Ata guidelines 2015 thyroid

Skip nav destination PDF split view of the content of article figures &- tables Video audio additional data current American Thyroid Association (ATA) Management guidelines for the treatment of differentiated thyroid cancer (DTC) stratify patients to decide on additional radiooid therapy (RAI) after surgery, and to predict recurrent/ongoing disease. However, studies to evaluate the detection of distant metastases and how these guidelines are presented in patients with distant metastases are scarce. To evaluate the 2015 ATA Guidelines in patients with DTK regarding 1) detection of distant metastases, and 2) the accuracy of its risk stratification system in patients with distant metastases. Patients and basic evaluation measures We retrospectively concluded 83 DTC patients diagnosed with distant metastases during initial therapy, and a control population of 472 patients (312 low-risk patients, 160 intermediate risks) who did not have a routine indication for RAI therapy. We used the control group to assess the percentage of distant metastases that would have been missed if RAI therapy was not performed. Two hundred and forty-six patients did not have a routine indication for RAI therapy, of which 4 (1.6%) had distant metastases. In addition, among 83 patients with distant metastases, 14 patients (17%) had an excellent answer, while 55 (67%) follow-up of 62 months. None of the 14 patients who received an excellent response had a relapse. In patients without a routine indication of RAI therapy under the 2015 ATA Guidelines, 1.6% of patients would initially lack distant metastases. In addition, in patients with distant metastases at diagnosis, 2015 the ATA Guidelines are an excellent predictor of both persistent disease and relapse. The global incidence of differentiated thyroid cancer (DTC) has steadily increased over the past 2 decades (1, 2). Since mortality remained stable to a slight increase, a less aggressive therapeutic approach appeared (1-4). In order to optimise the need for de-escalation of therapy and follow-up strategies, various systems were proposed and evaluated that predicted the risk of relapse and survival in patients with DTC (3, 5–9). Current 2015 American Thyroid Association (ATA) Guidance guidelines use their own risk stratification system to determine the need for radioiodine therapy (RAI) after surgery (3). However, this approach has been challenged by several experts in the field (10–12). Since one of the purposes of RAI therapy is to treat all other unknown cancerous tissues, skipping RAI therapy can leave undiscovered metastases untreated (11). Using the criteria set out in the 2015 ATA Guidelines, one study stated that a significant proportion of patients with remote metastatic disease would not be treated with RAI and would thus missed (13). However, this study also included patients in whom during tracing. Another study showed, in low- and medium-risk patients defined by the 2009 ATA Guidelines, that 1% of distant metastases would be missed by skipping RAI therapy (14). Several studies have shown that patients with remote metastases have a relatively poor prognosis (15–21). Risk factors such as age, RAI growth, tumor size, and follicular type influence this prognosis (15-23). However, as far as we know, there are no studies yet of the ATA risk stratification system 2015 in DTC patients with distant metastases in terms of its ability to predict prognosis, relapse and survival. We initiated this study as 1) there are very few studies that assessing the risk factors for metastatic disease identified before or during 2) only 2 studies, both with limitations, have so far assessed the consequences of skipping RAI therapy under the new ATA guidelines for proportion of possible undetected distant metastases (13, 14), a 2015 ATA risk stratification system has not yet been evaluated in patients with DTC patients with distant metastases. The purpose of our study is to evaluate the 2015 ATA guidelines in patients with DDI in relation to 1) the ratio of possible distant metastases and 2) the implementation of an ATA risk stratification system in patients with distant metastases. Materials and methods Study population and clinical results We retrospectively identified all patients, aged 16 years or older, who have been diagnosed and/or treated for papillary (PTC) or follicular (FTC) thyroid cancer (including Hürthle cell carcinoma) at Erasmus Medical Center, Rotterdam, Netherlands, from January 2002 to December 2016. For this study, we included all patients who underwent thyroid surgery followed by RAI therapy, which is in line with the 2015 Thyroid Cancer Guidelines (24). Patients included are 1) diagnosed with distant metastases or before the initial RAI therapy based on pathology or imaging, such as computed tomography (CT) (pre-RAI group) or directly thereon with the help of postoperative whole body scan (post-RAI group); or (2) classified DTC as low or intermediate risk ATA (under the 2015 ATA Guidelines). We used data from patients with distant metastases (pre- and post-RAI group) to assess the effectiveness of the risk stratification system. Low and intermediate risk groups served as control groups to calculate the proportion of undetected distant metastases when rai therapy was missed. In a previous publication (25), we assessed the 2015 ATA Guidelines for 236 high-risk DTC patients, including patients with metastatic disease, treated at our institute (n = 78). In the current study, which focused only on the metastatic group and examined this in much more detail, 74 of the patients in this previous publication plus some additional patients with metastatic metastatic patients, we received demographic, disease, treatment, response to therapy, relapse and mortality characteristics. Demographic variables include age at diagnosis, gender and year of diagnosis. Features of the disease include type of disease, TNM-stage (8th edition), tumor size, presence/absence of multifocal disease, presence/absence of vascular invasion, presence/absence of metastases of lymph node, and minor/gross extrathyroid expansion (ETE). Data on treatment consists of the degree of surgery, use of RAI, and use of other modality treatment (eg, beam therapy [EBRT]). In rai treatment, a retrospective assessment was made using the ATA guidelines (3) in 1) the post-RAI group, ignoring knowledge of detected distant metastases and (2) control groups. RAI therapy is routinely recommended in high-risk patients, should be considered in patients with ATA at intermediate risk, is not routinely recommended in patients with low risk in patients with tumors greater than 1 cm and less than 4 cm, and is not given in ATA patients with low risk with tumors of 1 cm or less. Current and past Dutch guidelines recommend always treating patients with RAI therapy after a totalitarianectomy; total thyroidectomy is always indicated in tumors ≥ 1 cm.Response to therapy is determined in accordance with 4 categories described in the 2015 ATP Guidelines and is continuously evaluated during follow-up (i.e. dynamic risk stratification [DRS]) (3). Patients are considered an excellent response to therapy (i.e. there is no evidence of disease [NED]) if they have had depressed thyroglobulin (Tg) < 0.2 ng/ml or thyrotropin (also known as thyrotropin stimulating hormone; TSH)-stimulated Tg < 1 ng/ml, no detectable antibodies and no evidence of structural disease on the image. Patients are considered to be a biochemical incomplete response if they have had a suppressed Tg ≥ 1 ng/ ml or stimulated Tg ≥ 10 ng/ mL or an increase in anti-Tg antibody levels, but there is no evidence of structural imaging disease. Patients are considered to have a structural incomplete reaction if they have structural evidence of disease in imaging. Finally, patients are considered to have an indeterminate response if they have had suppression of Tg < 1 ng/ml or stimulated Tg < 10 ng/ml, decrease or stable antibody-TN levels. Persistent disease is defined either as a structural or biochemical incomplete reaction. Response to treatment was recorded for the first time 6 to 18 months after the first therapy (i.e. initial DRS); then during and at the end of the follow-up. Relapse is defined as a new biochemical or structural disease after more than 12 months NED. Refractory RAI disease is defined according to the 2015 ATA Guidelines (3), i.e. 1) malignant/metastatic tissue is never concentrated RAI, 2) tumor tissue loses the ability to concentrate RAI after previous data on RAI-avid disease, 3) RAI is concentrated in some lesions, but not in others, 4) progresses metastatic disease despite the progression of metastatic disease concentration of RAI. Furthermore, we also consider patients with stimulated Tg ≥ 30 ng/mL without significant concentration of RAI as having rai-refractory disease. The last follow-up time, survival status and date and cause of death have been recorded. Survival is defined as the time of initial diagnosis until the last date of follow-up, death or end of the study (December 2017), whichever comes first. The cause of death was received by hospital or general practitioners. Patients with extensive or rapidly progressive thyroid cancer and no clear other cause of death are classified as death due to thyroid cancer. The study protocol was approved by the Erasmus Medical Centre Institutional Review Board. Statistical analysis For constant variables, mean values and standard deviations (SD) or medians with interquartyl ranges (IQR). Absolute numbers with percentages are recorded for absolute variables. To assess the impact of the 2015 ATA Guidelines on the emergence of possible undetected metastases in remote areas, we compared post-RAI and the control group. The differences in characteristics between the groups before and after ral were then assessed using the student's T-test or 2-test. Overall survival (OS) and disease-specific survival (DSS) were analysed using the Kaplan-Meier method for patients with distant metastases. The same analyses were performed for the pre- and post-RAI groups as well as for the control population individually. In the before and after RAI groups, single-ovarian and multi-variant logistical regression or cox-proportional hazards were used to investigate the effect of various (potential) risk factors on the response to therapy (at first and in the event of a final subsequent reaction) developing NED, relapse or survival. Data on these (potential) risk factors are missing in 4% of the values; due to this low percentage, the patient was omitted from the relevant analysis if there was no value. P values below 0,05 are considered significant. All analyses were performed using SPSS statistics for Windows (version 24.0). Results Characteristics of the population During the study period, a total of 85 patients with distant metastases, 312 with ATA low risk, and 160 with ATA medium risk diseases were eligible for study. Two patients with distant metastases were excluded due to insufficient follow-up data, with 83 patients available for analysis. Table 1 lists the characteristics of the studied population with distant metastases. The mean age was 56.3 years and 57 (69%) are women. Metastatic disease was established prior to RAI therapy (pre-order group) in 33 (40%) Patients. In these 33 patients, these metastases were detected either due to symptoms (30%; eg, pain), during preoperative discontinuation due to a large tumor load in the neck (27%), or accidentally detected on CT or emission tomography (FDG-PET) performed for another reason (21%). remains 50 (60%) patients, distant metastases were detected directly after RAI therapy from post-joint therapy with whole-body examination (post-RAI group). PTC was present in 53 (64%) patients (including 10 (19%) follicular version of PTC) and the remaining 30 patients (36%) including 7 patients (8%) cell carcinoma of Hürthle. The median follow-up time was 62 months; during follow-up, 30 patients (36%) 26 of which were caused by thyroid cancer. In all patients except 1 who have received hemidroidectomy, due to the presence of unilateral recurrent paralysis of the nerves. All patients received RAI therapy (19 [23%] once, 21 [25%] twice and 43 [52%] received more than 2 therapies). Neck dissection was performed in 40 (48%) 6 [7%], side at 5 [6%] and both at 29 [35%]). Patients in the pre-RAI group were significantly older (62.5 years versus 52.3 years; P < 0.001) had significantly more frequent FTC (58% vs. 22%; p = 0.001), and received more often EBRT (46% vs. 18%; p = 0.008) than those in the post-RAI group. There are no differences between groups before and after RAI in terms of elevated Tg, presence of metastases of lymph nodes or gross ETE. The only difference was that patients in the post-RAI group more often had multifocal disease (26). Table 1.Characteristics of the study population. Total population (n = 83)a . Group before RAI (n = 33)a . Group after RAI (n = 50)a . P Value . Age at diagnosis (years) 56.3 ± 20.0 62.5 ± 17.9 52.3 ± 20.4 <0.001 Women 57 (69%) 20 (61%) 37 (74%) 0.198 Histopathological subtype Papillaren 53 (64%) 14 (42%) 39 (78%) 0.001 Follicular 30 (36%) 19 (58%) 11 (22%) Hürthle cell 7 (8%) 5 (15%) 2 (4%) 0.074 AJCC/TNM System Shutdown (8th) I - 0.051 II 36 (43%) 10 (30%) 26 (52%) III - - IV 47 (57%) 23 (70%) 24 (48%) Tumour size (cm) 3.5 (2.0–5.2) 4.1 (1.7-6.6) 3.5 (2.1-5.0) 0.668 Metastatic disease 83 (100%) 34 (100%) 50 (100%) - Lung 64 (77%) 22 (67%) 42 (84%) 0.071 Bone 24 (29%) 12 (36%) 12 (24%) 0.145 Pulmonary and bone 12 (15%) 4 (12%) 8 (16%) 0.902 Surgery (TT or HT) 83 (100%) 33 (100%) 50 (100%) - HT 1 (1%) 1 (3%) - 0,216 TT 82 (99%) 32 (97%) 50 (100%) Neck dissection 40 (48%) 14 (42%) 24 (48%) 0.226 Central 6 (7%) 2 (6%) 4 (8%) 0.131 Side 5 (6%) 4 (12%) 1 (2%) Both 29 (35%) 8 (24%) 21 (42%) RAI treatment 83 (100%) 33 (100%) 50 (100%) - once 19 (23%) 11 (33%) 8 (16%) 0.115 twice as many as 21 (25%) 9 (27%) 12 (24%) ≥ 3 43 (52 %) 13 (39%) 30 (60%) Cumulative dose (mCi) 387 (193-599) 294 (146-598) 446 (271-599) 0.295 Other treatments EBRT 24 (29%) 15 (46%) 9 (18%) 0,008 TKI 11 (13%) 6 (18%) 5 (10%) 0.299 Follow-up (months) 62 (34-103) 56 (31–76) 75 (42–122) 0.088 Death 30 (36%) 16 (49%) 14 (28%) 0.057 Thyroid cancer 26 (31%) 13 (39%) 13 (26%) 0.198 Impact of ATA Guidelines 2015 We retrospectively reassess the indication for RAI treatment in 50 patients after RAI. In 1 patient, insufficient assessment of the initial risk category. By From 49 patients, 39 (80%) 12 (12%) intermediate risks and 4 (8%) were at low risk. These 4 patients with low-risk disease would not have been treated with RAI therapy under the 2015 ATA Guidelines, while RAI therapy should not have been considered for 6 low-risk patients (see Table 2). The 10-year DSS for these 49 patients was 100% at low, 80% in intermediates - and 68% in the high-risk group (P = 0.607). Table 2.Indication for RAI therapy (2015 ATA) in the post-RAI group, in which remote metastases would have been omitted if the rai indication was omitted. LOW RISK (n = 4)a. ATP Intermediate Risk (n = 6)a. High risk (n = 39)a. No - - Not routine 4 (8%) - Consider - 6 (12%) - Yes - 39 (80%) As already mentioned, the control population of low and medium risk ATA patients consisted of 472 patients who received a common thyroidectomy followed by RAI therapy according to the Thyroid Cancer Guidelines (26). According to the 2015 ATA Guidelines, 54 (11%) should not be taken, but 188 (40%) was not regularly treated with RAI, while in 230 (49%) treatment with RAI therapy (26). The 10-year DSS in the control group was 99.8%. The combination of groups in which RAI therapy should not be carried out or was not regularly administered, according to the 2015 ATA Guidelines, resulted in 246 patients (i.e. 4 + 54 + 188), of whom 4 (1.6%) metastatic disease that would initially have been missed if RAI therapy had not been given. The group in which RAI therapy should be considered consisted of 236 patients (i.e. 6 + 70 + 160), in which 6 (2.5 %) metastases would be omitted if a decision was taken not to treat RAI. It is not possible to thoroughly study possible risk factors for the identification of metastatic disease before the initial treatment in these patients is possible; characteristics of the 4 low-risk patients are presented in Table 3. 3.Characteristics of patients at low risk for ATA where distant metastatic would initially have missed gender, age. Year of diagnosis . Type of disease . 8th. Location of distant metastases . 100 mg /ml/ s-Tg (ng/ml) during the first RAI therapy. RAI therapy . Initial drs . time to an excellent answer . Female, 48 years 2014 PTC; Follicular version pT1bN0M1 SPECT/CT ternal lesion <0,9 (Tg-abs: (15,8 U/ml) Once; 143 mCi Excellent 17 months Female, 46 years 2006 PTC pTC pT2N0M1 Lung absorption of SPECT/CT 22.3 (Tg- abs: 22.3 U/mL) Two; 230 mCi structural incomplete 121 months Female, 32 years 2014 FTC; minimally invasive pT2N0M1 Spect/CT 2.9 Twice; 193 mCi Excellent 10 months Female, 52 years 2013 PTC pT2N0M1 Lung absorption of SPECT/CT 8.6 Twice; 192 mCi in 38 months Combining groups before and after RAI, while not taking into account knowledge of the presence of distant metastases that were known in advance, resulted in 5 patients with low-risk disease That 2015 ATA were treated with RAI therapy according to the 2015 ATA Guidelines. metastatic disease would have been omitted if RAI therapy had not been given. The number of patients at intermediate risk remains unchanged. Therefore, there was no effect on the percentage of potentially missed distant metastases in the group in which RAI therapy should be considered. Response to therapy and survival of patients with distant metastases In the first DRS after initial therapy (median 10 months), the majority of patients with distant metastases continued to have structural disease (87%), while an excellent response was observed only in 5 patients (6%). indefinitely (6%) Response. These percentages are similar for groups before and after RAI separately (see Table 4). None of the patients with an initial excellent response died of thyroid cancer during follow-up, while the 10-year DSS of patients with initial structural incomplete response was lower than 54%. Response to therapy after the first therapy. Total population (n = 83)a, b . Group before RAI (n = 33)a . Group after RAI (n = 50)a . P Value . Excellent 5 (6%) - 5 (10%) 0.998 Indefinite 5 (6%) 2 (6%) 3 (6%) Biochemical incomplete 1 (1%) - 1 (2%) 0.998 Structurally incomplete 72 (87 %) 31 (94%) 41 (82%) Persistent disease 73 (88%) 31 (94%) 42 (84%) 0.190 During follow-up, only 14 (17%) 45 months. During the rest of the follow-up (median 43 months), none of these patients had a relapse. NED appeared significantly more frequently in the post-RAI group (P = 0.044), but using a Cox proportional hazard model that represents time, this significant difference between the two groups disappeared (P = 0,106). None of the patients who achieved NED died during the remaining follow-up. Since none of the patients experienced a relapse, at the end of follow-up 14 patients (17%) received an excellent response. In the immediate vicinity of this, 55 patients (67%) disease (see Table 5). Other patients had either biochemical incomplete (1%) indefinitely (15%) Response. In most patients, the structural disease still existed as distant metastases (96%), but 40% also had a local disease in the neck area in addition to distant metastases. Patients who identified distant metastases of posttherapy more often showed an excellent response (25% vs. 6%; p = 0.044), and less often there are data on structural disease (55% vs. 85%; (100 mg/200 mg/200 mg/200 mg/200 mg/ Table 5.Response to treatment at the end of follow-up. Total population (n = 82)a . P Value . Excellent 14 (17%) 2 (6%) 12 (25%) 0.044 Unspecified 12 (15%) 2 (6%) 10 (20%) Biochemical incomplete 1 (1%) 1 (3%) - 0.998 Structurally incomplete 55 (67%) 28 (85%) 27 (55%) 0.007 Local 24 (43%) 11 (39%) (48%) Distant 53 (96%) 28 (100%) 25 (93%) Both 22 (40%) 11 (39%) 11 (41%) Persistent disease 56 (68%) 29 (88%) 27 (55%) 0.003 In terms of survival, the 10-year OP was 48.5% for the whole group, while 5- and 10-year-old DSS were 79.8% and 57.0% respectively (see Figure 1). The pre-RAI group had a significantly lower 10-year DSS (39.3% vs. 68.3%, respectively); (100 mg/200 mg/200 mg/200 mg/200 mg/ However, when adjusted for age and sex, the difference between the two groups loses statistical significance (P = 0.187; see also Table 6). Table 6.Effect of metastases detection time on survival. hazard ratio (95% CI). P Value . OS Model Ia 0.38 (0.18–0.79) 0.009 Model IIb 0.47 (0.22–1.00) 0.050 DSS model I 0.45 (0.2 0.0.21-00) 0.99) 0.047 Model IIb 0.58 (0.26–1.30) 0.187 Of the 4 patients with distant metastases who were not treated with RAI therapy, and from 6, under the 2015 ATA Guidelines. (see also Table 3) in the first DRS after initial therapy, 3 had an excellent response, while the others had an unspecified (n = 1) or structural incomplete response (n = 6). Six patients achieved NED and the median time to NED was 28 months. During the rest of the follow-up (median 29 months), none of these patients had a relapse or died. The other 4 patients had an unspecified (n = 1) or incomplete structural response (n = 3) at the end of the follow-up. Risk factors Increased postoperative stimulated-Tg just before RAI therapy, the presence of initial metastasis lymph nodes, older and larger tumor size increases the risk of lack of excellent response at the end of the follow-up of univariate analysis, while increased postoperatively stimulates-Tg, older, larger tumor, and taking FTC increases the risk of persistent disease at the end of follow-up (26). The presence of refractory disease RAI, older age, and larger tumor size led to increased all cause and thyroid cancer specific mortality (26). Increased postoperatively stimulated-Tg, the initial presence of metastases of lymph nodes, and older age leads to a lower chance of developing NED during follow-up (26). After adjusting for age and sex, we found that increased postoperative stimulating-Tg, initial presence of metastases of lymph nodes, and older age increases the risk of lack of excellent response at final follow-up, while these same factors (excluding increased postoperative stimulated-Tg) increases the risk of persistent disease (26). The presence of REI refractory diseases and older age still increases all cause and thyroid cancer specific mortality (26). Increased postoperatively stimulated-Tg, the initial presence of metastases of lymph nodes and older age still leads to a lower chance of developing NED during follow-up (26). A discussion in this study found that 1.6% of patients who did not routine indication for RAI therapy according to the 2015 ATA guidelines were established with remote metastases that would have been if RAI therapy is not given. This rate was 2.5% in the group of patients who should have considered RAI therapy. In addition, in patients with initial distant metastases, two-thirds still have a structural disease at the end of follow-up, while almost 20% achieve an excellent response. None of the patients with an excellent response had a relapse during the follow-up period. The recommendation in the 2015 ATA Guidelines not to give RAI therapy to patients at low risk of ATA is based on systematic reviews that are not beneficial for cancer-related therapy (3, 27, 28). Others argue that the occurrence of unnoticed metastatic disease in these patients is low, and an increase in TG levels during follow-up would require further research (27). In addition, it has been reported that RAI therapy in patients with hyperthyroidism can lead to an increased risk of mortality from secondary solid tumors, but not hematological cancers (29); However, a recent meta-analysis in patients with thyroid cancer has not provided a clear answer about the possible increased risk of secondary malignancies due to RAI therapy (30). In this retrospective study, we observed that 1.6% of 246 patients with no indication of RAI therapy according to the 2015 ATA Guidelines had distant metastases. Initially, these metastases would have been omitted if RAI therapy was not carried out. Although it can be argued that due to the characteristics of these patients (levels of TJ, presence of antibodies), closer monitoring is justified, which would lead to the detection of metastases, it is not clear whether this would affect the prognosis. Due to the small number of identified low-risk patients with remote metastatic disease, we were unable to look for factors that could identify those patients with remote metastatic disease before initial therapy. Albano et al found a slightly higher number, as 3.6% of their low-risk patients had distant metastases that would have been missed using the 2015 ATA Guidelines (13). However, they also included patients who were diagnosed with metastatic disease during follow-up. This group is probably a different subset of patients who would probably be tested for the possible presence of distant metastases during follow-up. By contrast, Agate et al found a smaller number of approximately 1% in low-risk patients with distant metastases who would have been missed (14). However, these results may not be fully comparable as they use the 2009 ATA guidelines to define low-risk ones. In addition, Avram et al. investigated the impact of the first full-body scan on braking and demonstrated distant metastases in 5 out of 116 (4.3%) tumours (≤ 2.0 cm) (31). However, since no information is available on the ATA risk category of this study, possible indications of cannot be determined by their study. Furthermore, it is not tumours (size > 2.0 cm to ≤ 4.0 cm). The 2015 ATA Guidelines recommend considering RAI therapy in patients with these recommendations based on literature that studies the effect of RAI therapy in patients who have one or more of the different intermediate risk criteria; since the data are contradictory, it is recommended to take rai therapy into account in these Since our Dutch guidelines recommend always treating patients with RAI therapy after treatment with thyroidectomy, our study population is suitable for assessing the proportion of possible undetected distant metastases when skipping RAI therapy in low-risk patients. We showed that 2.5% of patients had distant metastases that would have been missed if RAI therapy was not performed. Albano et al reported that 4.9% were omitted (13), while this percentage was 1.4% in the Agate et al study (14). The differences between these 2 studies and ours were mentioned in the previous paragraph. An ata system assessment for ATA 2015 in patients with distant metastases, two-thirds of our patients still had a structural disease at final follow-up, while 17% had NED. This suggests that initial risk stratification in patients with distant metastases such as ATA high risk is valid. Hirsch et al found an excellent response in 25% of their patients at the end of subsequent, but to determine an excellent response they used stimulated Tg < 2 ng/ml instead of < 1 ng/mL as used in our study and in 2015 ATA Guidelines (15). Earlier studies in high-risk patients, ATA, thus including patients with remote metastatic disease, showed a lower percentage of patients with persistent structural disease and a higher number of patients with Sun at final follow-up (32, 33). This difference is probably due to the fact that we only examined patients treated in a tertial targeting center with distant metastases. However, metastatic disease did not affect the response to therapy in an earlier study (25). Another factor may be age, since we have shown that an older person increases the risk of persistent diseases and without an excellent answer; population of 2 previous studies (32 and 33). Data on other factors, such as elevated postoperative stimulated-Tg unfortunately not available for these 2 studies. In patients who achieved an excellent response, no relapses occurred (the median time from NED to the end of follow-up was 43 months). Similar results were found by Hirsh et al (15). Chopra et al was found to have a relapse rate of 21% in patients with pulmonary metastases (34). However, their definition of excellent response is different (stimulated Tg < 10 ng/mL), and therefore their group also includes patients with an unspecified response under the 2015 ATA Guidelines. In addition, earlier studies in high-risk patients in ATA found relapses of 14% to 30% (9, 25, 32, 33, 35). to argue that successful therapy for distant metastatic metastatic is also able to destroy other thyroid cancer tissue (eg, due to gross ETE), which leads to a lower relapse in these patients. Therefore, the DRS of the ATA risk stratification system performs well in terms of predicting recurrent diseases after NED. 5- and 10-year DSS levels are 80% and 57% in our population, respectively. This is similar to earlier studies (20, 22, 33). On the other hand, Lee and al (16) and Goffredo et al (36) established 10-year DSS rates of 27% and 44%, respectively, while Nixon et al showed a 5-year DSS of 68% (18). The differences may be due to the fact that we only examined patients with distant metastases detected before or during initial therapy, while others also included patients who developed distant metastases later during follow-up (16), or patients who did not receive thyroid surgery (36). RAI-refractory disease and older age leads to increased all cause and thyroid cancer specific mortality. These factors have also been reported in previous studies, indicating the risk factors for reducing survival in patients with distant metastases (15–17, 20, 21, 36). One of the main strengths of this study is the significant number of patients who have distant metastases of well-differentiated thyroid cancer found before or during initial therapy with well-documented follow-up. This enabled us to evaluate the indications for RAI therapy of THE ATA Guidelines 2015, but also to study the results of the disease and prognostic factors. Moreover, unlike this study, many other studies evaluated well differentiated and poorly differentiated thyroid cancer as one group despite their different behavior (15, 16, 33). It is possible to limit the current study that patients were recruited by a university hospital, which can attract patients with a more aggressive disease due to the availability of advanced treatments. Finally, due to the retrospective nature of the study, the data set was incomplete in 4% of the (potential) risk factors. Since only 2 patients had insufficient follow-up information, it is unlikely that such a small proportion changed the overall outcomes. In conclusion, this study showed that in patients with DTK with no indication of RAI therapy or in whom RAI therapy should be considered 1, 6% and 2.5% respectively, they had distant metastases that would initially have been missed if RAI therapy was not performed. Therefore, further studies should focus on factors that predict that patients may not be treated during raptherapy safely without the risk of lack of metastatic disease. Secondly, the 2015 ATA Guidelines are an excellent predictor of both persistent disease and relapse in patients with initial metastatic disease, since at the end of two-thirds of patients still had a structural illness and none of the patients with an excellent response during follow-up had a recurrence at a later stage. Abbreviations American Thyroid Association Dynamic Risk Stratification survival differentiated thyroid cancer external radiotherapy fluorodeoxyglucose-positron emission tomography follicular thyroid carcinoma papillary thyroid carcinoma tyrotropin (tyrotropin-stimulating hormone) Recognition Disclosure Summary: Authors do not declare conflicts of interest and do not exist competing financial interests. Availability of data: All data generated or analyzed during this study are included in this published article or in the repositories of data listed in references. References 3. , et al. American Thyroid Association guidelines for management for adult thyroid patients nodes and differentiated thyroid cancer: the American Thyroid Association guidelines task force for thyroid nodes and differentiated thyroid cancer. ;:–.5. , , . 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