal radiation, and shorter exposure to high TSH levels (103,108,109,111,113). In the remainder of patients (incomplete tumor resection or persistent metastases), discontinuation of T4 over 3 or 4 weeks is still the most proper indication in the absence of clinical contraindications. The latter recommendation also applies to children and adolescents because although the use of recombinant TSH is safe and apparently efficacious in them (114), further studies are required. To perform 131I ablation or therapy, one ampoule of recombinant TSH (0.9 mg) is administered intramuscularly on two consecutive days followed by 131I administration 24 hours after the second dose. Recommendation 37 In the presence of clinical conditions potentially aggravated by hypothyroidism, recombinant TSH is the recommended pre-treatment (Recommendation A). In the absence of such conditions, the discontinuation of T4 is recommended in patients with known tumor persistence, as well as in both children and adolescents (Recommendation C). In the remainder of patients, recombinant TSH is recommended whenever it is available (Recommendation A). What 131I activity should be administered? In patients with low risk of persistent or recurrent disease and in whom a total thyroidectomy was properly performed, an activity of 30 mCi of 131I is efficacious to achieve remnant ablation (108,109,115-118) and exhibits low medium- and long-term relapse rates (67,93,117,119). In this regard, two major randomized trials with 438 (108) and 756 (109) patients stand out. Both studies showed clearly that the efficacy of 30 mCi for the purpose of ablation was the same compared to 100 mCi independent of the pre-treatment, i.e., discontinuation of T4 or recombinant TSH (108,109). When the size of the thyroid remnant is uncertain, the parameters to indicate an activity of 30 mCi are the volume measured on US (< 2 g), thyroid bed uptake [< 2% (108,109,115)], or postoperative Tg levels (97). Activities of 200 mCi or greater require caution when dosimetry is not available, particularly in the case of elderly or patients with diffuse lung metastases, because the maximum tolerated activity is commonly exceeded in such cases (120). Recommendation 38 In low-risk patients, an activity of 30 mCi is preferable, whereas a 100-mCi activity is reserved for cases with known large tissue remnants (Recommendation A). Recommendation 39 In patients without apparent disease, but intermediate or high risk, activity of 100 mCi is recommended (Recommendation B). Recommendation 40 In patients with local-regional tumor persistence, who are not candidates for surgical reintervention, activities of 100 or 150 mCi are recommended (Recommendation B). Recommendation 41 An activity of 200 mCi should only be considered for adults with known distant metastases (Recommendation B). What other recommendations are important in 131I ablation/therapy? A low-iodine diet, usually < 50 µg/day for 7 to 14 days before the administration of 131I, appears to increase the uptake and radiation dose in the lesions (121). Nevertheless, the influence of a low-iodine diet on the success rate of ablation/therapy has not yet been demonstrated in a convincing manner (121). The corresponding studies are few, and none included a long-term assessment of the relapse and mortality rates (121). In addition to diet, other sources of iodine should be investigated (e.g., medications, syrups, dietary supplements, topic solutions, cosmetics). In addition, iodinated contrast agents are an important source of contamination, whose complete elimination requires at least one month (71). Administration of furosemide and/or lithium before 131I may increase its uptake and the success rate of ablation performed with low 131I activity (116,118); however, the available evidence does not suffice to recommend it as routine. Recommendation 42 Despite its controversial benefit, a low-iodine diet must be prescribed due to its potentially positive effect and low cost (Recommendation B). Recommendation 43 Women of reproductive age should be subjected to clinical and laboratory assessment (measurement of human chorionic gonadotropin; b-hCG) to rule out a pregnancy before administration of 131I. Pregnancy and breastfeeding are absolute contraindications to the use of RAI (Recommendation A). Women are advised to avoid conception for 6 to 12 months after RAI, and men are similarly advised for 3 months (Recommendation B). What tests must be performed before and immediately after 131I ablation/therapy? When TSH levels are > 30 mIU/l, Tg levels after total thyroidectomy and immediately before ablation bear a direct correlation with the presence of persistent metastasis and WBS after treatment with RAI (67,97,122), are predictive of the success of the ablation (97,123), and behave as an important long-term prognostic factor (122,124,125). In addition, in the patients with elevated Tg levels after initial treatment, comparison with the Tg levels obtained during the ablation is predictive of the clinical outcome (124,125). WBS before RAI treatment exhibits a lower sensitivity for metastases compared to WBS after RAI treatment (126) and may also be associated with a risk of stunning, delayed treatment, and higher costs. Conversely, the post-treatment WBS exhibits higher sensitivity and is able to identify unsuspected metastases (67,87,91,97,98,109,111,122,126). Physiological uptake, or false-positive WBS results after treatment with RAI must be suspected when Tg is undetectable or low at the time of ablation [in the absence of anti-Tg antibodies (TgAb)], when there is a lack of radiological correspondence to uptake, or when uptake occurs in sites unusual for metastases, particularly when isolated (127). Recommendation 44 Measurement of serum Tg and TgAb must be performed immediately before 131I administration (Recommendation B). Recommendation 45 In patients with known anatomical-pathological and surgical data, WBS prior to treatment with RAI is not recommended (Recommendation B). Recommendation 46 WBS must be performed 5 to 7 days after 131I administration in any patient subjected to this therapy (Recommendation B). When the results of WBS after treatment with RAI are suggestive of metastasis, it is recommended to complement the assessment with an additional method to image the area corresponding to ectopic uptake (Recommendation B). What is the approach in patients already subjected to thyroidectomy but with insufficient anatomopathological data for risk stratification? In this circumstance, the assessment of the thyroid remnants and the determination of the presence of metastases are important. Initial assessment comprises clinical examination, serum Tg [T4] (i.e., without TSH stimulation) and TgAb levels, neck US, and simple chest x-rays. Surgical reintervention must be considered when large thyroid remnants (128) or lymph node metastases are found. When neither US nor x-rays show abnormalities, but Tg [T4] levels are higher than 1 ng/ml, it is recommended to administer 30 or 100 mCi of 131I based on Tg [T4] levels. When the initial assessment rules out persistent disease, stimulated Tg must be performed (following discontinuation of T4 or use of recombinant TSH) together with a diagnostic WBS. An activity of 100 mCi of 131I is recommended when stimulated Tg levels are greater than 10 ng/ml under hypothyroidism or 5 ng/ml after use of recombinant TSH and a negative WBS. An activity of 100 to 200 mCi is recommended when WBS shows ectopic uptake, depending on the extent of the metastases. Recommendation 47 In patients undergoing thyroidectomy, but whose anatomopathological data are not sufficient to establish appropriate risk stratification, a more thorough postoperative assessment is needed to determine the need for surgical reintervention and 131I ablation or therapy (Recommendation A). When must external radiotherapy be included in the initial treatment? Recommendation 48 External radiotherapy must be considered for patients with incomplete tumor resection, who are not candidates for surgical reintervention, and when the tumor remnants exhibit low 131I uptake (Recommendation B). When must T4 replacement be initiated? In very low-risk individuals without indication for 131I administration, T4 replacement must be initiated immediately after surgery. When recombinant TSH is used, there is no justification to delay T4 replacement. Similarly, in the case of low-risk patients in whom the decision to perform 131I ablation depends on the Tg level approximately 12 weeks after surgery, hormone replacement must be initiated early. Finally, when the clinical, histological, and radiological data indicate the need for 131I ablation/therapy, and the 131I ablation/therapy will be performed within four weeks, T4 replacement may be delayed following thyroidectomy. However, when 131I ablation/therapy is scheduled for a later period, T4 replacement must be initiated after surgery to avoid long-lasting hypothyroidism, and then discontinued. When 131I ablation/therapy is preceded by discontinuation of T4, hormone replacement must be restarted early, i.e., 48 hours after the administration of RAI, and at the full dose to promote rapid TSH reduction (113). Recommendation 49 T4 therapy must be initiated as early as possible (Recommendation B). What is the indicated TSH level following initial treatment? In patients with well-differentiated tumors, TSH suppression is an important adjuvant therapy. In individuals with known metastasis, TSH suppression has an inhibitory action on tumor growth and disease progression (67). In patients without apparent disease but with elevated Tg levels, low TSH levels contribute to the long-term negation of this marker (129). In addition, in cases without apparent disease but high risk of relapse, TSH suppression is associated with improved outcomes (130,131). Even in low-risk patients under full remission, TSH levels persistently over 2 mIU/ml are associated with worse long-term progression (132). Subclinical thyrotoxicosis is associated with bone mass compromise, especially among postmenopausal women (57,58,133), and morphological and functional heart disorders (57,58), which have more clinical repercussions among older adults. To minimize the adverse effects of suppressive therapy with T4, some steps are important. First, clinicians should pay attention to the fact that the TSH target must be individualized and subjected to constant reassessment (134), taking the presence of metastasis, Tg levels, and risk of relapse into account (Figure 2). Second, truly undetectable TSH is not necessary, and high serum T4 and especially T3 levels, must be avoided. Third, in addition to appropriate calcium and vitamin D intake (in all), periodic cardiovascular assessment (all) and bone densitometry (postmenopausal women) are recommended in patients subjected to TSH suppression for long periods of time. Finally, if the TSH suppression persists, in addition to their usual therapeutic indications, beta-blockers must be considered in patients with heart symptoms or morphological alterations, as well as the use of bisphosphonates in postmenopausal women with osteopenia (57,58). Figure 2. Recommended TSH levels after initial treatment in patients with differentiated thyroid cancer. To avoid long periods outside the target, it is recommended to measure TSH levels 6 to 8 weeks after the onset of replacement therapy or after any change in the dose or commercial formulation of T4 and every six months once the desired levels are achieved, provided the dose is kept unchanged. Recommendation 50 The level of TSH suppression must be individualized according to the ongoing disease state (Recommendation B). Measures to monitor and prevent the negative effects of TSH suppression must be applied to patients subjected to TSH suppression for long periods of time (Recommendation B). What are the recommendations relative to the method for thyroglobulin measurement? Measurement of Tg is not a trivial laboratory exam (135). Although a number of limitations are minimized by highly sensitive immunometric methods, others remain (135): Lack of international standards, resulting in variability of the available methods. Excessively high inter-assay variability, especially when we consider the usual interval between sample collections during the follow up of patients with differentiated carcinoma (6 to 12 months). Therefore, to reduce the inter-assay error, the laboratories should keep samples frozen for at least one year to process the older sample together with the newer one. Possibility of a "hook effect", especially in the immunometric assays, leading to inappropriately low results in patients with very high Tg levels. To avoid this effect, the tests should be systematically performed in two steps. The presence of TgAb in the serum can elicit false low Tg results in immunometric assays (136). Therefore, investigation of TgAb is mandatory, and whenever positive, the laboratory must call attention to the possibility of false-negative Tg results. In such cases, quantitative investigation of serum Tg mRNA may be an alternative (137); however, it is not yet available in clinical practice. What is the recommendation for the initial assessment of patients who were not given 131I? Recommendation 51 For very low-risk patients not subjected to treatment with 131I, it is recommended to measure Tg [T4] and TgAb levels and to perform a neck US six months after thyroidectomy. The patients with serum Tg [T4] levels < 1 ng/ml, no TgAb, and no abnormal findings on US are considered to be disease free; therefore, the measurement of stimulated Tg is not needed (Recommendation B). When Tg [T4] levels are higher than 1 ng/ml, or the TgAb assay is positive, patient management will depend on the behavior of these markers, i.e., a more thorough investigation (in case of increase) or only monitoring (in case of decrease) (Recommendation B). What exams must be performed at the initial assessment following ablation? In the patients in whom WBS after RAI treatment does not show ectopic uptake, six months after ablation, measurement of Tg [T4] and TgAb levels and neck US are recommended. At that moment, most patients exhibit Tg [T4] levels < 1 ng/ml, a negative TgAb, and no abnormal findings on US. In that case, stimulated Tg ought to be measured 9 to 12 months after ablation (138-140). Ultra-sensitive Tg tests (functional sensitivity < 0.2 ng/ml) are available in Brazil and may reduce the need to measure stimulated Tg (141). Indeed, when Tg is measured using these tests, stimulation becomes unnecessary in low-risk patients with undetectable Tg [T4] levels, no TgAc interference, and negative US findings (141-145). Diagnostic WBS concomitant with stimulated Tg may be helpful in intermediate- or high-risk patients (140); however, its value has not been established (138). In the patients with undetectable Tg [T4] levels and negative US findings but circulating TgAb, stimulated Tg associated with diagnostic WBS may be useful (146). However, if TgAb was assessed earlier, usually at the time of ablation, and the ongoing levels show a reduction of > 50% of their titer (147), neither stimulated Tg nor diagnostic WBS are necessary. To avoid stunning, diagnostic WBS must be performed with 123I, 2 mCi of 131I (148), or tracer activity of 5 mCi of 131I, provided that the 131I therapy (whenever necessary) is performed 3 to 5 days later (149). TSH levels > 30 mIU/ml are necessary to accomplish appropriate Tg stimulation and WBS and are achieved by a total (3 to 4 weeks) or partial (6 to 8 weeks) discontinuation of T4 (150) or administration of recombinant TSH. When hypothyroidism is contraindicated or endogenous TSH is unable to increase to appropriate levels, use of recombinant TSH is the only available option. In the remainder of cases, due to the above-mentioned advantages, use of recombinant TSH is systematically preferred, when available. For the purpose of Tg stimulation, one ampoule (0.9 mg) of TSH is administered intramuscularly on two consecutive days; the Tg levels should be measured 72 hours after the second dose. Recommendation 52 Measurement of serum Tg [T4] and TgAb levels and a neck US must be performed six months following ablation. Stimulated Tg (9 to 12 months after ablation) is recommended when the earlier results were negative, except for low-risk patients with undetectable Tg [T4] levels on an ultrasensitive test and no TgAb interference (Recommendation B). Diagnostic WBS (associated with stimulated Tg) may be useful in intermediate- or high-risk patients (Recommendation C). Recommendation 53 In patients with undetectable Tg [T4] levels and a negative US but circulating TgAb, stimulated Tg associated with a diagnostic WBS may be useful (Recommendation C); however, those tests are not necessary when the TgAb titers decrease by > 50% (Recommendation B). What is the recommended investigation in patients with high Tg and negative US? In patients with Tg [T4] levels > 1 ng/ml and a negative neck US, the initial step is to perform a chest and mediastinal CT. When no abnormalities are thus found, one may decide to merely monitor the Tg behavior later or to perform a more thorough investigation based on the Tg [T4] levels and the patient risk category. In the latter case, the traditional recommendation is to perform WBS after the use of radioiodine (100 mCi 131I) followed by 18FDG-PET (139,151); however, the latter might also be the first step (138,152,153). When negative Tg [T4] levels increase to levels above 1 ng/ml following TSH-induced stimulation and metastases are not found at the initial assessment, conservative management is recommended when Tg is less than 10 ng/ml following discontinuation of T4 or 5 ng/ml with use of recombinant TSH (91,124,125,138). When the Tg levels are higher, a more thorough investigation is recommended, as mentioned above. Many patients with elevated Tg and no apparent disease progress late into complete remission (91,112,124,125,138,151,152,154). Recommendation 54 In patients with Tg [T4] levels greater than 1 ng/ml or stimulated Tg higher than 5 ng/ml (with recombinant TSH) or 10 ng/ml (under hypothyroidism), chest and mediastinal CT followed by WBS after an empirical dose (of 100 mCi) of 131I and/or 18FDG-PET is recommended (Recommendation B). How should cervical lymphadenopathy be managed? US is the most sensitive method to detect neck metastases (122,140,142,144,155); however, its sensitivity depends on the examiner's experience and ability (156). Lymph nodes larger than 5 mm must be investigated only when they exhibit micro-calcifications or cystic degeneration or, in the absence of these findings, if they are round and lack an echogenic hilum or are hypervascular based on Doppler results (98,140,157-160). FNA is crucial to establish the nature of suspicious lymph nodes; therefore, the biopsied tissue must be subjected to cytological analysis and Tg should be measured in the needle washing fluid (158,160). Recommendation 55 US is the best method to assess neck lymph nodes. Cytological analysis of the FNA material and measurement of Tg in the aspirated fluid are recommended in suspicious lymph nodes (Recommendation B). How should patients who achieve complete remission after treatment be monitored? Recommendation 56 The patients who achieve complete remission (undetectable Tg, no TgAb, and negative findings on the imaging methods) following treatment are at low risk of relapse in the long term (87,90,91,112,138,143). Therefore, these patients may be assessed once per year by means of a clinical examination and measurement of serum Tg [T4] and TgAb levels (Recommendation B). Neck US must be performed annually the first five years in intermediate- or high-risk patients, whereas it is optional or may be performed at longer intervals in low-risk patients (Recommendation B). The long-term recommended TSH levels are shown in Figure 2. In case TgAb or Tg [T4] levels become persistently detectable, and more particularly, when they exhibit progressive increase, and US shows no abnormal findings, investigation must include other imaging methods such as chest and mediastinal CT, WBS after RAI treatment, or FDG-PET (Recommendation B). The need to repeat stimulated Tg in patients who maintain negative findings of Tg [T4], TgAb, and US is doubtful. If it is, indeed, performed, it should not be too soon after the first negative stimulated Tg test [i.e., < five years (161)]. Recommendation 57 In the cases where only the TgAb are elevated, an annual measurement of Tg [T4] and TgAb levels and the performance of the US are recommended (Recommendation B). Abnormalities on the US, the persistent and progressive increase of TgAb titers, and elevated Tg [T4] levels point to tumor recurrence, indicating the need for further investigation by means of other imaging methods (Recommendation B). Conversely, disappearance of TgAb with undetectable Tg [T4] and negative US findings are indicative of remission (Recommendation B). How should the patients with elevated thyroglobulin without apparent disease at the initial assessment be monitored? Recommendation 58 When the initial assessment does not reveal disease, monitoring by means of serum Tg [T4] and TgAb l levels, a neck US, and maintenance of TSH suppression (Figure 2) are recommended. In the cases where elevated stimulated Tg is the only finding, a second test is recommended 18-24 months later. Whenever Tg increases, the clinical investigation must be furthered (chest and mediastinal CT, WBS following the use of an empirical 131I dose, FDG-PET). As long as Tg levels are stable or decreasing, no further investigation is needed, and the clinical outcome will be most likely be satisfactory (91,112,124,138,151,154). Finally, the patients with undetectable stimulated Tg should be monitored as if they were in complete remission (Recommendation B). Metastatic disease When surgical treatment and 131I therapy associated with TSH suppression (< 0.1 mIU/L) (162) do not suffice to control metastatic disease, external radiotherapy should be considered depending on the site. Conventional chemotherapy has proven to induce a limited benefit but considerable morbidity in patients with progressive disease, in spite of the measures described above (163). New therapeutic approaches based on molecular targeted therapies are currently emerging as promising alternatives in such cases (164,165). However, the recommendation to use those new drugs in clinical practice must be cautious, as a large number of the new drugs are still under investigation and their availability is limited. In addition, their high cost and significant side effects (heart, gastrointestinal, and skin) must be considered. Whether synergistic drug combinations exhibit better cost-benefit ratios and less morbidity remains to be determined (166). What is the approach for local-regional disease? Five to 20% of patients with DTC exhibit local or regional recurrence, which is approximately twice the frequency of the distant metastases (67,72,167). The most widely indicated treatment of local-regional disease is surgical excision, especially in the absence of distant metastases. Most surgeons recommend extending the exploration beyond the apparently affected compartments because the extent of the metastatic disease tends to be larger than suggested by the imaging exams, but this exploration should preserve the vital structures (168). Approximately 30-50% of the patients attain complete remission shortly after surgical reintervention (169). In recent years, US-guided percutaneous ethanol injection of metastatic lymph nodes has emerged as a therapeutic possibility for patients with papillary carcinoma and a limited number of metastases (170,171). In tumors that invade the upper airway and/or digestive tract, aggressive surgery seeking to resect as much affected tissue as possible, while preserving organ function is recommended. Surgery may include tracheal resection with anastomosis or esophagopharyngectomy (172). Recommendation 59 Therapeutic dissection is indicated in metastases located in the central compartment; and careful pre- and perioperative assessment is required to define the extent of the procedure in the lateral compartments (Recommendation B). Therapeutic dissection is indicated in metastases located in the lateral compartments (Recommendation B), and dissection of the central compartment lymph nodes is also indicated when it was not performed initially (Recommendation B). Recommendation 60 When surgical resection is not complete or possible, and the tumor has 131I uptake, the patient should be subjected to treatment with 131I (Recommendation B). In patients treated with 131I, lack of ectopic uptake on WBS after treatment, associated with negative stimulated Tg is predictive of low risk of relapse (173). Recommendation 61 Whenever it is technically possible, extensive surgery is indicated for tumors that invade the upper airway and/or digestive tract, provided that the surgery can be performed by surgeons with broad experience in these procedures and reinterventions and can subsequently be combined with radioactive iodine therapy when the tumor demonstrates 131I uptake (Recommendation B). Recommendation 62 External radiotherapy is indicated in patients with clinically significant, non-resectable, local-regional disease without 131I uptake (Recommendation B). Distant metastases: general considerations The patients with DTC and distant metastases exhibit increased mortality and morbidity (67,72). Nevertheless, the negative impact of metastases depends on their number, localization, and size as well as on the patient age and tumor 131I uptake (174,175). Whenever metastases are resectable, surgery is the treatment of choice, provided its associated morbidity is acceptable. In this regard, it is advisable for the procedure to be performed by a surgeon with wide experience in major surgery and reinterventions. The procedure must be aggressive, while seeking to preserve organ function. In this regard, the indication for highly aggressive surgical procedures that compromise the overall state of the patients without likelihood of curing them, or in the presence of multiple additional metastases, must be questioned. What is the approach in patients with lung metastases? The treatment of lung macrometastases with 131I uptake is similar to the treatment of micrometastases. However, as the 131I uptake is not adequate in such tumors, therapeutic alternatives must be taken into consideration, such as surgical resection of the metastases, which must be performed whenever possible; palliative external radiotherapy in symptomatic intrathoracic tumors; drainage of symptomatic pleural or pericardial effusions; tumor redifferentiation attempts (178); or use of the novel molecular-targeted drugs, which appear to induce better responses specifically in lung metastases (179,180). Traditional chemotherapy has not proven to be useful in patients with non-resectable tumors that do not exhibit 131I uptake (163). Recommendation 63 Patients with lung micro- or macrometastases that demonstrate 131I uptake must be given 100 to 200 mCi of 131I every 6 months during the first two years and then once per year. Most remissions occur at an accumulated activity < 600 mCi. Above this level, the eventual benefit of additional radioactive iodine therapy must be balanced with its potential risks (Recommendation B). Recommendation 64 A large number of patients with lung macrometastases kept under suppressed TSH levels (< 0.1 mIU/L) have a good outcome and can be monitored in a conservative manner (Recommendation B). Other cases of lung macrometastases exhibit a more aggressive progression, and thus the palliative treatment of symptomatic lesions must be considered, including surgical resection, external radiotherapy, and endobronchial laser ablation (Recommendation B). Recommendation 65 Patients with progressive or symptomatic lung metastatic disease that is not responsive to conventional treatment should be encouraged to enroll in clinical trials for new drugs when available. For patients not included in clinical trials, the off-label use of drugs commercially available for other malignant tumors and previously investigated in DTC may be considered (Recommendation C). What is the approach in patients with bone metastases? Up to 40% of the patients with DTC and distant metastases exhibit bone involvement, which is associated with a poorer prognosis (176). The survival of the patients with bone metastases is usually reduced due to the therapeutic challenge posed by the localization and extent of the lesions, which usually do not exhibit 131I uptake. In addition to the lower survival rates, the development of bone metastases may result in significant morbidity due to pathologic fractures, intense pain, immobility, and reduced quality of life (181). In clinical studies, the term skeletal-related events (SRE) is used to quantify the morbidity associated with bone metastases (181). The clinical determinants that compose the SRE include spinal cord compression, pathologic fractures, and the need for external radiotherapy or surgery to afford pain relief or control tumor-related hypercalcemia (181). The patients frequently exhibit pathologic fractures that can involve the vertebrae, resulting in severe neurological problems, including disabling pain and paraplegia (182). In addition to the clinical data, imaging resources are crucial to identify the presence, location, and extent of the bone lesions; skeletal CT or MRI and FDG-PET/CT are the best currently available methods for this purpose (176). When the number of bone metastases is limited, surgical resection significantly improves patient prognosis and survival and may eventually also be curative (176,183,184). Bone lesions that exhibit 131I uptake are also associated with improved survival (176,184). The recommended 131I activity varies from 150 to 200 mCi per cycle. In tumors located in critical areas close to neural structures, 131I-induced edema can cause nerve compression associated with severe pain and functional disability (182). In such cases, external radiotherapy combined with corticosteroids must be considered (176,182). Radiotherapy is also indicated for non-resectable metastases that do not exhibit 131I uptake. Other procedures such as intra-arterial embolization, periodic pamidronate or zoledronate infusions, or cement injections may also be useful (185,186). Selumetinib - a MEK1 and MEK2 inhibitor - represents a recent perspective in the treatment of bone metastases, which appear to be more resistant to tyrosine kinase inhibitors; this drug significantly increases 131I uptake and reverts the refractoriness to 131I (165). Recommendation 66 Bone metastases must be subjected to surgical treatment whenever possible. The treatment of non-resectable bone lesions that have 131I uptake consists of the administration of 150 or 200 mCi 131I per cycle. These therapeutic approaches improve patient quality of life and survival (Recommendation B). Recommendation 67 In areas where the expansion of bone metastases induced by 131I or high TSH levels may cause neurological complications or pain, corticosteroid use is recommended (Recommendation B). Recommendation 68 External radiotherapy is recommended for non-resectable metastases that are painful or symptomatic and are located in sites where the 131I-induced expansion is problematic or where they do not demonstrate 131I uptake (Recommendation B). Recommendation 69 Patients with progressive or symptomatic bone metastatic disease non-responsive to conventional treatment must be encouraged to enroll in clinical trials of new drugs when they are available (Recommendation C). What is the approach for brain metastases? Brain metastases are rare complications of DTC and occur more frequently among older adults with advanced stages of the disease. Nevertheless, these lesions may be the first manifestation or the first metastasis of thyroid cancer (187). Imaging exams such as CT and gadolinium-based MRI (preferably) are usually able to reveal the tumor location and extent. A biopsy is frequently necessary to confirm that a lesion is a thyroid cancer metastasis (188). Initial treatment is surgical and must attempt a full resection of the metastases, as a full resection is associated with improved survival (187,188). These lesions do not usually exhibit 131I uptake, and treatment must thus include external radiotherapy or target-directed therapy (189). Recommendation 70 The treatment of choice for brain metastases is the full surgical resection of the lesions (Recommendation B). As the lesions often do not exhibit 131I uptake, external radiotherapy is indicated when surgery is not possible (Recommendation B), or the use of novel drugs must be considered, as indicated in R65 (Recommendation C). When should recombinant TSH be used in metastatic disease? The possible use of recombinant TSH in the treatment of metastases that have 131I uptake has been assessed, and the response was seemingly similar to T4 withdrawal (182,190,191). A retrospective study showed that the five-year survival rate was similar in patients with lung or bone metastases prepared with either T4 withdrawal or recombinant TSH before 131I therapy (190). Recommendation 71 In the treatment of metastases with 131I, preparation with recombinant TSH is indicated in patients presenting with clinical conditions that contraindicate discontinuation of T4 (and the consequent hypothyroidism), who are unable to increase the endogenous TSH to satisfactory levels, are very debilitated, or old (Recommendation B). Pre-treatment with corticosteroids is recommended in metastatic sites where the risk of expansion due to edema and bleeding might be problematic (Recommendation B).

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Correspondence: Pedro Weslley Rosário Instituto de Ensino e Pesquisa Santa Casa de Belo Horizonte Rua Domingos Vieira, 590 30150-240 - Belo Horizonte, MG, Brazil pedrorosario@globo.com

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