Evaluation of the 2015 ATA Guidelines in Patients With Distant Metastatic Differentiated Thyroid Cancer

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Context: Current American Thyroid Association (ATA) Management Guidelines for the treatment of differentiated thyroid cancer (DTC) stratify patients to decide on additional radioiodine (RAI) therapy after surgery, and to predict recurring/persisting disease. However, studies evaluating the detection of distant metastases and how these guidelines perform in patients with distant metastases are scarce.

Objective: To evaluate the 2015 ATA Guidelines in DTC patients with respect to 1) the detection of distant metastases, and 2) the accuracy of its Risk Stratification System in patients with distant metastases.

Patients and Main Outcome Measures: We retrospectively included 83 DTC patients who were diagnosed with distant metastases around the time of initial therapy, and a control population of 472 patients (312 low-risk, 160 intermediate-risk) 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 no RAI therapy was given.

Results: Two hundred forty-six patients had no routine indication for RAI therapy of which 4 (1.6%) had distant metastases. Furthermore, among the 83 patients with distant metastases, 14 patients (17%) had excellent response, while 55 (67%) had structural disease after a median follow-up of 62 months. None of the 14 patients that achieved an excellent response had a recurrence.

Conclusions: In patients without a routine indication for RAI therapy according to the 2015 ATA Guidelines, distant metastases would initially have been missed in 1.6% of the patients. Furthermore, in patients with distant metastases upon diagnosis, the 2015 ATA Guidelines are an excellent predictor of both persistent disease and recurrence. (*J Clin Endocrinol Metab* 105: 1–9, 2020)

Key Words: differentiated thyroid cancer, survival, prognosis, recurrence, American thyroid association guidelines, distant metastases

The worldwide incidence of differentiated thyroid cancer (DTC) has been steadily increasing over the last 2 decades (1, 2). As mortality has remained stable to slightly

increasing, a less aggressive therapeutic approach seems appropriate (1–4). To optimize the need for de-escalation of therapy and follow-up strategies, different systems that predict the risk of recurrence and survival in patients with DTC have been proposed and evaluated (3, 5–9).

The current 2015 American Thyroid Association (ATA) Management Guidelines use their own Risk Stratification System to determine the need for radioiodine (RAI) therapy after surgery (3). However, this approach has been challenged by several experts in the field (10–12). Because one of the aims of RAI therapy is to treat any remaining unknown cancer tissue, omitting RAI therapy might leave undetected metastases untreated (11). Using the criteria defined in the 2015 ATA Guidelines, one study claimed that a substantial proportion of patients with distant metastatic disease would not have been treated with RAI and thereby would have been missed (13). However, this study also included patients in whom metastatic disease was diagnosed during follow-up. Another study showed, in low- and intermediate-risk patients defined by the 2009 ATA Guidelines, that 1% of the distant metastases would have been missed with omission of RAI therapy (14).

Several studies show that patients with distantly metastasized DTC have a relative poor prognosis (15–21). Risk factors such as age, RAI avidity, tumor size, and follicular type influence this prognosis (15–23). However, to our knowledge, no studies yet evaluated the 2015 ATA Risk Stratification System in DTC patients with distant metastases with respect to its ability to predict prognosis, recurrence, and survival.

We initiated the current study because 1) there are very few studies evaluating risk factors in distant metastatic disease identified before or during initial therapy, 2) only 2 studies, both having limitations, have so far evaluated the consequences of omitting RAI therapy according to the new ATA Guidelines on the proportion of possible undetected distant metastases (13, 14), and 3) no studies have yet evaluated the 2015 ATA Risk Stratification System in DTC patients with distant metastases. The aim of our study was to evaluate the 2015 ATA Guidelines in DTC patients with respect to 1) the proportion of possible distant metastases, and 2) the performance of the ATA Risk Stratification System in patients with distant metastases.

Materials and Methods

Study population and clinical outcomes

We retrospectively identified all patients, aged 16 years or older, who were diagnosed and/or treated for either papillary (PTC) or follicular (FTC) thyroid carcinoma (including Hürthle cell carcinoma) at the Erasmus Medical Center, Rotterdam, The Netherlands, from January 2002 to December

2016. For the current study, we included all patients who underwent thyroid surgery followed by RAI therapy, which is in line with the 2015 Dutch Thyroid Cancer Guidelines (24). Patients included were 1) diagnosed with distant metastases either before initial RAI therapy based on pathology or imaging such as computed tomography (CT) (pre-RAI group) or directly afterwards using the posttherapy whole-body scan (post-RAI group); or 2) had DTC classified as either ATA low- or intermediate-risk (according to the 2015 ATA Guidelines). We used data from the patients with distant metastases (pre- and post-RAI group) to assess the performance of the Risk Stratification System. The ATA low- and intermediate-risk groups served as control groups for the calculation of the proportion of undetected distant metastases when omitting RAI therapy. In a previous publication (25), we evaluated the Risk Stratification System of the 2015 ATA Guidelines in 236 high-risk DTC patients, also including patients with metastatic disease treated in our institute (n = 78). In the current study, which only focuses on the metastatic group and investigates this in much greater detail, we included 74 of the patients from this previous publication plus some additional patients with metastatice disease.

From patient records, we obtained demographic, disease, treatment, response to therapy, recurrence, and mortality characteristics. Demographic variables included age at diagnosis, sex, and year of diagnosis. Disease characteristics included disease type, TNM-stage (8th edition), tumor size, presence/absence of multifocal disease, presence/absence of vascular invasion, presence/absence of lymph node metastases, and minor/gross extrathyroidal extension (ETE). Data regarding treatment consisted of extent of surgery, use of RAI, and use of other treatment modalities (eg, external beam radiation therapy [EBRT]).

Indication for RAI therapy was retrospectively reassessed using the 2015 ATA Guidelines (3) in 1) the post-RAI group, ignoring knowledge about the found distant metastases, and 2) the control groups. RAI therapy is routinely recommended in ATA high-risk patients, should be considered in ATA intermediate-risk patients, is not routinely recommended in ATA low-risk patients with tumors larger than 1 and smaller than 4 cm, and is not given in ATA low-risk patients with tumors of 1 cm or smaller. The current and past Dutch Guidelines recommend to always treat patients with RAI therapy after a total thyroidectomy; a total thyroidectomy is always indicated in tumors ≥ 1 cm.

Response to therapy was defined according to the 4 categories described in the 2015 ATA Guidelines and was continually assessed during follow-up (ie, dynamic risk stratification [DRS]) (3). Patients were considered to have an excellent response to therapy (ie, no evidence of disease [NED]), if they had a suppressed thyroglobulin (Tg) < 0.2 ng/mL or thyrotropin (also known as thyroid-stimulating hormone; TSH)-stimulated Tg < 1 ng/mL, no detectable antibodies, and no evidence of structural disease on imaging. Patients were considered to have biochemical incomplete response if they had a suppressed Tg ≥ 1 ng/mL or stimulated Tg ≥ 10 ng/mL or rising anti-Tg antibody levels, but no evidence of structural disease on imaging. Patients were considered to have structural incomplete response if they had structural evidence of disease on imaging. And finally, patients were considered to have indeterminate response if they had a suppressed Tg < 1 ng/mL or a stimulated Tg < 10 ng/mL, declining or stable anti-Tg

antibody levels. Persistent disease was defined as either structural or biochemical incomplete response. Response to therapy was recorded for the first time 6 to 18 months after the first therapy (ie, initial DRS); thereafter during and at end of follow-up. A recurrence was defined as new biochemical or structural disease after longer than 12 months of NED.

RAI refractory disease was defined according to the 2015 ATA Guidelines (3), ie, 1) the malignant/metastatic tissue never concentrated RAI, 2) the tumor tissue loses the ability to concentrate RAI after previous evidence of RAI-avid disease, 3) RAI is concentrated in some lesions but not in others, 4) metastatic disease progresses despite significant concentration of RAI. Additionally, we also considered patients with a stimulated Tg ≥ 30 ng/mL without significant concentration of RAI as having RAI-refractory disease.

Time to last follow-up, survival status, and date and cause of death were recorded. Survival was defined as the time of initial diagnosis to either last date of follow-up, death, or end of study (December 2017), whichever occurred first. Cause of death was obtained from hospital or general practitioner records. Patients with extensive or rapidly progressive thyroid cancer and no clear other cause of death were classified as death due to thyroid cancer. The study protocol was approved by the institutional review board of the Erasmus Medical Center.

Statistical analysis

For continuous variables, means and standard deviations (SD), or medians with interquartile ranges (IQR) were calculated. For categorical variables, absolute numbers with percentages were recorded. To assess the influence of the 2015 ATA Guidelines on the occurrence of possible undetected distant metastases, we compared the post-RAI and control group. Thereafter, differences in characteristics between the pre- and post-RAI groups were assessed using the Student's t-test or χ^2-test. Overall survival (OS) and disease-specific survival (DSS) were analyzed using the Kaplan-Meier method for the patients with distant metastases. The same analyses were also performed for the pre- and post-RAI groups, and for the control population separately. In the pre- and post-RAI groups, univariate and multivariate logistic regression or Cox proportional hazards models were used to examine the effect of different (potential) risk factors on either response to therapy (at first DRS and at final follow-up), developing NED, recurrence, or survival. Data on these (potential) risk factors were missing in 4% of the values; due to this low percentage, a patient was left out from the corresponding analysis if a value was missing. P values below 0.05 were considered significant. All analyses were performed using SPSS Statistics for Windows (version 24.0).

Results

Population characteristics

During the study period, a total of 85 patients with distant metastases, 312 with ATA low-risk, and 160 with ATA intermediate-risk disease were eligible for the study. Two of the patients with distant metastases were excluded because of insufficient data on follow-up, leaving 83 patients available for analyses.

Table 1 lists the characteristics of the study population with distant metastases. Mean age was 56.3 years, and 57 (69%) were women. Distant metastatic disease was identified before RAI therapy (pre-RAI group) in 33 (40%) patients. In these 33 patients, these metastases were discovered either because of symptoms (30%; eg, pain), during preoperative staging because of large tumor burden in the neck (27%), or incidentally discovered on a CT or fluorodeoxyglucose-positron emission tomography (FDG-PET) made for another reason (21%). On the other hand, in the remaining 50 (60%) patients, the distant metastases were detected directly after RAI therapy by the posttherapy whole-body scan (post-RAI group). PTC was present in 53 (64%) patients (including 10 (19%) with follicular variant of PTC), and the remaining 30 patients (36%) had FTC, including 7 patients (8%) with Hürthle Cell carcinoma. Median follow-up time was 62 months; during follow-up, 30 patients (36%) died, of which 26 were due to thyroid cancer. Total thyroidectomy was performed in all patients except 1 who received a hemithyroidectomy because of presence of one-sided recurrent nerve paralysis. 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%) patients (central in 6 [7%], lateral in 5 [6%], and both in 29 [35%]). Patients in the pre-RAI group were significantly older (62.5 years vs 52.3 years; P < 0.001), had significantly more often 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 were no differences between the pre- and post-RAI groups regarding elevated Tg, presence of lymph node metastases or gross ETE. The only difference was that patients in the post-RAI group more often had multifocal disease (26).

Influence of the 2015 ATA guidelines

We retrospectively re-evaluated the indication for RAI therapy in the 50 post-RAI patients. For 1 patient, insufficient information was available to assess the initial risk category. Of the remaining 49 patients, 39 (80%) were ATA high-risk, 6 (12%) were intermediate-risk, and 4 (8%) were low-risk. These 4 patients with low-risk disease would not have been treated with RAI therapy according to the 2015 ATA Guidelines, while for the 6 intermediate-risk patients, RAI therapy should have been considered (see Table 2). The 10-year DSS for these 49 patients was 100% in the low-, 80% in the intermediate-, and 68% in the high-risk group (P = 0.607).

As previously mentioned, the control population of ATA low- and intermediate-risk patients consisted of 472 patients who all received total thyroidectomy

Table 1.   Characteristics of the Study Population

	Total Population (n = 83)[a]	Pre-RAI Group (n = 33)[a]	Post-RAI Group (n = 50)[a]	P Value[b]
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				
Papillary	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 Staging system (8th)				
I	-	-	-	0.051
II	36 (43%)	10 (30%)	26 (52%)	
III	-	-	-	
IV	47 (57%)	23 (70%)	24 (48%)	
Tumor 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%)	-
Pulmonary	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
Lateral	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	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

Significant P values displayed in bold.

Abbreviations: EBRT, external beam radiation therapy; HT, hemi-thyroidectomy; IQR, interquartile range; mCi, milliCurie; RAI, radioactive iodine; SD, standard deviation; TKI, tyrosine kinase inhibitor; TT, total thyroidectomy.

[a]Values are means (± SD), medians (25–75 IQR), or numbers (percentages).

[b]P value comparing metastases pre- and post-RAI groups.

Table 2.   Indication for RAI Therapy (2015 ATA Guidelines) in the Post-RAI Group in Whom Distant Metastases Would Have Been Missed if RAI Therapy was Omitted

RAI Indication	ATA Low-Risk (n = 4)[a]	ATA Intermediate-Risk (n = 6)[a]	ATA High-Risk (n = 39)[a]
No	-	-	-
Not routine	4 (8%)	-	-
Consider	-	6 (12%)	-
Yes	-	-	39 (80%)

[a]Values are numbers (percentages). Abbreviations: ATA, American Thyroid Association.

followed by RAI therapy according to 2015 Dutch Thyroid Cancer Guidelines (26). According to the 2015 ATA Guidelines, 54 (11%) should not, and 188 (40%) would not routinely have been treated with RAI, while in 230 (49%) treatment with RAI therapy should have

been considered (26). The 10-year DSS in the control group was 99.8%. Combining the groups in which RAI therapy should not or would not routinely have been given according to the 2015 ATA Guidelines resulted in 246 patients (ie, 4 + 54 + 188) of whom 4 (1.6%) had distant metastatic disease that would have been initially missed if no RAI therapy would have been given. The group in which RAI therapy should be considered consisted of 236 patients (ie, 6 + 70 + 160) in which 6 (2.5%) distant metastases would have been missed if it were decided not to treat them with RAI. No in-depth investigation of possible risk factors to identify distant metastatic disease before initial therapy was possible in these patients; characteristics of the 4 low-risk patients are presented in Table 3.

Combining the pre- and post-RAI groups, while purposefully not accounting for the knowledge of the presence of distant metastases that was known upfront,

Table 3.　Characteristics of the ATA Low-Risk Patients in Whom Distant Metastatic Would Have Been Initially Missed

Gender, Age	Year of Diagnosis	Disease Type	TNM (8th)	Location of Distant Metastases	s-Tg (ng/ml) during first RAI therapy	RAI Therapy	Initial DRS	Time Until Excellent Response
Female, 48 years	2014	PTC; Follicular variant	pT1bN0M1	Sternal lesion on SPECT/CT	<0.9 (Tg-abs: (15.8 U/mL)	Once; 143 mCi	Excellent	17 months
Female, 46 years	2006	PTC	pT2N0M1	Uptake in Lungs on SPECT/CT	22.3 (Tg- abs: 22.3 U/mL)	Twice; 230 mCi	Structural Incomplete	121 months
Female, 32 years	2014	FTC; minimally invasive	pT2N0M1	Uptake in Lungs on SPECT/CT	2.9	Twice; 193 mCi	Excellent	10 months
Female, 52 years	2013	PTC	pT2N0M1	Uptake in Lungs on SPECT/CT	8.6	Twice; 192 mCi	Indeterminate	38 months

Abbreviations: ATA, American Thyroid Association; DRS, Dynamic Risk Stratification; FTC, follicular thyroid cancer; mCi, milliCurie; PTC, papillary thyroid cancer; RAI, radioactive iodine; s-Tg, stimulated thyroglobulin; Tg-abs, thyroglobulin antibodies.

Table 4.　Response to Therapy After First Therapy

	Total Population (n = 83)[a, b]	Pre-RAI Group (n = 33)[a]	Post-RAI Group (n = 50)[a]	P Value[b]
Excellent	5 (6%)	-	5 (10%)	0.998
Indeterminate	5 (6%)	2 (6%)	3 (6%)	0.991
Biochemical Incomplete	1 (1%)	-	1 (2%)	0.998
Structural Incomplete	72 (87%)	31 (94%)	41 (82%)	0.134
Persistent Disease	73 (88%)	31 (94%)	42 (84%)	0.190

[a]Values are numbers (percentages).
[b]P-value comparing pre- and post-RAI groups.

Table 5.　Response to Therapy at End of Follow-up

	Total Population (n = 82)[a]	Pre-RAI Group (n = 33)[a]	Post-RAI Group (n = 49)[a]	P Value[b]
Excellent	14 (17%)	2 (6%)	12 (25%)	**0.044**
Indeterminate	12 (15%)	2 (6%)	10 (20%)	0.089
Biochemical Incomplete	1 (1%)	1 (3%)	-	0.998
Structural Incomplete	55 (67%)	28 (85%)	27 (55%)	**0.007**
Local	24 (43%)	11 (39%)	13 (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**

Significant P values displayed in bold.
[a]Values are numbers (percentages).
[b]P-value comparing pre- and post-RAI groups.

resulted in 5 patients with low-risk disease who would not have been treated with RAI therapy according to the 2015 ATA Guidelines. This resulted in 247 patients (ie, 5 + 54 + 188), in whom 5 (2.0%) distant metastatic disease would have been missed if no RAI therapy would have been given. The number of intermediate-risk patients remained the same. Therefore, there was no influence 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

At the first DRS after initial therapy (median 10 months), the majority of the patients with distant metastases continued to have structural disease (87%), while an excellent response was seen in only 5 patients (6%). The other patients had either biochemical incomplete (1%) or an indeterminate (6%) response. These percentages were similar for the pre- and post-RAI groups separately (see Table 4). None of the patients with an initial excellent response died from thyroid cancer during follow-up, while the 10-year DSS of

patients with an initial structural incomplete response was as low as 54%.

During follow-up, only 14 (17%) patients achieved NED after a median of 45 months. During the rest of follow-up (median 43 months), none of these patients experienced a recurrence. NED occurred significantly more often in the post-RAI group (P = 0.044), but using a Cox proportional hazards model accounting for time, this significant difference between both groups disappeared (P = 0.106). None of the patients that achieved NED died during remaining follow-up.

As none of the patients experienced a recurrence, at the end of follow-up, 14 patients (17%) had an excellent response. Next to this, 55 patients (67%) still had structural disease (see Table 5). The other patients had either biochemical incomplete (1%) or indeterminate (15%) response. In the majority of patients, structural disease was still present as distant metastases (96%), but 40% also had local disease in the neck region in addition to the distant metastases. The patients in whom the distant metastases were identified on the posttherapy scan,
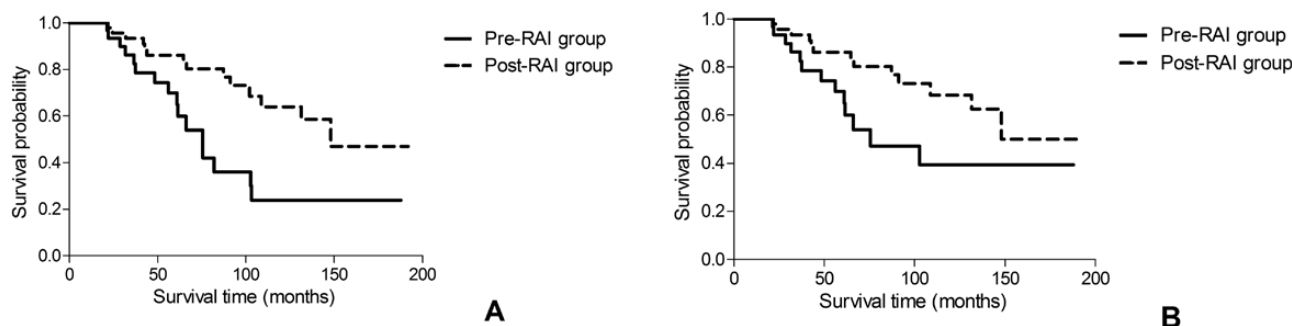
Figure 1. Kaplan-Meier curves for overall survival (OS) (A) and disease-specific survival (DSS) (B).

exhibited an excellent response more often (25% vs 6%; *P* = 0.044), and less frequently had evidence of structural disease (55% vs 85%; *P* = 0.007).

With respect to survival, 10-year OS was 48.5% for the whole group, while 5-year and 10-year DSS were 79.8% and 57.0%, respectively (see Fig. 1). The pre-RAI group had a significantly lower 10-year DSS (39.3% vs 68.3% respectively; *P* = 0.042). However, when adjusting for age and sex, the difference between both groups lost statistical significance (*P* = 0.187; see also Table 6).

Of the 4 patients with distant metastases who would not have been treated with RAI therapy, and of the 6 for whom RAI therapy would have been considered, according to the 2015 ATA Guidelines (see also Table 3), at the first DRS after initial therapy, 3 had an excellent response, while the others had either indeterminate (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 follow-up (median 29 months), none of these patients experienced a recurrence nor died. The other 4 patients had either indeterminate (n = 1) or structural incomplete response (n = 3) at end of follow-up.

Risk factors

An elevated postoperative stimulated-Tg just before RAI therapy, presence of initial lymph node metastases, older age, and larger tumor size increased the risk of not having an excellent response at end of follow-up in a univariate analysis, while an elevated postoperative stimulated-Tg, older age, larger tumor size, and having FTC increased the risk of having persistent disease at end of follow-up (26). Presence of RAI refractory disease, older age, and larger tumor size resulted in an increased all-cause and thyroid cancer specific mortality (26). An elevated postoperative stimulated-Tg, initial presence of lymph node metastases, and older age resulted in a lower chance of developing NED during follow-up (26).

After adjusting for age and sex, we determined that an elevated postoperative stimulated-Tg, initial presence of lymph node metastases, and older age

Table 6.   Effect of Metastases Detection Time on Survival

	Hazard Ratio (95% CI)	*P* Value[c]
OS		
Model I[a]	0.38 (0.18–0.79)	**0.009**
Model II[b]	0.47 (0.22–1.00)	0.050
DSS		
Model I[a]	0.45 (0.21–0.99)	**0.047**
Model II[b]	0.58 (0.26–1.30)	0.187

Significant *P* values displayed in bold.
Abbreviations: CI, confidence interval; DSS, disease specific survival; OS, overall survival.
[a]Model I; unadjusted.
[b]Model II; adjusted for age and sex.
[c]*P* value comparing pre- and post-RAI groups (pre-RAI group as reference group).

increased the risk of not having an excellent response at final follow-up, while these same factors (except for an elevated postoperative stimulated-Tg) increased the risk of having persistent disease (26). The presence of RAI refractory disease and older age still increased all-cause and thyroid cancer specific mortality (26). An elevated postoperative stimulated-Tg, initial presence of lymph node metastases and older age still resulted in a lower chance of developing NED during follow-up (26).

Discussion

This study determined that 1.6% of the patients who did not have a routine indication for RAI therapy according the 2015 ATA Guidelines were found to have distant metastases that would have been missed initially if no RAI therapy was given. This percentage was 2.5% in the patient group in whom RAI therapy should have been considered. Furthermore, in patients with initial distant metastases, two-thirds still had structural disease at end of follow-up, while almost 20% achieved an excellent response. None of the patients with an excellent response experienced a recurrence during the period of follow-up.

The recommendation in the 2015 ATA Guidelines not to give RAI therapy in ATA low-risk patients is based on systematic reviews which did not find a significant benefit of RAI therapy on cancer-related death (3, 27, 28). Others have argued that the occurrence of undetected metastatic disease in these patients is low, and rising Tg levels during follow-up would warrant the need for further investigations (27). In addition, it has been reported that RAI therapy in patients with hyperthyroidism might lead to an increased mortality risk from secondary solid tumors, but not hematologic cancers (29); however, a recent meta-analysis in thyroid cancer patients did not provide a clear answer on the possible increased risk of secondary malignancies due to RAI therapy (30). In the current retrospective study we observed that 1.6% of the 246 patients without an indication for RAI therapy according to the 2015 ATA Guidelines had distant metastases. Those metastases would initially have been missed if no RAI therapy was given. Although one might argue that due to the characteristics of these patients (Tg-levels, presence of antibodies), closer follow-up was warranted which would have led to detection of the metastases, it is unclear whether this would have affected prognosis. Due to the small number of identified low-risk patients with distant metastatic disease, we were unable to search for factors that could have identified those patients with distant 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 in whom metastatic disease was diagnosed during follow-up. This group is probably a different subset of patients, who would probably have been investigated for possible presence of distant metastases during follow-up. In contrast, Agate et al found a lower number of approximately 1% in low-risk patients with distant metastases that would have been missed (14). However, these results might not be totally comparable as they used the 2009 ATA Guidelines low-risk definition. Further, Avram et al. investigated the impact of the first whole-body scan on staging, and demonstrated distant metastases in 5 out of 116 (4.3%) patients with pT1 tumors (size ≤ 2.0 cm) (31). However, because no information about the ATA risk category is available from this study, the possible indications for RAI therapy could not be determined from their study. Furthermore, no separate numbers regarding pT2 tumors (size > 2.0 cm to ≤ 4.0 cm) were given.

The 2015 ATA Guidelines recommend to consider RAI therapy in ATA intermediate-risk patients; these recommendations are based on literature investigating the effect of RAI therapy in patients having one or more of the different intermediate-risk criteria; since data are conflicting, the recommendation is given to consider RAI therapy in these patients (3). As our Dutch guideline recommends to always treat patients with RAI therapy after a total thyroidectomy, our study population is suited to evaluate the proportion of possible undetected distant metastases when omitting RAI therapy in ATA intermediate-risk patients. We showed that 2.5% of the patients had distant metastases that would have been missed if no RAI therapy was given. Albano et al reported that 4.9% would have been missed (13), while this proportion was 1.4% in the study of Agate et al (14). Differences between these 2 studies and ours were mentioned in the previous paragraph.

Evaluating the 2015 ATA Risk Stratification System in patients with distant metastases, two-thirds of our patients still had structural disease at final follow-up, whereas 17% had NED. This suggests that the initial risk stratification of patients with distant metastases as ATA high-risk is valid. Hirsch et al found an excellent response in 25% of their patients at the end of follow-up, but to define an excellent response they used a stimulated Tg < 2 ng/mL, rather than < 1 ng/mL as used in our study and in the 2015 ATA Guidelines (15). Earlier research in ATA high-risk patients, thus including patients with distant metastatic disease, showed lower percentages of patients with persistent structural disease and higher numbers of patients with NED at final follow-up (32, 33). This difference is probably due to the fact that we only studied patients treated at a tertiary referral center with distant metastases. However, metastatic disease did not influence response to therapy in an earlier study (25). Another factor might be age, as we showed that older age increases the risk of having persistent disease and not having an excellent response; our population is older than the populations of 2 earlier studies (32, 33). Data on other factors, such as elevated postoperative stimulated-Tg was unfortunately unavailable for these 2 studies.

In patients that achieved an excellent response, no recurrences occurred (median time from NED to end of follow-up was 43 months). Similar results were found by Hirsh et al (15). Chopra et al found a recurrence rate of 21% in patients with lung metastases (34). However, their definition of an excellent response was different (stimulated Tg < 10 ng/mL), and therefore their group also included patients having an indeterminate response according to the 2015 ATA Guidelines. Further, earlier studies in ATA high-risk patients found recurrences rates of 14% to 30% (9, 25, 32, 33, 35). One might argue that a successful therapy for distant metastatic disease is also able to destroy other thyroid cancer tissue (eg, due to gross ETE), resulting in a lower recurrence in these patients.

Therefore, the DRS of the ATA Risk Stratification System performs well regarding the prediction of recurrent disease after NED.

The 5- and 10-year DSS rates were respectively 80% and 57% in our population. This is similar to earlier studies (20, 22, 33). On the other hand, Lee et al (16) and Goffredo et al (36) found 10-year DSS rates of respectively 27% and 44%, while Nixon et al showed a 5-year DSS of 68% (18). Differences might be due to the fact that we studied only 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 that did not receive thyroid surgery (36). RAI-refractory disease and older age resulted in an increased all-cause and thyroid cancer specific mortality. These factors were also reported in earlier studies identifying risk factors for decreased survival in patients with distant metastases (15–17, 20, 21, 36).

One of the main strengths of this study is the substantial number of patients having distant metastases of well-differentiated thyroid carcinoma discovered before or during initial therapy with a well-documented follow-up. This enabled us to evaluate the indications for RAI therapy of the 2015 ATA Guidelines, but also to investigate disease outcome and prognostic factors. Furthermore, unlike this study, many other studies evaluated well-differentiated and poorly-differentiated thyroid cancer as one group despite their different behavior (15, 16, 33). A possible limitation of the current study is that patients were recruited from a single tertiary university hospital, which might attract patients with more aggressive disease because of the availability of advanced treatments. Finally, because of the retrospective character of the study, our dataset was incomplete in 4% of the (potential) risk factors values. As only 2 patients had insufficient follow-up information, it is unlikely that such a small proportion would have altered the overall results.

In conclusion, this study shows that in DTC patients without an indication for RAI therapy or in whom RAI therapy should be considered respectively 1.6% and 2.5% have distant metastases that initially would be missed if no RAI therapy is given. Further research should therefore focus on factors predicting in which patients RAI therapy could be omitted safely without the risk of missing distant metastatic disease. Secondly, the 2015 ATA Guidelines are an excellent predictor of both persistent disease and recurrence in patients with initial metastatic disease, since at the end of follow-up, two-thirds of the patients still had structural disease, and none of the patients with an excellent response during follow-up experienced a recurrence later-on.

Acknowledgments

References

1. La Vecchia C, Malvezzi M, Bosetti C, et al. Thyroid cancer mortality and incidence: a global overview. *Int J Cancer.* 2015;**136**:2187–2195.
2. Davies L, Welch HG. Increasing incidence of thyroid cancer in the United States, 1973–2002. *JAMA.* 2006;**295**:2164–2167.
3. Haugen BR, Alexander EK, Bible KC, et al. American Thyroid Association Management guidelines for adult patients with thyroid nodules and differentiated thyroid cancer: the American Thyroid Association guidelines task force on thyroid nodules and differentiated thyroid cancer. *Thyroid.* 2016;**26**:1–133.
4. Lim H, Devesa SS, Sosa JA, Check D, Kitahara CM. Trends in thyroid cancer incidence and mortality in the United States, 1974–2013. *JAMA* 2017;**317**:1338–1348.
5. Tuttle RM, Haugen B, Perrier ND. Updated American Joint Committee on cancer/tumor-node-metastasis staging system for differentiated and anaplastic thyroid cancer (Eighth Edition): what changed and why? *Thyroid.* 2017;**27**:751–756.
6. Edge SB, Compton CC. The American Joint Committee on Cancer: the 7th edition of the AJCC cancer staging manual and the future of TNM. *Ann Surg Oncol.* 2010;**17**:1471–1474.
7. van Velsen EFS, Stegenga MT, van Kemenade FJ, et al. Comparing the prognostic value of the eighth edition of the American Joint Committee on cancer/tumor node metastasis staging system between papillary and follicular thyroid cancer. *Thyroid.* 2018;**28**:976–981.
8. Pacini F, Schlumberger M, Dralle H, Elisei R, Smit JW, Wiersinga W; European Thyroid Cancer Taskforce. European consensus for the management of patients with differentiated thyroid carcinoma of the follicular epithelium. *Eur J Endocrinol.* 2006;**154**(6):787–803.
9. Lee SG, Lee WK, Lee HS, et al. Practical performance of the 2015 American Thyroid Association guidelines for predicting tumor recurrence in patients with papillary thyroid cancer in South Korea. *Thyroid.* 2017;**27**:174–181.
10. Treglia G, Aktolun C, Chiti A, et al. The 2015 Revised American Thyroid Association guidelines for the management of medullary thyroid carcinoma: the "evidence-based" refusal to endorse them by EANM due to the "not evidence-based" marginalization of the role of Nuclear Medicine. *Eur J Nucl Med Mol Imaging* 2016;**43**:1486–1490.
11. Verburg FA, Luster M, Giovanella L. Adjuvant post-operative I-131 therapy in differentiated thyroid carcinoma: are the 2015 ATA guidelines an exact science or a dark art? *Eur J Nucl Med Mol Imaging* 2017;**44**:183–184.
12. Luster M, Aktolun C, Amendoeira I, et al. European Perspective on 2015 American Thyroid Association management guidelines for adult patients with thyroid nodules and differentiated thyroid cancer: proceedings of an interactive international symposium. *Thyroid.* 2019;**29**:7–26.
13. Albano D, Bertagna F, Bonacina M, et al. Possible delayed diagnosis and treatment of metastatic differentiated thyroid

cancer by adopting the 2015 ATA guidelines. *Eur J Endocrinol* 2018;**179**:143–151.

14. Agate L, Bianchi F, Brozzi F, et al. Less than 2% of the low- and intermediate-risk differentiated thyroid cancers show distant metastases at post-ablation whole-body scan. *Eur Thyroid J.* 2019;**8**(2):90–95.

15. Hirsch D, Levy S, Tsvetov G, et al. Long-term outcomes and prognostic factors in patients with differentiated thyroid cancer and distant metastases. *Endocr Pract.* 2017;**23**(10):1193–1200.

16. Lee J, Soh EY. Differentiated thyroid carcinoma presenting with distant metastasis at initial diagnosis clinical outcomes and prognostic factors. *Ann Surg.* 2010;**251**(1):114–119.

17. Durante C, Haddy N, Baudin E, et al. Long-term outcome of 444 patients with distant metastases from papillary and follicular thyroid carcinoma: benefits and limits of radioiodine therapy. *J Clin Endocrinol Metab.* 2006;**91**(8):2892–2899.

18. Nixon IJ, Whitcher MM, Palmer FL, et al. The impact of distant metastases at presentation on prognosis in patients with differentiated carcinoma of the thyroid gland. *Thyroid.* 2012;**22**:884–889.

19. Kim H, Kim HI, Kim SW, et al. Prognosis of differentiated thyroid carcinoma with initial distant metastasis: a multicenter study in Korea. *Endocrinol Metab (Seoul).* 2018;**33**(2):287–295.

20. Albano D, Panarotto MB, Durmo R, Rodella C, Bertagna F, Giubbini R. Clinical and prognostic role of detection timing of distant metastases in patients with differentiated thyroid cancer. *Endocrine.* 2019;**63**:79–86.

21. Sampson E, Brierley JD, Le LW, Rotstein L, Tsang RW. Clinical management and outcome of papillary and follicular (differentiated) thyroid cancer presenting with distant metastasis at diagnosis. *Cancer.* 2007;**110**(7):1451–1456.

22. Lang BH, Wong KP, Cheung CY, Wan KY, Lo CY. Evaluating the prognostic factors associated with cancer-specific survival of differentiated thyroid carcinoma presenting with distant metastasis. *Ann Surg Oncol.* 2013;**20**:1329–1335.

23. Kim HJ, Lee JI, Kim NK, Min YK, Kim SW, Chung JH. Prognostic implications of radioiodine avidity and serum thyroglobulin in differentiated thyroid carcinoma with distant metastasis. *World J Surg.* 2013;**37**(12):2845–2852.

24. IKNL. *2015 Dutch Thyroid Cancer Guidelines.* 2015. https:// www.oncoline.nl/schildkliercarcinoom.

25. van Velsen EFS, Stegenga MT, van Kemenade FJ, et al. Evaluating the 2015 American Thyroid Association risk stratification system in high-risk papillary and follicular thyroid cancer patients. *Thyroid.* 2019;**29**:1073–1079.

26. van Velsen EFS, Stegenga M, van Kemenade FJ, et al. Evaluation of the 2015 ATA guidelines in patients with distant metastatic differentiated thyroid cancer - supplemental material. 2019. https:// repub.eur.nl/pub/119137.

27. Lamartina L, Durante C, Filetti S, Cooper DS. Low-risk differentiated thyroid cancer and radioiodine remnant ablation: a systematic review of the literature. *J Clin Endocrinol Metab.* 2015;**100**(5):1748–1761.

28. Sawka AM, Brierley JD, Tsang RW, et al. An updated systematic review and commentary examining the effectiveness of radioactive iodine remnant ablation in well-differentiated thyroid cancer. *Endocrinol Metab Clin North Am.* 2008;**37**(2):457–480.

29. Kitahara CM, Berrington de Gonzalez A, Bouville A, et al. Association of radioactive iodine treatment with cancer mortality in patients with hyperthyroidism. *JAMA Intern Med* 2019.

30. Yu CY, Saeed O, Goldberg AS, et al. A systematic review and meta-analysis of subsequent malignant neoplasm risk after radioactive iodine treatment of thyroid cancer. *Thyroid.* 2018;**28**:1662–1673.

31. Avram AM, Fig LM, Frey KA, Gross MD, Wong KK. Preablation 131-I scans with SPECT/CT in postoperative thyroid cancer patients: what is the impact on staging? *J Clin Endocrinol Metab.* 2013;**98**(3):1163–1171.

32. Pitoia F, Bueno F, Urciuoli C, Abelleira E, Cross G, Tuttle RM. Outcomes of patients with differentiated thyroid cancer risk-stratified according to the American thyroid association and Latin American thyroid society risk of recurrence classification systems. *Thyroid.* 2013;**23**:1401–1407.

33. Shah S, Boucai L. Effect of age on response to therapy and mortality in patients with thyroid cancer at high risk of recurrence. *J Clin Endocrinol Metab.* 2018;**103**(2):689–697.

34. Chopra S, Garg A, Ballal S, Bal CS. Lung metastases from differentiated thyroid carcinoma: prognostic factors related to remission and disease-free survival. *Clin Endocrinol (Oxf).* 2015;**82**(3):445–452.

35. Tuttle RM, Tala H, Shah J, et al. Estimating risk of recurrence in differentiated thyroid cancer after total thyroidectomy and radioactive iodine remnant ablation: using response to therapy variables to modify the initial risk estimates predicted by the new American Thyroid Association staging system. *Thyroid.* 2010;**20**:1341–1349.

36. Goffredo P, Sosa JA, Roman SA. Differentiated thyroid cancer presenting with distant metastases: a population analysis over two decades. *World J Surg.* 2013;**37**(7):1599–1605.