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**Original Research**

# Tumor size and presence of metastases in differentiated thyroid cancer: comparing cohorts from two countries

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## Abstract

**Objective:** Incidence of thyroid cancer varies widely, even across neighboring countries. Data on this phenomenon are largely lacking but are likely related to differences in health care systems. Therefore, we explored whether there are differences between populations from these 2 countries with respect to the relationship between tumor size and advanced disease.

**Methods:** We retrospectively studied 2 cohorts of adult differentiated thyroid cancer (DTC) patients from a Dutch and a German university hospital. We analyzed the presence of lymph node metastases with respect to tumor size for papillary thyroid cancer (PTC), and the presence of distant metastases for DTC, and PTC and follicular thyroid cancer (FTC) separately.

**Results:** We included 1771 DTC patients (80% PTC, 20% FTC; 24% lymph node and 8% distant metastases). For PTC, the proportion of patients with lymph node metastases was significantly higher in the Dutch than in the German population for tumors ≤ 1 cm (45% vs. 14%; $P < .001$). For DTC, distant metastases occurred particularly significantly more frequently in the Dutch than in the German population for tumors ≤ 2 cm (7% vs. 2%; $P = .004$).

**Conclusion:** The presence of lymph node and distant metastases is significantly higher in pT1 DTC cases in the Dutch compared to the German cohort, which might be caused by differences in the indication for and application of diagnostic procedures eventually leading to DTC diagnosis. Our results implicate that one should be cautious when extrapolating results and guidelines from 1 country to another.

**Keywords:** differentiated thyroid cancer, papillary thyroid cancer, tumor size, lymph node metastases, distant metastases

### Significance

Data are largely lacking on the influence of differences in health care systems with respect to the detection of advanced thyroid cancer. Such differences include factors such as restrictive (the Netherlands) or ubiquitous (Germany) use of thyroid ultrasound screening. In the current study, we showed that the presence of lymph node and distant metastases is significantly higher in differentiated thyroid cancer (DTC) tumors ≤ 2 cm in the Dutch compared to the German cohort, which might be caused by differences in the indication for and application of diagnostic procedures eventually leading to DTC diagnosis. Our results implicate that one should be cautious when extrapolating results and guidelines from 1 country to another.

## Introduction

The worldwide incidence of differentiated thyroid cancer (DTC) has increased steadily over recent decades,[1,2] but mortality has not. Therefore, in recent years, a less aggressive therapeutic approach has been advocated frequently,[1-4] although this has not yet resulted in consensus: guidelines are uniform neither in their risk estimates nor in their resulting advice with regard to extent of surgery and the need for radioiodine therapy.[4-8]

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For instance, the 2015 American Thyroid Association (ATA) Guidelines recommend a hemithyroidectomy in case of low-risk DTC with tumors ≤ 4 cm[4] based on large national USA DTC database studies.[9] Furthermore, the Japanese Association of Endocrine Surgery posed a consensus statement that one might consider active surveillance in patients with papillary thyroid cancer (PTC) ≤ 1 cm with low-risk features.[10] However, results from earlier studies showed that there are many differences in baseline factors that may contribute to differences in disease characteristics of DTC patients.[11,12] Such differences may also include air pollution,[13] or differences in health care systems, which include the indication for and application of diagnostic procedures eventually leading to DTC diagnosis. A good example of this is the Dutch guidelines stating that, in general, incidentally discovered thyroid nodules on CT or MRI scans do not require routine investigation,[6] whereas to date, no such guidelines exist in Germany. Another example is the availability and use of thyroid ultrasound in first-line health care services for screening for thyroid nodules. Based on a very low incidence of symptomatic goiter because of a >70-year history of legally mandated iodine supplementation, thus eliminating iodine sufficiency, the Netherlands has barely incorporated thyroid ultrasound in first-line healthcare, especially not for screening purposes. In contrast, in Germany, a country still classified as iodine deficient, many primary care physicians have an ultrasound machine available and actively use this for screening for thyroid nodules in this iodine-insufficient country, likely contributing to the steep rise in incidence of especially small, low-risk PTC seen over the past 2 decades in Germany.[14]

It was established in previous research that increasing DTC tumor size is associated with an increasing risk of lymph node and distant metastases.[15] However, it is unknown whether healthcare system–related differences may influence this relationship between tumor size and the risk of advanced disease features such as lymph node and distant metastases in those cases diagnosed in clinical practice.

Therefore, the aim of the current study is to explore whether there are differences in disease characteristics related to primary tumor size between 2 large ethnically similar Western European DTC populations from different healthcare systems.

## Materials and methods

### Study population

For the current study, we compared data from 2 established, well-described populations from Rotterdam (the Netherlands) and Würzburg (Germany).[16-27]

In short, from the Erasmus Medical Center (Erasmus MC), Rotterdam, the Netherlands, we retrospectively obtained data from patients, aged 18 years or above, who were diagnosed and/or treated for either PTC or follicular thyroid cancer (FTC) between January 2002 and December 2015. All patients underwent thyroid surgery and were treated according to the Dutch Guidelines valid at the time of treatment (eg[6]); the extent of lymph node surgery was based on the location of the lymph node metastases, and usually, no prophylactic lymph node resection was performed. Before surgery, a cervical ultrasound was performed to determine possible existence of lymph node metastases. Demographic, disease, and treatment characteristics were obtained from patient records. Cause of death was obtained from hospital or general practitioner records. Survival was defined as the time from the date of the initial diagnosis to either the date of the last-known follow-up, death, or end of study (December 2017), whichever occurred first. The study protocol was approved by the Institutional Review Board of the Erasmus MC, and informed consent was waived.

From the University of Würzburg (UKW), Würzburg, Germany, we retrospectively obtained data on patients, aged 18 years or above, who were treated for either PTC or FTC between January 2002 and December 2015. All patients underwent thyroid surgery and were treated further in accordance with the standards of the respective time period as described previously.[20,21] In general, the extent of lymph node surgery was based on the location of the lymph node metastases, and usually, no prophylactic lymph node resection was performed. Before surgery, a cervical ultrasound was performed to determine possible existence of lymph node metastases. Demographic, disease, and treatment data were immediately recorded at each patient visit. Cause of death was obtained from hospital or general practitioner records or public registration offices. Survival was defined as the time of initial diagnosis to either last date of follow-up, death, or end of study data collection (December 2016), whichever occurred first. The Würzburg Thyroid Cancer Database was maintained with approval of and continuous monitoring by Institutional Review Board, which also waived informed consent and approved this study.

This study complies with the Declaration of Helsinki.

### 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. Differences in characteristics between Erasmus MC and UKW were assessed using Student's *t*-test, log-rank test, or $\chi^2$-test as appropriate.

The presence of lymph node (based on pathology results) and distant metastases (based on radiology and/or pathology results) according to tumor size, comparing both populations, was analyzed using logistic regression (adjusted for age and sex). Analyses regarding lymph node metastases were performed for PTC, while the analyses for distant metastases were performed for PTC and FTC separately and combined as DTC. In case no tumor inside the thyroid was discovered, the tumor size was considered as 0.0 cm.

Overall survival (OS) and disease-specific survival (DSS) were analyzed using the Kaplan–Meier method, and both populations were compared using the log-rank test.

*P*-values below .05 were considered significant. All analyses were performed using SPSS Statistics for Windows (version 25.0).

## Results

### Population characteristics

Our database query yielded a total of 1931 DTC patients. In 160 of these (35 [2%] from Erasmus MC, and 125 [6%] from UKW), reliable information on tumor size was missing, and therefore, the final study cohort consisted of 1771 patients (712 patients from Erasmus MC and 1059 from UKW). Table 1 displays the characteristics of the study population.

PTC was present in 1425 patients (80%), whereas the remaining 346 patients (20%) had FTC. 132 patients (8%) had distant and 432 (24%) had lymph node metastases at presentation. Thyroid surgery was performed in all included

**Table 1.** Characteristics of the study population.

| | Total population ($n = 1771$)[a] | Erasmus MC ($n = 712$)[a] | UKW ($n = 1059$)[a] | *P*-value[b] |
|---|---|---|---|---|
| Age at baseline (years) | 48.7 ± 15.4 | 48.1 ± 16.2 | 49.1 ± 14.9 | .197 |
| Sex | | | | .746 |
| Male | 547 (30.9) | 223 (31.3) | 324 (30.6) | |
| Female | 1224 (69.9) | 489 (68.7) | 735 (69.4) | |
| Disease | | | | .334 |
| Papillary | 1425 (80.5) | 565 (79.4) | 860 (81.2) | |
| Follicular | 346 (19.5) | 147 (20.6) | 199 (18.8) | |
| T-stage | | | | **<.001** |
| T0 | 10 (.6) | 10 (1.4) | — | |
| T1 | 943 (53.2) | 283 (39.7) | 660 (62.3) | |
| T2 | 459 (25.9) | 193 (27.1) | 266 (25.1) | |
| T3 | 284 (16.0) | 177 (24.9) | 107 (10.1) | |
| T4 | 74 (4.2) | 48 (6.7) | 26 (2.5) | |
| Lymph node metastases | | | | |
| Not present | 1339 (75.6) | 486 (68.3) | 853 (80.5) | **<.001** |
| Present[c] | 432 (24.4) | 226 (31.7) | 206 (19.5) | |
| N1a | 147 (8.3) | 56 (7.9) | 91 (8.6) | |
| N1b | 244 (13.8) | 168 (23.6) | 76 (7.2) | |
| Distant metastases | | | | |
| Not present | 1639 (92.5) | 640 (89.9) | 999 (94.3) | **<.001** |
| Present | 132 (7.5) | 72 (10.1) | 60 (5.7) | |
| Tumor size (mm) | 18 (10-32) | 25 (12-40) | 15 (9-26) | |
| Surgery (TT or HT) | | | | |
| HT | 99 (5.6) | 26 (3.7) | 73 (6.9) | **.004** |
| TT | 1672 (94.4) | 686 (96.3) | 986 (93.1) | |
| Neck dissection[d] | | | | |
| Yes | n/a | 212 (29.8) | n/a | |
| No | n/a | 497 (69.8) | n/a | |
| RAI treatment | | | | **.001** |
| Yes | 1620 (91.5) | 670 (94.1) | 950 (89.7) | |
| No | 151 (8.5) | 42 (5.9) | 109 (10.3) | |
| Follow-up (months) | 57 (32-110) | 96 (50-140) | 44 (25-79) | **<.001** |
| Vital status at the end of follow-up | | | | |
| Alive | 1612 (91.0) | 628 (88.2) | 984 (92.9) | |
| Died (all cause) | 159 (9.0) | 84 (11.8) | 75 (7.1) | **<.001** |
| Died (thyroid cancer) | 56 (3.2) | 46 (6.5) | 10 (.9) | **<.001** |
| Survival | | | | |
| 10-year OS (%) | 85.2 ± 1.3 | 86.1 ± 1.6 | 82.4 ± 2.5 | .295 |
| 10-year DSS (%) | 94.5 ± 0.8 | 92.4 ± 1.2 | 96.6 ± 1.3 | **<.001** |

Significant *P*-values displayed in bold.
[a]Values are means (±standard deviation), medians (25-75 IQR) or numbers (percentages).
[b]*P*-value comparing Erasmus MC and UKW.
[c]Information on location is missing in 41 patients.
[d]Information on neck dissection is missing in 3 patients.
OS, overall survival; DSS, disease-specific survival; HT, hemi-thyroidectomy; TT, total thyroidectomy; RAI, radioactive iodine; n/a, not available.

patients, of which 1672 patients (94%) received a total thyroidectomy.

During follow-up, 159 patients (9.0%) died, of which 56 (3.2%) were due to thyroid cancer.

Significantly more patients died in the Erasmus MC population compared to UKW ($P < .001$). Additionally, 10-year DSS was significantly lower for the Erasmus MC cohort compared to UKW (92.4% vs. 96.6%; $P < .001$). Additional analyses revealed that this difference is mainly caused by patients with AJCC/TNM stage IV (8 edition) who have a significantly lower 10-year DSS in the Erasmus MC cohort compared to UKW (35.5% vs. 77.9%; $P = .002$). On the other hand, there were no differences with respect to 10-year OS (31.2% vs. 29.5%; $P = .601$).

## Comparing both populations

Patients from the Erasmus MC significantly more often had lymph node (32% vs 20%; $P < .001$) and distant metastases (10% vs. 6%; $P = .001$) at diagnosis than those from UKW. Furthermore, the median tumor diameter was significantly larger in the Erasmus MC than in the UWK population (median 25 mm vs. 15 mm; $P < .001$). Additionally, patients from Erasmus MC received significantly more often total thyroidectomy and RAI therapy ($P = .004$ and $P = .001$, respectively).

For PTC, lymph node metastases were significantly more frequent in the Erasmus MC than in the UKW population for tumors ≤ 4 cm (OR 1.96 [95% CI 1.52-2.54], $P < .001$; see also Table 2 and Figure 1), which was primarily caused by tumors ≤ 1 cm (OR 5.22 [95% CI 3.22-8.48], $P < .001$). Further, of all patients with lymph node metastasis, 31% for Erasmus MC and 19% for UKW had tumors ≤ 1 cm. For DTC and PTC and FTC separately, distant metastases were significantly more often present in the Erasmus MC than in the UKW population in tumors ≤ 2 cm (OR 3.78 [95% CI 1.86-7.68], $P < .001$; OR 3.41 [95% CI 1.45-7.99], $P = .005$; OR 6.90 [95% CI 1.53-31.21], $P = .012$; see also Table 3 and Figures 2 and 3). No differences in frequency

**Table 2.** Lymph node metastases by primary tumor diameter.

| | ≤1.0 cm | 1.1-2.0 cm | ≤2.0 cm | 2.1-4.0 cm | ≤4.0 cm | >4.0 cm |
|---|---|---|---|---|---|---|
| PTC | | | | | | |
| Erasmus MC[a] | 69/153 (45%) | 43/137 (31%) | 112/290 (39%) | 55/173 (32%) | 167/463 (36%) | 41/102 (40%) |
| UKW[a] | 40/292 (14%) | 84/320 (26%) | 124/612 (20%) | 54/198 (27%) | 178/810 (22%) | 17/50 (34%) |
| OR (95% CI)[b] | 5.22 (3.22-8.48) | 1.33 (0.84-2.11) | 2.50 (1.81-3.45) | 1.22 (0.78-1.91) | 1.96 (1.52-2.54) | 1.26 (0.62-2.59) |
| *P*-value[c] | **<.001** | .218 | **<.001** | .385 | **<.001** | .526 |

Significant *P*-values displayed in bold.
[a]Numbers and percentage of lymph node metastases present at this tumor diameter.
[b]Odds ratio with 95% CI, adjusted for age and sex. UKW as reference.
[c]*P*-value comparing both groups, adjusted for age and sex.

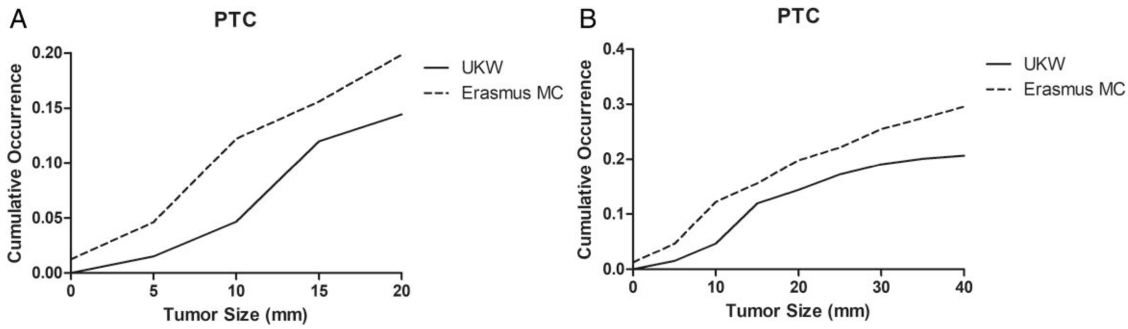


**Figure 1.** Presence of lymph node metastases by tumor size for PTC tumors (A) up to 20 mm and (B) up to 40 mm.

**Table 3.** Distant metastases by primary tumor diameter.

| | ≤1.0 cm | 1.1-2.0 cm | ≤2.0 cm | 2.1-4.0 cm | ≤4.0 cm | >4.0 cm |
|---|---|---|---|---|---|---|
| DTC | | | | | | |
| Erasmus MC[a] | 8/158 (5%) | 13/159 (8%) | 21/317 (7%) | 18/226 (8%) | 39/543 (7%) | 33/169 (20%) |
| UKW[a] | 5/306 (2%) | 8/369 (2%) | 13/675 (2%) | 25/282 (9%) | 38/957 (4%) | 22/102 (22%) |
| OR (95% CI)[b] | 3.20 (1.02-10.07) | 4.36 (1.75-10.88) | 3.78 (1.86-7.68) | 1.01 (0.53-1.92) | 2.03 (1.27-3.24) | 0.95 (0.51-1.75) |
| *P*-value[c] | **.046** | **.002** | **<.001** | .989 | **.003** | .862 |
| PTC | | | | | | |
| Erasmus MC[a] | 5/153 (3%) | 9/137 (7%) | 14/290 (5%) | 13/173 (8%) | 27/463 (6%) | 17/102 (17%) |
| UKW[a] | 4/292 (1%) | 5/320 (2%) | 9/612 (2%) | 12/198 (6%) | 21/810 (3%) | 7/50 (14%) |
| OR (95% CI)[b] | 2.35 (0.62-8.98) | 4.53 (1.48-13.83) | 3.41 (1.45-7.99) | 1.34 (0.59-3.03) | 2.41 (1.34-4.32) | 1.26 (0.48-3.31) |
| *P*-value[c] | .211 | **.008** | **.005** | .488 | **.003** | .636 |
| FTC | | | | | | |
| Erasmus MC[a] | 3/5 (60%) | 4/22 (18%) | 7/27 (26%) | 5/53 (9%) | 12/80 (15%) | 16/67 (24%) |
| UKW[a] | 1/14 (7%) | 3/49 (6%) | 4/63 (6%) | 13/84 (15%) | 17/147 (12%) | 15/52 (29%) |
| OR (95% CI)[b] | — | 8.72 (1.04-72.78) | 6.90 (1.53-31.21) | 0.66 (0.20-2.20) | 1.56 (0.65-3.75) | 0.83 (0.35-1.95) |
| *P*-value[c] | — | **.046** | **.012** | .501 | .324 | .661 |

Significant *P*-values displayed in bold.
[a]Numbers and percentage of distant metastases present at this tumor diameter.
[b]Odds ratio with 95% CI, adjusted for age and sex. UKW as reference.
[c]*P*-value comparing both groups, adjusted for age and sex.

between both populations were seen for tumors ≥ 4 cm regarding lymph node and distant metastases (see Tables 2 and 3).

## Discussion

In the present study, combining 2 well-described, ethnically similar large DTC patient cohorts from 2 neighboring European countries with considerable differences in health care systems due to infrastructure-related aspects of thyroidology, leading to the diagnosis of DTC, we showed that lymph node metastases are significantly more frequently present in PTC tumors ≤ 1 cm and distant metastases in tumors ≤ 2 cm in patients from an iodine-sufficient country with restrictive use of ultrasound for thyroid screening (the Netherlands) when compared to those from an iodine-insufficient country with ubiquitous availability of thyroid ultrasound screening in the primary care setting (Germany).

Thus far, to the best of our knowledge, no studies exist which have sought to examine specific differences in DTC disease characteristics as a function of tumor diameter between populations. However, it is well established that disease characteristics differ between populations. This was illustrated already over 35 years ago by Hannequin et al.,[28] who showed that applying specific methods for deriving prognostic scoring

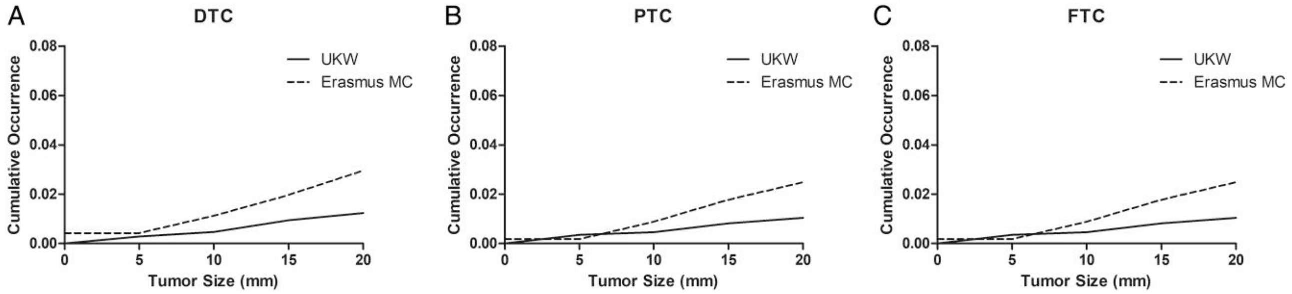


**Figure 2.** Presence of distant metastases by tumor size for tumors up to 20 mm for (A) DTC, (B) PTC, and (C) FTC.

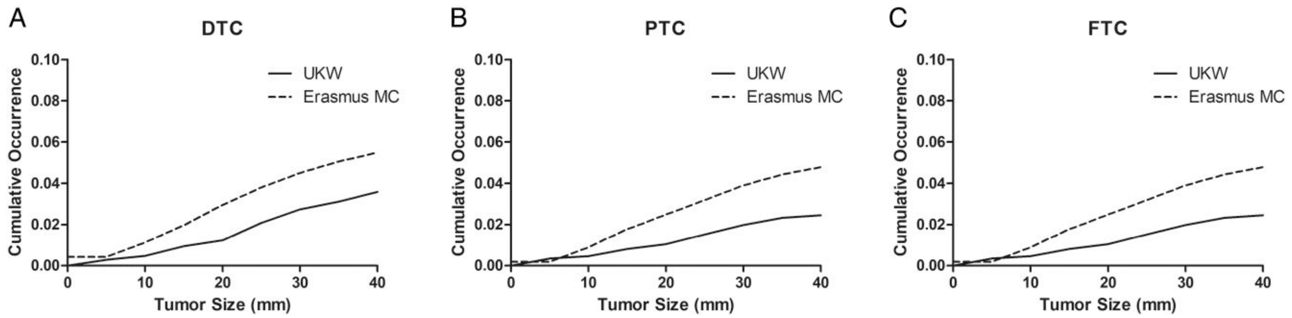


**Figure 3.** Presence of distant metastases by tumor size for tumors up to 40 mm for (A) DTC, (B) PTC, and (C) FTC.

systems to a different population yielded a different system than the one constructed based on the initial test population. Many studies that followed also identified varying risk factors in different populations.[29-32]

A significant difference in the relationship between primary tumor diameter and occurrence of lymph node and distant metastases was seen for tumors ≤ 2 cm (ie, pT1). There are a number of potential factors which could theoretically be responsible for this, such as a difference in iodine sufficiency, air pollution, the Dutch guidelines stating that, in general, incidentally discovered thyroid nodules on CT or MRI scans do not require routine investigation, and the influence from the difference in availability of ultrasound screening for thyroid. Regarding the latter 2, the far larger proportion of small tumors in the UKW population, 62% of the patients had T1 tumors vs. only 39% in the Erasmus MC population (see Table 1), indicates a comparative overdiagnosis of small tumors without lymph node or distant metastases or, conversely, shows that likely a far larger proportion of patients in the Erasmus MC population had symptomatic and/or metastatic disease than in the UKW population. Differences between Erasmus MC and UKW were also seen in the mortality statistics as significantly more patients died from thyroid cancer in the Erasmus MC population compared to UKW, which was mainly caused by patients with by AJCC/TNM (eighth edition) stage IV disease. However, no differences with respect to overall survival were seen in those with stage IV disease suggesting that those from the UWK cohort died from another cause before they could die from thyroid cancer, or differences regarding the registration of the cause of death exist between both cohorts. In 2015, the incidence rate for thyroid cancer (including all other types) is almost twice as high in Germany compared to the Netherlands (8.30 per 100 000 vs. 4.23 per 100 000 per year), while differences for mortality rates are less pronounced (0.90 per 100 000 vs. 0.54 per 100 000 per year). This may suggest that on a population level, health care differences do not result into a worse survival. However, this is difficult to confirm as data per thyroid cancer subtype were lacking with respect to the mortality data.

The present results have direct consequences for medical practice. A significantly more frequent occurrence of lymph node metastases was seen for PTC tumors ≤ 4 cm in the Erasmus MC population, which was primarily caused by a significantly higher proportion of patients with lymph node metastases in patients with a primary tumor diameter ≤ 1 cm (pT1a). However, based on a recent consensus statement of the Japanese Association of Endocrine Surgery, one might consider active surveillance in patients with PTC ≤ 1 cm with low-risk features,[10] which excludes those having known lymph node and/or distant metastases. Ito et al. showed that during an active surveillance of 10 years, 3.8% developed lymph node metastases,[33] observations later confirmed in essence by studies by Tuttle et al. and Molinaro et al.,[34,35] whereas the percentage of those who have such metastases at 1 cm diameter in the population of patients presenting to the Erasmus MC is already at 45%, suggesting that most clinically non-relevant microcarcinoma cases are not even diagnosed in the Netherlands as these tumors rarely cause clinical complaints. Based on such observations of relatively mild courses of disease in smaller tumors, the current 2015 ATA Guidelines advise to consider a hemithyroidectomy only in case of low-risk DTC with tumors ≤ 4 cm.[4] It is important to note that the studies and guidelines on which such de-escalating treatment studies are based are mostly, if not exclusively, from countries with a comparatively ubiquitous availability of ultrasound thyroid screening, thus leading to overdiagnosis of clinically non-relevant small tumors with likely an indolent course and a comparatively low frequency of advance disease characteristics in the population diagnosed with small tumors. The differences between the Erasmus MC and UKW population, however, indicate this may result in differences between populations, and consequently prognosis. Supporting this, Lee et al. showed that the risk of recurrence of PTC was significantly lower for incidentalomas (hazard rate [HR] 0.4 [95% CI 0.2-0.9; $P = .033$]), and significantly higher when PTC was diagnosed after a palpable neck mass was found (HR 2.7 [95% CI 1.1-6.4; $P = .025$]).[36] Unfortunately, we could not perform such an analyses, because information on how patients were initially diagnosed was not available for our populations. An adaptation of treatment recommendations according to baseline population characteristics seems appropriate, as the present study implies that de-escalating treatment guidelines may not apply to all countries. Therewith, our results fuel the discussion on the benefits and harms of ubiquitous availability of ultrasound thyroid screening, in which one might even consider to restrict thyroid ultrasound screening to reduce overdiagnosis of low risk cases. A recommendation also following from the previously described South Korea's thyroid cancer "epidemic."[37,38] For future international, multi-population guidelines, it therefore seems essential that recommendations should no longer be based on tumor diameter alone, but rather on risk levels for having advanced disease features such as lymph node metastases—it is then up to the individual center to determine with which tumor diameter such a risk level is associated.

Strengths of the current study include the substantial proportion of patients with lymph node (>20%) and distant (>5%) metastases in 2 in itself already large patient cohorts, which enabled us to robustly investigate the relationship between tumor size and metastases. Furthermore, both the Erasmus MC and UKW populations are cohorts with representative populations for their own countries. Also, our population included a substantial proportion of FTC patients which enabled us to also investigate PTC and FTC separately with respect to distant metastases.

A possible limitation of our study is that patients were recruited from 2 tertiary university hospitals, which might, at least in theory, have resulted in a disproportionately high percentage of patients with more aggressive DTC seeking advanced care. However, as both UKW and Erasmus MC are the primary referral centers for I-131 therapy of DTC in their respective region of adherence, the proportion of patients needing I-131 therapy not being seen at these centers is likely so small as not to cause a significant bias with respect to the representability of these population for their own countries. Further, it is known that the extent of surgery determines the pathological characteristics, eg, prophylactic central neck dissection would lead to more N1a patients. However, in both centers during the whole study, usually, no prophylactic lymph node resection was performed, and therefore, we feel it is unlikely this could have influenced the current results. Furthermore, unfortunately, information regarding in which way DTC was diagnosed (eg, ultrasound screening, palpable mass or coincidental finding upon surgery for benign thyroid disease) was not available for the large majority of patients in our cohorts, and therefore, we were unable to confirm the assumption that DTC was more frequently diagnosed due to ultrasound screening in Germany compared to the Netherlands. Additionally, as is inherent to retrospective studies over the course of a longer period, some influence on the results may be caused by changing standards over time. It is possible that an (unknown) proportion of DTC patients would in present times be classified otherwise, such as non-invasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP). Unfortunately, the retrospective nature of our study precludes any ascertainment in this respect.

## Conclusions

The present study shows that in a large European population of patients with DTC, both lymph node and distant metastases are more frequently present in pT1 tumors in patients from the Netherlands compared to the German patients, which might be caused by differences between both health care systems, such as the indication for and application of diagnostic procedures eventually leading to DTC diagnosis. Our results implicate that one should be cautious when extrapolating results and guidelines from 1 country to another, and perhaps, treatment related recommendations in guidelines should be associated with risk levels for advanced disease characteristics rather than absolute levels.

## Disclosure

Frederik A. Verburg has received consultancy fees from Sanofi, EISAI, and Jubilant Draximage as well as speaker honoraria from Sanofi. Robin P. Peeters received teaching fees from Sanofi and Bayer. Evert F.S. van Velsen, W. Edward Visser, Merel T. Stegenga, Uwe Mäder, Christoph Reiners, Folkert J. van Kemenade, and Tessa M. van Ginhoven declare no conflicts of interest and that no competing financial interests exist. W. Edward Visser and Frederik A. Verburg are on the editorial board of EJE. They were not involved in the review or editorial process for this paper, on which they are listed as authors.

## Authors' contributions

Evert F.S. van Velsen, Frederik A. Verburg, and W. Edward Visser designed the current study. Evert F.S. van Velsen, W. Edward Visser, Merel T. Stegenga, Robin P. Peeters, Uwe Mäder, Christoph Reiners, and Frederik A. Verburg created and/or managed the original databases to collect the clinical data. Evert F.S. van Velsen conducted the statistical analyses, and Evert F.S. van Velsen and Frederik A. Verburg wrote the initial manuscript. All authors reviewed and revised the manuscript to improve its intellectual and technical content.

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