The Impact of Regional Variation in Clinical Practice on Thyroid Cancer Diagnosis: A National Population-Based Study

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Keywords

Thyroid cancer · Incidence · Fine-needle aspiration · Thyroid weight · Overdiagnosis

Abstract

Objective: Regional variation in thyroid cancer incidence in Belgium, most pronounced for low risk cancer, was previously shown to be related to variation in clinical practice, with higher thyroid surgery rates and lower proportions of preoperative fine-needle aspiration (FNA) in regions with high thyroid cancer incidence (period 2004–2006). The objective of this study was to investigate regional thyroid cancer incidence variation in relation with variation in thyroid surgery threshold in a more recent Belgian thyroid cancer cohort. **Methods:** A population-based cohort of thyroid cancer patients that underwent a (near) total thyroidectomy in the period 2009–2011 ($n = 2,329$ patients) was identified and studied by linking data from the Belgian cancer registry and the Belgian health insurance companies, and case-by-case study of the pathology protocols. The execution of preoperative FNA and the thyroid resection specimen weight were compared between high and low thyroid cancer incidence regions. Thyroid weight in the pT1a-restricted group was studied as a proxy for surgical threshold for benign nodular goiter. Furthermore, time trend analyses were performed for the execution of FNA for the period 2004–2012. **Results:** Al-

though a lower proportion of FNA in the high thyroid cancer incidence region persisted in the period 2009–2011 (41.2% [31.9–50.9] vs. 72.9% [64.9–79.7] in the low-incidence region (LIR), $p < 0.001$), a positive time trend was observed for the period 2004–2012. The median thyroid surgical specimen weight was lower in the high incidence region compared to the LIR (27.0 g [IQR 18.0–45.3] vs. 36.0 g [IQR 22.0–73.0], $p < 0.0001$), and this finding was corroborated in the pT1a-restricted group. **Conclusion:** Interregional differences in use of FNA and surgical thyroid specimen weight are consistent with an inverse relation between thyroid cancer incidence and thyroid surgery threshold, carrying risk for overdiagnosis.

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Introduction

In Belgium, higher thyroid cancer incidence – most pronounced for microcancers (T1a) – is present in the Southern region, Wallonia, compared to the Northern region, Flanders. In a pioneer national population-based study studying the cohort of patients with thyroid cancer

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diagnosis in the period 2004–2006, we showed that this geographical thyroid cancer incidence variation was paralleled by differences in clinical practice. Compared to Flanders or the further designated low-incidence region (LIR), in Wallonia or the further designated high incidence region (HIR) higher imaging rates were observed that might uncover a reservoir of subclinical disease. Although more thyroid surgery was performed, proportionally less thyroid surgery was preceded by fine-needle aspiration (FNA), suggesting less selective surgery, and the proportion of histological thyroid cancer diagnosis after total thyroidectomy was lower. Finally, in the HIR, less thyroid cancer patients had been submitted to a presurgical FNA or a lymph node dissection at first surgery [1].

The overall low proportion of thyroid cancer patients with FNA before surgery in Belgium and especially in the HIR (only 1 out of 3 patients) in our previous study was surprising and suggested disbelief in FNA and/or surgery being a substitute for FNA [2]. The 2006 and 2009 international guidelines emphasized the benefit of FNA [3–5]. However, to date, limited evidence is available regarding the local adherence to international guidelines.

Geographical variation of imaging and surgical rates frequently reflects variation in clinical management. Nevertheless, variation in disease prevalence may be present. In the case above, a slightly lower iodine intake in the HIR as compared to the LIR [6] might result in a higher prevalence of goiter in the HIR. A higher rate of goiter/volume-related complaints might drive imaging and surgical rates. The latter hypothesis assumes an equal or higher median weight of the thyroid resection specimens in the HIR as compared to the LIR. To our knowledge, the link between thyroid cancer incidence, surgical rates, and the weight of the surgical specimens has not been studied yet.

In the current study, we aimed to examine 2 measures related to thyroid surgery threshold, the use of preoperative FNA and the weight of the thyroid resection specimen across regions in Belgium, in a more recent cohort with thyroid cancer diagnosis after the publication of the 2006 and 2009 international guidelines.

Materials and Methods

Description of Data Sources

The Belgian cancer registry (BCR) collects information regarding new cancer diagnoses at the Belgian level since 2004, covering the Belgian population at an estimated 98% [7]. Based on notifications from both the oncology care programs and the laboratories of pathology, a broad set of patient and tumor characteristics is

registered, using the national social security number as a unique patient identifier. This identifier allows a deterministic coupling of the cancer registration database with reimbursement data covering diagnostic and therapeutic acts, as recorded by the health insurance companies (HIC). Health insurance being obligatory in Belgium, the HIC data can also be considered quasi complete (99%) at the Belgian population level.

Patient Selection

As shown in Figure 1, all thyroid cancer patients with a diagnosis of thyroid cancer between January 1, 2009, and December 31, 2011, were retrieved from the BCR database ($n = 2,659$, of which 2,368 with differentiated thyroid cancer [DTC]). Standard patient (incidence date, age, sex, residence, vital status, multiple tumor status) and tumor (histology, topography, behavior, clinical and pathological TNM stage, differentiation grade) characteristics were available. More detailed tumor characteristics were derived from the pathology reports sent to the BCR as part of the pathology notification flow. The pathology reports, available for 94% of this cohort, were reviewed case-by-case to extract information on the weight of the thyroidectomy specimen, the histology result and the exact tumor size, allowing identification of pT1a lesions.

For the time trend analysis, all thyroid cancer patients with a diagnosis of thyroid cancer between January 1, 2004, and December 31, 2012, were retrieved from the BCR database ($n = 7,026$, of which 6,294 with DTC).

By linkage between the BCR and the HIC databases, patient information on medical procedures was available from January 1 of the year preceding the year of incidence till December 31 of the fifth year following the year of incidence, limited to the end of the year 2013.

Identification of Surgery

Surgically treated patients were identified by reimbursement codes for near-total or total thyroidectomy charged within 3 months around the incidence date, and concerned 2,329 patients for the period 2009–2011 (Fig. 1), and 5,584 DTC patients for the period 2004–2012. All analyses compared results between LIR and HIR, where the region was determined by the geographical location of the center which performed the thyroid surgery. Consequently, patients that were operated in the Brussels-Capital Region (Fig. 2) were not considered for final analyses.

Identification of FNA before Surgery

The execution of FNA before surgery was identified by either a charged thyroid FNA procedure or thyroid cytology analysis in the year preceding surgery. In comparison to our previously published results, cytology analyses were added as the result of a cross validation of the HIC-retrieved FNA procedures with the procedures mentioned by the pathology reports. Subgroups were DTC patients and DTC patients after excluding patients with prior thyrotoxicosis or micropapillary thyroid cancer (PTC) pT1a. In the latter group, a high rate of presurgical FNA is expected, as the indication for FNA in patients with thyrotoxicosis (especially in the context of Graves' disease) and patients with the postoperative finding of a micropapillary thyroid cancer is much less likely. Prior thyrotoxicosis was defined as described before [1]. For the time-trend analysis (period 2004–2012), FNA before surgery was assessed in 4,022 surgically treated DTC patients without prior thyrotoxicosis.

Fig. 1. Flow diagram for patient selection, identification of surgery, identification of FNA performance, evaluation of thyroid specimen weight. ^aIdentified via BCR; ^bidentified via reimbursement codes (health insurance companies); ^cassignment of region based on region of surgery; ^dbased on pathology report, with exclusion of preoperative thyrotoxicosis identified by reimbursement codes. DTC, differentiated thyroid cancer; FNA, fine-needle aspiration; LIR, low-incidence region; HIR, high-incidence region.

Assessment of Thyroid Specimen Weight in Surgically Treated Thyroid Cancer Patients

Of the 2,329 surgically treated patients, 2,140 had a pathology report available, of whom 2,030 had no evidence of prior thyrotoxicosis, defined as described before [1]. Restricting to patients operated in LIR or HIR ($n = 1,567$), the thyroid weight was available for 1,223 (78%) patients and is expressed in grams. Patients with surgery for hyperthyroidism for Graves' disease, with expected lower thyroid weight, are thereby excluded. The PTC pT1a subgroup consisted of 516 patients of whom thyroid weights were known in 416 patients (81%). Patients with surgery for benign nodule/goiter volume-related complaints are expected to be represented in this subgroup. Therefore, thyroid weight in this patient group could serve as a proxy for surgical threshold for goiter surgery.

Statistical Analysis

Age-standardized incidence rates according to the European population (ESR), that is, the incidence that would be observed if the population had the structure of the European population, were calculated using the direct method [8]. Similarly, age-standardized proportions were calculated using the direct method of standardization and the European standard population. The 95% CI for each proportion was calculated using a normal approximation on

the logit scale. To allow comparison between the regions, z -scores and corresponding p values were computed. For the interregional comparison of the surgical thyroid gland weights, Moods median tests were performed. Trend over time (2004–2012) for FNA pre-surgery was evaluated by means of a linear probability model having the proportion (p) as dependent variable and the year of incidence as independent variable ($p = B_0 + B_1$ [year of incidence]). B_1 corresponds to the average increase of p by year. For each calculated trend, the p value of B_1 has been reported. Significant differences were defined as $p < 0.05$. All analyses were performed with SAS version 9.3 (SAS Institute, Cary, NC, USA).

Results

Geographical Variation in Thyroid Cancer Incidence in Belgium in the Period 2009–2011 and Time Trend for T1 Cancer Incidence for the Period 2004–2012

Thyroid cancer incidence in the period 2009–2011 was lower in Flanders or the LIR as compared to Wallonia or the HIR (Fig. 2a–b). In accordance with earlier findings, the

Fig. 2. **a** Map of Belgium and its regions. **b** The incidence of thyroid cancer, being lower in the Northern region Flanders as compared to the Southern region Wallonia (further designated as, respectively, LIR and HIR). **c–e** The incidence of thyroid cancer (white bars represent LIR, dark bars represent HIR) by histological type (**c**) and T category (**d**), and the incidence of T1 PTC (**e**). All data represent age-standardized incidence rates, using the Eu-

ropean Standard Population (number per 100,000 person years); based on BCR database where region corresponds to the region of residence, for incidence years 2009–2011. **f** Proportion of FNA before surgery in DTC patients without prior thyrotoxicosis for LIR and HIR, for the period 2004–2012. * $p < 0.05$, ** $p < 0.001$. LIR, low-incidence region; HIR, high-incidence region; BCR, Belgian cancer registry.

difference mainly reflects a variation in PTC (Fig. 2c). With regard to tumor size, the interregional differences are most pronounced for T1 cancers (Fig. 2d), especially T1a (Fig. 2e). A significant increase of T1 cancers was observed over time (years 2004–2012) in both regions, with an annual increase of 2.40% (95% CI [1.47–3.32], $p < 0.0001$) in the LIR and 2.17% (95% CI [1.11–3.24], $p < 0.0001$) in the HIR.

Use of FNA before Surgery in Thyroid Cancer Patients in the Period 2009–2011 and FNA Time Trend for the Period 2004–2012

In the 2009–2011 cohort, FNA before surgery was performed in 72.9% of the DTC patients in the LIR and 41.1% in the HIR ($p < 0.001$). The proportions were higher in the

restricted DTC group (after exclusion of thyrotoxic and PTC pT1a patients), with a similar regional difference (Table 1a). This regional difference was present across all T-categories and statistically significant in T1 and T2 tumors and in tumors of unknown T category (Table 1b).

In the large DTC cohort without prior thyrotoxicosis (2004–2012), preoperative FNA was performed in 74.6% (95% CI [69.8–78.9]) in the LIR as compared to 38.8% (95% CI [33.4–44.5]) in the HIR ($p < 0.0001$). As shown in Figure 2f, a time-trend analysis for the period 2004–2012 showed a significant increase in the use of FNA before surgery for all DTC in patients without prior thyrotoxicosis in the HIR ($p < 0.0001$). In the LIR, the use of FNA was stable over time ($p = ns$).

Table 1. FNA before surgery**a** FNA before surgery in DTC patients (2009–2011)

	All DTC patients			DTC patients after exclusion of thyrotoxic and PTC T1a patients		
	LIR	HIR	<i>p</i> value	LIR	HIR	<i>p</i> value
Total	831	666		555	334	
Number	583	235		431	149	
Proportion	70.2 (67.0–73.3)	35.3 (31.7–38.9)		77.7 (74.2–81.1)	44.6 (39.2–50)	
Age-standardized proportion	72.9 (64.9–79.7)	41.1 (31.9–50.9)	<0.001	79.2 (69.9–86.1)	48.3 (36–60.9)	<0.01

b FNA before surgery, according to T category (2009–2011)

T category	LIR		HIR		<i>p</i> value
	number	age-standardized proportion	number	age-standardized proportion	
T1	430	66.7 (55.3–76.3)	456	35.7 (25.3–47.7)	<0.01
T2	185	80.5 (65.0–90.2)	100	48.0 (30.0–66.5)	<0.05
T3 and T4	185	76.1 (55.9–88.9)	97	50.2 (28.1–72.2)	ns
Unknown	31	82.4 (46.3–96.2)	13	31.1 (22.2–41.7)	<0.01

Data are expressed as age-standardized proportions (% (95% CI)). FNA, fine-needle aspiration; LIR, low-incidence region; HIR, high-incidence region; DTC, differentiated thyroid cancer; PTC, papillary thyroid cancer; ns, not significant.

Table 2. Thyroid weight in surgically treated thyroid cancer patients after exclusion of thyrotoxicosis (2009–2011)

	All patients		DTC patients		PTC pT1a patients	
	LIR	HIR	LIR	HIR	LIR	HIR
Surgically treated thyroid cancer patients						
Number	854	713	767	646	209	307
Thyroid weight known						
Number	627	596	564	546	150	266
Median	36.0	27.0	34.5	27.3	37.5	29.8
Q1–Q3	22.0–73.0	18.0–45.3	21.0–70.8	18.0–45.0	25.5–71.7	19.0–46.0
Age 0–39 years						
Number	149	142	145	131	32	44
Median	25.9	22.0	25.0	22.0	31.0	23.5
Q1–Q3	18.0–45.3	15.0–32.0	18.2–36.0	14.5–31.5	18.5–54.5	14.3–42.5
Age 40–69 years						
Number	377	387	343	360	108	199
Median	38.0	29.5	38.0	29.5	39.5	30.0
Q1–Q3	23.0–71.0	18.5–46.0	23.0–71.7	19.0–46.0	26.0–72.1	20.0–46.7
Age 70+ years						
Number	101	67	76	55	10	23
Median	79.0	44.0	79.5	44.0	89.0	37.0
Q1–Q3	35.0–134.0	24.0–76.0	36.0–130.0	25.0–69.9	30.0–151.0	25.0–51.0

Data are expressed as median thyroid weight in grams and interquartile range. LIR, low-incidence region; HIR, high-incidence region; DTC, differentiated thyroid cancer; PTC, papillary thyroid cancer.

Thyroid Specimen Weight in Thyroid Cancer Patients in the Period 2009–2011

For all thyroid cancer patients diagnosed in the period 2009–2011 that underwent a near-total or total thyroidectomy, the median thyroid weight was significantly higher in the LIR, 36.0 grams, as compared to the HIR, 27.0 g ($p < 0.0001$). Analysis by age groups showed an age-related increase of the resected thyroid gland weight, revealing consistently higher weights in the LIR as compared to the HIR (Table 2). The regional difference in median weight of the resected thyroid gland was confirmed in DTC patients ($p < 0.0001$). Analysis of the PTC pT1a subgroup showed a median thyroid weight of 37.5 g as compared to 29.8 g in the LIR and the HIR, respectively ($p < 0.0001$). Analyses by age groups in the DTC and PTC pT1a cohorts confirmed gradual increases in thyroid weights for older patients.

Discussion

The previously observed geographical variation in thyroid cancer incidence in Belgium, with a clear North-South gradient and highest incidence in the South mostly explained by small and thus low-risk tumors, has been confirmed in the recent years with as most recent figures an age-standardized incidence rate of 3.2 and 10.7/100,000 person years in males and females in the year 2016 in the Northern region compared to 5.5 and 14.5/100,000 person years in males and females in the Southern region (http://www.kankerregister.org/media/docs/Cancer-FactSheets/Cancer_Fact_Sheet_ThyroidCancer_2016.pdf, consulted December 29, 2018). In a pioneer population-based study analyzing the thyroid cancer patient cohort with diagnosis in the years 2004–2006 (corresponding to the first 3 years of cancer registration at national level in Belgium), we demonstrated a correlation between regional variation in thyroid cancer incidence and variation in clinical practice with higher imaging and surgical rates in the HIR and lower use of presurgical FNA, suggestive of a lower surgical threshold and higher chances of finding occult thyroid cancer. Using a comparable methodologic approach for the study of a more recent, postguideline, surgically treated thyroid cancer cohort (incidence years 2009–2011), we dissected in more depth measures related to thyroid surgery threshold. In the present study, we first investigated whether presurgical FNA underuse persisted in the post-guideline era and whether interregional differences in the execution of FNA persisted. Furthermore, we questioned whether the

median weight of surgical resection specimens differed across regions. An equal or higher median thyroid weight would favor a higher incidence of goiter in the HIR, whereas a lower median thyroid weight would favor a lower surgical threshold, in line with the underuse of FNA.

First, in this cohort, the regional difference in thyroid cancer incidence is confirmed to be most pronounced for very low-risk T1a cancers, most probably representing incidental thyroid cancer findings in most cases.

The execution of a FNA constitutes a determinant for the preoperative risk evaluation for thyroid cancer, and the indications for this highly cost-effective diagnostic test were clearly pointed out in the 2006 international recommendations [3, 4] as well as in following revised versions [5, 9]. Nevertheless, a persistent underuse of preoperative FNA was observed in the HIR in the more recent DTC cohort. The proportions were slightly higher after exclusion of thyrotoxic and PTC T1a patients, but regional differences persisted with FNA being performed in approximately 50 and 80%, respectively, in surgically treated DTC patients in the HIR and LIR. Remarkably, also of the surgically treated T3/T4 DTC patients only half underwent a presurgical FNA in the HIR, leaving a wide room for improvement and implementation of guidelines in the clinical practice. Underuse of FNA and wide geographical variation in its use were also observed in recent population-based studies in Germany and France [10, 11]. However, evaluating the broader period from 2004 to 2012, a positive time trend is observed regarding the use of preoperative FNA that was most pronounced for the HIR, suggesting the onset of a catch-up dynamic potentially leading to a better preoperative cancer risk evaluation, according to guidelines. At present, the reasons for a persistent underuse of FNA are not clear. Although FNA has been shown and is generally proposed as the preferred minimally invasive, highly performant, and cost-effective diagnostic tool in the evaluation of nontoxic thyroid nodules [12, 13], several reasons for a persistent underuse of FNA might (still) exist, such as a (variable) risk for a nondiagnostic, inconclusive, or false-negative result and a low reimbursement rate for the FNA procedure. Also the decision for surgery based on clinical symptoms or imaging characteristics or the wish of the patient may contribute. As the execution of FNA in this study is based on reimbursement codes, an underestimation cannot be ruled out. Interestingly, a US survey performed in 2016 and recently published revealed that mainly nonsurgeons (radiologists and endocrinologists) perform FNA [14].

Besides surgical rates and the use of preoperative FNA, the thyroid specimen weight could provide information on the threshold for thyroid surgery. Especially the study of the thyroid gland weight of PTC T1a patients, in whom thyroid cancer is assumed to represent an incidental histologic finding in most cases, could serve as a proxy for thyroid surgical threshold. In the 2009–2011 surgically treated thyroid cancer cohort, the median thyroid weight was 30% higher in the LIR, consistent with a higher surgical threshold. This finding was corroborated in the DTC subgroup as well as the in PTC T1a-restricted group, strengthening the finding of a regional difference in surgical threshold for nontoxic nodular thyroid disease, eventually leading a different chance of finding an occult microcancer and thus impacting (very) low-risk thyroid cancer incidence figures. A lower resected thyroid gland weight across age groups in the HIR further favors the hypothesis of a lower surgical threshold and not a higher prevalence of goiter driving higher surgical rates. Historical, sociocultural, and educational reasons could contribute to the regional differences in the management of thyroid nodular disease both at physician and patient level between the Dutch-speaking Northern region and the French-speaking Southern region. Literature data on surgical thyroid specimen weight are sparse. The mean thyroid weight in PTC T1a (57 ± 52 g in the LIR and 38 ± 29 g in the HIR) in our study is lower than in a large Polish surgical cohort of patients with nontoxic, multinodular goiter. However, this was a monocentric study with estimated weights assessed by preoperative ultrasound, without data on postoperative specimen weights [15]. Of note, thyroid cancer incidence is substantially higher in Belgium than in Poland (<http://eco.iarc.fr/eucan>, consulted September 13, 2018). Our register-based study does not allow to relate thyroid specimen weight with preoperative factors such as nodule characteristics, globus symptoms, or radiological thyroid volume.

The present study is a large population-based study in a recent cohort of DTC patients confirming an inverse relation between thyroid cancer incidence and thyroid specimen weight. To our knowledge, this is the first epidemiologic study introducing thyroid specimen weight as a measure of surgical selection. Our study underlines the importance of monitoring implementation of international guidelines, especially in an ever-evolving era of thyroid cancer management, where even active surveillance is increasingly advocated in case of very low-risk T1a DTC [9, 16–19]. Our study has several limitations. Due to the type of data used, other factors involved in the decision to perform thyroid surgery cannot be ruled out, such

as globus symptoms or the cytology result. The geographical region was assigned by the place of thyroid surgery, not to the region of FNA execution, potentially impacting the results.

In conclusion, in spite of increased use of FNA and thus a more adequate preoperative cancer risk evaluation of thyroid nodules – in accordance with the international guidelines – clear geographical variation in FNA use persists. Thyroid cancer incidence across regions is negatively correlated with thyroid surgery threshold, assessed by execution of presurgical FNA and thyroid specimen weight in PTC T1a patients following (near) total thyroidectomy, consistent with variable overdiagnosis. Our findings highlight the need for additional and by preference international studies on the impact of geographical variation in clinical practice on thyroid cancer incidence.

Acknowledgments

The authors thank Evelien Vaes, Kris Henau, Bérengère Snyers, and Liesbet Van Eycken (BCR).

Statement of Ethics

The Ethics Committee of the University Hospitals Leuven approved the study, which conforms to the Declaration of Helsinki.

Disclosure Statement

There is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

Funding Sources

This work was supported by a research grant (fund Rondou, 2015) to B.D. from the KOOR (Klinische Onderzoeks-en Opleidingsraad), University Hospitals Leuven, Belgium.

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