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Article

Bilaterality, not multifocality, is an independent risk factor for recurrence in low-risk papillary thyroid cancer

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Abstract

Background: The impact of multifocality and bilaterality on recurrence in patients with low-risk papillary thyroid cancer (PTC) is relevant when considering patients for a de-escalated treatment strategy: hemithyroidectomy instead of total thyroidectomy followed with or without radioactive iodine. This study aims to analyze contralateral tumor probability in patients treated for low-risk PTC and assess multifocality and bilaterality as possible predictors for recurrence.

Methods: Patients with low-risk PTC treated with total thyroidectomy followed with or without radioactive iodine in the Netherlands between 2005 and 2015 were included in this study. Patients were identified from the Netherlands Comprehensive Cancer Organization (IKNL) and linked with the nationwide network and registry of Pathology in the Netherlands (PALGA). Contralateral tumor probability and recurrence were assessed.

Results: Of 791 included patients, 41.8% (331 of 791) had multifocal disease, with 68.9% (228 of 331) of those patients having bilateral disease. The contralateral tumor probability after hemithyroidectomy was 24.6% (150 of 610) for patients with unifocal disease and 43.1% (78 of 181) for patients with multifocal disease. We found a higher trend of recurrence in patients with bilateral disease, regardless of multifocality: in patients with contralateral disease after precompletion diagnosed unifocal disease 7.3% (11 of 150) had recurrent disease, and patients without contralateral disease after precompletion diagnosed multifocal disease 1.9% (2 per 103) had recurrence. Cox regression analysis showed that bilaterality (hazard ratio = 3.621, 95% confidence interval = 1.548 to 8.471) was the sole statistically significant risk factor for recurrence.

Conclusion: Low recurrence rates are found in patients with either multifocal or bilateral disease with low-risk PTC. Bilaterality should be taken into account when considering these patients for de-escalated treatment strategy.

The incidence of thyroid cancer has increased worldwide in the past 30 years, with well-differentiated thyroid cancer as the main contributor (1). Incidence rates in the Netherlands are now estimated to be 2 of 100 000 in men and 4.5 of 100 000 in women and are still increasing (2). To date, total thyroidectomy with or without radioactive iodine (TT+/-RAI) is considered as standard treatment for most patients with well-differentiated thyroid cancer (3). With this approach, low-risk, well-differentiated thyroid cancer has an excellent prognosis, with reported 10-year overall survival rates of 96%-98% (4,5). However, a number of studies report similar recurrence rates for patients with low-risk, well-differentiated thyroid cancer after hemithyroidectomy (HT) compared with treatment with TT+/-RAI. Also, HT has a lower reported incidence of treatment-related complications (6,7). Therefore, the 2015 American Thyroid Association (ATA) guidelines recommend HT instead of TT +/- RAI in selected patients of well-differentiated, low-risk thyroid cancer (3). Eligible patients for this de-escalated approach with HT are those who have less than 4 cm well-differentiated thyroid cancer without aggressive features on final pathology, which are associated with disease recurrence, including lymph angioinvasion, extrathyroidal extension (ETE), and multifocality. Multifocal disease is present in approximately 18%-87% of all patients with well-differentiated thyroid cancer (8,9). However, its clinical significance remains a topic of debate, not in the least because of conflicting results from several studies investigating multifocal disease as a potential risk factor for recurrence (10-15). Additionally, with HT as a treatment option for low-risk, well-differentiated thyroid cancer, a risk of missed multifocality is introduced in patients in whom only unifocal disease is found in the resected lobe. The rate of missed

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multifocality as well as the potential clinical consequence of missed bilateral disease is currently unknown (16,17). The question rises whether the lower morbidity in patients treated with HT only, when compared with TT+/-RAI, could outweigh the clinical impact of "missed" contralateral tumors. Therefore, the aim of this study is to analyze contralateral tumor probability in patients with 0-4 cm low-risk papillary thyroid cancer (PTC) and to investigate risk factors for recurrence, including bilateral and/or multifocal disease.

Methods

All patients who underwent TT for well-differentiated thyroid cancers sized 0-4 cm in the Netherlands between 2005 and 2015 were identified from the Netherlands Comprehensive Cancer Organisation (IKNL) database. Data from PALGA (the nationwide network and registry of histo- and cytopathology in the Netherlands) were collected and linked on patient level to the data from the IKNL. Patients were only included when laterality of the multifocal disease was available from the pathology report. Patients aged younger than 18 years, with unknown tumor stage (Tx), tumor size of more than 4.0 cm, node positive, noninvasive follicular thyroid neoplasm with papillary-like features, venous invasion, and patients with ETE were excluded. Also, 1-stage TT was excluded as the index thyroid lobe may be unclear while assessing contralateral tumor incidence. To ensure a minimum of 4 years of follow-up for detecting recurrence, pathology data from the PALGA database was collected up to December 2019. The pathology reports were used to restage according to the TNM eighth edition of the American Joint Committee for Cancer Manual for staging (18). Core data elements from pathology reports including age at diagnosis, sex, initial surgical treatments, multifocality, bilaterality, and recurrent disease were reviewed and collected. Vital status was collected from the patient-level data from IKNL. This study was approved by the medical ethical committee of Amsterdam University Medical Center, location VUmc, Cancer Center Amsterdam (IRB00002991).

Endpoints and definitions

The primary outcome of this study is contralateral tumor probability in patients treated with low-risk PTC. Completion thyroidectomy had to be performed less than 1 year after initial HT. If completion thyroidectomy was performed more than 1 year after HT, the patient was considered as treated with HT only and therefore excluded from this study. The secondary outcome is recurrence as defined by pathologically confirmed disease after at least 1 year after thyroidectomy.

Patients were divided into 4 groups based on number of lesions and site of cancer. Group A consists of patients with truly unifocal disease. Group B consists of patients with unifocal tumor in the index thyroid lobe and tumor localization in the contralateral lobe after completion thyroidectomy. According to the 2015 ATA guidelines, these patients are at risk of undertreatment because multifocality would be missed after initial HT. Group C consists of patients with multifocal tumor in the index thyroid lobe and no tumor in the contralateral lobe (unilateral multifocal disease) after completion thyroidectomy. This group of patients does not show bilateral disease. Group D consists of patients with multifocal disease in the thyroid lobe that was resected first and tumor localization in the contralateral lobe as well. Groups B, C, and D include patients with multifocal disease, and groups B and D include all patients with bilateral disease. Recurrence rates are compared between groups, and the impact of multifocality and bilateral disease on recurrence was analyzed.

Thyroglobulin levels and/or RAI single-photon emission computed tomography scan outcomes were not available in the used database registries. Therefore, recurrence was defined as pathology-proven recurrence only. Also, to adjust for the possible delayed treatment of patients with actual persistent disease, recurrent tumor was considered only when diagnosed more than 1 year after the date of initial thyroidectomy. Recurrence was subdivided in locoregional (the thyroid bed, central or lateral cervical nodal levels) or distant (all disease locations other than locoregional recurrence). Multifocality was defined as 2 or more thyroid cancer nodules of any size smaller than 4 cm, as proven by histo- or cytopathology. Bilaterality was defined as cancer presence in both thyroid lobes, as proven by histo- or cytopathology.

Statistical analysis

All statistical analyses were performed using SPSS version 27 (SPSS, Inc, Chicago, IL, USA). Baseline characteristics are presented as means with standard deviations for data with a normal distribution and compared using Student *t* test. Baseline data with nonnormal distribution are presented as medians with interquartile range for data and compared using the Mann–Whitney U test. Categorical data are presented as percentages and compared with the χ^2 test. Data from continuous variables with a normal distribution from more than 2 groups were compared using the 1-way analysis of variance. Kaplan–Meier curves and log-rank tests were used to evaluate recurrence-free survival over time. Multivariate Cox regression was performed using recurrence as the outcome. Backward Wald selection was used for selection of variables and assessment of confounding (increase in B coefficient of >10%) and effect modification (significant interaction term). Significant factors were reported in hazard ratio (HR) with complementary 95% confidence intervals (CIs). The multivariate Cox regression accounted for preset potential risk factors: sex, age, T stage, multifocality, and bilaterality.

Results

Baseline characteristics

A total of 3763 patients who underwent surgical treatment for well-differentiated thyroid cancer during the period 2005-2015 were identified and linked on a patient-to-patient level to the PALGA database. A total of 2972 patients were excluded according to our exclusion criteria (Figure 1), resulting in 791 patients with low-risk PTC eligible for analysis, with a median follow-up of 8.0 years. Baseline patient and tumor characteristics are presented in Table 1. Patients were predominantly female (n = 656, 82.9%), and the mean age was 46.4 (13.6) years. In total, 22.3% (176 of 791) patients had a PTC less than 1 cm, defined as papillary thyroid microcarcinoma (PTMC). The remaining 77.7% (615 of 791) had 1.1-4.0 cm tumors. Tumor nodule sizes ranged from 0.5 to 40 mm. Median tumor nodule size was 18 mm. A total of 83.8% (663 of 791) patients were treated with RAI after TT. Only 0.6% (5 of 791) of patients were treated with a lymph node dissection; these patients had no pathology-proven lymph node metastasis and were therefore not excluded from our cohort. Of all 791 patients, 331 (41.8%) patients had multifocal disease, and 460 (58.2%) had unifocal disease. Of the patients with multifocal disease, 228 (68.9%) patients had bilateral disease.

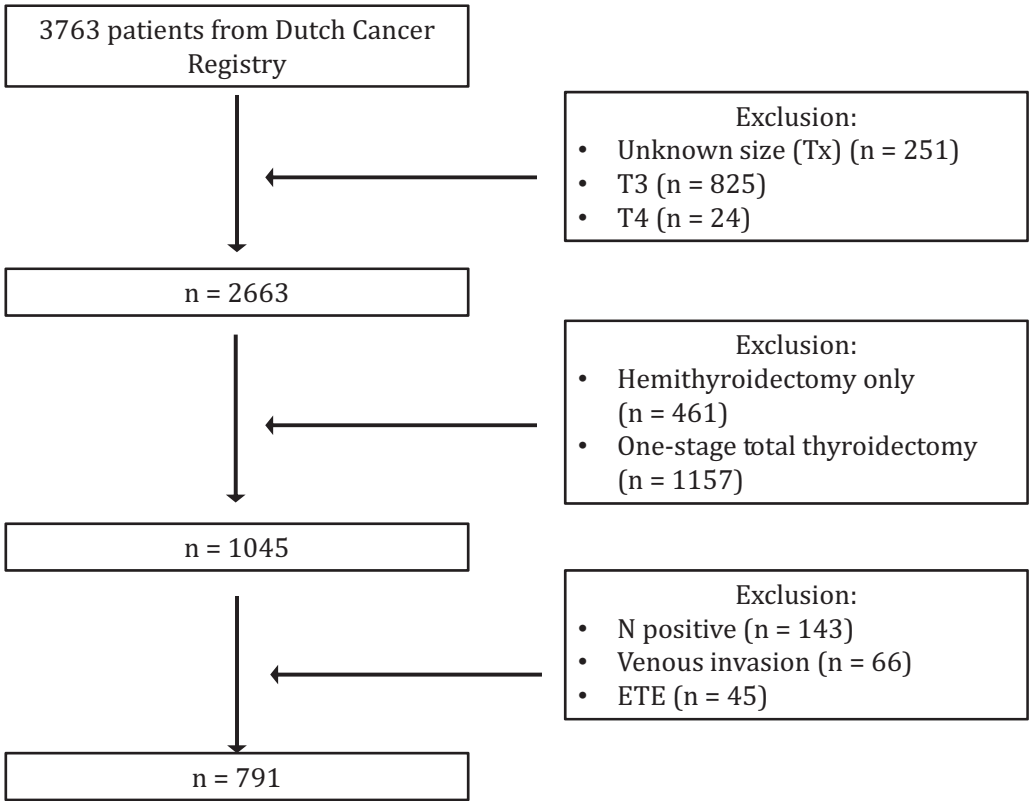

Figure 1. Flowchart of reasons for exclusion. ETE = extrathyroidal extension.

Table 1. Overall patient characteristics of included patients

Characteristics	Total (n = 791)	Group A Unifocal-unilateral (n = 460)	Group B Unifocal-bilateral (n = 150)	Group C Multifocal-unilateral (n = 103)	Group D Multifocal-bilateral (n = 78)
Age, mean (SD)	46.36 (13.55)	45.66 (13.94)	48.60 (13.05)	45.46 (14.06)	47.35 (10.92)
Sex, No. (%)					
Men	135 (17.1)	71 (15.4)	23 (15.3)	22 (21.4)	19 (24.4)
Women	656 (82.9)	389 (84.6)	127 (84.7)	81 (78.6)	59 (75.6)
Follow-up median time, y	8.0	8.1	8.3	7.6	7.8
pT stage, No. (%)					
T1a	176 (22.3)	79 (17.2)	35 (23.3)	33 (32.0)	29 (37.2)
T1b	281 (35.5)	171 (37.2)	56 (37.3)	25 (24.3)	29 (37.2)
T2	334 (42.2)	210 (45.7)	59 (39.3)	45 (43.7)	20 (25.6)
pN stage, No. (%)					
Nx	636 (80.4)	371 (80.7)	121 (80.7)	85 (82.5)	59 (75.6)
N0	155 (19.6)	89 (19.3)	29 (19.3)	18 (17.5)	19 (24.4)
pM-stage, No. (%)					
Mx	791 (100)	460	150	103	78
Median nodule size, mm	18	20	18.5	16	14
BRAFV600, No. (%)					
Positive	9 (1.1)	2 (0.4)	4 (2.7)	2 (1.9)	1 (1.3)
Negative	24 (3.0)	11 (2.4)	7 (4.7)	2 (1.9)	4 (5.1)
Surgical margin, No. (%)					
R0	671 (84.8)	394 (85.7)	129 (86.0)	89 (86.4)	59 (75.6)
R1	49 (6.2)	26 (5.7)	9 (6.0)	8 (7.8)	6 (7.7)
R2	38 (4.8)	14 (3.0)	12 (8.0)	2 (1.9)	10 (12.8)
Radioactive iodine therapy, No. (%)	663 (83.8)	378 (82.2)	124 (82.7)	92 (89.3)	69 (88.5)
Neck dissection, No. (%)	5 (0.6)	3 (0.7)	1 (0.7)	0	1 (1.3)
Multifocal, No. (%)					
Unifocal disease	460 (58.2)	460	0	0	0
Multifocal disease	331 (41.8)	0	150	103	78
Bilaterality, No. (%)					
Unilateral	563 (71.2)	460	0	103	0
Bilateral	228 (28.8)	0	150	0	78
Recurrence, No. (%)	22 (2.8)	7 (1.5)	11 (7.3)	2 (1.9)	2 (2.6)

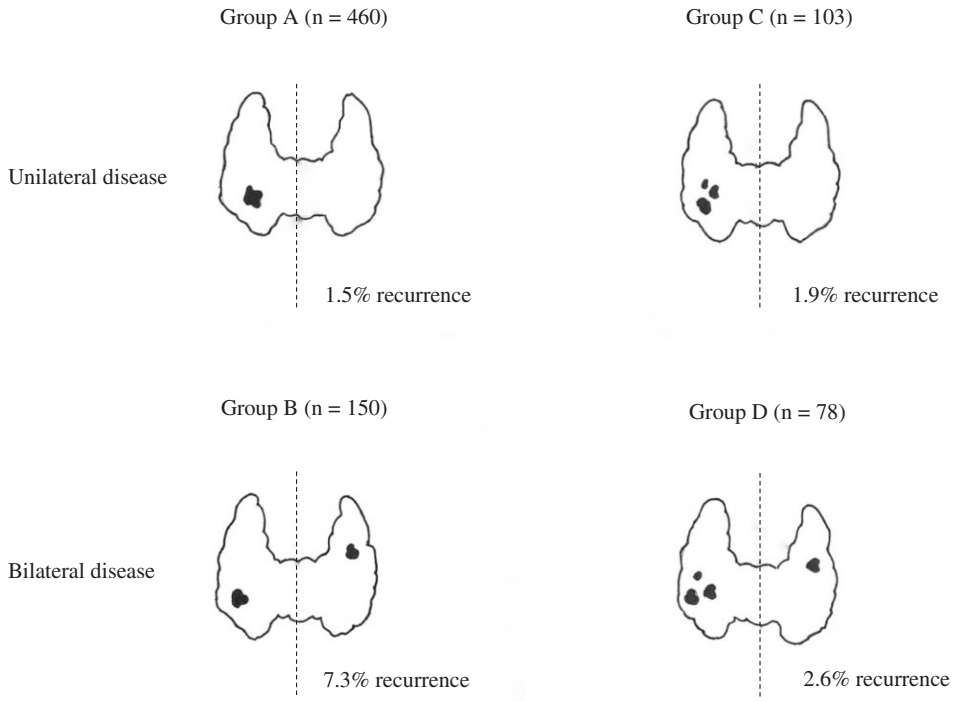

Figure 2. Recurrence in patients with papillary thyroid carcinoma as stratified for bilaterality and multifocality. Group A: patients with unifocal-unilateral disease. Group B: patients with unifocal tumor in the index thyroid lobe and tumor localization in the contralateral lobe after completion thyroidectomy. Group C: patients with multifocal tumor in the index thyroid lobe and no tumor in the contralateral lobe (unilateral multifocal disease) after completion thyroidectomy. Group D: patients with multifocal disease in the thyroid lobe that was resected first and tumor localization in the contralateral lobe as well.

Contralateral tumor probability

Contralateral tumor localizations were assessed according to the 4 groups based on diagnosis after HT and the outcome of completion thyroidectomy (groups A, B, C, and D) (Figure 2). In total, there were 77% (610 of 791) patients with unifocal disease in the index thyroid lobe (groups A and B). Of these, 460 of 610 (75.4%) patients did not show disease in the contralateral lobe (group A), and 150 of 610 (24.6%) patients showed disease in the contralateral thyroid lobe (group B). The contralateral tumor probability (bilateral disease) in patients with unifocal disease in the index thyroid lobe was therefore 24.6% (150 of 610). In total, there were 22.9% (181 of 791) patients with multifocal disease in the index thyroid lobe (groups C and D). Of these, 103 of 181 (56.9%) patients did not show disease in the contralateral lobe (group C). Consequently, 78 of 181 (43.1%) patients showed disease in the contralateral thyroid lobe (group D). The contralateral tumor probability in patients with multifocal disease in the index thyroid lobe was therefore 43.1% (78 of 181).

Recurrence

Of 791 patients, 20 patients had recurrent disease in the thyroid bed, and 2 other patients had cervical nodal recurrence. There were 25 (3.2%) patients who died during follow-up. Unfortunately, no data on cause of death were available. Recurrence was assessed according to the 4 groups based on diagnosis after HT and the outcome of completion thyroidectomy (groups A, B, C, and D) (Figure 2). In group A, 7 of 460 (1.5%) patients had recurrence. In group B, 11 of 150 (7.3%) patients had recurrence. In group C, 2 of 103 (1.9%) had recurrence. In group D, 2 of 78 (2.6%) patients had recurrence. Multivariate Cox regression analysis showed that bilaterality (HR = 3.621, 95% CI = 1.548 to 8.471) was the only statistically significant risk factor for recurrence, whereas other included risk factors (sex, age, T-stage, multifocality) were not statistically significant (Table 2). For illustration purposes, a Kaplan–Meier curve was plotted to show the significant effect of bilaterality (Figure 3).

Discussion

In this retrospective cohort study of 791 patients, we report contralateral tumor probability rates after unifocal and multifocal disease in the index thyroid lobe (24.6% and 43.1%, respectively), which are in line with rates reported in an international multicenter study performed (19). We showed that bilaterality was the only statistically significant risk factor for recurrence (HR = 3.621, 95% CI = 1.548 to 8.471). Thus, we did not find multifocality as a statistically significant risk factor.

This is in contrast to current ATA guidelines including multifocality as a (intermediate) risk factor and many other studies reporting on the significance of multifocality as a risk factor for recurrence (3,8-10), including a meta-analysis written by Jospeh et al. (10), which showed the association of multifocality with increased risk of recurrence (HR = 2.81, 95% CI = 1.07 to 7.36; $I^2 = 95.85$; $P < .001$). Kim et al. (20) reported on both multifocality and bilaterality in PTC patients. They found multifocality to be a risk factor for disease recurrence (odds ratio [OR] = 1.45, 95% CI = 1.01 to 2.10; $P = .04$) but did not find an association between bilaterality and recurrence (OR = 0.98, 95% CI = 0.64 to 1.48; $P = .92$). However, they did not focus on low-risk patients only and the subsequent de-escalation movement. A recent review and meta-analysis by Cui et al. (21) reported on the clinical outcomes of multifocal PTC and showed that multifocal disease is more aggressive in contrast to unifocal disease and that it is accompanied by an increased risk of recurrence. They did not mention bilaterality. Mao et al. (22) reported no correlation between

Table 2. Multivariate Cox regression hazard model for recurrence in patients with T1-2N0 thyroid cancer[a]

Characteristics	HR (95% CI)	P
Sex		
Men and women	4.496 (0.605 to 33.437)	.142
Age, y		
Younger than 55 years and older than 55 years	0.994 (0.389 to 2.543)	.990
T stadium		
T1a	Referent	
T1b	0.468 (0.166 to 1.317)	.150
T2	0.507 (0.187 to 1.371)	.181
Multifocal	1.205 (0.248 to 5.852)	.817
Bilaterality	3.621 (1.548 to 8.471)	.003

[a] CI = confidence interval; HR = hazard ratio.

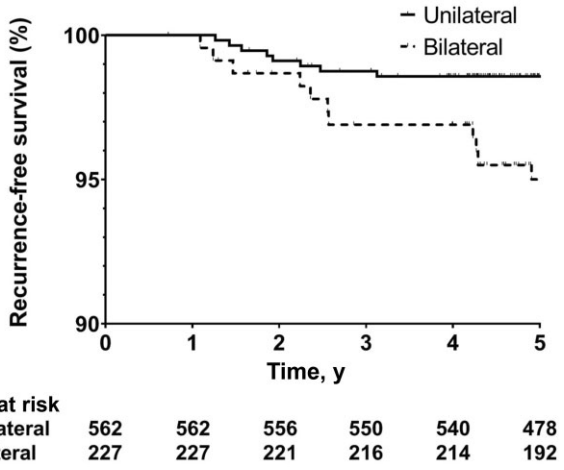

Figure 3. Multivariate Cox regression hazard model for recurrence in patients with low-risk papillary thyroid cancer.

bilaterality and lymph node metastasis. In our cohort, only 2 patients showed recurrence in lymph nodes. Bilaterality is reported as an independent risk factor by multivariate analysis in the study of Wang et al. (17). They reported a statistically significantly poorer prognosis in bilateral disease. Kartal et al. (23) reported that patients with bilateral disease would be at higher risk of advanced T-stage, higher ETE rates, and lymph node metastasis.

Against the background of surgical de-escalation of low-risk thyroid cancer, we specifically focused on groups B and C of our cohort. In theory, patients in group B could be at risk for undertreatment in a de-escalated treatment setting as these patients are mistakenly categorized as ATA low risk instead of ATA intermediate risk. Contrarily, patients with multifocal disease in the index thyroid lobe and no disease in the contralateral lobe (group C) could theoretically be at risk of overtreatment as these patients receive a completion thyroidectomy, and no disease is present at the contralateral thyroid lobe. The results of our study underline the importance of awareness of the risks of under- and overtreatment. The recurrence rates are low, regardless multifocality. Importantly, these results suggest the possibility of omitting a completion thyroidectomy in patients with unilateral multifocal disease. A recent meta-analysis by Hsiao et al. (24) suggests a lower risk of complications in less extensive surgery (and only a small increase in recurrence rates). Our results could suggest the possibility of bilaterality being an independent risk factor, not multifocality. However, as overall recurrence rate in patients with bilateral disease (groups B and D) is 5.7% (13 of 228), this subsequently means that in 94.3% of patients with bilateral tumors, no recurrence is detected in our cohort. Clinical consequences of recurrence and/or implications on patient morbidity and quality of life are difficult to correlate with incidence of contralateral disease in patients initially treated with HT. Regardless multifocality or bilaterality, recurrence rates remain low. The potential benefits of reduced morbidity in patients treated with HT rather than TT+/-RAI could outweigh the clinical impact of recurrent disease in low-risk thyroid cancer. In case of less extensive treatment strategy, the contralateral lobe should be closely monitored for potential bilateral disease. Active surveillance with ultrasound examination by a dedicated head and neck radiologist could be of great value for this purpose. Prospective studies focusing on the clinical value of active surveillance by head and neck ultrasound after HT are needed. Unfortunately, clinical information regarding the presence of a known identifiable nodule in the contralateral lobe at the time of initial HT was not available for this study.

Some limitations must be considered while weighing these study results. Only histology- and/or cytology-proven recurrence was recorded in this study, as no information on thyroglobulin levels and/or RAI single-photon emission computed tomography scan outcomes was available in the database registries used for this study. In addition, all patients in our study cohort were treated with TTx+/-RAI, which may underestimate true recurrence rates in the de-escalated setting. Inherently to the retrospective study design, missing data in pathology reports account for a bias in the estimation of parameters, and statistical analysis was complicated because of this. We opt for standardized pathology forms to reduce missing data in pathology reports. For example, lack of reporting size of nodules found in the contralateral lobe prevented us from reporting exact nodule sizes and any associations between histological findings of the ipsilateral and/or contralateral thyroid lobe and treatment outcomes. The multivariate Cox regression analysis should be interpreted with caution as well, because of the relatively low recurrence rates per predictor.

In patients with low-risk PTC, bilateral disease seems to be an independent risk factor for recurrence. In a de-escalated setting following the 2015 ATA guidelines for treatment of well-differentiated thyroid cancer, patients with unifocal disease after HT could be at risk of downstaging because of missed bilaterality and thus be undertreated, and patients with unilateral multifocality could benefit from less aggressive surgery as bilateral disease is a stronger predictor for recurrence than multifocality. Recurrence rates remain low, however. Reduced morbidity in patients treated with HT only possibly outweighs the clinical impact of missed contralateral tumors.

Data availability

The data underlying this article will be shared on reasonable request to the corresponding author.

Author contributions

Pedro Manuel Rodriguez Schaap, MD (Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Project administration; Writing—original draft), Jia Feng Lin, MD (Data curation; Writing—original draft), Madelon J.H. Metman, MD (Data curation; Writing—original draft), Koen M.A. Dreijerink,

MD, PhD (Writing—review & editing), Thera P Links, MD, PhD (Supervision), H. Jaap Bonjer, MD, PhD (Supervision), Els J.M. Nieveen van Dijkum, MD, PhD (Conceptualization; Supervision; Validation; Writing—review & editing), Chris Dickhoff, MD, PhD (Project administration; Supervision; Validation; Writing—original draft; Writing—review & editing), Schelto Kruijff, MD, PhD (Conceptualization; Resources; Supervision; Writing—review & editing), and Anton F. Engelsman, MD, PhD (Conceptualization; Formal analysis; Methodology; Project administration; Supervision; Visualization; Writing—review & editing).

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Conflicts of interest

None declared.

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