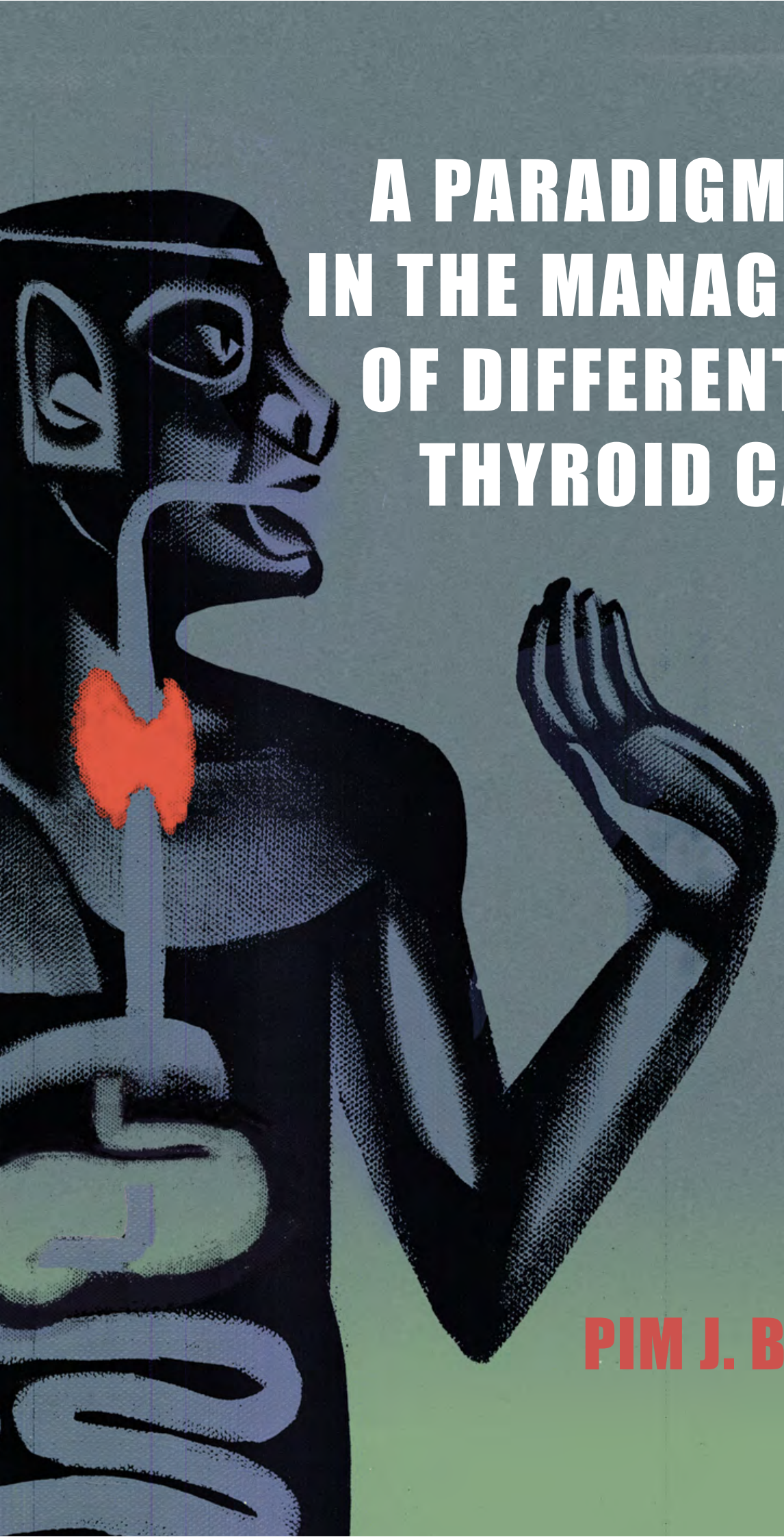
A PARADIGM SHIFT IN THE MANAGEMENT OF DIFFERENTIATED THYROID CANCER



PIM J. BONGERS

A PARADIGM SHIFT IN THE MANAGEMENT OF DIFFERENTIATED THYROID CANCER

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A paradigm shift in the management of differentiated thyroid cancer
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Cover: 'Belle Wahallah' originally by Lupo Avanti and edited by wenz iD
The original cover of the album Belle Wahallah of the Sierra Leonean Kondi Band. Originally the stomach was highlighted instead of the thyroid. It illustrates that the singer's belly is giving him so much trouble that he would rather sell it than fix the problem. It is a Nomoli depiction of a life of poverty in Freetown, Sierra Leone.
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A paradigm shift in the management of differentiated thyroid cancer

Een paradigma verschuiving in de behandeling van gedifferentieerde schildklierkanker
(met een samenvatting in het Nederlands)

Proefschrift

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... voor Nolet

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CHAPTER 1

Introduction

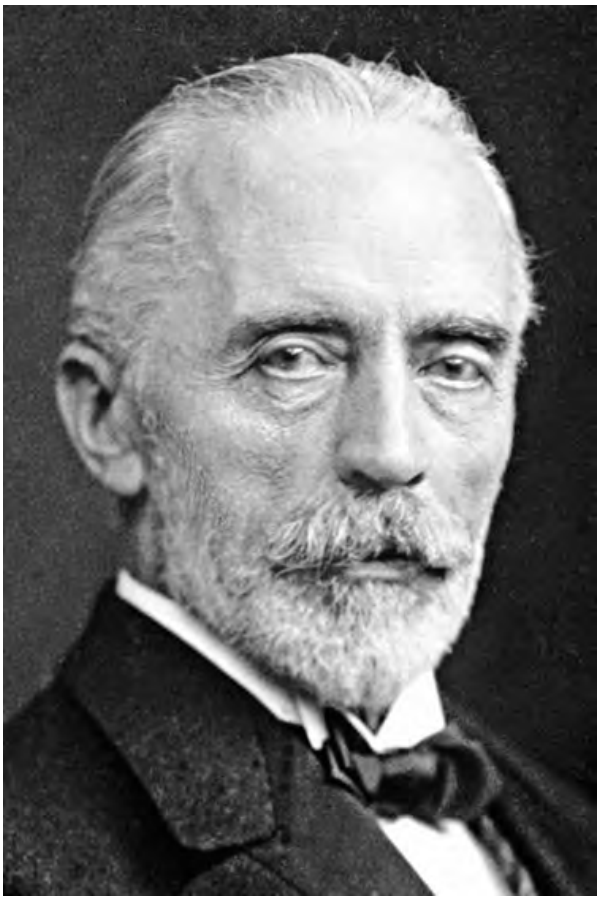
History of thyroid surgery

It was in 1511, Leonarda da Vinci made the first anatomical pictures of the thyroid gland as a bilobed butterfly shaped organ located in the lower half of the anterior neck *(figure 1)*. He presumed that the purpose of the thyroid was to fill the interval occurred by a deficit of muscles, in doing so holding the trachea away from the sternum.[1] It was not until the second half of the nineteenth century that the function of the hormone producing organ was revealed. Surgeon Theodor Kocher, of Bern, was among the first that connected cretinism, myxedema, and a person's psychological state after removal of the thyroid body *(figure 2)*. All three a result of insufficient thyroid hormone production we know nowadays.[2] When Kocher in 1883 became aware of a peculiar postoperative course in one of his patients, he called in to examine 101 patients he performed thyroid surgery on in the preceding years. He found symptoms after removal of the thyroid gland (total thyroidectomy) that were unmistakably similar to those found in patients with cretinism and myxedema who he had seen during his training.[3] The side effects of a total thyroidectomy, he named 'cachexia strumi priva', did not occur in patients that underwent a partial thyroidectomy (synonyms hemithyroidectomy and lobectomy) that still had a functioning remnant of the thyroid. This findings led to his advise expressed in the work *"Uber Kropfextirpation und ihre Folgen"*, translating loosky to, "not to remove a thyroid gland completely" but rather perform a hemithyroidectomy.[3] He underscored the risks of extensive thyroid surgery with his famous quote "*a surgeon knows when to operate, and when not to".*[3] Theodor Kocher was also known for a dramatic decrease in mortality of thyroid surgery with common rates up to 40.0% before his era to 0.5% in the 5000 operations he performed.[4] William S. Halsted observed both surgeons Theodor Kocher and Theodor Billroth, and believed that Billroth's older technique ensuring a quick but often bloody operation field was far less desirable than Kocher's technique that was concerned with precise ligation of vessels and fine dissection around the thyroid capsule.[5] Theodor Kocher

Figure 1. *First drawing of the thyroid by Leonardo da Vinci*[1]

received in 1909 the Nobel Prize in Physiology and Medicine for his extensive work on thyroid surgery, his prompt surgical audit of his therapeutic interventions and the investigation of unanticipated effects.[6] Despite impressive discoveries in surgical anatomy and the physiology related to surgery of the thyroid gland, the biology of thyroid cancer was poorly understood at Kocher's time. While there have been large strides in the understanding of thyroid cancer, there continues to be a gap in knowledge required to provide diagnoses and individualized care to those with thyroid cancer.

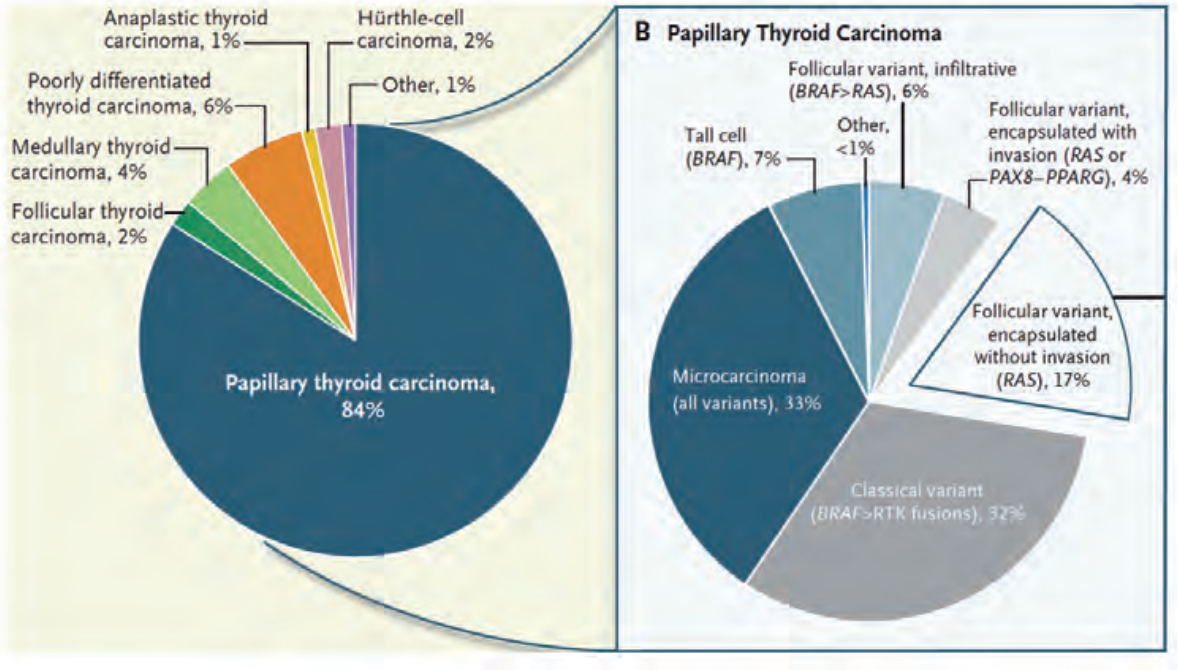
Figure 2. *Surgeon professor Theodor Kocher of Bern*[33]



Thyroid cancer

Thyroid cancer can be divided in different groups depending on the originating cells and the extent of de-differentiation (*figure 3*).[7] The transformation of endodermal-derived thyroid follicular cells or neural crest–derived thyroid C cells leads to distinct types of cancer. Follicular cells give rise to two main forms of differentiated thyroid cancer (DTC): the most common type papillary thyroid carcinoma (PTC) and the much more rare form follicular thyroid carcinoma (FTC). Main driver mutations for malignant transformation are mutually exclusive for the different subtypes of DTC. PTC is mainly driven by BRAF V600E or RAS mutations whereas FTC and follicular variants of papillary thyroid cancer (FVPTC) are driven by RAS or PAX8–PPARG fusion oncogenes.[8] DTC accounts for the vast majority (>90%) of all thyroid cancers[9]. Poorly differentiated and anaplastic thyroid carcinomas are comparatively rare tumors that also arise from follicular cells and are associated with aggressive disease with median survival of less than a year.[10] Medullary thyroid carcinomas derive from thyroid C-cells and have distinct biologic features, often relating to a familial syndrome.[11] This entire booklet will focus on DTC.

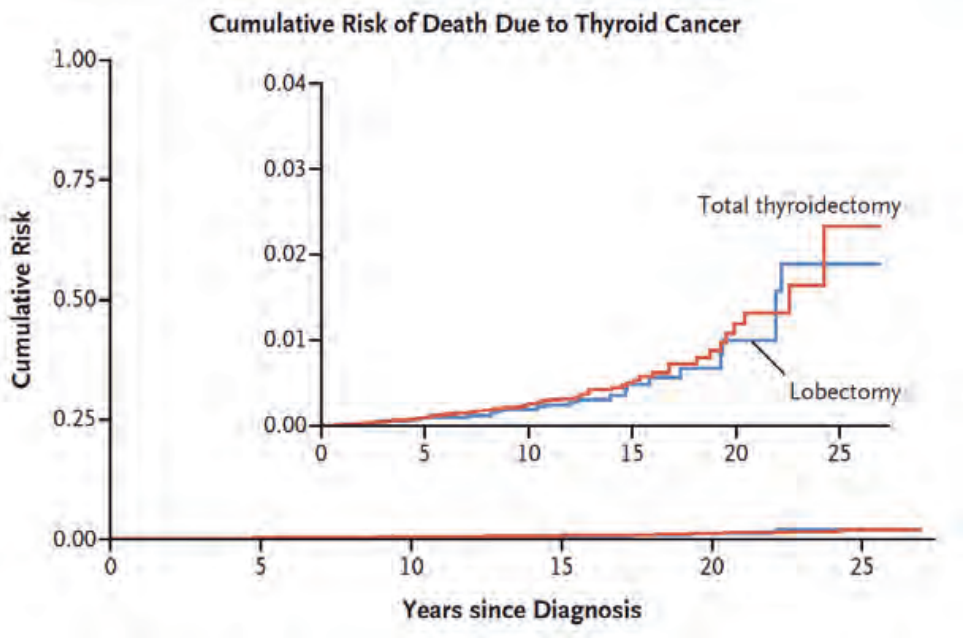
Figure 3. *Subgroups of thyroid cancer*[8]



A paradigm shift

DTC incidence has been on the rise both in the Netherlands and worldwide. Most of the increase is related to incidentaly discovered tumors which has led to diagnosis of mainly low-risk lesions.[12] This disease, that is not destined to cause clinical illness or death, is resulting in a phenomenon of overdiagnosis.[12,13] DTC has historically been treated by the removal of the entire thyroid gland followed by ablative therapy using radioactive iodine (RAI). Because survival rates are excellent, a shift started over the past decade towards de-escalation of treatment and an aim for a more patient-specific approach based on the specific risk profile of the cancer.[14] As a reflection of this phenomenon, clinicians have begun abonding RAI treatment for carcinomas below 1cm and only resecting the affected lobe of the thyroid, known as a hemithyroidectomy.[15] This "less is more"-movement included larger differentiated thyroid carcinomas up to 4cm in recent international guidelines and has extended to a Prof Miyauchi's watch-and-wait approach in patients with papillary microcarcinoma.[16–18] The 25-year risk of death due to DTC up to 2cm is as low as 2% and is unaffected by the choice of procedure, as shown in *figure 4*.[19] The shift in management of DTC is closely tied to societal acceptance of evidence adoption. This is illustrated by the treatment that varies considerably around the world. Various factors could explain the international differences such as quality of diagnostics, a priori chance of thyroid malignancy, cultural beliefs or revenue incentives.[14] In **chapter 2** we query what the hypothetical change in surgical

Figure 4. *Mortality risk after total thyroidectomy and hemithyroidectomy*[19]



The graph shows the 25-year risk of death due to thyroid cancer among 52,117 patients treated with either total thyroidectomy or lobectomy. The inset shows the same data on an enlarged y axis. Data are from the Surveillance, Epidemiology, and End Results database, 1988–2014

management of a Dutch cohort treated for DTC would be when the current "2015 American Thyroid Association Management Guidelines for Adult Patients with Thyroid Nodules and Differentiated Thyroid Cancer" (ATA guidelines) would have been followed.

Who to treat?

Recognizing that overdiagnosis plays a role in the rising incidence of DTC, it is important that providers exercise appropriate judgement in deciding who benefits from screening and when to perform adjunct diagnostics. DTC originates from thyroid nodules, hyperplastic follicular cells that are palpably or ultrasonographically distinct from surrounding thyroid parenchyma.[9] A thyroid nodule can be either clinically detected (on the basis of symptoms and signs), screening-detected (purposefully found with either examination or ultrasound imaging, but asymptomatic), or incidentally detected (an incidentaloma found during imaging studies unrelated to the thyroid in an asymptomatic patient).[20] Fortunately, only around 5% of the thyroid nodules are found to be malignant.[21] For this reason a selection of cases needs further assessment. Once ultrasound is completed, the indication for fine needle aspiration cytology (FNAC, thyroid biopsy) of the nodule is based on patient history, physical

examination, biochemical markers and ultrasound characteristics. FNAC result can either increase or decrease the suspicion of thyroid cancer, based on the Bethesda classification system, with subsequent surgical or non-surgical management recommendations.[22] When the FNAC result is benign, those nodules are often still followed indefinitely, sometimes with both multiple ultrasounds and subsequent FNACs based upon growth of the nodule. In **chapter 3** we use data of a large population from within a closed health care system to define the long-term risk of thyroid cancer of an initially benign thyroid nodule.

While **chapter 3** gives insight on the natural history of thyroid nodules in a general population, there are subsets where these malignancy patterns may not be generalizable. Specifically, patients with Multiple Endocrine Neoplasia type 1 (MEN1) may harbour thyroid nodules and perhaps applying investigation and treatment algorithms used currently may not be optimized. These patients develop hyperparathyroidism, often as first symptom of a syndrome with multiple endocrine tumors.[23] While screening for parathyroid adenomas MEN1 patients will repetitively have ultrasounds of the neck and the thyroid will be imaged due to the anatomical relation between the parathyroid and thyroid gland. When present, thyroid nodules will be unevitably detected. It is unclear whether these incidentally found nodules (thyroid incidentalomas) are related to the MEN1 syndrome and if there is an altered risk profile. Should surgical management of these patients' thyroid nodules be more aggressive or can prevailing guidelines of the general population be followed? To get more insight in this, we compared in **chapter 4** the prevalence of thyroid tumors in MEN1 patients to a matched non-MEN1 cohort and verified by immunohistochemistry the relationship of tumorigenesis and MEN1.

Risk stratification

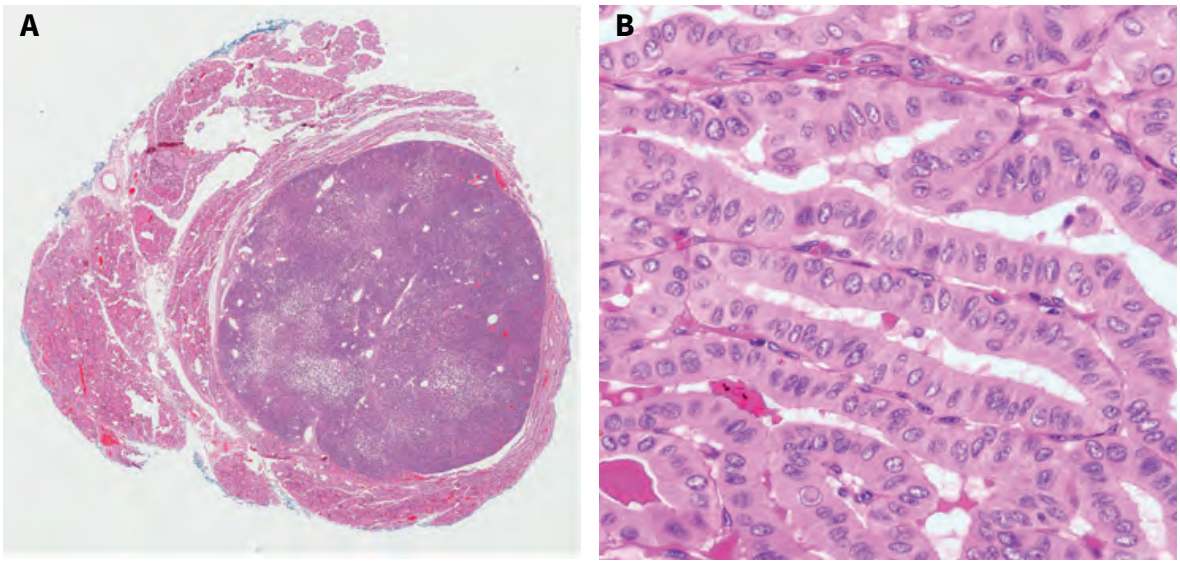
In order to adequately or not "overtreat" thyroid cancer, clinicians must be able to predict which patients will have true low-risk disease and which will have more aggressive variants. Within the recent past, a subset of thyroid cancer, encapsulated follicular variant of papillary thyroid cancer (EFVPTC), has been shown to potentially act as a benign tumor. Given this, a pathology group published a series of these lesions, that met strict criteria as shown in *figure 5,* in which none of them had malignany potential.[24] This entity was renamed into "noninvasive follicular thyroid neoplasm with papillary-like nuclear features" (NIFTP) and removed from the list of malignant tumors (*figure 6a*).[24] In **chapter 5** we validated these data in a large single center institution and had multiple subspecialist endocrine pathologists review all patients who met criteria. In **chapter 6** we highlighted the drawbacks of describing EFVPTC types as "non-malignant".

Figure 5. *Diagnostic criteria for noninvasive follicular thyroid neoplasm with papillary-like nuclear feature (NIFTP)*[34]

1.	Encapsulation or clear demarcation[a]
2.	Follicular growth pattern[b] with <1% Papillae No psammoma bodies <30% Solid/trabecular/insular growth pattern
3.	Nuclear score 2-3
4.	No vascular or capsular invasion[c]
5.	No tumor necrosis
6.	No high mitotic activity

a Thick, thin, or partial capsule or well circumscribed with a clear demarcation from adjacent thyroid tissue
b Including microfollicular, normofollicular, or macrofollicular architecture with abundant colloid
c Requires adequate microscopic examination of the tumor capsule interface
d High mitotic activity defined as at least 3 mitoses per 10 high-power fields (400×)

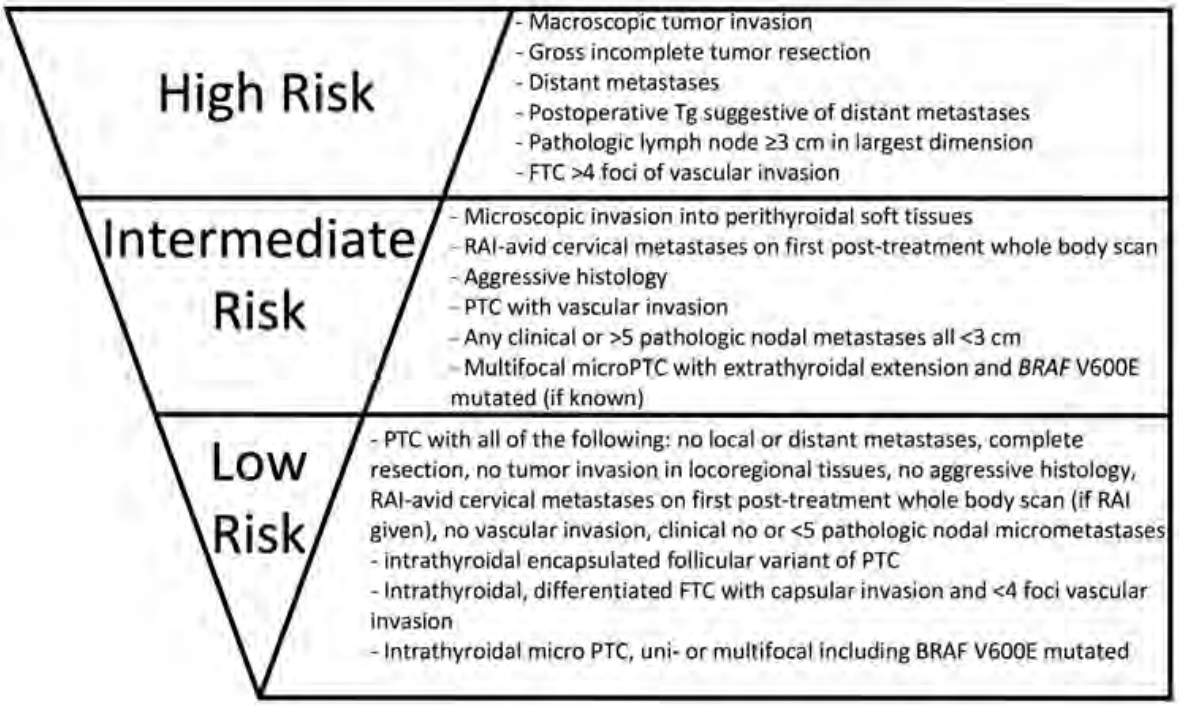
Figure 6. *Examples of subgroups of differentiated thyroid cancer*



a: Example of a noninvasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP)
b: Tall cell variant of papillary thyroid cancer

To match the correct treatment for a specific thyroid malignancy, the clinician estimates or stratifies the risk of the tumor. Given the excellent overall prognosis of DTC, clinicians are concerned with its recurrence rather than mortality as this occurs far more frequently than death. Currently the most commonly used model for the stratification for risk of recurrence is found in the 2015 ATA guidelines.[18] The model stratifies low-risk, intermediate-risk and high-risk groups, with risk of structural disease recurrence of respectively <5%, 5-20% and >20%. The risk stratification, as illustrated in *figure 7*, is mainly based on TNM-stage,

Figure 7. *ATA stratification for risk of recurrence*



Adapted from Haugen et al.[18]
Tg serum thyreoglobulin; RAI radioactive iodine; FTC follicular thyroid cancer; PTC papillary thyroid cancer

histologic findings, BRAF V600E mutation and post-treatment iodine scan and derived from existing best available evidence. The risk stratification guides initial surgical treatment strategy. Using these guidelines, in low-risk patients a hemithyroidectomy is now a viable alternative to a total thyroidectomy as surgical treatment. Specifically, in the preoperative decision making, a hemithyroidectomy could be planned if the tumor diameter is up to 4cm (T1a-T3 stage) and no lymph node and distand metastasis are clinically suspected (N0 and M0). A total thyroidectomy is warranted for large tumors or suspected extrathyroidal growth (T4) or clinically suspected/proven metastatic disease (N1a/b or M1). There may be additional reasons for peforming a total thyroidectomy, such as bilateral suspicious thyroid nodules, a history of head and neck radiation or a positive family history of thyroid cancer.[18] To optimize initial management and to prevent the need for additional surgeries preoperative risk stratification is paramount. Preoperative ultrasound with identification of cervical lymph nodes is standard of care when thyroid cancer is suspected, but there is increased recognition that cross-sectional imaging with contrast enhanced computed tomography of the neck (CT) can aid in the surgical planning and reduce the rate of treatment failure and later identification of residual disease.[25,26] In **chapter 7** we identified the impact of adding a preoperative CT of the neck on the surgical management in a prospective cohort of patients with otherwise low-risk DTC based on preoperative ultrasound.

In defining low-risk disease, accurate and precise pathology assessment is requisite. Once the initial surgical management is complete, specimen analysis can reveal new findings that may increase the risk of recurrence, updated from the preoperative assessment. Examples of histology findings with increased risk are extrathyroidal growth, vascular invasion, non-microscopic lymph node metastasis, incomplete resection or presence of aggressive histologic variants of PTC. The tall cell variant is such an aggressive variant of PTC, that confers a prognosis persuant to ATA intermediate-risk of recurrence and may warrant RAI therapy.[18] Tall cell variants are characterized by a predominance of tall columnar tumor cells whose height is at least two to three times their width (*figure 6b)*.[27] At molecular level alterations are found that are associated with worse disease outcome such as higher prevalence of BRAFV600E mutations and TERT promoter mutations.[28] There is evidence showing that the current definition of 30% presence of tall cells in the tumor to define it a tall cell variant may not be adequate.[29] In **chapter 8** we describe a series of tall cell variants and compare outcomes to patients with tall cell change in the specimen, not meeting the 30% criteria for the tall cell variant status. We should ensure that we use the correct cutoff to highlight those patients who may benefit from a total thyroidectomy and RAI remnant ablation.

Health related quality of life

Health related quality of life (HRQoL) is an individual's or a group's perceived physical and mental health over time and entails both positive and negative aspects of life.[30] Although DTC can have a generally indolent course, studies showed that the HRQoL of thyroid cancer survivors may be as bad as the HRQoL of survivors of cancers with worse prognosis.[31] The impaired HRQoL of this population may be rooted in the classical treatments for thyroid cancer, such as thyroid hormone replacement, RAI therapy and the morbidity of surgical complications. All may negatively impact psychological well-being and social functioning.[32] The recent ATA guidelines highlight the importance of integrating HRQoL outcomes into the treatment decision-making process of physicians.[18] Although there is a paucity of research focusing on long-term HRQoL in surgical literature, one may hypothesize that less aggressive surgery may lead to long-term improvement in HRQoL. On the other hand de-intensifying care may increase patients' anxiety regarding persistent or recurrent disease in the body.[19] To assist the practicioner in counseling patients we focused in **chapter 9** on the influence of treatment strategy on the long-term HRQoL of survivors of low-risk DTC.
Theodor Kocher's legacy of balancing the risks of more extensive treatment such as with surgery, RAI therapy and thyroid hormone suppression (resulting in complications or affected quality of life) against minimal treatment with active surveillance and the spectrum in-between is still today of utmost relevance. Improved risk stratification tools will be essential

to individualize treatment especially in an era of increasing number of patients with low-risk DTC. This bundled work is meant to be of any help in further refining the appropriate management of patients suspected of or diagnosed with DTC.

Research aims per chapter

Chapter 2: To investigate the proportion of a Dutch cohort of DTC patients that would have been eligible for less extensive surgery using the 2015 ATA risk stratification criteria.

Chapter 3: To define the risk of being diagnosed with thyroid cancer in long-term follow-up of those with a initial benign thyroid biopsy.

Chapter 4: To assess the prevalence of thyroid incidentalomas in patients with MEN1 syndrome compared to non-MEN1 patients and to verify whether thyroid tumorigenesis is MEN1 related.

Chapter 5: To document the incidence and the clinical outcomes of reclassifying encapsulated follicular variant of papillary thyroid cancer (EFVPTC) to noninvasive follicular thyroid neoplasm with papillary-like nuclear feature (NIFTP).

Chapter 6: To demonstrate the drawbacks of renaming a low-risk malignancy into a noninvasive entity.

Chapter 7: To investigate the impact of standard preoperative contrast enhanced CT on surgical management in patients with clinically low-risk DTC due to detection of lymph node metastasis not located by ultrasound of the neck.

Chapter 8: To compare the outcome and adverse tumor characteristics of PTC with focal tall cell change (<30% cell change in the entire tumor volume) to tall cell variant PTCs (≥30% cell change) and classical PTC without tall cell change.

Chapter 9: To assess the influence of treatment strategy on the long-term HRQoL of survivors of low-risk DTC.

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CHAPTER 2

Is our treatment of well-differentiated thyroid cancer too aggressive? Hemithyroidectomy versus total thyroidectomy

[originally published in Dutch]

Bongers PJ, Kluijfhout WP, Vriens MR, Mastboom WJ, Lutke Holzik MF

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Abstract

Recent literature shows that hemithyroidectomy is a safe alternative for total thyroidectomy in the treatment of patients with differentiated thyroid cancer up to 4 cm in diameter and a low-risk of recurrence. According to criteria of the 2015 American Thyroid Association guidelines, more than 28% of patients with differentiated thyroid cancer of a Dutch cohort would be eligible for hemithyroidectomy instead of the total thyroidectomy they actually underwent. However, standardisation and high quality pre- and postoperative diagnostics are required for responsible implementation of this new guideline in Dutch healthcare.

A healthy 31-year-old woman was referred to the endocrinologist for a lump on the anterior side of her neck. There was no family history of thyroid cancer or radiation exposure to the neck. The patient had normal TSH, T3 and T4. Ultrasound of the neck showed a single 3.3 cm solid nodule located in the left thyroid lobe. Fine needle aspiration cytology (FNAC) of the nodule showed a Bethesda IV lesion, suspicious for a follicular neoplasm, with an estimated malignancy risk of 25%.[1] A diagnostic hemithyroidectomy of the left lobe was performed for the definitive diagnosis. Pathologic examination revealed a 3.0 cm papillary thyroid carcinoma. It was a unifocal lesion with negative margins, no vascular invasion, no aggressive histology and no lymph node metastasis in the specimen found. Is it safe to suffice with a hemithyroidectomy in this patient, or should the entire thyroid gland be removed? Consisting with the current Dutch national guidelines, a second surgery was performed to remove the remaining lobe, a procedure known as a completion thyroidectomy. The patient needed to be admitted for two days due to hematoma formation. Pathologic examination showed no abnormalities in the specimen of the second surgery. After a low-iodine diet the patient underwent radioactive iodine ablative therapy (RAI). The post-treatment whole body scan showed no foci suspected for persistent or metastatic disease. Due to the removal of the entire thyroid gland, the patient depends lifelong on thyroid hormone replacement therapy. At present, two years after surgery, no recurrent disease is suspected.

This case tells us about a patient who, according to Dutch management guidelines, underwent a total thyroidectomy and RAI ablation therapy. Worldwide trends among updates of thyroid cancer guidelines are focusing on avoidance of overtreatment. The dogma of maximal surgical resection with adjuvant therapies is being replaced by treatment based on patient-tailored risk assessment with the aim to both optimize oncologic outcomes and minimize morbidity. In this manuscript we put these international developments in the light of the Dutch health care and thyroid cancer management.

Differentiated thyroid cancer

Over 90% of thyroid malignancies are well-differentiated. This group consists of papillary and follicular thyroid carcinoma; both have a good prognosis.[2] Rare other thyroid malignancies, including medullary and anaplastic thyroid carcinoma, have a more aggressive course of disease that requires different treatment strategies and will not be discussed in this work. Incidence of differentiated thyroid cancer (DTC) has increased over the past decades. For example in the United States the annual incidence has quadrupled between 1975 and 2014.[3] One of the explanations of this rise is the increased usage of imaging modalities on which incidental thyroid abnormalities are found due to unintended visualization of the thyroid gland.[4] One study predicts that in 2019 DTC will be the third most common malignancy

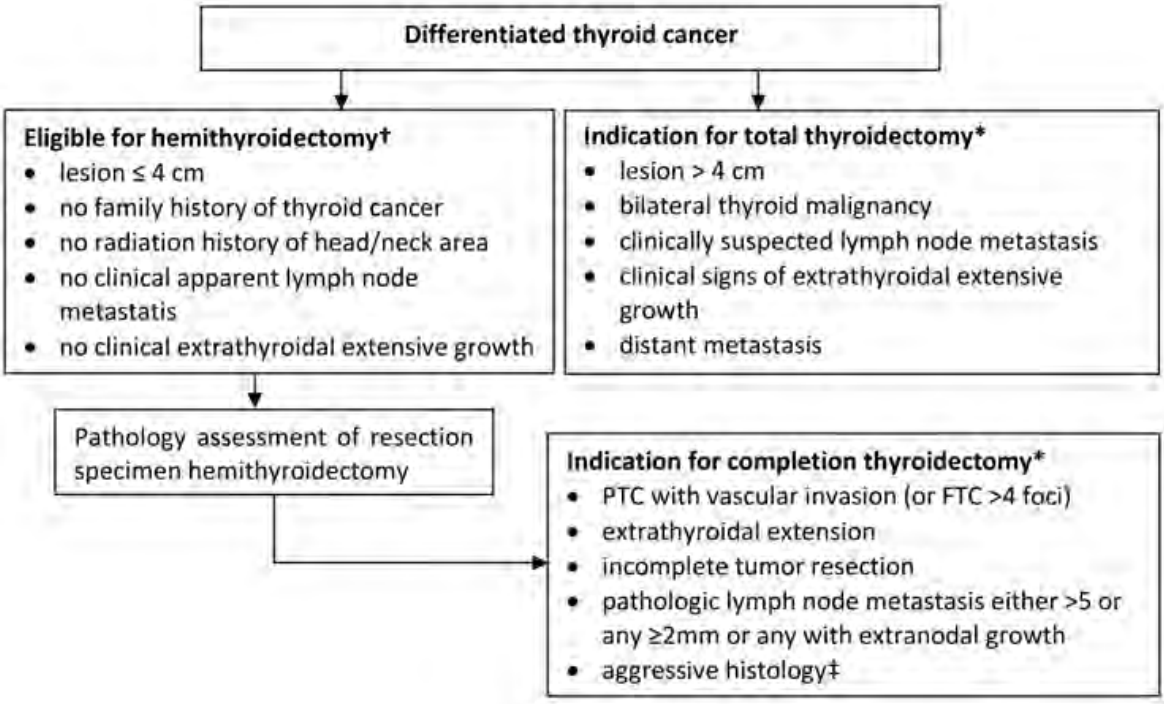
in women in the United States, with 2.4 billion dollars of total health care costs.[5] With 613 new diagnoses of DTC in 2015 the incidence in the Netherlands is also rising.[6] The management of patients with thyroid cancer requires a multidisciplinary approach including family medicine, endocrinology, radiology, pathology, nuclear medicine, and surgery. In the Netherlands common treatment for DTC >1cm is a total thyroidectomy followed by RAI.[7] Often first the diagnosis is confirmed by removal of the affected lobe (diagnostic hemithyroidectomy), and if malignancy is present the remnant lobe is removed during a completion thyroidectomy as preparation for RAI remnant ablation. This treatment regimen was supported until very recently, mainly due to a publication of Bilimoria et al. which showed a better survival after total thyroidectomy compared to hemithyroidectomy in 52,173 patients.[8] However, there is increasing evidence over the past years that there is no benefit in disease-free and overall survival of total thyroidectomy over hemithyroidectomy for selected patients with low-risk DTC.[9] This has resulted in significant changes in international guidelines, including the "2015 American Thyroid Association management guidelines for differentiated thyroid cancer in adults" (2015 ATA guidelines). According to these guidelines patients with DTC ≤4cm in largest diameter, in absence of high-risk features, are now eligible for hemithyroidectomy as surgical treatment.[10-12] The risk assessment is based on pre-, intra-, and postoperative characteristics of patient and tumor, as shown in *figure 1*. In addition to potential lower health care costs, less extensive treatment has benefits for the patients.[13] There is less risk of injury to the recurrent laryngeal nerve, which innervates the vocal cord, the patient has a larger chance of maintaining sufficient endogenous thyroid hormone production, and there are no side effects of the RAI.[14-16] Finally, a hemithyroidectomy only exposes two of the four parathyroid glands to trauma thereby negating the risk of postoperative hypocalcemia.[14] An example of a potential drawback of a hemithyroidectomy as definitive treatment could be the patient's anxiety and fear of persistent or future cancer in the remaining thyroid lobe.

We looked into the potential impact when the 2015 ATA guidelines would have been followed in the Netherlands. We accomplished this by analysing in a regional Dutch cohort the amount of patients with DTC that underwent a total thyroidectomy but would have been eligible for a hemithyroidectomy as per the new 2015 ATA guidelines.

Regional analysis

The case at the beginning of this manuscript is one of 60 adult patients with DTC that has been treated since 2013 in three hospitals in the eastern part of the Netherlands. The hospitals are together responsible for the care of DTC of around one million inhabitants. As presented in *table 1* the average age is 53 years and 68.3% were female. The data from eight of these patients was insufficient for a proper risk assessment following the 2015 ATA guidelines

Figure 1. *Surgical strategy for differentiated thyroid cancer*



Adapted from American Thyroid Association Guidelines Task Force on Thyroid Nodules and Differentiated Thyroid Cancer[10]
PTC papillary thyroid carcinoma; FTC follicular thyroid carcinoma
** With/without radioactive iodine ablation therapy*
† Other considerations could play a role in the choice of surgical strategy, such as hyperthyroidism, comorbidities, difficulties in adequate follow-up, patient's preference
‡ Examples are hobnail-, tall cell- en columnar cell-variants of papillary thyroid carcinoma

(*figure 1*). Examples of incomplete data are; the lack of noticing the presence of contralateral nodules in ultrasound report or not mentioning vascular invasion and size of nodal metastasis in the pathology report. According to the 2015 ATA guidelines in 17 patients a hemithyroidectomy would have been an acceptable alternative for the performed total thyroidectomy and RAI. This is 28.3% of all patients treated for DTC in this cohort.

Considerations

We tried to put worldwide developments in treatment of DTC in the context of the Dutch health care using a sample of Dutch patients with DTC. As mentioned, 28.3% of the patients from our retrospective cohort would have been eligible for a hemithyroidectomy when applying the 2015 ATA guidelines, with possible advantages for both the patient and the health care system. However, when discussing revision of the Dutch policy for DTC treatment, other factors need to be taken into consideration.

Table 1. *Patient characteristics of a cohort surgically treated for differentiated thyroid cancer*

Variable	**n (%)***
Number of patients	60
Age, mean in years (range)	53 (26-79)
Female	41 (68.3)
Total nights admitted, mean (range)	2.67 (0-10)
Subtype thyroid carcinoma	
papillar carcinoma	32 (53.3)
follicular carcinoma	11 (18.3)
follicular variant of papillar carcinoma	17 (28.3)
Final surgical treatment	
hemithyroidectomy	15 (25.0)
hemi + completion thyroidectomy	32 (53.3)
total thyroidectomy	13 (21.7)
Tumor-stage	
Ia	11 (18.3)
Ib	13 (21.7)
II	15 (25.0)
III	16 (26.7)
IV	5 (8.3)
Nodal-stage	
0/X	42 (70.0)
Ia	10 (16.7)
Ib	8 (13.3)
Metastasis-stage	
0/X	59 (98.3)
I	1 (1.7)

** unless otherwise stated*

The surgical treatment is preceded by a complex diagnostic work up that includes history taking, physical examination, ultrasonography and FNAC of the thyroid lesion. If the result of the FNAC is indeterminate a diagnostic hemithyroidectomy is often performed for definitive diagnosis. When ultrasonography is of high quality in experienced hands with compliance to strict ultrasound criteria to indicate FNAC, the number of indeterminate results of FNAC, and hence the amount of diagnostic hemithyroidectomies, could be minimized. Additionally, there is currently an ongoing Dutch trial that investigates if PET-CT of indeterminate nodules can decrease the number of diagnostic hemithyroidectomies in a cost-effective manner.[17] Molecular testing on the presence of cancer related genetic alterations, such as the presence of BRAFV600E, RAS, or TERT mutations and RET/PTC-translocations, can contribute to the improvement of preoperative diagnostics of thyroid nodules and the risk stratification of DTC. In modern health care the patient is well informed about the different treatment options to allow a deliberate treatment choice together with the clinician. The principle is also known as ‘shared decision making’. DTC ≤4cm without a history of radiation or familial thyroid

cancer, and no clinical suspicion of contralateral malignancy, extrathyroidal extensive growth or metastasis, can be treated adequately with a hemithyroidectomy according to current literature. Still, factors such as anxiety of the patient for recurrent disease or the burden of long-term follow-up with ultrasounds of the remnant lobe can be arguments to chose for a total thyroidectomy as treatment of proven DTC with low-risk of recurrence. Traditionally, an argument for a total thyroidectomy is that follow-up with serum thyreoglobulin concentration (Tg) is a reliable marker for recurrence. Thyreoglobulin is the precursor of the thyroid hormone thyroxin. Because after a hemithyroidectomy thyreoglobulin-producing thyroid tissue is still present in the body it was assumed previously that Tg was an unreliable marker for follow-up. Technologic developments of Tg-assays now allow that reliable and timely recurrent disease can be predicted in patients that underwent a hemithyroidectomy by observing trends of sequential Tg measurements.[18] The time of follow-up that is needed after treatment for DTC is still not fully clarified by international guidelines. Recurrences, both locoregional and distant metastasis, can still occur up to ten years after surgery.[19] This could be an argument to follow both patients after a hemithyroidectomy and total thyroidectomy long-term using ultrasonography and sequential Tg measurements.

Back to the case

This patient had a DTC of ≤4cm without other high-risk features. After pathology assessment of the hemithyroidectomy specimen no additional treatment was needed according to the current 2015 ATA guidelines (see *figure 1*). It is recommended to follow the patient long-term with both ultrasounds of the neck and sequential Tg measurements.[10]

Let the discussion start

Being less aggressive in treatment of patients with low-risk DTC is only possible when the risk stratification is reliable. Ultrasonography and pathology assessment are crucial and therefore quality assurance and standardisation is important. High quality often goes hand in hand with increase of expertise, which can be accomplished for example by centralisation of care. Centralisation and introduction of quality standards for both diagnostics and treatment are part of the recommendations from the recent report on thyroid cancer of the Dutch Cancer Society.[20] Following international guidelines and up to date literature, but also taking into account the characteristics of our health care system, we encourage a debate to optimize our management of DTC. In our opinion, in properly selected patients with low-risk DTC, a hemithyroidectomy treatment can be considered as a viable alternative for a total thyroidectomy with RAI.

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CHAPTER 3

Long-term risk of thyroid cancer after initially negative thyroid biopsy results

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Research letter
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Introduction

Thyroid nodules are common, occurring in over 50% of the general population.[1] Historically, nodules characterized as benign were followed indefinitely, often with multiple subsequent biopsies based upon growth. Current evidence derived from sampled populations suggests that the rate of malignant neoplasms among benign nodules after long-term follow-up is low.[2] We used data from an entire population to define the risk of being diagnosed with thyroid cancer in long-term follow-up of individuals with initially benign thyroid biopsy results.

Patients and Methods

Cross-sectional analysis of population-based data from a comprehensive administrative health database of Ontario, Canada was performed. All thyroid biopsies in the province performed from January 1, 1991 to December 31, 2010, were identified from the provincial single payer physician-billing plan and linked to the Ontario Cancer Registry until December 31, 2014, to detect all cases of differentiated thyroid cancer with follow-up of up to 24 years. Thyroid cancers diagnosed previously or within one year after first biopsy were not regarded as benign and excluded from further analyses. This study was approved by the research ethics board of Sunnybrook Health Sciences Centre, Toronto, Canada. Patient consent was waived by this board because health care databases were anonymously linked using encrypted identifiers to safeguard confidentiality. Investigators had no direct access to the study population.

Results

During the study period, 146,014 individuals had at least one thyroid biopsy. Results of 135,676 biopsies (92.9%) were initially benign. Of the patients with a benign nodule, the mean (SD) age at biopsy was 52.2 (13.4) years, 81.2% were females, and 18.8% were males. During the study period, the number of biopsies performed in the province that were initially benign increased from 2,280 per year in 1991 (22.1 per 100,000 inhabitants) to 12,074 per year in 2010 (91.5 per 100,000 inhabitants) as shown in *figure 1.*

Of the patients with initially benign biopsies, 6,354 patients had a diagnosis of thyroid malignant neoplasm during the follow-up period (396 per 100,000 person years). The cumulative risk of being diagnosed with thyroid cancer within the follow-up period was 4.6% after 10 years and 7.5% after 24 years (*figure 2*).

Figure 1. *Population standardized annual number of initial benign biopsies and the risk of subsequently developing cancer (%)*

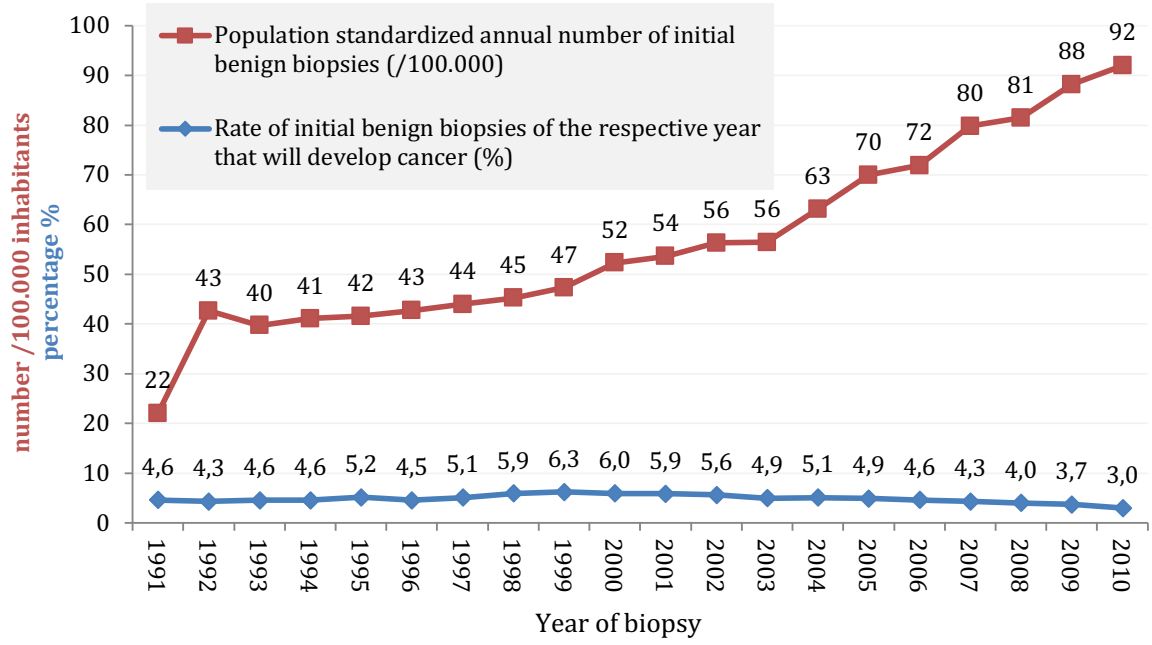
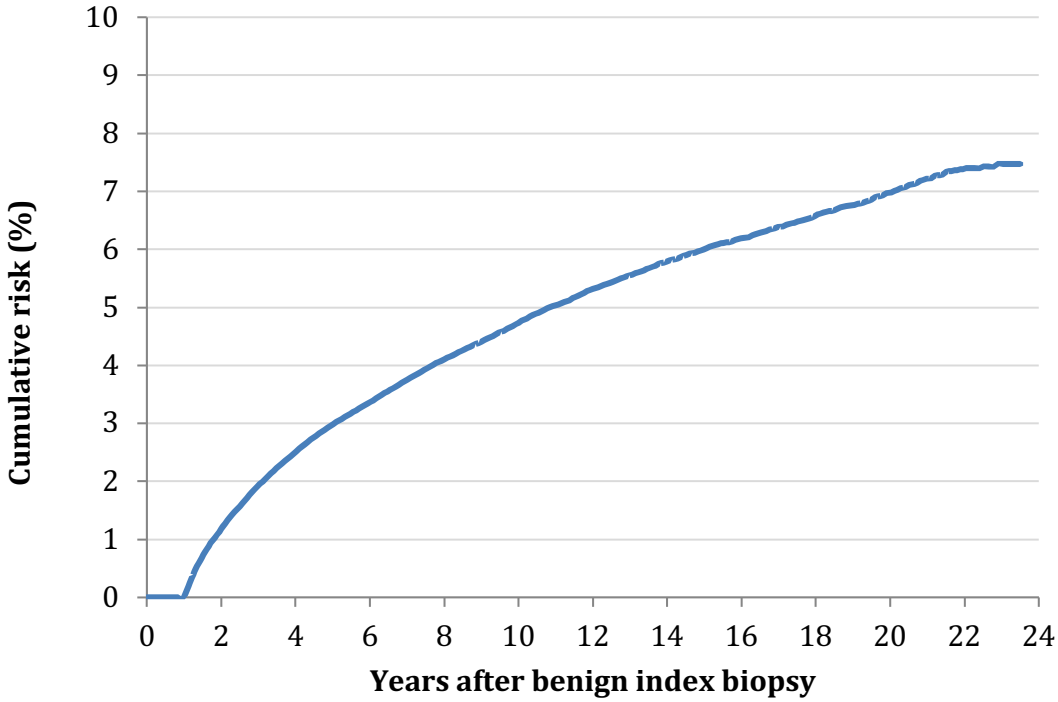


Figure 2. *Cumulative risk of being diagnosed with thyroid cancer after a benign index biopsy*



Vertical axis has been rescaled from 0 to 10% to better demonstrate the cumulative risk curve

Discussion

In this population-based, longitudinal study, the cumulative risk of developing thyroid cancer among patients with an initially negative thyroid biopsy who were followed long-term was 7.5% after 24 years. Consistent with literature thyroid biopsy performance increased 4.1-fold between 1991 and 2010.[3] The risk of a malignant neoplasm after benign results of an index biopsy in our population was higher compared to recent literature showing rates between 0.3 and 2.4% after less than ten years of follow-up.[2,4] There are some differences that may explain the rates seen in this large population. First, the definition of benign cytology in Ontario has, until Bethesda classification adoption, been variable. Since this cohort spans 24 years, and begins in 1991, there was at least 15 years of patient data where cytology was not standardised. Further insight into the cancer rate we found within the population could be related to the substantially longer follow-up period and therefore may include delayed malignant transformation of nodules not captured in shorter follow-up studies.[5]

The study design strengthens the validity of these results. The administrative health databases from Ontario are more than 95% complete for cancer diagnosis and procedures.[6] By capturing an entire population, our study was less susceptible to the types of selection biases and confounding that may have influenced other studies.

Limitations to this study include the lack of patient-specific clinical information such as results of ultrasonography and pathologic results. In addition, changes in specimen management and diagnostic criteria over time may have influenced the rate of carcinoma because of more incidentally found microcarcinomas. Although the rate of carcinoma may have increased, these diagnoses may be predominantly due to a clinically irrelevant entity.

Based on a large provincial population followed long-term after initially benign results of thyroid biopsy, the rate of malignant neoplasms was low, which questions the need of follow-up biopsies for all patients. Since cumulative risk of thyroid cancer in these patients is higher than the baseline lifetime risk of the population, further large risk stratification studies incorporating standard ultrasound biopsy data are needed to identify those requiring long-term follow-up.

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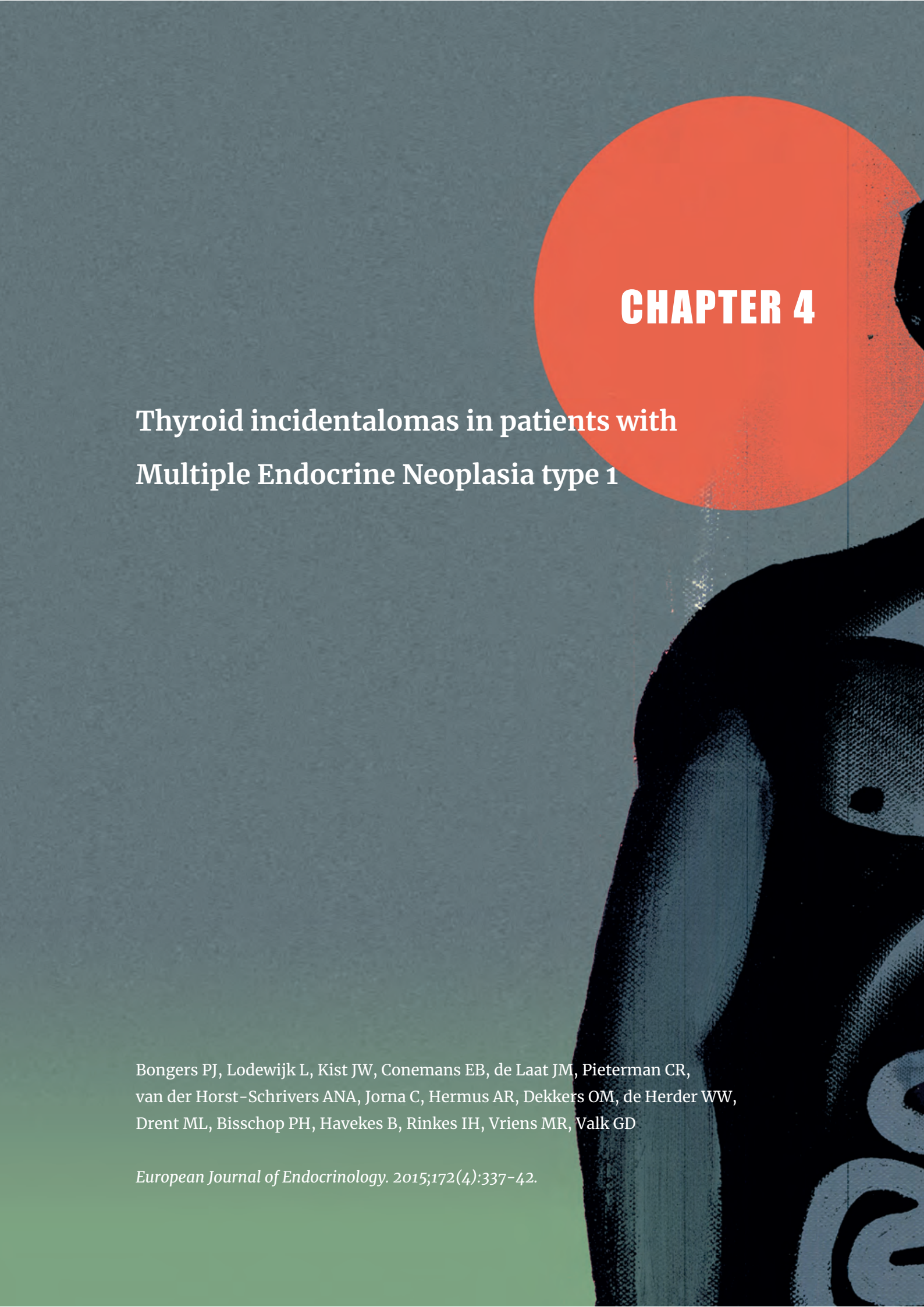
CHAPTER 4

Thyroid incidentalomas in patients with Multiple Endocrine Neoplasia type 1



Bongers PJ, Lodewijk L, Kist JW, Conemans EB, de Laat JM, Pieterman CR, van der Horst-Schrivers ANA, Jorna C, Hermus AR, Dekkers OM, de Herder WW, Drent ML, Bisschop PH, Havekes B, Rinkes IH, Vriens MR, Valk GD

European Journal of Endocrinology. 2015;172(4):337-42.

Abstract

Objective

Currently, little is known about the prevalence of thyroid tumors in multiple endocrine neoplasia type 1 (MEN1) patients and it is unclear whether tumorigenesis of these thyroid tumors is MEN1-related. The aim of the study was to assess the prevalence of thyroid incidentalomas in MEN1 patients compared with non-MEN1 patients and to verify whether thyroid tumorigenesis is MEN1-related.

Design

A cross-sectional study.

Methods

The study included two groups: patients with MEN1and a matched non-MEN1 control group without known thyroid disease, who underwent an ultrasound of the neck for the localisation of parathyroid adenoma. Ninety-five MEN1 patients underwent ultrasound of the neck and were matched on gender and age with non-MEN1 patients. The prevalence of thyroid incidentalomas described in the ultrasound report was scored. Multinodular goiters, solitary nodes, and cysts were scored as
incidentalomas. Presence of nuclear menin expression was evaluated by menin immunostaining of the thyroid tumors.

Results

In the MEN1 group, 43 (45%) patients had a thyroid incidentaloma compared with 48 (51%) in the non-MEN1 group, of which 14 (15%) and 16 (17%), respectively, were solitary nodes. Menin was expressed in the nuclei of all evaluated thyroid tumors.

Conclusions

MEN1 patients do not have a higher prevalence of thyroid incidentalomas compared with primary hyperparathyroidism patients without the diagnosis of MEN1. Menin was expressed in the thyroid tumors of MEN1 patients.

Introduction

Multiple Endocrine Neoplasia type 1 (MEN1) syndrome is characterized by the combined occurrence of pituitary tumors, primary hyperparathyroidism, pancreatic and duodenal neuroendocrine tumors (NET), adrenal adenomas, and NETs of stomach, lung and thymus.[1] Recently, MEN1 also turned out to be a breast cancer susceptible syndrome.[2] The syndrome is caused by an inactivating germline mutation in the *MEN1* gene, which encodes for the tumor suppressor protein menin. Tumorigenesis of MEN1-related tumors is characterized by loss of menin expression or the production of nonfunctional menin in case of missense (or in-frame) alterations of the *MEN1* gene.[3] At present, little is known about the prevalence of thyroid tumors in MEN1 patients. Marx et al. found a prevalence of 12% thyroid tumors (8% follicular adenoma and 5% papillary thyroid carcinoma) in 130 MEN1 patients. These patients were screened for all types of endocrine abnormalities.[4] The recent published MEN1 guideline reports that thyroid tumors (adenomas, colloid goiters and carcinomas) occur in more than 25% of patients with MEN1. Subsequently, the guideline states that 'because of the high prevalence of thyroid abnormalities in the general population the association of thyroid abnormalities in MEN1 may be incidental and not significant'.[1] However, the lack of evidence regarding the clinical relevance of thyroid tumors might cause an extra dilemma for both endocrinologist and endocrine surgeon treating patients with MEN1.

Primary hyperparathyroidism (pHPT) occurs in 90% of the MEN1 patients. Therefore, a substantial part of this population undergoes a neck ultrasound to localize parathyroid adenomas.[5] Because of to the anatomical relationship between thyroid and parathyroid glands it is inevitable that the thyroid is imaged during the neck ultrasound, which increases the chance of incidentally finding a thyroid tumor.

The aim of this study was to assess the prevalence of thyroid incidentalomas in the Dutch MEN1 population compared with a matched reference group of non-MEN1 patients. To support the epidemiologic findings we studied menin expression in thyroid tumors of MEN1 patients by immunohistochemistry to assess whether loss of nuclear menin was present.

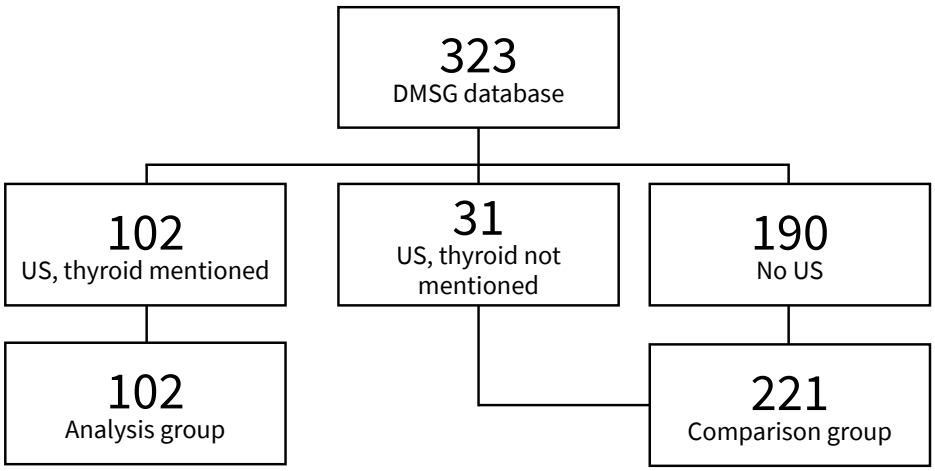
Methods

Study group

All MEN1 patients in the Dutch MEN1 Study Group (DMSG) database were identified as described previously (325 patients).[6] From this database, data regarding demographics, mutation status (according to the Human Genome Variation Society nomenclature), MEN1 manifestations, imaging, surgery, and histology reports were extracted.[7] For further analysis patients were selected who had a neck ultrasound because of pHPT in which the thyroid was

described (102 patients, *figure 1*). The baseline characteristics of 102 patients were compared with the other MEN1 patients to verify whether it was a representative subgroup.
As a non-MEN1 reference group, 201 consecutive patients who underwent neck ultrasound between 2003 and 2012 for pHPT, not having MEN1 or known thyroid disease, were identified from the hospital radiology database of the University Medical Centers of Utrecht and Groningen in The Netherlands. This reference group will further be referred to as the non-MEN1 group. As age and gender differed significantly in the MEN1 and the non-MEN1 group, patients were matched (1:1) on these variables via the 'case-control matching' extension in SPSS. For age, a spread of three years was accepted for the matching. In total 95 patients could be matched. Seven MEN1 patients had to be excluded because no match was available. These consisted of five females and two men with a median age of 21 years, ranging from 15 to 33 years. Of those seven patients, two patients had a cyst.
Multinodular goiters, solitary nodes and cysts that were identified by the ultrasounds of the neck were scored. By definition these tumors are incidentalomas.

Figure 1. *Flowchart of patients from the DMSG database*



US, neck ultrasound.

Immunohistochemistry

As proxy, for menin expression, immunohistochemistry was performed on formalin-fixed paraffin-embedded (FFPE) tissues from five thyroid samples and a negative control sample. However, certain types of the *MEN1* mutations do not lead to an altered expression of menin, but due to these mutations there is a nonfunctional protein. Therefore, we listed the mutations per sample in t*able 1*. All thyroid tumors were selected and evaluated by a dedicated pathologist (PJvD). As a negative control, we used a sample in which, by sequencing of the DNA, loss of heterozygosity (LOH) was proven. This sample was from a patient with infiltrative ductal

Table 1. *Type of germline mutation of MEN1 patients used for menin immunohistochemistry and whether altered protein expression was expected based on the mutation.*

Patient	Diagnosis	Type mutation	Altered protein expression expected	Mutation
A	Infiltrative ductal carcinoma of the breast	Nonsense	Yes	c.377G>A(p.Trp126X)
B	Hyperplastic node	Missense	No	c.552G>T (p.Glu184Asp)
C	Micro-invasivie medullary thyroid cancer	Frameshift	Yes	c.1430dupG(p.Glu478fs)
D	Multinodular goiter	Nonsense	Yes	c.1099A>T(p.Lys367X)
E	Follicular adenoma	Nonsense	Yes	c.1594C>T(p.Arg532X)
F	F Micro-invasive follicular thyroid carcinoma	In-frame deletion	No	c.358_360del (p.Lys120del)

carcinoma of the breast with a germline nonsense mutation (c.377G>A(p.Trp126X)).[2] All tissues were sampled from surgical specimen according the standard procedure in the University Medical Center Utrecht. The slides were deparaffinized with xylene and rehydrated in decreasing ethanol dilutions. Endogenous peroxidase activity was blocked with 3% hydrogen peroxide. Antigen retrieval was achieved by boiling slides in citrate buffer (pH 6.0) for 20 min. The slides were then incubated with the rabbit polyclonal antibody against menin (Menin, A300-105A, Bethyl Laboratories, Inc., Montgomery, TX, USA), dilution 1:1600, for 1 hour at room temperature. For detection of primary antibodies, goat anti-mouse poly-HRP (Powervision, Immunologic, Immunovision Technologies, Brisbane, CA, USA) was used. All slides were developed with diaminobenzidine (DAB). The slides were counterstained with filtered hematoxylin, dehydrated through a graded series of ethanol, immersed in xylene and mounted. Menin staining was reviewed by an experienced pathologist and compared with the negative control.

Statistical analysis

Continuous variables are expressed as means with a standard deviation (SD) if normally distributed and as median (25% and 75% percentile) if not. Categorical and dichotomous variables are expressed as absolute numbers (%). Matching was performed by the case-control-matching function available in SPSS. Student's *t*-test, Mann-Whitney *U* test, and Pearson's χ^2 test were used where appropriate. Statistical significance was reached when p-value was smaller than 0.05. Calculations were performed using SPSS version 23 (IBM Corporation, Armonk, NY, USA).

Results

Baseline comparison

The presence of thyroid was mentioned in the report of the neck ultrasound in 102 patients (32%) of a total of 323 MEN1 patients. In 31 (10%) patients, an ultrasound was performed but the presence of thyroid was not mentioned in the report. No ultrasound was performed between 1990 and 2010 in 190 (59%) MEN1 patients (*figure 1*). Patient characteristics of the groups with and without a neck ultrasound were compared with baseline characteristics (*table 2*). The group that underwent ultrasound of the neck consisted of more female patients (68 (66.7%) vs 120 (54.3%)) and was significantly older (51.9 (14.8) vs 46.7 (16.5)). There was no difference in mean follow-up time and the type of mutation between the groups with and without a neck ultrasound.

Table 2. *Baseline comparison between MEN1 patients with or without neck ultrasound.*

	Comparison group (n= 221)	**Analysis group (n= 102)**	**p-value**
Female, n (%)	120 (54.3)	68 (66.7)	0.04
Age, mean in years (SD)	46.7 (16.5)	51.9 (14.8)	0.01
Follow-up, mean in years (SD)	10.2 (9.9)	10.5 (8.5)	0.82
pHPT, n (%)	161 (73.6)	102 (100.0)	0.00
Type of mutation, n (%)			0.29
Clinical diagnoses*	15 (6.8)	15 (14.7)	
Nonsense	30 (13.6)	18 (17.6)	
Missense	43 (19.5)	18 (17.6)	
Frameshift	68 (30.8)	32 (31.4)	
Splice	12 (5.4)	2 (2.0)	
Unclassified	2 (0.9)	0 (0.0)	
Large deletions**	48 (21.7)	15 (14.7)	
Unknown***	3 (1.4)	2 (2.0)	

**Clinical diagnosis are patients with 2 or more of the major manifestations of MEN1 without a germline mutation **Large deletions include in-frame deletions, deletions of exon 1 and 2, deletions of exon 1, 2, and 3 and deletions of the entire MEN1 gene. ***Unknown consists of patients with clinical diagnosis of MEN1 in whom either no genetic testing is performed or the exact location of the mutation is unknown. Abbreviations: SD, standard deviation; pHPT, primary hyperparathyroidism.*

Thyroid incidentalomas

In 43 MEN1 patients (45%) and in 48 non-MEN1 patients (51%), incidentalomas of the thyroid were found on neck ultrasound. The tumors consisted of 25 (26%) and 29 (31%) multinodular goiters, 14 (15%) and 16 (17%) solitary nodes, four (4%) and four (4%) cysts in the MEN1 group and the non-MEN1 group, respectively. No significant differences were found (*table 3*). When reported, size of the solitary nodes was also analysed. The median

size of the solitary nodes was 6 mm (interquartile range (IQR) 4.5 – 11 mm) in the MEN1 group and 8 mm (IQR 4.0 – 9.0 mm) in the non-MEN1 group it was (p-value 0.94).

Table 3. *Thyroid incidentalomas in MEN1 patients compared to a matched control group.*

	MEN1 n=95	**non-MEN1 n= 95**	**p-value**
Female, n (%)	63 (66)	63 (66)	-
Age at date of ultrasound, mean (SD)	48.3(14.3)	46.6(13.8)	-
Incidentaloma, n (%)	43 (45)	48 (51)	NS
Multinodular goitre, n (%)	25 (26)	29 (31)	NS
Solitary node, n (%)	14 (15)	16 (17)	NS
Cyst, n (%)	4 (4)	4 (4)	NS

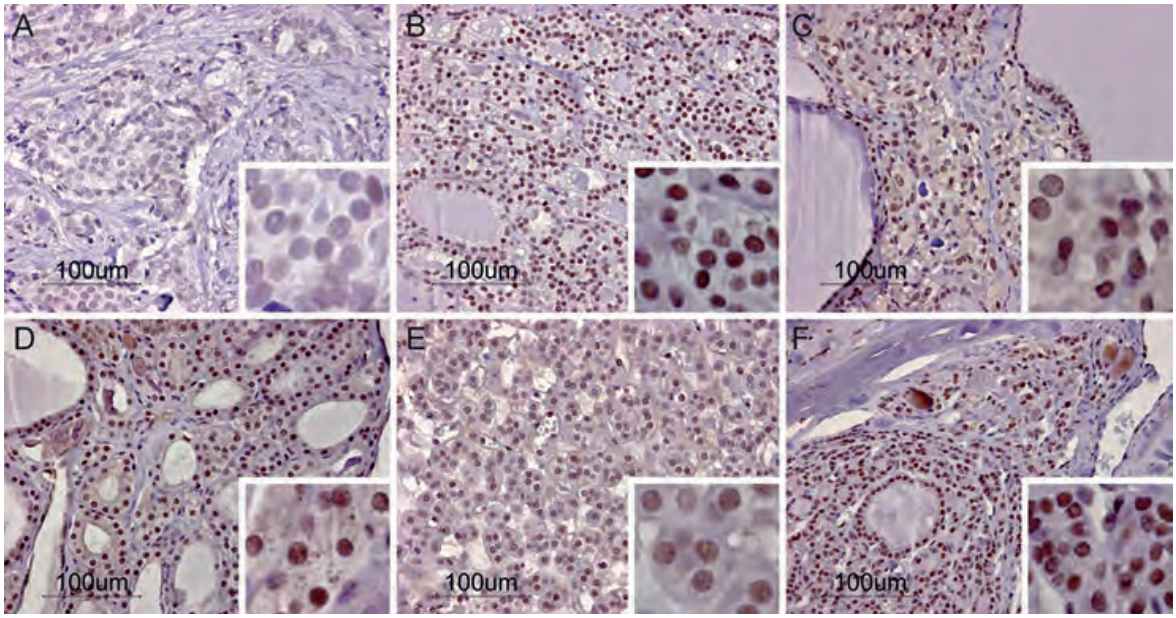
Thyroid histology

From 17 MEN1 patients, the histology reports of the thyroid tumors were available and the diagnoses are given in *table 4*. Follicular adenomas and nodular dysplasia were most prevalent. Immunohistochemistry was performed in a representative subset of the different types of thyroid tumors. In all thyroid tumors, we tested whether menin was present by immunohistochemical staining in the nucleus of adjacent normal and tumor tissues. In the control sample, no menin expression was found, indicating loss of heterozygosity (*figure 2* and *figure 3*).

Table 4. *Diagnoses of the thyroid tumors after histologic examination in MEN1 patients.*

	(n=17)
Multifocal micro-invasive medullary thyroid carcinoma	1
Micro-invasive follicular thyroid carcinoma	1
Follicular adenoma	4
Multinodular goiter	2
Nodular dysplasia	5
Nodular hyperplasia	3
Lymphocytic thyroiditis	1

Figure 2. *Immunohistochemical analysis of menin protein expression in the nuclei of five thyroid tumors from MEN1 patients and absence of expression in one infiltrating ductal carcinoma of the breast from a MEN1 patient with proven LOH.*



Pictures are taken with a 20x magnification, inlays with 40x magnification. A. infiltrative ductal carcinoma of the breast; B. hyperplastic node; C. micro-invasive medullary thyroid carcinoma; D. multinodular goiter; E. Follicular adenoma; F. micro-invasive follicular thyroid carcinoma.

Discussion

The results of this study show that the prevalence of thyroid incidentalomas in patients with MEN1 is equal to a matched reference group with non-MEN1 patients. These results are in line with the suggestion in the recently updated guideline, that the high percentage (25%) of thyroid tumors occurring in MEN1 patients is incidental and not significant.[1] These epidemiologic results are strongly supported by the immunohistochemistry, which shows a positive menin staining indicating the presence of intact nuclear menin expression in a representative subset of thyroid tumors found in patients with MEN1.

The non-MEN1 patients were considered the best available control group facing the fact that a neck ultrasound was performed for the same indication as in the MEN1 patients. As MEN1 patients present with pHPT at a young age, not all MEN1 patients could be matched. Also in this young patient group a very low prevalence of thyroid incidentalomas was found which is in line with what one can expect in the general population.

In literature, prevalence rates for solitary nodes in healthy individuals are around 10% compared to 15% in our study.[8-11] Owing to the retrospective character of the study, all patients (n=31) who underwent a neck ultrasound in which the thyroid was not mentioned in the

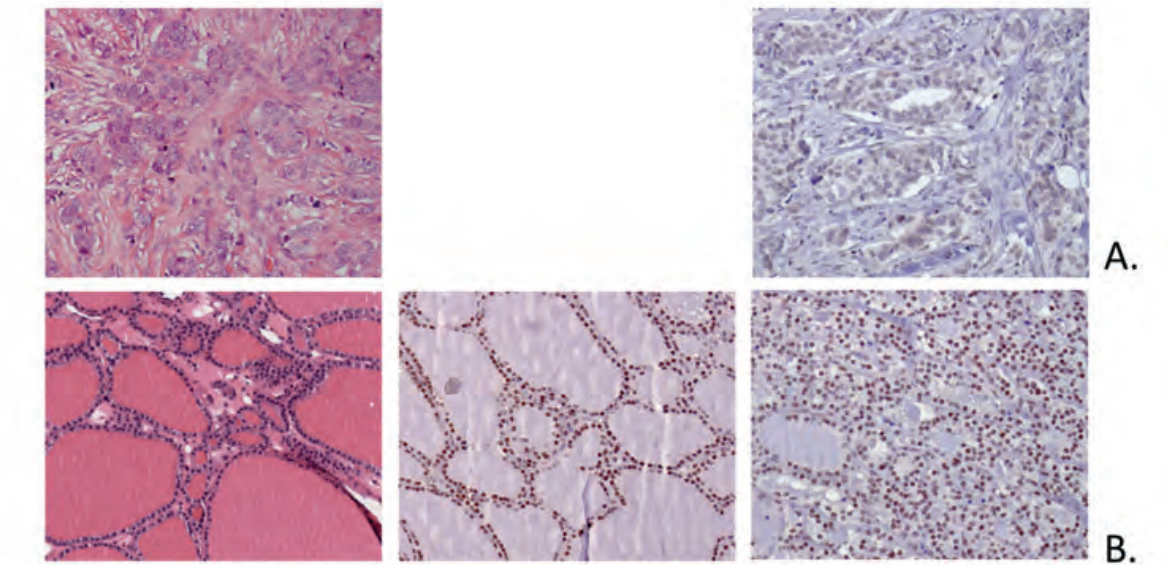
report were excluded. If we assume that there was no solitary node in those 31 neck ultrasounds, our prevalence would be similar (11%) to the prevalence rates reported in literature.

From 17 MEN1 patients, histology reports were available from thyroid tumors found by ultrasound. Of those 17 patients, one patient had a microinvasive medullary thyroid carcinoma and one patient had a microinvasive follicular thyroid carcinoma, and the other 15 showed benign pathology. MEN1-related tumors are characterized by loss of the second allele of *MEN1* gene, encoding for the protein menin, resulting in no functional copies of the gene.[12] In four case series of MEN1 patients with thyroid carcinoma, loss of heterozygositiy (LOH) was examined. The results did not show any LOH, which indicates no etiological relation between the presence of MEN1 mutation and thyroid carcinoma.[13-16] We assessed loss of menin expression by immunohistochemistry in a representative subset of diagnoses; in all evaluated tissue menin was expressed throughout the tumor and adjacent normal thyroid tissue. This indicates that there is no haploinsufficiency, i.e. the intact copy of the *MEN1* gene produces enough protein to bring about a wild-type condition.

It is a clinical challenge for both endocrinologists and surgeons to deal with thyroid incidentalomas in MEN1 patients. On the one hand, the burden of the patient needs to be as low as possible, and on the other hand, malignancies need to be identified and treated as early as possible. Our results indicate that in case of a thyroid incidentaloma in MEN1 patients, prevailing guidelines for thyroid incidentalomas in the general population can be followed.

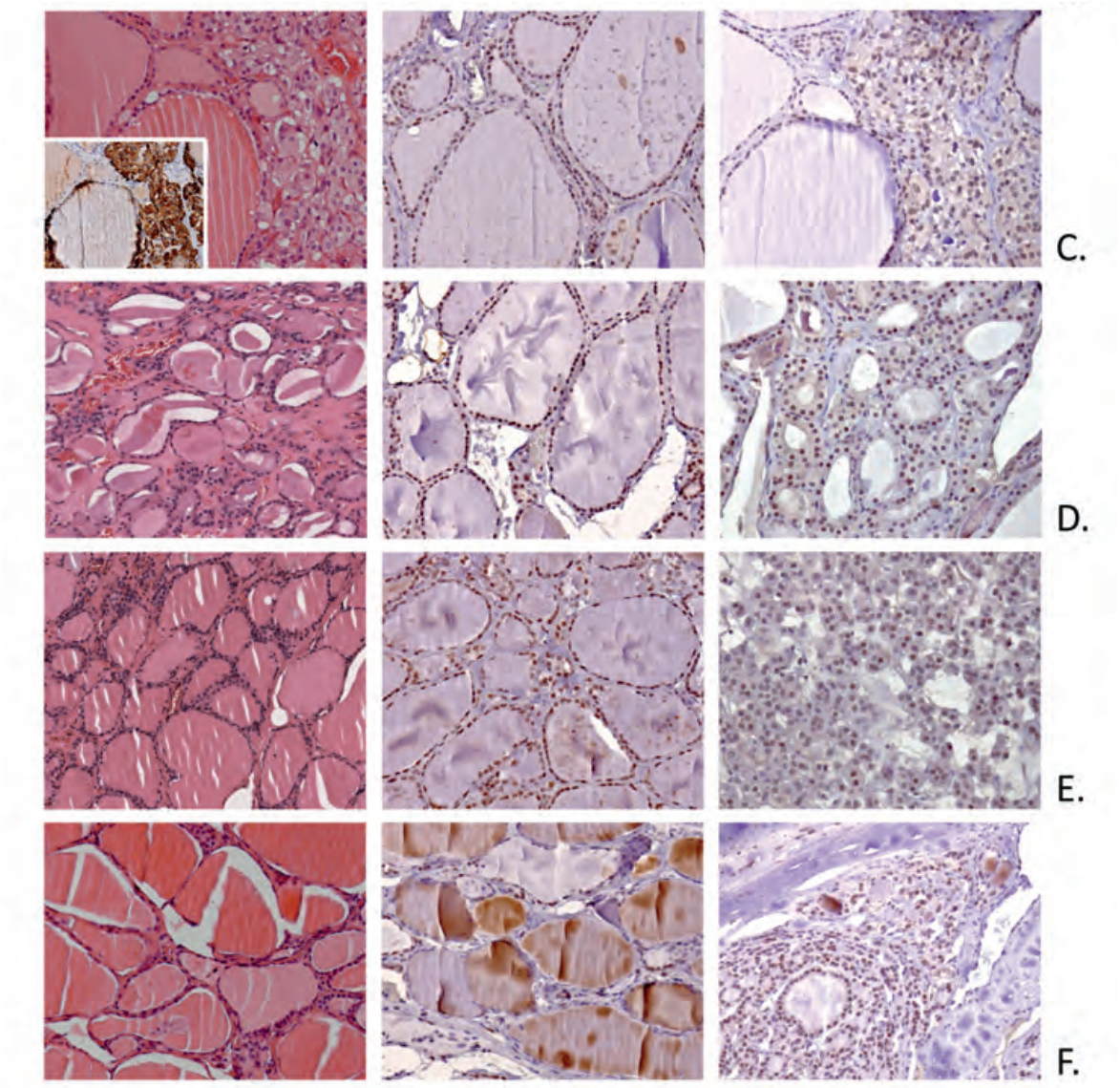
In conclusion, our results show no difference in the prevalence of thyroid incidentalomas in MEN1 patients compared with patients with pHPT without the diagnosis of MEN1. The epidemiologic findings were validated by menin expression in the nuclei.

Figure 3. *Additional immunohistochemical pictures of patients presented in figure 2*



see next page for the continuation of this figure.

Figure 3. *Continued*



Left column shows H&E staining, middle column shows menin staining in normal thyroid tissue, right column shows menin staining in thyroid tumor. A. infiltrative ductal carcinoma of the breast; B. hyperplastic node; C. micro-invasive meduallary thyroid carcinoma (inlay is calcitonin staining); D. multinodular goiter; E. follicular adenoma; F. micro-invasive follicular thyroid carcinoma.

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CHAPTER 5

Clinical safety of renaming encapsulated follicular variant of papillary thyroid carcinoma: Is NIFTP truly benign?

Parente DN, Kluijfhout WP, Bongers PJ, Verzijl R, Devon KM, Rotstein LE, Goldstein DP, Asa SL, Mete O, Pasternak JD

Reply, letter to the editor. World Journal of Surgery. 2018;42(2):321-326.

Abstract

Background

Renaming encapsulated follicular variant of papillary thyroid carcinoma (EFVPTC) to noninvasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP) was recently suggested to prevent the overtreatment, cost and stigma associated with this low-risk entity. The purpose of this study is to document the incidence and further assess the clinical outcomes of reclassifying EFVPTC to NIFTP.

Methods

We searched synoptic pathologic reports from a high-volume academic endocrine surgery hospital from 2004 to 2013. The standard of surgical pathology practice was based on complete submission of malignant thyroid nodules along with the nontumorous thyroid parenchyma. Rigid morphological criteria were used for the diagnosis of noninvasive EFVPTC, currently known as NIFTP. A retrospective chart review was conducted looking for evidence of malignant behaviour.

Results

One hundred and two patients met the strict inclusion criteria of NIFTP. The incidence of NIFTP in our cohort was 2.1% of papillary thyroid cancer cases during the studied time period. Mean follow-up was 5.7 years (range 0–11). Five patients were identified with nodal metastasis and one patient with distant metastasis. Overall, six patients showed evidence of malignant behaviour representing 6% of patients with NIFTP.

Conclusion

Our study demonstrates that the incidence of NIFTP is significantly lower than previously thought. Furthermore, evidence of malignant behaviour was seen in a significant number of NIFTP patients. Although the authors fully support the de-escalation of aggressive treatment for low-risk thyroid cancers, NIFTP behaves as a low-risk thyroid cancer rather than a benign entity and ongoing surveillance is warranted.

Introduction

The incidence of thyroid cancer has steadily increased in the United States since the early 1990s with similar trends in Canada.[1,2] This is largely related to the rise of low-risk well-differentiated thyroid cancers which have low rates of recurrence and are found predominantly incidentally.[3,4] Specific outcomes of differentiated thyroid cancers, including follicular variant papillary thyroid cancer, have shown to be specifically favourable resulting in a widespread belief that these tumors may represent indolent malignancies.[5] As healthcare costs have rapidly increased associated with the treatment and follow-up of thyroid cancer, debate has ensued regarding the importance of sub-categorizing thyroid cancers based on their malignant potential. One example of this is the extensive literature on distinct classification and treatment strategies for papillary thyroid microcarcinoma (PTMC), namely those thyroid cancers with a size <1 cm.

Separate from PMTC, encapsulated follicular variant of papillary thyroid cancer (EFVPTC) is a particularly indolent variant of PTC when it lacks evidence of invasion beyond its clear demarcation or encapsulation. This has prompted recent work to rename this tumor "noninvasive follicular thyroid neoplasm with papillary-like nuclear features" (NIFTP).[6] The renaming of noninvasive EFVPTC to NIFTP has de-escalated the once malignant diagnosis into what is now described as a benign entity by some experts.[7] The long-term effects of reclassifying this entity to benign have yet to be studied large cohort.

The objective of this study was to characterize the incidence of NIFTP within a large tertiary care endocrine surgery cohort and determine its malignant potential.

Methods

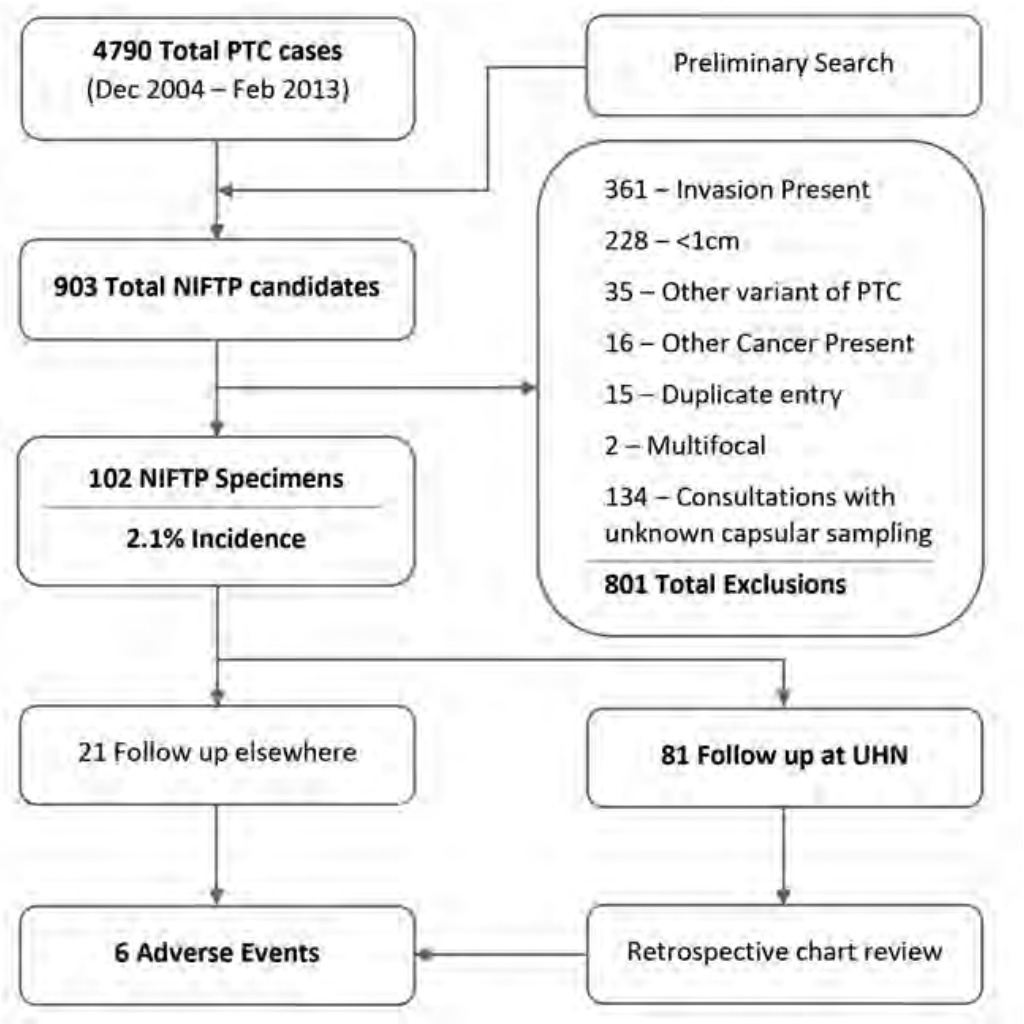
This is a retrospective cohort study conducted from a single, high-volume academic endocrine surgical center in North America. This academic center services a large geographical region both by providing primary specialty care as well as tertiary and quaternary referrals for a population of over 4 million people. For the purposes of this study, synoptic pathologic reports were evaluated from December 2004 to February 2013. Throughout this time period, standard evaluation of EFVPTC specimens by the pathology department at our institution involved complete capsular evaluation by sampling the tumor capsule and nontumorous parenchyma in toto. This ensures not only the accuracy of the diagnosis in that the entire capsule is examined for invasion, but virtually eliminates other non-dominant tumors as confounders. Synoptic reports were generated for all thyroidectomies; when staged procedures were performed, the synoptic report included comprehensive data from the previous thyroidectomy specimens, which also were reviewed in toto. The synoptic reports included information

about tumor classification, tumor architecture and cytology (e.g., oncocytic change, tall cell change), presence of intact capsule, local invasion, lymphatic spread and angioinvasion. These synoptic data were used to select appropriate cases from a large series.
All follicular variant of papillary thyroid carcinoma (FVPTC) specimens were reviewed by the expert endocrine pathology team to determine whether they met the criteria for NIFTP. Clinical data were then reviewed. With the exception of arbitrary cut-off of 1% papillae, all other inclusion criteria were adapted from the index paper on NIFTP in the literature.[6] FVPTC greater than 1 cm in size with clear demarcation or encapsulation and no evidence of local invasion of the capsule, or where there was no capsule, into the surrounding parenchyma, were included in the study. Variants other than FVPTC, tumors with any true papillae, as well as tumors with solid or trabecular growth were excluded. Tumors with high mitotic rate, tumor necrosis, positive resection margins, lymphatic or vascular invasion, perineural invasion, or extrathyroidal extension were similarly excluded. Cases were only included if the tumor was unifocal, thus eliminating any potential influence by other tumor foci. Consultations with review of slides were excluded as the thoroughness of capsule sampling could not be ensured. Patients who underwent thyroidectomy for the purpose of treating a non-thyroid lesion were not included in the study.
Primary outcome was defined as an 'adverse oncologic event' which signified patients who were found to have neck lymphadenopathy at time of initial treatment, local neck recurrence or distant metastasis. Statistical analysis was performed using SPSS version 23 (IBM Corporation, Armonk, NY, USA). The study protocol was approved by the institution Research Ethics Board.

Results

Initial screening of synoptic reports identified 903 NIFTP candidates from 4790 PTC cases between December 2004 and February 2013. After manual review of reports and pathology slides, 102 patients were found to meet the strict inclusion criteria of the study. This provided an incidence of 2.1% of all PTC cases at our institution during the study period. Of the total 102 NIFTP specimens, 81 were followed at our center and 21 were followed elsewhere (*figure 1*).
The characteristics of the NIFTP cohort are outlined in *table 1* and are compared with the cohort from Nikiforov et al.[6] The average age of our cohort was 46.8 years, and 77% of the cohort was female. The average tumor size was 3.1 cm. Forty-two percent of the tumors were between 2 and 4 cm in size, classified as pT2 (n=43). There was no statistically significant difference between this cohort and the Nikiforov cohort with respect to age, gender and average tumor size.[6] The most common surgical intervention in this cohort was a total

Figure 1. *Study flow diagram with incidence*



thyroidectomy (n=79, 77%), followed by 23 (23%) patients who underwent hemithyroidectomy alone. Adjuvant treatment with radioactive iodine (RAI) ablation was completed in 45 (44%) patients with 38 (84%) of treatments occurring prior to 2010. Mean follow-up for this cohort was 5.7 versus 14.4 years in the Nikiforov cohort.[6] Despite this, there were 6 (6%) adverse oncologic events compared to none found in the Nikiforov cohort.[6] The most common adverse oncologic event was local lymph node metastasis (n=5, 5%), followed by distant metastatic disease in the lung (n=1, 1%), and no neck recurrence. The details of patients with adverse oncologic events are presented in *table 2*. During our study period, there were no mortalities attributable to thyroid cancer. There was no correlation between number of adverse oncologic outcomes and T-stage (p=0.92) (*figure 2*).

Table 1. *Summary of data*

Characteristic	University Health Network NIFTP Cohort (n = 102)	Nikiforov et. al NIFTP Cohort [a] (n=109)	P Value
Age, mean (range), y	46.8 (15 – 81)	45.9 (21 – 81)	0.65
Sex, No. (%)			0.20
Male	24 (24 %)	18 (17 %)	
Female	78 (77 %)	91 (83 %)	
Tumor Size, mean (range), cm	3.1 (1.1 – 10)	3.1 (1.1 – 9.0)	1.0
T Stage, No. (%)			
T1a	0	-	
T1b	38 (37 %)	-	
T2	43 (42 %)	-	
T3	21 (21 %)	-	
T4a	0	-	
T4b	0	-	
Extent of Surgery, No. (%)			0.0001
Hemithyroidectomy	23 (23 %)	67 (61 %)	
Total Thyroidectomy	79 (77 %)	42 (39 %)	
Radioactive iodine ablation, No. (%)	45 (44 %)	-	
Follow-up			
No. (%)	81 (79 %)	109 (100 %)	
Mean (range), y	5.7 (0 – 11)	14.4 (10 – 26)	0.0001
Adverse events, No. (%)	6 (6 %)	0	
Locoregional	0	-	
Nodal metastases	5 (5 %)	-	
Distant metastases	1 (1 %)	-	
Death secondary to disease	0	-	

a. Nikiforov YE, Seethala RR, Tallini G, Baloch ZW, Basolo F, Thompson LD, et al. Nomenclature Revision for Encapsulated Follicular Variant of Papillary Thyroid Carcinoma: A Paradigm Shift to Reduce Overtreatment of Indolent Tumors. JAMA Oncol. 2016 Aug 1;2(8):1023-9.

Discussion

To our knowledge, this study represents the most rigorous methodology used to evaluate the malignant potential of the new entity described as NIFTP. Our data provide new insights into the value and significance of this reclassification proposal.

First, the incidence of NIFTP has been proposed to be as high as 16–23% of all PTC cases in North American and European populations.[6,8] However, this study showed the overall incidence to be much lower than expected, at 2.1%. This lower proportion has also been shown in recent NIFTP populations in Asia.[9,10] Although there can be variability in cancer rates in disparate populations, the implication of pathologic interpretation may be a key explanation.

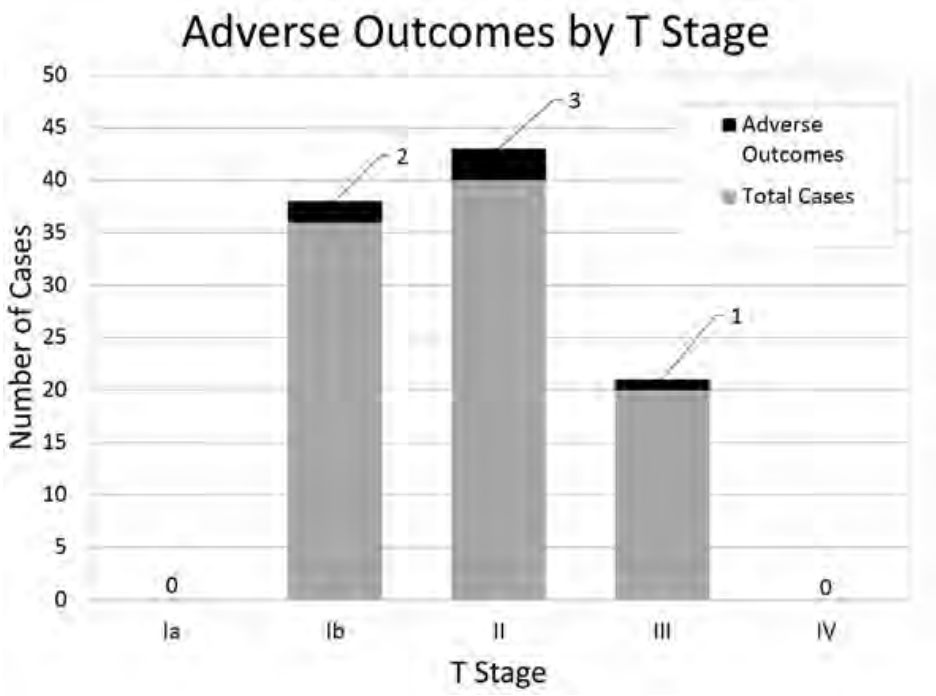
Table 2. *Patients with adverse oncologic events*

Study No.	Age	Gender	Tumor Size	Adverse Event Type	Treatment
40	69	Male	3.0 cm	Level VI nodal metastasis, 1/1 nodes	Total Thyroidectomy, Adjuvant RAI
119	60	Male	3.0 cm	Level VI nodal metastasis, 1/2 nodes	Total Thyroidectomy, Unknown Adjuvant RAI
140	37	Female	1.2 cm	Level VI nodal metastasis, 1/2 nodes	Total Thyroidectomy, Adjuvant RAI
161	42	Female	2.7 cm	Level VI nodal metastasis, 1/4 nodes (+ nodes in completion specimen)	Hemi Thyroidectomy with completion thyroidectomy, Adjuvant RAI
240	47	Female	1.7 cm	Level VI nodal metastasis, 1/8 nodes	Total Thyroidectomy, No Adjuvant RAI
248	44	Female	6.4 cm	Lung metastasis, No neck nodes retrieved	Total Thyroidectomy, Adjuvant RAI

Radioactive Iodine (RAI)

There has been previous work published on the significant inter-observer variation in reporting of thyroid tumors.[11–13] Further, when reporting on EFVPTC cases, it has been shown that there is complete agreement among expert pathologists in only 10% of cases.[14] This idea is highlighted in the Nikiforov paper, as the interobserver agreement requirement to label a specimen as NIFTP was set at only 50%.[6] The incidence of NIFTP may therefore be highly center-specific depending on institutional specimen preparation protocols (evaluation of the capsule in toto) or interpretation of the criteria. We also restricted this diagnosis to cases with no papillae, rather than the 1% cutoff initially proposed, since a few papers have identified BRAFV600E mutations in some tumors classified as NIFTP.[15] Likely due to this lax definition, we wanted to ensure that the cohort was truly limited to RAS-like thyroid neoplasms. Similarly, another recent paper highlighted that no papillae should be allowed in the diagnosis of NIFTP.[10] In addition, the requirement for examination of the complete tumor capsule limits the ability of many centers to perform accurate retrospective reviews; in our center, this was a standard of care for the duration of the study period and may have resulted in the identification of higher rates of microscopic invasion. Furthermore, despite the complete submission of the tumor nodule along with the adjacent parenchyma, the current series had a 6.4-cm noninvasive tumor that developed a lung metastasis. Similarly, five tumors presented with nodal involvement. These findings underscored that the absence of invasive growth in the plane of sections examined does not necessarily predict the possibility of an indolent behaviour. In fact, one should think that each paraffin-embedded block contains an average of 3 mm thickness of tumor tissue and often a single section of 3 micron is typically subjected to routine light microscopic assessment. Currently, there are no pathology practice guidelines addressing to the need of deeper and/or serial sections when

Figure 2. *Adverse outcomes by T Stage*



dealing with a noninvasive follicular variant papillary thyroid carcinoma. Although rare, this limitation should also be kept in mind when linking an indolent behaviour to NIFTP.

Our results show that while there is a clear benefit to the de-escalation of invasive treatment for low-risk thyroid cancers, the application of this new terminology limits the absolute benefit because of the low incidence of NIFTP. The adverse oncologic events seen in this cohort of patients are not consistent with a benign diagnosis. Our cohort demonstrated malignant behaviour in 6% of 102 patients with unifocal NIFTP, including one patient with lung metastasis. A similar trend has been seen in a Korean cohort of patients which demonstrated a 3% rate of nodal metastasis.[10] While the Korean study performed prophylactic central neck dissection which may have overestimated clinically relevant nodal deposits, our center does not routinely perform central neck dissection in the absence of preoperatively suspicious lymph nodes. This further supports the clinical relevance of neck nodes found in this study. The practical implications of de-classification of these tumors are not inconsequential, since the approach may discourage follow-up and monitoring for recurrence or metastasis. The American Thyroid Association has recognized this and recently published a statement suggesting that a NIFTP diagnosis should not affect the management and follow-up of patients with very low-risk differentiated thyroid cancer.[16] Implications on quality of life for patients with a change to the diagnosis from cancer to a benign entity but with the same treatment and follow-up need to be examined.

Our study is limited by its retrospective nature and that only 80% of the patients with NIFTP had follow-up at our institution. This design may have underestimated the rate of adverse oncologic events. Inter-observer reliability may also be a concern in any retrospective pathology review. This limitation is mitigated in our center by the subspecialty practice model in which all thyroids are reported by expert, high-volume endocrine pathologists who reviewed all of the patient samples with a high rate of intradepartmental consultation to ensure concordance. Further, pathology practice at our institution is unique in total capsular sampling for FVPTC specimens was standard practice. This ensures a high degree of confidence in the lack of invasion necessary to meet the strict NIFTP criteria in a retrospective fashion. Finally, our cohort had a high proportion of patients who underwent total thyroidectomy as their treatment for NIFTP. This may have been done to facilitate RAI ablation as 84% of the RAI was given pre-2010.

In summary, we present a large cohort of patients seen in a tertiary care academic endocrine surgery center with a reliable diagnosis of noninvasive EFVPTC that would qualify as NIFTP. Within this center, the incidence of NIFTP among PTC patients was 2.1%, lower than previously described. Furthermore, within the NIFTP cohort we documented adverse oncologic outcomes, mainly lymph node metastasis but also including distant metastasis, in 6% of patients. Our data support the proposal that patients with noninvasive EFVPTC have an excellent prognosis; however, clinicians should continue to follow these patients for evaluation of adverse oncologic outcomes until larger prospective studies can determine optimal surveillance strategies. Ongoing capture of this very low-risk thyroid malignancy in cancer registries would continue to provide epidemiologic data required for continued monitoring of this entity.

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CHAPTER 6

Noninvasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP): Trading six for a risky half dozen: Reply

Parente DN, Bongers PJ, Verzijl R, Kluijfhout WP, Devon KM, Rotstein LE, Goldstein DP, Asa SL, Mete O, Pasternak JD

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Since the term noninvasive follicular neoplasm with papillary-like nuclear features (NIFTP) was introduced, its existence has been controversial. The resultant debate has left clinicians confused as to how to counsel and follow their patients diagnosed with this entity. The authors would like to thank dr. Rosàrio for his support with respect to our recent article on the clinical safety of renaming encapsulated follicular variant of papillary thyroid carcinoma (EFVPTC).[1] The authors believe that a continued academic discourse as well as further research on the topic is necessary to clarify the ongoing uncertainty.

After Nikiforov et al.[2] published their article suggesting that the nomenclature for the low-risk thyroid

cancer variant EFVPTC be changed to NIFTP, the authors found that the experience at the University Health Network was significantly different with respect to both incidence and malignant potential.[1] In addition to Parente et al., there have been several studies indicating that EFVPTC has both malignant potential and a low incidence.[1,3,4] The authors certainly support the de-escalation of treatment of these low-risk thyroid cancers including the use of thyroid lobectomy and more selective radioactive iodine ablation. However, the avoidance of the term ‘‘cancer’’ for an entity with malignant potential may result in undertreatment or inappropriate lack of surveillance of patients with these tumors. In this regard, change in terminology is not a substitute for meaningful patient education and multidisciplinary discussion to highlight the low-risk nature of these cancers. Until future research can clarify the current controversy in the literature, clinicians should continue to follow and counsel patients about this low-risk malignant entity. Furthermore, ongoing capture of this diagnostic category by Cancer Registries is essential for both quality improvement and investigational study.

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CHAPTER 7

Preoperative Computed Tomography changes surgical management in clinically low-risk well-differentiated thyroid cancer

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Abstract

Background

In current guidelines for differentiated thyroid cancer (DTC) computed tomography of the neck (CT) has a limited role. We hypothesized that adding CT to work-up of clinically low-risk DTC ≤ 4cm changes surgical management in a portion of patients due to detection of clinically significant lymph node metastases not located by ultrasound of the neck (US).

Methods

A prospective cohort of DTC patients at an academic referral center between 2012-2016 was reviewed. All patients with fine needle aspiration cytopathology results that were suspicious for malignancy or malignant (Bethesda category V or VI, respectively) underwent CT prior to surgery. Clinically low-risk DTC patients were selected if 1) tumor diameter ≤ 4cm, and 2) no evidence for local invasion or suspicious lymph nodes was seen on US. Outcomes focused on alteration in surgical plan based on CT and correlation with pathology.

Results

Twenty-five (22.5%) of 111 patients with clinically low-risk DTC had a change in surgical management based on CT findings. Of these 25 patients, 16 (14.4% of the entire cohort) benefited due to the removal of clinically significant lymph node disease not seen on US. When categorizing the change in management group, 6 of 7 (85.7%) lateral neck dissections and 10 of 18 (55.6%) central neck dissections (CND) harboured metastatic nodes larger than 2mm.

Conclusions

In patients with clinically low-risk DTC, CT changed surgical management in a substantial number of patients with clinically significant nodal disease not detected by US. This highlights that in certain practice settings adding CT to the preoperative staging may be of added value to detect nodal metastasis.

Introduction

The incidence of differentiated thyroid carcinoma (DTC) has risen substantially in recent decades.[1] As most of these cancers are considered low-risk DTC with almost universal 10-year disease-specific survival, de-escalation of treatment is being pursued.[2-4] Currently, the extent of surgical treatment is determined by preoperative staging. If deemed clinically 'low-risk', the patient is considered for treatment with hemithyroidectomy rather than previously suggested total thyroidectomy.[5,6] Ultrasonography of the neck (US) has been shown to be accurate in the assessment of the thyroid gland itself, especially in detecting small thyroid nodules and possible extrathyroidal extension (ETE). US can also detect suspicious lymph nodes, which are not found on physical examination.[7-10] However, there is inconsistent data whether US is the optimal imaging modality for the detection of clinically relevant lymph node metastases. Contrast-enhanced computed tomography of the neck (CT) might have additional value in detecting lymph node metastases and invading disease in areas that are less well visualized by US.[5,11-14] Presence of macrometastatic lymph node disease or invasive disease implies more extensive surgery in lateral and/or central neck compartments and possible treatment with radioactive iodine remnant ablation (RAI). Nevertheless, the role of CT defined by the "2015 American Thyroid Association (ATA) Management Guidelines for Adult Patients with Thyroid Nodules and Differentiated Thyroid Cancer" (ATA guidelines) is limited.[15] It states that CT is only recommended as an adjunct to US in patients with clinical or ultrasound evidence of lymph node metastases or locally invasive tumors. We hypothesized that adding CT to the preoperative work-up of clinically low-risk DTC will change surgical management in a significant portion of patients with lymph node metastases that may be clinically relevant but not detected on US.

Materials and methods

Patient selection

We used prospectively collected data from a high volume tertiary care referral center. All adult patients with fine needle aspiration cytology (FNAC) suspicious for thyroid malignancy or malignant (Bethesda category V or VI, respectively) that underwent surgical treatment for DTC at the general surgery department between January 1, 2012 and December 31, 2016 received a standard preoperative CT of the neck with iodine contrast. For this study, patients were retrospectively selected as clinically low-risk if they had a thyroid mass up to 4 cm (cT1a-2) without evidence for local invasion or lymph nodes metastases (cN0) based on physical examination and US.[16] Patients with incomplete US reports (defined as not mentioning lymph nodes status in the neck) or non-iodine contrast CT were excluded from

study analysis. In this practice, suspicious lymph nodes were not routinely biopsied preoperatively.

Change in surgical plan

During the work-up for all patients, the surgeon noted the surgical management plan in the patients' electronic medical records after the initial consultation and review of FNAC and US findings and subsequently ordered a preoperative CT scan of the neck for each patient. Once the CT scan had been completed, the surgeon logged into each patient's medical record whether a change in surgical management plan (i.e. addition of neck dissection) was made or not. The surgical planning was based on the ATA guidelines that were present at that time. A compartment-orientated neck dissection was performed based on the location of suspicious lymph nodes found on imaging. Central neck dissection (CND), the removal of all lymph nodes from the central neck compartment (level VI), was performed if there was lymphadenopathy seen on imaging. When the suspicion for lymph node metastasis on imaging was mild or dubious this led to a plan of only ipsilateral removal of the mildly suspected nodes (limited CND). A lateral neck dissection (LND) was planned if there were suspicious lymph nodes in the lateral neck (level I-V) seen on imaging and this was always combined with at least an ipsilateral CND. The surgeon's intra-operative judgement for the central neck compartment could change planned procedure, although for analysis purposes these were not regarded as change in management based on CT.

Interpretation of radiology

Different radiologists, either at the tertiary referral hospital or at external diagnostic imaging clinics, performed the US as per usual care. Interpretation of US was based on the radiology reports. CT was assessed by both the surgeon and a dedicated head and neck radiologist and interpretative inconsistencies were resolved by discussion. Highly suspicious nodes in a patient with known thyroid malignancy were defined as nodes that had a combination of the following attributes: avid enhancement, cystic change, punctate calcification, central necrosis, peripheral ill-definition, presenting on a high-risk location such as low level III, level IV, level VI, and the retropharynx. Mildly suspicious nodes were those with mild or faint enhancement on a high-risk location.

Histopathology

The results of preoperative changes in planned surgical strategy were correlated to the pathological analyses of the resected lymph nodes. A change in surgical plan was considered true positive if significant metastatic lymph node disease (i.e. at least five metastatic lymph nodes or any metastatic lymph node larger than 2mm) was within the compartments that warranted the surgery. False positive results were assigned to the surgical plan if

Table 1. *Preoperative baseline characteristics*

	Total group n = 111	**Management change (n=25)**	**No management change n = 86**	**P-value**
Age at surgery, *mean (SD)*	48.0 (14.6)	44.4 (15.2)	49.0 (14.4)	0.168
Female sex	89 (80.2)	23 (92.0)	66 (76.7)	0.152
Family history of DTC	98 (88.3)	21 (84.0)	77 (89.5)	0.484
Radiation exposure history	4 (3.6)	1 (4.0)	3 (3.5)	0.999
Diagnosis				0.835
Incidental	32 (28.8)	6 (24.0)	26 (30.2)	
Asymptomatic	58 (52.3)	14 (56.0)	44 (51.2)	
Symptomatic	5 (4.5)	1 (4.0)	4 (4.7)	
FNA result				0.376
Bethesda V	28 (25.2)	8 (32.0)	20 (23.3)	
Bethesda VI	83 (74.8)	17 (68.0)	66 (76.7)	
Ultrasound tumor stage				0.301
T1a	16 (14.4)	2 (8.0)	14 (16.3)	
T1b	55 (49.5)	11 (44.0)	44 (51.2)	
T2	40 (36.0)	12 (48.0)	28 (32.6)	

Data are expressed as n (%) unless stated otherwise. SD: standard deviation, DTC: differentiated thyroid cancer, FNA: fine needle aspiration

micrometastatic lymph nodes (i.e. less than five metastatic lymph nodes each ≤ 2mm) or no metastatic lymph nodes were found in the compartments that underwent surgical resection based on preoperative CT.

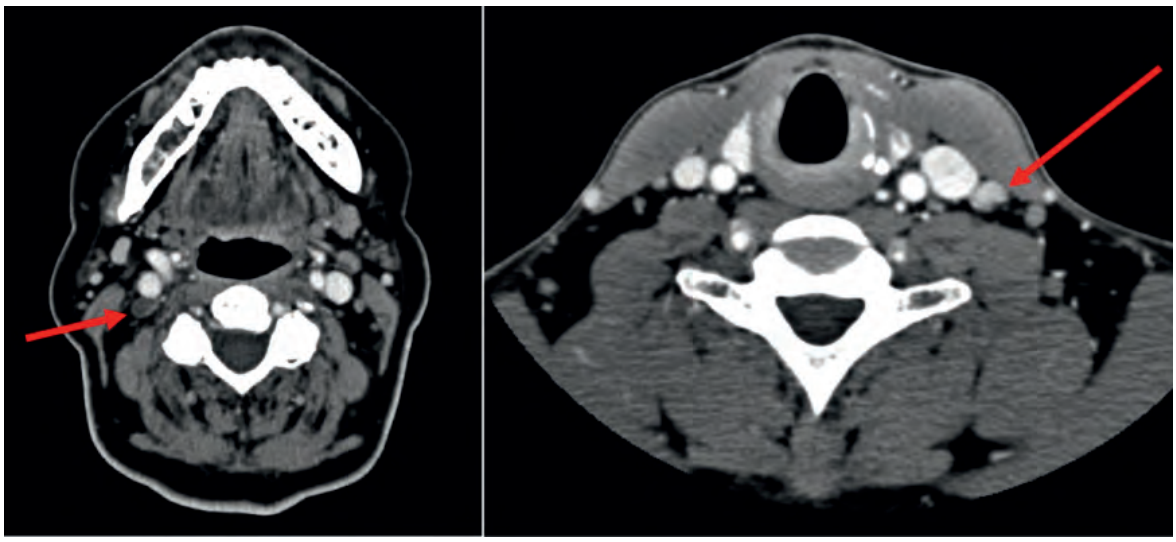
Statistical analysis

Clinical baseline features were compared between all patients. Parametric data are presented as mean with standard deviation (SD), and for non-parametric data as median with interquartile range (IQR). Independent-samples t-tests were used to calculate significance of parametric data. Mann-Whitney U tests were used for non-normally distributed variables. Chi-square tests were used for categorical variables. A p-value of < 0.05 was considered significant. Statistical analyses were performed using SPSS version 24 (IBM Corporation, Armonk, NY, USA). Institutional Research Ethics Board approved this study.

Results

During the inclusion period, a total of 199 patients with a diagnosis or suspicion of thyroid malignancy (Bethesda V/VI) underwent surgery at the tertiary referral hospital. Forty-eight patients were excluded due to incompleteness of their US reports that lacked information

Figure 1. *CT scan of two patients with an altered surgical plan due to preoperative lymph node findings on CT not noted in initial assessment*



regarding cervical lymph node status, and 40 patients were excluded as they did not have low-risk DTC. A total of 111 patients with clinically low-risk DTC were included for analysis. Mean age was 48.0 (SD 14.6) years and 89 (80.2%) patients were women (*table 1*). Thirteen (11.7%) patients had a positive family history for DTC and four (3.7%) had a history of radiation exposure to the neck. Eighty-three (74.8%) patients had proven (Bethesda VI) thyroid malignancy on FNAC and 28 (25.2%) had suspicion of malignancy (Bethesda V). The group of patients with a change in surgical plan based on preoperative CT did not statistically significantly differ on any of the preoperative baseline characteristics from the group without a change in management (*table 1*).

Changes in surgical plan based on CT

Twenty-five (22.5%) patients had a change in surgical plan based on CT findings (*table 1*). Of the patients with a change in surgical plan, two (8%) had a primary tumor smaller than 1cm (T1a stage) and 23 (92%) had a primary tumor of 1-4cm (T1b-T2 stage). Twelve patients (48.0%) with a change in surgical plan based on CT findings underwent RAI compared to 26 (30.2%) patients in the group of patients without a change in surgical plan after CT imaging (p=0.017).

Table 2 focuses on the patients with a change in surgical plan based on CT findings. A LND was indicated in seven patients (6.3% of the entire cohort) with suspicion of metastatic disease in the lateral neck not noted at initial clinical and US assessment (*figure 1*). Six of these seven (85.7%) patients were found to have pathological macrometastatic lateral neck disease. The average number of lymph nodes removed from the lateral neck in these patients was 37.1

Table 2. *Analysis of changes in surgical plan after CT*

	Change in surgical plan	Percentage of entire cohort (n=111)
Total	**25**	**22.5 %**
True positive	16 (64.0%)	
False positive	9 (36.0%)	
Lateral neck dissection	**7**	**6.3 %**
True positive	6 (85.7%)	
False positive	1 (14.3%)	
Central neck dissection	**18**	**16.2 %**
True positive	10 (55.6%)	
False positive	8 (44.4%)	

(range 15-68), of which on average 7.3 (range 0-20) had metastases. In 18 patients (16.2% of the entire cohort), more extensive central neck compartment surgery was planned based on CT findings. Of those, 10 (55.6%) had macrometastatic disease in the removed lymph nodes of the central compartment. Seven out of the eight unnecessarily performed CNDs consisted of a limited CND because mildly suspicious nodal disease was seen on CT. This is reflected in the difference in average number of lymph nodes resected from the central compartment: 3.5 lymph nodes were on average removed in the patients that underwent an unjustified limited CND compared to the removal of 7.9 lymph nodes in the CNDs that did harbour macrometastatic disease.

The operative reports showed that in 12 of the 18 (66.7%) cases wherein CND was planned based on new CT findings, suspicious-looking lymph nodes in the central neck were also seen on intraoperative assessment by the surgeon. However, in five of the 12 (41.7%) cases, these suspicious lymph nodes were negative for metastases based on histopathological examination. Of the six cases with a planned CND based on CT findings but without abnormalities seen intraoperatively by the surgeon, three had non-microscoscopic lymph node metastases.

Of the 25 patients that underwent a neck dissection based on new CT findings, one patient needed long-term replacement therapy for hypocalcaemia that developed after surgery for thyroid malignancy with lateral lymph node metastasis. No other direct complications (haematoma or bilateral laryngeal nerve paralysis) or persistent complications six months after surgery (spinal accessory nerve palsy or unilateral laryngeal nerve paralysis seen on laryngoscopy) were reported.

Discussion

This study shows that performing a standard preoperative CT of the neck in patients with clinically low-risk DTC, defined as having less than 4cm noninvasive tumors without suspicious lymph nodes on US, changed planned surgical management in 22.5% of patients. Sixteen out of 25 patients benefited from the CT-directed change in management due to the removal of non-microscopic lymph node disease not seen on US. LNDs (level I-V) were performed in 6.3% of the entire cohort based on the additional information of CT with a true positive rate of 85.7%.

While previous reports compared the diagnostic performances of both US and CT in patients with DTC, this study investigated the clinical consequence of CT on surgical planning in patients with clinically low-risk DTC.[14,17] Studies exploring the effect on surgical decision-making are consistent with our data. In line with our results, *Lesnik et al.* found that adding CT to the work up of newly-diagnosed papillary thyroid cancer patients changed the surgical plan in 25% due to macroscopic lymph node disease in the central and/or lateral neck compartments.[14]

To help the surgeon plan the extent of the thyroid operation, poorly visualized areas on US can be readily visualized through CT. This includes retropharyngeal and mediastinal lymph node localisation as well as tracheal, oesophageal, laryngeal, or vascular invasion.[18,19] Another important advantage of CT is that it is widely available, even in low-volume settings where many thyroid cancers are currently treated. Many studies have shown that US assessment is operator-dependent and this supports the idea that CT may be used in practice setting where high-volume interpreters are not available.[20-22] Nevertheless, potential disadvantages of performing standard preoperative CT exist and need to be taken into account, such as costs and radiation exposure.[14,23] One argument against CT focuses on the iodide contrast use in thyroid cancer patients needing RAI therapy. Recent studies show that preoperative administration of contrast for CT purposes does not cause long-term iodine retention and should not lead to hesitancy in using this modality.[24-26]

A large body of evidence has shown that macroscopic lymph node metastasis has significant prognostic significance.[27-31] A structurally incomplete response to initial therapy gives significantly worse outcomes and as such, a complete resection of cancerous tissue from the thyroid and from cervical macroscopic lymph nodes is essential.[32,33] In discussing the addition of CT imaging to the standard preoperative work-up, it is also important to consider the consequences of unnecessarily performed neck dissections or RAI that were based on the additional CT findings. In our study cohort, no patient that underwent an unjustified CND or LND based on CT findings had any intraoperative or postoperative complications up to 6 months. Only one of the nine patients who underwent an unnecessary CND or LND, in this case it was a CND, underwent subsequent RAI therapy. The reason for adding RAI for this pT1aN0 patient was based on the patient's advanced age (> 60 years) and thyroid histology

(20% tall cell), not on the preoperative CT findings. Long-term follow-up data is needed to determine whether the surgical intervention done based on the addition of preoperative CT does in fact lead to lower recurrence rates.

This study also intended to identify specific patient or clinical tumor characteristics that might predict helpfulness of CT.[15] As shown in *table 1*, we found no statistically significant characteristics that were linked to a change in management and thus we were unable to narrow the indication for a preoperative CT in patients with clinically low-risk DTC. As an example, in two of the 16 T1a tumors the CT led to a neck dissection that harboured macrometastatic nodal disease.

Different factors needs to be considered when determining the cost-effectiveness of adding CT to the standard work-up of clinically low-risk DTC. Our results show that for every patient that benefits from the CT findings, 6.9 patients with clinically low-risk DTC underwent a CT scan and 8.1% of the patients had unnecessary and potentially harmful lymph node dissections. The incremented costs of a standard CT scan should be weighed against future costs saved by the prevention of treatments for clinically relevant recurrences and their impacts on quality of life. A previous study calculated that the cost of surveillance of low-risk disease to detect a recurrence is over six times more costly when compared to detection of recurrence in an intermediate- or high-risk patient.[34]

The strength of this study is the standardisation of all thyroid cancer patients receiving preoperative CT in a prospective cohort who were evaluated and treated by the same surgeons and radiologists. This ensured homogeneity in surgical planning and treatment.

A limitation to this study is the heterogeneity in the performance of the US in the preoperative work up. Many US were performed outside of the academic center (48.7%). This could have caused inconsistency in the comprehensiveness of the US imaging, supported by the finding that 24.0% of the ultrasounds lacked description of cervical lymph nodes and had to be excluded from analysis. This may ultimately be a good reflection of this study's external validity because it may be a realistic reflection of current clinical practice.

Conclusions

In a prospective cohort of clinically low-risk DTC patients, a standard preoperative CT changed the surgical management for a substantial number of the patients, leading to more extensive operations involving central and/or lateral neck dissections for clinically significant nodal disease. This highlights the fact that in certain practice settings with variable-quality US imaging available, adding a preoperative staging CT scan may be of added value for detecting clinically significant metastatic nodal disease. Further long-term clinical correlation with postsurgical recurrence and cost-effectiveness assessment will be helpful for informing CT use in future preoperative thyroid cancer guidelines.

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CHAPTER 8

Papillary thyroid cancers with focal tall cell change are as aggressive as tall cell variants and should not be considered as low-risk disease

Bongers PJ, Kluijfhout WP, Verzijl R, Lustgarten M, Vermeer M, Goldstein DP, Devon K, Rotstein LE, Asa SL, Brierley JD, Tsang RW, Ezzat S, Vriens MR, Mete O, Pasternak JD

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Abstract

Background

Tall cell variant of papillary thyroid carcinoma (PTC) is as an aggressive histological variant. The proportion of tall cells needed to influence prognosis is debated.

Methods

Patients with PTC and tall cells, defined as having a height-to-width ratio of ≥3:1, seen at a high-volume center between 2001-2015 were reviewed. Specimens were classified as 1) focal tall cell change, containing <30% tall cells; 2) tall cell variant, ≥30% tall cells and 3) control cases selected from infiltrative classical PTCs without adverse cytologic features. Univariate, sensitivity and multivariable analyses were performed with persistent/recurrent disease as primary outcome.

Results

We identified 96 PTCs with focal tall cell change, 35 with tall cell variant and 104 control cases. Factors associated with poor clinical prognosis were significantly greater in those with focal tall cell change and tall cell variants. Regarding primary outcome hazard ratios were 2.3 (95%CI 1.0-5.7) for focal tall cell change and 3.4 (95%CI 1.2-8.7) for tall cell variants compared to controls. Five-year disease-free survival was higher for the control group (92.7%, 95%CI 87.4-98.0) compared to focal tall cell change (76.3%, 95%CI 66.1-86.5) and tall cell variant (62.2%, 95%CI 43.2-81.2). When stratified in groups consisting of tall cell proportions (<10%, 10-19%, 20-29% and ≥30%), identification of ≥10% tall cell change was associated with worse outcome (p=0.002).

Conclusions

PTCs with ≥10% tall cell change have worse prognosis than those without tall cells. Our data indicate that thyroid cancer management guidelines should consider PTCs with focal tall cell change outside of the low-risk classification.

Introduction

Papillary thyroid carcinoma (PTC) is generally indolent with excellent 10-year survival rates greater than 95%.[1] However, some histologic variants of PTC demonstrate more aggressive behaviour leading to higher rates of metastasis, recurrence, and resistance to radioactive iodine (RAI) therapy.[2] Among these, tall cell variant of PTC has been recognized for its aggressive biology.

In 1976, Hawk and Hazard first reported the tall cell variant of PTC.[3] Tall cells are characterized by a cell height that is at least two or three times its width, eosinophilic cytoplasm, basal nuclei and the classic nuclear features of PTC.[4,5] At a molecular level, higher prevalence of *BRAFV600E* mutation (80-100%), *TERT* promoter mutations, somatic copy number alteration of 1q, and oncogenic miR-21 have been identified in this variant.[6-9]

There is a noticeable variability in descriptive reports of the tall cell variant of PTC, with a wide range of prevalence (3-19% of PTCs), recurrence (0-66.3%) and disease-specific death rates (1.5-42.9%).[10-15] Some of the variability is attributed to the thresholds for pathological identification of tall cell change. These criteria are ultimately used to define the tall cell variant which include the ratio of 2 or 3 for height:width, and the proportion of tall cell change within the entire tumor ranging from 30 to 75%.[4,15-21] Most experts have adopted 30% proportion rather than the previously more common 50% as diagnostic criteria for a tall cell variant PTC.[22] The 4th edition of the World Health Organization classification of endocrine tumors revised the cut-off value for tall cell change as ≥30% for tall cell variant designation.[23] The most recent 2015 American Thyroid Association Management Guidelines for Adult Patients with Thyroid Nodules and Differentiated Thyroid Cancer (ATA guidelines) included tall cell variant as an independent factor indicating intermediate- rather than low-risk PTC.[24] Interestingly, Beninato *et al,* found that aggressive behaviour can already be seen in PTC with ≥10% tall cell change.[25] Others also reported increased risk in those with other proportions of tall cell change.[8,26,27] The outcome implications of focal tall cell change (<30%) in a classical variant PTC remains unaddressed in the risk stratification of most guidelines.

As there is a paucity of evidence to support the clinical relevance of PTC with less than 30% tall cells, we compared outcome and adverse tumor characteristics of PTC with focal tall cell change (<30% cell change in the entire tumor volume) and tall cell variant PTCs (≥30% cell change) in our series of thyroid cancers. We hypothesized that even small proportions of tall cell change within a PTC portend more aggressive tumor biology and ultimately worse clinical outcome.

Materials and methods

Case selection and pathology review

A retrospective review was performed of all patients with any tall cell changes in PTC managed at a high volume university hospital between 2001 and 2015. Patients were identified from the institutional pathology database. Institutional research ethics board approved the study. All tall cell variant PTCs and PTCs with focal tall cell change that were >1cm and had available follow-up data were included. Tall cell variants with a synchronous focus of other cytomorphology (e.g. columnar cell, hobnail cell change) and dedifferentiation were excluded. A control group consisted of all patients with classical PTCs >1cm with available follow-up from a three year period (2011-2013).

Tall cells were defined as cells with their height three times their width and having an eosinophilic cytoplasm with the characteristic nuclear features of PTC. A PTC was classified as tall cell variant when tall cell change accounted for at least 30% of the entire tumor volume. A diagnosis of PTC with focal tall cell change was made when the PTC had focal tall cell change accounting for less than 30% of the entire tumor volume. The pathologic definition for classical PTC as control group was an infiltrative PTC with classical papillary architecture and with no evidence of adverse cytomorphological features; including absence of all the following: tall cell, columnar cell, or hobnail cell change, increased mitotic activity (>3 per 10 high power fields), tumor cell necrosis, and dedifferentiation.

Standard practice has been to submit the entire tumor for pathologic examination as well as documentation of focal adverse cytomorphological features including focal tall cell change. Two experienced endocrine pathologists (OM, SLA) independently reviewed all cases. The pathology department used digital pathology routinely since 2011 and when a PTC displayed borderline tall cell-like changes, pathologists used whole slide images to confirm the height-to-width ratio. During re-review of cases for the purposes of this study, when a discordance was present with respect to focal tall cell change, the whole slide images were used to objectively estimate the volumetric extent of tall cell change within the entire tumor volume. By doing this, a mutual agreement was achieved in all study cases.

Clinicopathologic characteristics and follow-up

Demographic information, synoptic pathology reports, clinical and imaging data were obtained from the electronic patient records. Persistent or recurrent disease was defined as histologically or cytologically confirmed structural disease present or found after the initial surgery and radioactive iodine treatment. Serum thyroglobulin increase without structural disease or small indeterminate lesions were not considered recurrence for the purposes of this study. Follow-up time was defined as the time between surgery and the last clinical visit related to the thyroid cancer reported in the institutional electronic patient records up to January 1st 2017.

Statistical analysis

Descriptive data were summarized using descriptive statistics. Differences in clinical and pathological features between each of the three groups (classical PTC without any adverse features, those with focal tall cell change and tall cell variant groups) were tested using Chi-square, One-way ANOVA or Kruskal-Wallis tests as appropriate, with Sidak and Holm–Bonferroni correction being applied once pairwise comparisons were made between the subgroups.

The relationship of subgroups of PTC and persistent or recurrent disease was evaluated by univariate methods (Kaplan-Meier survival curve and log-rank test) and corrected for confounders using multivariable methods (Cox-proportional hazards analysis). Forward stepwise regression was employed given the large amount of potential confounders and relatively low event rate (recurrence). The forward stepwise regression procedure included variables that both differed among the three subgroups of PTC and were univariately associated ($p<0.10$) with persistent or recurrent disease. Those candidate confounders were entered step by step, starting with the highest p-value in the univariate analysis, and eliminating non-significant variables until all variables in the model were statistically significant. Sensitivity analysis was performed to understand thresholds of tall cell impact on outcome by stratifying patients with specific reported percentage of tall cell features in groups consisting of tall cell proportion of a) <10%, b) 10-19%, c) 20-29% and d) ≥30%.

Significance was determined at p-value < 0.05. Statistical analyses were performed using SPSS version 24 (IBM Corporation, Armonk, NY, USA).

Results

There were 131 patients with tall cell change identified; 96 patients had focal tall cell change and 35 patients had tall cell variant PTC. We collected 104 patients to serve as a control group with classical PTC.

Table 1 summarizes the clinical and pathological features of the tumor subgroups. Control group patients with classical PTC and those with focal tall cell change were younger compared to those with tall cell variant PTC (mean age ± SD: 45.6±13.5; 48.5±14.7 and 55.3±17.2 years, respectively). The median tumor size differed between the control group, PTC with focal tall cell change and tall cell variant PTC [median (interquartile range, IQR) size: 17.0 (13.0-31.5); 26.0 (16.0-39.5) and 40.0 (21.0-48.0) millimetres, respectively]. Median (IQR) follow-up time among tumor groups was 49.5 (28.0) months for the control group, 43.5 (31.0) months for PTC with focal tall cell change and 35.0 (87.0) months for tall cell variant PTC. These differences were not statistically significant (p=0.521). Factors significantly associated with both tall cell variant and focal tall cell change but not the control group included vascular invasion, gross

Table 1. *Baseline clinicopathologic features per subgroup of papillary thyroid cancer*

	Infiltrative classical PTC (control group) n=104	**PTC with focal tall cell change n=96**	**Tall cell variant PTC n=35**	**p-value**
Age in years, mean (SD)	45.6 (13.5)	48.5 (14.7)	55.3 (17.2)	0.003*
Female	77 (74.0)	63 (65.6)	19 (54.3)	0.083
Tumor size in mm, median (IQR)	17.0 (13.0-31.5)	26.0 (16.0-39.5)	40.0 (21.0-48.0)	<0.001**
Vascular invasion	14 (13.5)	30 (31.3)	14 (40.0)	0.001#
Gross extrathyroidal extension	1 (1.0)	13 (13.5)	7 (20.0)	<0.001#
Positive margins	25 (24.0)	43 (44.8)	22 (62.9)	<0.001#
Lymph node metastasis at diagnosis	56 (53.8)	66 (68.8)	25 (71.4)	0.047^
Distant metastasis at diagnosis	0	5 (5.2)	3 (8.6)	0.024#
Hemithyroidectomy as definitive treatment	7 (6.7)	2 (2.1)	1 (2.9)	0.241
RAI remnant ablation	64 (61.5)	80 (83.3)	31 (88.6)	<0.001#

*Data are expressed as n (%) unless stated otherwise. PTC: Papillary thyroid carcinoma, IQR: interquartile range, RAI: radioactive iodine. Significant differences between: * Classical PTC vs. tall cell variant; ** All groups; # Classical PTC vs. focal tall cell change / tall cell variant; ^ Classical PTC vs. focal tall cell change*

extrathyroidal extension, positive resection margins and distant lung metastasis. Lymph node metastases at time of initial diagnosis were more frequent in patients with PTCs displaying focal tall cell change (68.8%) than those with classical PTC (53.8%) (p= 0.031).

Disease Specific Outcome

Within the entire cohort one patient died of disease. This patient had a tall cell variant PTC with lymph node metastasis and positive resection margins and died of disease after rapid progression with extensive local invasion into the trachea and distant metastases to bone and brain.

The likelihood of persistent or recurrent disease was higher in patients with PTC displaying focal tall cell change (21.9%, p=0.002) and tall cell variant PTC (37.1%, p=0.001) compared to the control group with classical PTC (6.7%). Of the control group 6.7% had locoregional lymph node metastasis and none had distant metastasis whereas these rates were 14.6% and 8.9% for PTC with focal tall cell change and 14.3% and 22.9% for tall cell variant PTC.

Table 2 shows the final multivariate Cox-proportional hazards model for persistent or recurrent disease after the forward stepwise selection procedure. The Hazard Ratio (HR) for the PTC subgroup with focal tall cell change was 2.3 (95% Confidence Interval (CI) 1.0-5.7; p=0.062) and was 3.3 (95% CI 1.2-8.7; p=0.020) for the tall cell variant PTC, adjusted for tumor size and gross extrathyroidal extension.

Table 2. *Forward Cox-regression analysis for persistent or recurrent disease*

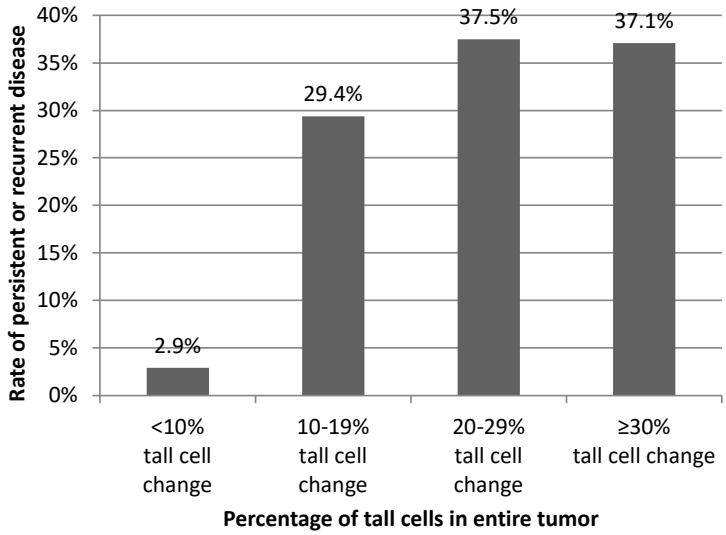
		Hazard ratio (95% confidence interval)	p-value
Subgroup of PTC	Classical PTC	1.0 (reference)	
	PTC with focal tall cell change	2.3 (1.0-5.7)	0.062
	Tall cell variant PTC	3.4 (1.2-8.7)	0.020
Tumor size in mm		1.0 (1.0-1.1)	0.003
Gross extrathyroidal extension		2.6 (1.1-5.8)	0.024

PTC: papillary thyroid carcinoma
Potential confounders that entered the forward stepwise selection procedure were tumor size, vascular invasion, gross extrathyroidal extension, positive resection margins, lymph node metastasis at time of initial diagnosis and RAI remnant ablation.

Sensitivity Analysis

The relationship between the extent of tall cell change and persistent or recurrent disease is shown in *figure 1*. This included thirty-five cases with less then 10% tall cell change, 17 between 10-19%, 24 between 20-29% and 35 tall cell variants had recurrence rates of 2.9%, 29.4%, 37.5% and 37.1%, respectively. PTCs exhibiting less than 10% tall cell change had less persistent or recurrent disease compared to PTCs with 10% or more tall cell change (p=0.002).

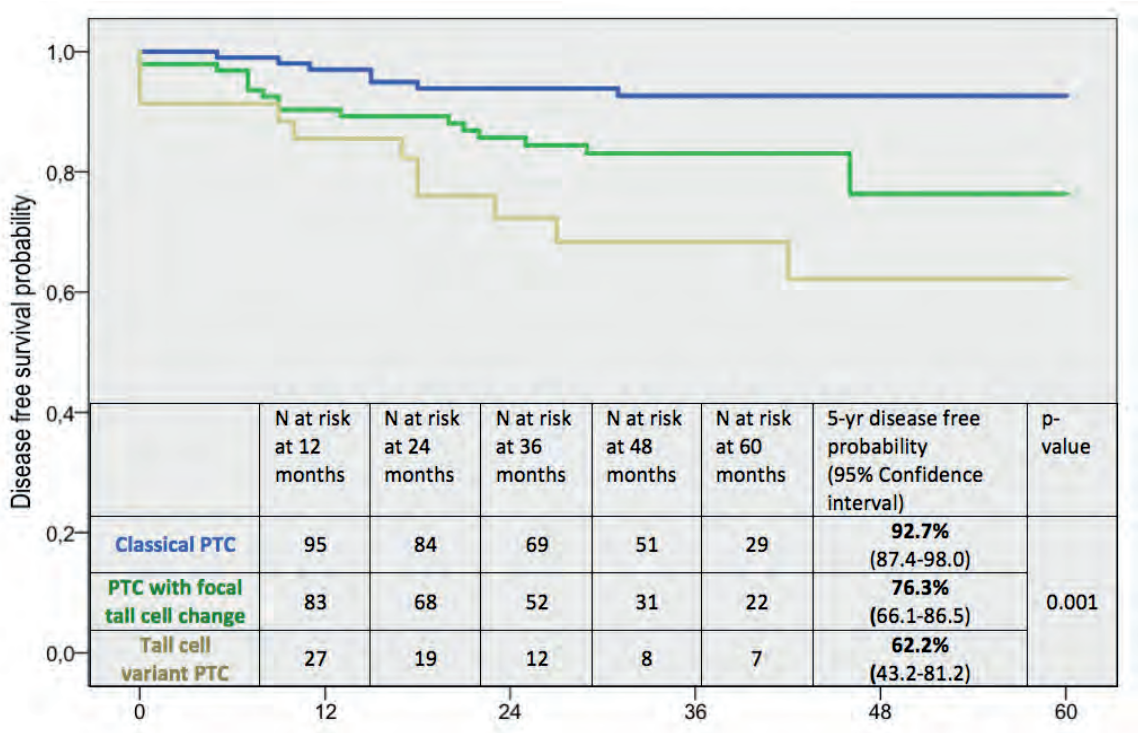
Figure 1. *Persistent or recurrent disease rate stratified per amount of tall cells present in the papillary thyroid carcinoma*



Disease-free survival

As demonstrated in *figure* 2**,** infiltrative classical PTCs (control group) had a higher 5-year disease-free survival of 92.7% compared to PTCs displaying focal tall cell change (76.3%, p=0.010) and tall cell variant PTCs (62.2%, p=0.001). There was no significant difference between PTCs with focal tall cell change and tall cell variant PTCs with respect to 5-year-disease free survival (p=0.120).

Figure 2. *Five-year disease-free survival curve*



	N at risk at 12 months	N at risk at 24 months	N at risk at 36 months	N at risk at 48 months	N at risk at 60 months	5-yr disease free probability (95% Confidence interval)	p-value
Classical PTC	95	84	69	51	29	**92.7%** (87.4-98.0)	0.001
PTC with focal tall cell change	83	68	52	31	22	**76.3%** (66.1-86.5)	
Tall cell variant PTC	27	19	12	8	7	**62.2%** (43.2-81.2)	

PTC: papillary thyroid carcinoma

Discussion

This study highlights the elevated risk profile of PTCs with small percentages of tall cell change. Tumors with focal tall cell change (defined as <30% of the entire tumor volume) had more worse prognostic features than a control group of classical PTCs and resembled those of tall cell variants. PTCs with focal tall cell change and tall cell variant PTCs had comparable rates of persistent or recurrent disease. Moreover, focal tall cell change showed a trend to be independently associated with persistent and recurrent disease. When the percentage of tall cells in the PTC was greater than 10%, the recurrence/persistence rate increased 10 fold from 3% to 30%.

The tall cell variant of PTC stands out as an aggressive variant. The extent of tall cell change required to negatively affect prognosis remains unclear.[3,4,15-21] The most recent 4th edition of the WHO classification adopted the cut-off of 30% and a recent survey of expert thyroid pathologists showed that no consensus has been reached yet on diagnostic criteria for this variant.[22,23] In that particular report, only 7 of 14 experts identified that they use the 30% cut-off to define a tall cell variant.[22] In recent years, there has been a tendency to use lower thresholds in defining tall cell variants. This has been influenced by studies that found adverse when only 10% tall cell change is seen in sections examined.[8,25,27] Poor survival and higher rates of lymph node metastasis were independently associated with tall cell variant PTCs correlating with other known risk factors for poor outcome such as patient age, tumor size and extrathyroidal extension.[10,12,28,29] In this study, these risk factors were seen more commonly in both the tall cell variant and focal tall cell groups compared to the control group.
One ongoing difficulty in making a diagnosis of tall cell variant involves thyroid specimen evaluation. Currently, there are no evidence-based guidelines addressing the amount of thyroid tumor that needs to be submitted for histological examination when making a diagnosis of tall cell variant PTC.[22] In this study, all thyroidectomy specimens were submitted in toto for microscopic examination and were reviewed by two expert endocrine pathologists. This enabled us to determine the extent of the tall cell change within the entire tumor volume rather than the percent of tall cells in representative sections, the latter, a method commonly used in most North American surgical pathology practices. In addition, this unique advantage secured accurate selection of the control group.
With the de-escalation of treatment of thyroid cancer, further discussion on surgical approach for patients with tall cell change is warranted. Within the sensitivity analysis in this cohort, PTCs with <10% tall cell change had a recurrence/persistent rate of 3%, consistent with low-risk disease that would likely be candidates for hemithyroidectomy alone. In contrast, patients with ≥10% tall cell change (but less than 30%) had 30% chance of recurrence or persistence. This suggests a possible benefit of more aggressive management, including total thyroidectomy and RAI remnant ablation, usually reserved for higher-risk disease. At least five of the 41 patients (12.2%) with 10-30% tall cell features would be classified as "low-risk" according to the recent ATA guidelines. It is important to note that these changes in management can only be applied after the initial surgical management given a diagnosis of tall cell containing PTC requires a histological examination.
There are several limitations to this study. Data regarding mortality may be missing as follow-up data was collected retrospectively and information regarding mortality outside of the electronic hospital record is unavailable. Further, since our center is a tertiary care endocrine surgery referral center, selection bias may explain why our control group of infiltrative classical PTC had a somewhat worse outcome compared to the literature.[30,31] If true, this bias would underestimate the aggressiveness of focal tall cell change compared to controls.

We did not perform molecular profiling of tumor subgroups. While tall cell variants of PTC are frequently associated with *BRAFV600E* mutations, data from the Cancer Genome Atlas showed that these tumors are also enriched in synchronous *TERT*-promoter mutations, somatic copy number alterations and gain of 1q (*SCNA-low-1q amp*) as well as a distinct epigenetic signature including *miR-21* expression.[9,27] Future studies will employ genetic testing which may allow clinicians to have indications on aggressive tumors possibly within a preoperative fine needle aspiration.

Conclusions

As treatment of thyroid cancer becomes less aggressive and more targeted to higher risk patients, selecting those in low and higher risk categories is imperative to minimize recurrence and optimize quality of life. Patients with PTCs displaying focal tall cell change without other intermediate or high-risk characteristics are currently classified as low-risk. The five-year recurrence rate of 23.7% in our study indicate that patients with focal tall cell change have a risk association which is more consistent with tall cell variant PTCs than classical variant PTC. Further, those patients with greater than 10% tall cell composition of PTC had recurrence rates in the range of 30% compared to 3% for those with less than 10% components. Our data suggest a potential re-classification of low-risk PTC with at least 10% composition of tall cells.

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CHAPTER 9

Differences in long-term quality of life between hemithyroidectomy and total thyroidectomy in patients treated for low-risk differentiated thyroid carcinoma

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Abstract

Background

The long-term health-related quality of life (HRQoL) implications of treating low-risk differentiated thyroid cancer (DTC) with total thyroidectomy (TT) or hemithyroidectomy (HT) is important to patients, but remains poorly understood.

Methods

Using a cross-sectional mailed survey, we compared long-term HRQoL in low-risk DTC survivors treated with HT to those treated with TT between 2005-2016 at a university hospital. EORTC QLQ-C30, QLQ-THY34, and the Assessment of Survivor Concerns (ASC) questionnaires were used. Our primary outcome was the global scale of quality of life. Exploratory outcomes included differences among other HRQoL items after correction for potential confounders in the multivariable regression analyses.

Results

The response rate was 51.0% (270/529) of which 59 patients (21.9%) were treated with HT. Main outcome score global quality of life did not differ between groups (HT-76.9 vs TT-77.7, p=0.450). Exploratory analyses showed HT to be associated with more worry about recurrence on the ASC questionnaire (HT-2.4 vs TT-2.1, p=0.021).

Conclusions

Long-term quality of life was not significantly different between low-risk DTC patients treated with TT compared to HT. In secondary analyses, worry about recurrence appeared to be higher in individuals treated with HT. These data highlight previously unreported impact of surgical regimen to the HRQoL for low-risk DTC patients.

Introduction

Health-related quality of life (HRQoL) is a major concern for patients with differentiated thyroid cancer (DTC) given the excellent prognosis of this disease. In comparison to the general population, HRQoL deficiencies have been found in DTC patients in areas such as insomnia, fatigue, and limitations of daily functioning.[1,2] HRQoL parameters may continue to be negatively impacted for up to twenty years after curative treatment.[3] Furthermore, the quality of life of those treated for DTC has been reported to be similar or worse than the quality of life of survivors of cancers with poorer prognoses.[4] Given the high long-term survival rates and rising incidence of DTC, additional focus must be directed towards strategies for improving quality of life.[5] The recent American Thyroid Association Management Guidelines for Differentiated Thyroid Cancer (ATA guidelines) highlight the importance of integrating long-term HRQoL outcomes into the treatment decision-making process of physicians.[6] The impaired HRQoL of this population may be rooted in the classic treatments for thyroid cancer, such as thyroid hormone replacement, radioactive iodine remnant ablation (RAI) and surgical complications, negatively impacting psychological well-being and social functioning.[2,7] The ATA guidelines recommend a hemithyroidectomy (HT) as an alternative treatment to a total thyroidectomy (TT) and RAI in low-risk DTC patients.[6] This new recommendation stems from findings, which have shown no benefit of a TT and RAI over a HT in regards to the prevention of disease recurrence and associated mortality.[8,9] One possible strategy for improving HRQoL in patients with DTC may be the reduction in the extent of surgical treatment. A recent retrospective review of patients undergoing treatment for thyroid cancer in Australia, suggested HT to be less detrimental compared to TT with respect to HRQoL in the immediate postoperative period.[10] Although research focusing on long-term HRQoL is mostly absent from the literature, one may hypothesize that less aggressive surgery may lead to long-term improvement in HRQOL.

We sought to determine differences in long-term HRQoL of low-risk DTC patients who had previously undergone HT to those treated with TT by using both validated questionnaires and a new thyroid cancer-specific HRQoL questionnaire.

Methods

Study design and eligibility criteria

A cross-sectional, self-administered survey of thyroid cancer patients was performed in parallel with a retrospective chart review. The targeted population consisted of a consecutive cohort of adults treated for DTC with ATA low-risk of recurrence between January 1, 2005 and June 30, 2016 at University Health Network in Toronto, Canada. The patients were

identified from our institutional database and electronic medical records were reviewed for eligibility. ATA low-risk of recurrence was defined as DTC ≤4 cm, without vascular invasion, extrathyroidal extension (ETE), gross positive resection margins, aggressive histologic variants (e.g. tall cell, columnar cell, hobnail cell variants of papillary thyroid carcinoma), or distant metastasis.[6] Patients with benign indications for surgery with incidentally found papillary microcarcinoma and otherwise benign pathology were excluded. Preoperative diagnosis was based on fine needle aspiration conclusion divided into non-diagnostic results, preoperative presumed benign (Bethesda II), indeterminate (Bethesda III-V), or malignant (Bethesda VI). The survey package and instructions were written in English and mailed to eligible patients in September of 2017, with a first reminder to non-responders three weeks later and a second reminder after address verification via primary care physicians. A self-addressed, postage-paid envelope was provided for return of the survey, and patient consent was implied by return of the completed questionnaire. The participants were not reimbursed for their participation. The study was approved by the University Health Network Research Ethics Board.

Questionnaires description

The survey package included a coversheet explaining the study and the following components: the European Organisation for Research and Treatment of Cancer Quality of Life core Questionnaire version 3.0 (EORTC QLQ-C30); the supplementary Thyroid Cancer specific questionnaire module version 2.0 (EORTC QLQ-THY34); the Assessment of Survivor Concerns (ASC) questionnaire; and self-reported disease related questions (last physician visit; self-reported disease status; active comorbidities; current use of thyroid hormone replacement medication; or calcitriol, a surrogate for hypoparathyrodism). The permission of developers was obtained for use of questionnaires where appropriate and all questionnaires were scored as per the developers' instructions.

EORTC QLQ-C30 version 3.0

This is a widely used and validated HRQoL questionnaire to evaluate quality of life in oncology patients, including thyroid cancer patients.[11,12] This questionnaire incorporates a global quality of life scale, five functional scales (physical, role, cognitive, emotional, and social), three symptom scales (fatigue, pain, and nausea/vomiting), and a number of single items assessing additional symptoms commonly reported by cancer patients (dyspnoea, loss of appetite, insomnia, constipation and diarrhoea) and perceived financial impact of the disease. The time frame of the questions is the previous week, and each item is scored on a four-point response scale ranging from 1, 'not at all' to 4, 'very much,' with the exception of the global quality of life scale, which is scored on a seven- point modified linear analogue scale ranging from 1, 'very poor' to 7, 'excellent'. After linear transformation, all scales and single item

measures range in score from 0–100, with 100 reflecting the best score possible for functioning scales and the worst score for symptom scales. The primary outcome of this study was chosen to be the global scale of quality of life of the EORTC QLQ-C30 questionnaire. For this scale, 10-15 points mean difference has been previously reported as a medium clinically relevant effect.[13]

EORTC QLQ-THY34 version 2.0

The Thyroid Cancer Module is a supplementary questionnaire module employed in conjunction with the EORTC QLQ-C30 for the evaluation of HRQoL in thyroid cancer patients. Thyroid cancer related HRQoL items are combined in the following scales: discomfort in the head and neck (DI), fatigue (FA), fear (FE), hair problems (HA), restlessness (RE), social support (SO), swallowing (SW), worry about important others (WO), tingling or numbness (TI), and voice concerns (VO). Single item scales include altered body image (BI), cramps (CR), dry mouth (DM), altered temperature tolerance (TO), impact on job or education (JE), joint pain (JP), and shoulder function problems (SH). The time frame of the questions is the previous week, and each item is scored on a four-point response scale ranging from 1, 'not at all' to 4, 'very much'. Following the EORTC QLQ-THY34 guidelines, raw scores were combined and transformed into abovementioned scales with standardized scores ranging from 0 to 100, with 100 presenting worst possible score for symptom scales.[14]

Assessment of Survivor Concerns (ASC)

ASC is a questionnaire to evaluate cancer-related worry that has been previously used in thyroid cancer survivors.[15,16] This questionnaire includes three items that focused on the construct of cancer worry (cancer worry subscale), specifically worries about the following: diagnostic tests, another type of cancer, or cancer coming back. The ASC also includes two items that focused on health worry (health worry Subscale), specifically addressing worries about dying and personal health. An item regarding child's health worry was removed as per the developers' recommendations. ASC questions are scored on a Likert Scale of agreement, with responses for individual items ranging from 1 (least worry) to 4 (most worry). Results for cancer worry and health worry subscales are calculated by summing the scores of all questions in their respective categories. Similarly, the overall ASC score is calculated by summing the results of all questions. Aside from the validated subsets, we included single-items of the ASC in the analysis.

Data collection and entry

Two investigators (PB, CG) conducted retrospective chart review to collect demographic, clinical, and pathologic data. Data collected from the chart review and questionnaire data was entered in an Excel spreadsheet. Duplicate entry of a random sample (ten percent) was

checked for accuracy by a third study member (RH). Incomplete questionnaires were handled as per the developers' recommendations.[12,17]

Statistical analyses

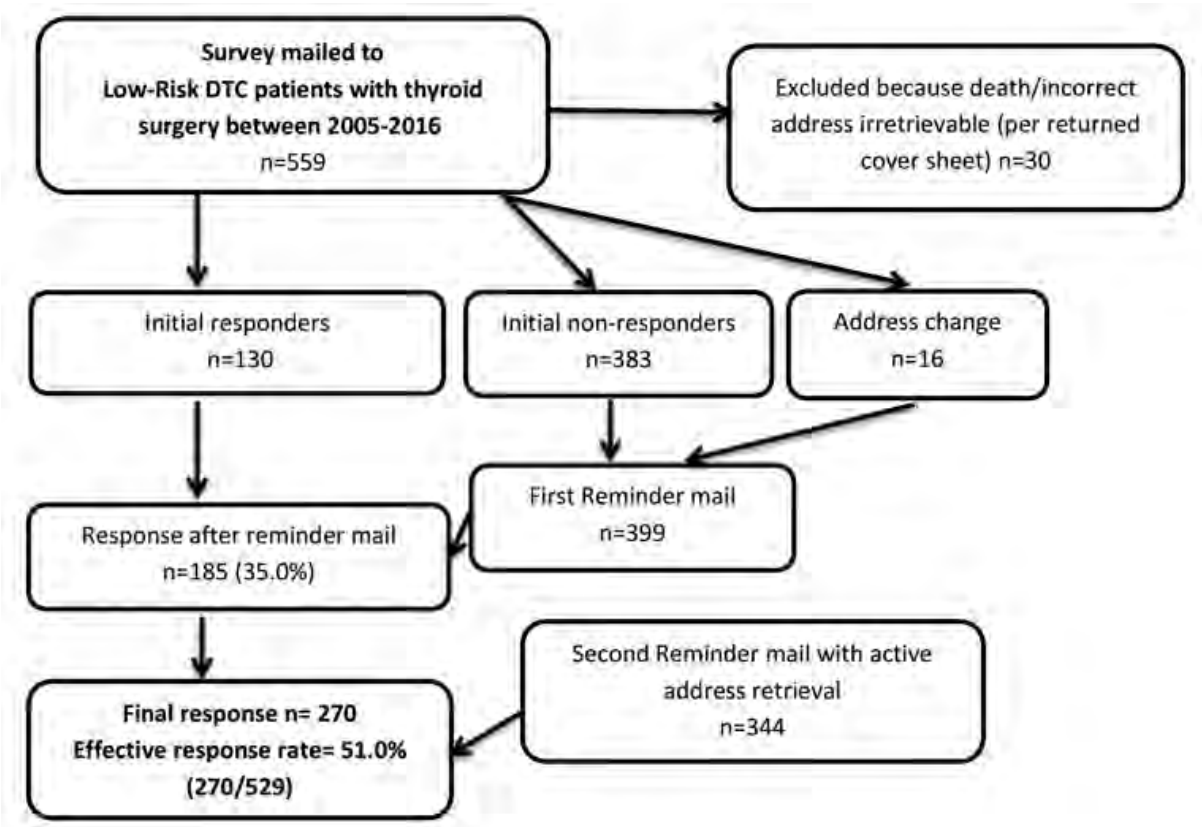
Descriptive demographic and clinic data were summarized according to extent of thyroidectomy. Univariate comparisons according to surgical treatment group were conducted using the Mann whitney U test for non parametric data and the Students' t-test for parametric data. Potential demographic and clinicopathologic confounders were identified by univariate analysis for each HRQoL domain that differed between HT and TT, using a criterion of $p<0.10$. To understand the adjusted influence of surgical strategy on HRQoL domains a multivariable regression analysis was performed with the covariates that were identified as potential confounders. To have a robust model we performed backward stepwise selection procedure of the covariates starting with removal of variables with the highest non-significant p-value, until only true confounders in the model ($p\leq0.05$) remained. Bootstrapping with 1000 times sampling was performed given the non-parametric nature of the data. Since other studies have shown that quality of life may continue to improve years after cancer diagnosis, we analysed cancer survivorship between 1-5 years after initial surgery as "early", and those ≥ 5 years after initial surgery as "late".[2,15] Statistical analyses were performed using SPSS version 24 (IBM Corporation, Armonk, NY, USA).

Results

Characteristics of the study population

The survey was mailed to 559 individuals. Of these individuals, 30 were excluded because of either an incorrect, irretrievable address, or because the patient had died from causes unrelated to thyroid cancer. The effective response rate was 51.0% (270/529), as shown in figure 1. Of the respondents, 59 (21.9%) underwent a HT and 211 (78.1%) a TT as definitive treatment. Table 1 demonstrates the demographic characteristics and differences between the HT and TT respondents. Thirty-five (59.3%) of the patients treated with a HT and 57 (27.0%, $p<0.001$) of the patients treated with a TT were early survivors, meaning that they completed the survey 1-5 years after initial surgery. The TT group consisted of 69 (32.7%) patients that underwent a two-staged thyroidectomy. Of respondents with a history of a TT 43.6% received RAI as part of initial treatment. More respondents that underwent a HT had T1a tumors (HT-62.7% vs TT-24.6%, $p=0.001$). Compared to TT, a fewer but still a significant number of patients received chronic thyroxine supplementation after a HT (HT-66.0% vs TT-100%, $p<0.001$). Long-term calcitriol supplementation, likely indicating permanent hypoparathyroidism, was not seen after HT, but was seen in 6.2% of participants after a TT

Figure 1. *Study flow*



(p=0.001). Recurrence rates were 3.4% (2/59) in the HT group and 1.9% (4/211) in the TT group. All underwent additional surgery and did not have evidence of disease at the time of the survey.

Health-related Quality of Life differences between HT and TT

HRQoL scores for HT and TT groups are shown in Table 2. The number of missing responses to single questions ranged from 0.0 to 2.6%. The primary outcome, the global quality of life score of the EORTC QLQ-C30, did not differ between HT and TT groups [mean 76.9 (SD 16.2) and 77.7 (SD 19.1) respectively, p= 0.450]. Sub analysis within the TT group showed no difference between patients who underwent a one-stage thyroidectomy or two-stage thyroidectomy [mean 77.1 (SD 19.3) and 78.9 (18.6) respectively, p=0.537]. The EORTC QLQ-C30 domains that showed significant or trends towards significant differences related to surgical strategy were cognitive functioning (HT-75.6 vs TT-82.1, p=0.022) and social functioning (HT-84.2 vs TT-90.0, p=0.094). In the EORTC QLQ-THY34 questionnaire trends were seen for the domains altered body image (HT-16.4 vs TT-10.9, p=0.078), fear (HT-21.3 vs TT-16.1, p=0.062), and impact on job (HT-18.1 vs TT-7.4, p=0.098). For the ASC questionnaire, worry about cancer recurrence significantly differed between HT (mean 2.4,

Table 1. *Demographic statistics of study participants*

Characteristics	**Of respondents with hemithyroidectomy** *n= 59*	**Of respondents with total thyroidectomy** *n= 211*	**p-value**
Female sex	50 (84.7)	178 (84.4)	0.942
Age			0.259
≤30 y	6 (10.2)	8 (3.8)	
31-49 y	22 (37.3)	91 (43.1)	
50-65 y	24 (40.7)	85 (40.3)	
>65 y	7 (11.9)	27 (12.8)	
History of neck radiation	2 (3.4)	12 (5.7)	0.294
Family history of thyroid cancer	3 (5.1)	15 (7.1)	0.582
Income <90,000CAD/y	24 (40.7)	38 (18.4)	**<0.001**
Time since first surgery for thyroid cancer			**<0.001**
1-2 y	10 (16.9)	5 (2.4)	
2-5 y	25 (42.4)	52 (24.6)	
5-10 y	15 (25.4)	102 (48.3)	
>10 y	9 (15.3)	52 (24.6)	
Preoperative diagnosis			0.651
Non diagnostic	4 (6.8)	13 (6.2)	
Presumed benign	5 (8.5)	28 (13.3)	
Indeterminate	23 (39.0)	89 (42.2)	
Malignant	27 (45.8)	81 (38.4)	
pT-stage			**<0.001**
Ia	37 (62.7)	52 (24.6)	
Ib	15 (25.4)	82 (38.9)	
II	7 (11.9)	77 (36.5)	
Histologic subtype			0.124
Papillary thyroid carcinoma	28 (47.5)	71 (33.6	
Follicular thyroid carcinoma	0 (0.0)	2 (0.9)	
Follicular variant of PTC	31 (52.5)	138 (65.4)	
Thyroiditis present in resection specimen	25 (42.4)	96 (45.5)	0.670
Central neck dissection/node sampling	5 (8.5)	28 (13.3)	0.336
Admission >2 days	1 (1.7)	47 (22.3)	**<0.001**
RAI	0 (0.0)	92 (43.6)	**<0.001**
Recurrent disease	2 (3.4)	4 (1.9)	0.491
On thyroxine replacement medication	33 (55.9)	199 (94.3)	**<0.001**
On calcitriol supplementation	0 (0.0)	13 (6.2)	**0.051**
Persistent laryngeal nerve damage	0 (0.0)	0 (0.0)	-
Self-reported active comorbities at time of survey			
Other cancer	1 (1.7)	15 (7.2)	0.117
Cardiovascular	1 (1.7)	15 (7.2)	0.117
Pulmonary	2 (3.4)	14 (6.7)	0.344
Mental health	8 (13.6)	26 (12.5)	0.829

Presented as number (%); p-value based on chi-square test; y year; CAD Canadian dollar; RAI Radioactive iodine remnant ablation

SD 1.0, answered range 1-4) and TT (mean 2.1, SD 1.0, answered range 1-4, p=0.021). Trends were seen for the item worry about their health (HT-2.6 vs TT-2.3, p=0.089), the cancer worry subscale score (HT-7.2 vs TT-6.5, p=0.062), and the ASC overall score (HT-11.7 vs TT-10.6, p=0.069).

Potential confounders

Potential demographic and clinicopathologic confounders of the relationship between surgical strategy and HRQoL domains were identified when p<0.10 in the univariate analysis as shown in table 3. Potential confounders included for HRQoL domain 'cognitive function' tumor stage, and time since first surgery; for 'social functioning'- RAI; for 'body image altered'- calcitriol supplementation at time of survey, RAI and time since first surgery; for 'fear'- time since first surgery; for 'impact on job'- RAI and time since first surgery; for 'worry about recurrence'- time since first surgery; for ASC Health Worry subscale- days of hospital admission at initial treatment; and for ASC Overall Score- days of hospital admission at initial treatment. After backward stepwise selection procedure of these potential confounders and bootstrapping method the final multivariable model showed that the ASC single item score regarding 'worry about recurrence' was significantly influenced by the surgerical strategy (p=0.021). For survivors who underwent a HT, the score for 'worry about recurrence' was estimated to be 0.3 points higher (95%CI 0.1-0.6) than survivors who underwent a TT, on the 1-5 likert-scale with 5 being the most worry. The extent of surgery did not remain significantly associated with other HRQoL domains of this survey. The following covariates remained as confounders in the final multivariable regression model: 1) supplementation of calcitriol at time of the survey for the EORTC QLQ-C30 domain 'body image altered' [beta coefficient -10.9, (95% CI -14.6, -7.5), p=0.001] and 2) hospital admission of >2 days for the ASC subscale Health Worry [beta coefficient -0.3, (95% CI -0.06, -0.01), p=0.048].

Table 2. *HRQoL domains: mean differences between hemithyroidectomy and total thyroidectomy*

		Hemi thyroidectomy n=59	Total thyroidectomy n=211	p-value
EORTC QLQ-C30 (range 0-100)	Global scale for quality of life	76.9 (16.2)	77.7 (19.1)	0.450
	Physical functioning	91.6 (11.6)	91.7 (13.4)	0.630
	Role functioning	88.5 (19.3)	91.1 (17.6)	0.341
	Emotional functioning	73.6 (24.7)	77.4 (21.9)	0.279
	Cognitive functioning	**75.6 (23.4)**	**82.1 (21.7)**	**0.022**
	Social functioning	**84.2 (26.6)**	**90.0 (21.6)**	**0.094**
	Fatigue	27.0 (24.8)	22.8 (21.5)	0.333
	Nausea/vomiting	3.2 (7.9)	4.4 (12.0)	0.704
	Pain	10.5 (18.0)	12.5 (20.1)	0.493
	Dyspnoe	9.2 (20.5)	9.5 (19.2)	0.729
	Sleep disturbances	37.4 (35.4)	29.0 (29.4)	0.139
	Appetite loss	6.3 (19.2)	5.8 (16.4)	0.817
	Constipation	14.3 (24.5)	13.7 (25.2)	0.795
	Diarrhea	7.6 (17.8)	7.9 (16.3)	0.653
	Financial difficulties	12.1 (28.4)	7.3 (20.1)	0.333
EORTC THY34 (range 0-100)	Fatigue	28.2 (26.4)	23.2 (22.4)	0.246
	Discomfort neck	11.5 (16.9)	8.7 (13.5)	0.230
	Voice concerns	9.0 (15.9)	9.4 (17.0)	0.920
	Hair problems	16.1 (26.3)	18.6 (28.3)	0.648
	Swallowing	5.9 (13.8)	7.4 (17.1)	0.715
	Dry mouth	20.3 (29.7)	20.9 (27.7)	0.725
	Temperature intolerance	31.1 (33.3)	24.9 (28.9)	0.241
	Body image altered	**16.4 (26.5)**	**10.9 (22.1)**	**0.078**
	Restlessness	18.9 (20.2)	17.8 (19.3)	0.765
	Shoulder functioning	6.2 (15.8)	4.5 (13.9)	0.368
	Fear	**21.3 (20.3)**	**16.1 (18.5)**	**0.062**
	Joint pain	26.6 (27.5)	30.8 (30.1)	0.365
	Tingling/numbness	12.1 (18.8)	12.3 (16.7)	0.665
	Cramps	22.0 (28.1)	25.8 (27.8)	0.277
	Worry about important others	25.7 (27.2)	17.8 (21.4)	0.169
	Impact on job	**18.1 (21.7)**	**7.4 (21.0)**	**0.098**
	Social support	**67.0 (29.9)**	**73.7 (29.7)**	**0.076**
ASC[a]	Cancer Worry (3-12)	**7.2 (2.6)**	**6.5 (2.5)**	**0.062**
	* future tests (1-4)	2.2 (0.9)	2.0 (0.9)	0.201
	* new cancer (1-4)	2.6 (1.0)	2.4 (0.9)	0.234
	* recurrence (1-4)	**2.4 (1.0)**	**2.1 (1.0)**	**0.021**
	General Health Worry (2-8)	4.5 (1.7)	4.1 (1.6)	0.151
	* death (1-4)	1.9 (0.9)	1.9 (0.9)	0.589
	* health (1-4)	**2.6 (0.9)**	**2.3 (0.8)**	**0.089**
	Overall (5-20)	**11.7 (4.0)**	**10.6 (3.8)**	**0.069**

Data presented as mean (SD); bold when p<0.10. Missing values per domain scale ranged between 0-7. [a] *Range of each domain scale is presented between brackets behind its name.*

Table 3. *Univariate analysis of associations between clinicopathologic characteristics and the outcomes of HRQoL domains*

	EORTC-QLQ-C30		EORTC-QLQ-THY34				ASC			
	Cognitive functioning	**Social functioning**	**Body image altered**	**Fear**	**Impact on job**	**Social support**	**Cancer worry**	**Worry about recurrence**	**Health worry**	**Overall**
Income > 90,000CAD[a]	4.1; p=.207	2.5 p=.569	-2.4 p=.633	-1.0 p=.593	-1.5 p=.389	5.1 p=.349	0.2 p=.559	0.1 p=.696	0.1 p=.440	0.4 p=.443
Admission >2 days[b]	5.8 p=.173	4.4 p=.168	-0.4 p=.816	0.3 p=.699	-0.9 p=.600	4.2 p=.364	-0.6 p=.136	-0.2 p=.129	-0.3 **p=.020**	-1.1 **p=.070**
RAI [c]	5.2 p=.114	5.2 **p=.075**	-4.6 **p=.013**	-2.5 p=.275	-5.2 **p=.015**	5.0 p=.228	-0.3 p=.345	-0.1 p=.269	-0.2 **p=.025**	-0.7 p=.145
T-stage Ib/II [d]	7.0 **p=.054**	5.6 p=.196	-0.4 p=.303	0.3 p=.847	-2.7 p=.530	5.4 p=.128	-0.1 p=.778	-0.1 p=.657	-0.2 **p=.042**	-0.4 p=.425
<5 year time since first surgery[e]	-5.7 **p=.009**	-4.1 p=.169	6.9 **p=.003**	5.1 **p=.024**	7.2 **p=.011**	-3.7 p=.326	0.4 p=.226	0.2 **p=.068**	0.1 p=.211	0.6 p=.205
Thyroxine suppletion[f]	4.1 p=.285	6.1 p=.253	-0.3 p=.445	-3.3 p=.269	-5.7 p=.681	4.5 p=.246	-0.5 p=.425	-0.1 p=.633	-0.2 p=.354	-0.7 p=.472
Calcitriol supplementation[g]	5.5 p=.281	6.4 p=.586	-12.7 **p=.029**	-4.6 p=.573	-9.0 p=.116	9.4 p=.411	0.2 p=.772	0.1 p=.975	-0.3 p=.110	-0.2 p=.859

Data are expressed as difference between mean scores of each group, p-value of mann whitney U test (for EORTC QLQ-C30 and EORTC QLQ-THY34 domains); Students' t-test used with unequal variances assumed (for ASC domains); bold when p<0.10
CAD Canadian dollars; RAI Radioactive iodine remnant ablation; y years; FU follow-up
[a]compared to ≤ 90,000 CAD yearly income; [b]compared to ≤2 days of postoperative admission; [c]compared to no RAI; [d]compared to T1a stage; [e]compared to ≥5 year time since first surgery; [f]compared to no self reported thyroid replacement therapy; [g]compared to no self-reported calcitriol supplementation therapy

Discussion

From this cross-sectional survey, we found that the type of surgery performed, namely HT or TT, for patients with low-risk DTC does not seem to influence general quality of life in the long-term. In an exploratory analysis of a wide range of HRQoL domains, single item worry about recurrence appeared to be significantly higher for those undergoing HT.

Quality of life is an especially important outcome measure of thyroid cancer treatment since the number of thyroid cancer survivors increases and the long-term prognosis is excellent.[18] From an oncological standpoint, HT and TT are both viable treatment options for low-risk differentiated thyroid cancer. Given the results of this study, from the perspective of long-term global quality of life, both of these treatment options seem acceptable.

Although other studies have reviewed quality of life differences between HT and TT, our study is among the first with extended follow-up in a population of low-risk DTC patients.[10,19,20] Nickel *et al.* reported better HRQoL outcomes in patients treated with HT, though median time between diagnosis and interview was less than six months and the study population was not limited to those with ATA low-risk DTC.[10] Similarly, a Korean study with shorter follow-up after thyroid cancer treatment, found that the global quality of life scores of the EORTC QLQ-C30 questionnaire were better for those who were treated with HT.[19] Of note, the compared baseline global quality of life score for their patients was significantly lower (mean 57.9) than in our population (mean 77.5). Possible explanations for this difference may be that the Korean study population contained a portion of higher risk disease and that their patients were surveyed closer to their date of surgery. With regards to our primary outcome, the global quality of life score of our study was similar to the scores of a large Dutch cohort of long-term thyroid cancer survivors.[2] Unfortunately, this cohort did not report HRQoL outcomes by surgical intervention.

As seen in this and other similar studies, thyroid cancer survivors may carry an increased worry about cancer recurrence which persists through long-term follow-up.[16] In a study conducted by Hedman *et al.* only 7% of thyroid cancer patients had disease recurrence, but as many as 48% of the patients experienced concerns about recurrence and had significantly affected HRQoL outcomes.[21] This was confirmed by a Canadian study on worry among thyroid cancer survivors.[16] Our explorative results suggest that there is a relationship between the extent of surgery performed in thyroid cancer patients and future concern of recurrence. This phenomenon has been previously suggested, however quantitative data comparing different surgical strategies is lacking. Most of the research that has been conducted on the association between extent of treatment and the worry about disease recurrence has been done in the field of early stage breast cancer. For breast carcinoma, although there is support for the relationship between many patient factors and fear of recurrence, the association with less extensive treatment, such as breast conserving surgery, has not been universally supported

by evidence.[22,23] International surveys of thyroid cancer survivors have indicated that the care of almost half of the respondents could be improved and worry reduced by introducing patients to a patient support group or by referring them to a psychologist.[24,25]

A strength of this study was the use of a relatively homogenous cohort from a high-volume endocrine surgery center with a substantial portion of patients having HT. In addition, HT had been employed at this center for low-risk DTC prior to the release of the most recent ATA guidelines which has allowed for the long-term follow-up of patients after a HT. Another strength of this study design is the use of a thyroid cancer specific questionnaire that helps to standardize language and provides a structure for further discussion in this area of thyroid cancer research.

The limitations of this study include the moderate response rate of 51.0%, and the potential bias of the study population, given that individuals with more HRQoL complaints might have been more likely to respond to the survey. A possible reason for the low response rate that we observed may lie in the nature of mailing a survey to patients after a long period of follow-up for a low-risk disease without providing any personal benefit or compensation for their participation. The EORTC QLQ-C30 is commonly used to evaluate HRQoL in various types of cancer, but because of a lack in validation for a low-risk DTC population as well as a lack in specific reference values, our conclusions should be interpreted with caution. In comparison to reference data from a validated group of all head and neck cancers, which included a small number of thyroid cancers, the global scale for quality of life from the EORTC QLQ-C30 had lower values (mean 64.1, SD 22.7) than our study population (mean 77.5, SD 18.5). Our study size was adequate for medium sized effects although may have been underpowered for smaller effects with less clinical relevance.

In summary, in this cross-sectional patient survey, individuals with low-risk DTC had similar scores for HRQoL whether they had previously been treated with a TT or a HT. In our hypothesis-generating secondary analyses there appeared to be more worry about recurrence in individuals treated with HT compared to TT. While further independent confirmation is required, these data highlight previously unreported impact of surgical regimen to the long-term quality of life for low-risk DTC patients.

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CHAPTER 10

Conclusions per chapter

Chapter 2
When using criteria adopted from the 2015 ATA guidelines over a quarter of patients from a Dutch retrospective cohort treated for DTC would have been classified as low-risk and therefore eligible for hemithyroidectomy as viable alternative for the total thyroidectomy they actually underwent. However, standardisation and high quality pre- and postoperative diagnostics are required for responsible implementation of this new guideline in Dutch healthcare.

Chapter 3
Based on a longitudinal population study within the closed health-care system of Ontario, Canada, the cumulative risk of developing thyroid cancer among patients with initially negative thyroid biopsy results was 7.5% after 24 years. Because cumulative risk of thyroid cancer in these patients is higher than the baseline lifetime risk of the population, further large risk stratification studies incorporating standard ultrasound biopsy data are needed to identify those requiring long-term follow-up.

Chapter 4
The prevalence of thyroid incidentalomas in patients with MEN1 is not higher compared with a non-MEN1 population. Thyroid incidentalomas in patients with MEN1 show different tumorigenesis than MEN1 related tumors and therefore should be treated as thyroid incidentalomas found in non-MEN1 patients.

Chapter 5
The incidence of NIFTP among patients with PTC in a large cohort of a tertiary care academic endocrine surgery center is lower than previously reported. Furthermore, evidence of malignant behaviour was seen in a significant number of NIFTP patients. Although de-escalation of aggressive treatment for low-risk thyroid cancers is warranted, NIFTP behaves as a low-risk thyroid cancer rather than a benign entity.

Chapter 6
The avoidance of the term ‘cancer’ for an entity with malignant potential may result in undertreatment or inappropriate lack of surveillance of patients with these tumors. Until future research can clarify the current controversy in the literature, clinicians should continue to follow and counsel patients about NIFTP as low-risk malignant entity.

Chapter 7
In a prospective cohort of patients with clinically low-risk DTC, a standard preoperative CT of the neck changed surgical management in a substantial number of patients with clinically

significant nodal disease not detected by cervical ultrasonography. This suggests that in certain practice settings adding CT to the preoperative staging may be favourable to detect nodal metastasis.

Chapter 8

Patients with PTC with focal tall cell change (≥10% and <30% cell change in the entire tumor volume) have worse prognosis than those without tall cells and comparable outcomes to those with tall cell variant PTCs (≥30% cell change). Our data indicate that thyroid cancer management guidelines should consider PTCs with focal tall cell change outside of the low-risk classification.

Chapter 9

In this cross-sectional patient survey, long-term HRQoL was not significantly different between low-risk DTC patients treated with total thyroidectomy compared to those treated with a hemithyroidectomy. In our hypothesis-generating secondary analyses there appeared to be more worry about recurrence in individuals treated with hemithyroidectomy compared to total thyroidectomy. While further independent confirmation is required, these data highlight previously unreported impact of surgical regimen to the long-term HRQoL for low-risk DTC patients.

CHAPTER 11

General discussion and future perspectives

Initiating an optimal strategy for the treatment of patients with differentiated thyroid cancer (DTC) relies on understanding which of our patients are best treated with the maximisation of treatment, and which patients would have an excellent prognosis with more conservative therapies. This chapter provides a general discussion using evidence-based recommendations from this booklet which will outline management for patients with suspected or diagnosed DTC and directions for future research.

A paradigm shift

Worldwide, the incidence of thyroid cancer has steadily increased over the past decades.[1] This is mainly due to the rise of low-risk DTC which has nearly complete 20-year survival rates.[2] The number and attitude of physicians toward cancer care and the use of new diagnostics and screening practices have been shown to correlate with the probability of detecting thyroid diseases and subsequently with the incidence of DTC. Not surprisingly, treatment patterns differ substantially even across the richest countries.[3–5] In several high-income countries diagnostic changes such as ultrasound utilisation, account for >60% of cases diagnosed in the last decade.[6] An example of this phenomenon is the Republic of Korea. Introduction of thyroid cancer screening with ultrasonography in 1999 led to a 15-fold increase of thyroid cancer over one decade.[7] Overdiagnosis in the setting of thyroid cancer refers to the detection of indolent or very slow-growing cancers that are unlikely to cause symptoms or death.[8] Finding these cancers is detrimental when it leads to overtreatment where the risks of harm or complications from surgery and radioactive iodine (RAI) ablation therapy outweigh the survival benefit. Historically, treatment with a total thyroidectomy, postoperative RAI ablation and thyroid suppression was a nearly universal paradigm for DTC.[9] The identification of the overdiagnosis and overtreatment problem has shifted the professional ethos towards an individualized less-is-more treatment philosophy, reducing side-effects and complications risks of treatments. Common aims of thyroid cancer guidelines are to define specialist referral indications, improve overall and disease-free survival, reduce complications, and enhance quality of life of patients.[10,11] A variation in environments, risk factors, and epidemiology, public awareness, screening practices, and health care infrastructure, may explain differences between international guidelines.[12] Despite those differences, common trends among most guidelines include avoidance of overtreatment, risk stratification, and shared decision-making.[13–16] In **chapter 2** we illustrated the hypothetical influence of adapting more progressive international guidelines on the surgical management of DTC in the Dutch setting. The American Thyroid Association (ATA) guidelines are heavily endorsed by specialists groups worldwide, and were updated most recently in 2015.[14] The consideration of a hemithyroidectomy as a reasonable approach for DTC measuring

1–4 cm is fundamentally different from previous guidelines that advised a total thyroidectomy. This recommendation is based on evidence showing that most patients are adequately treated with this more conservative approach and salvage surgery is an effective treatment option for the few patients with future locoregional recurrence.[14] Moreover, the indications for RAI therapy have narrowed, as few patients are thought to benefit from it.[17] Also active surveillance is acknowledged as treatment option in selected cases of DTC. This is based on work from the Japanese who have been the leaders in the global movement towards treatment de-escalation. Their landmark publications, led by Prof Miyauchi at the Kuma Clinic, describe safe long-term surveillance practices for DTC <1cm.[18] The 2010 Japanese guidelines already suggested hemithyroidectomy over total thyroidectomy with RAI for the majority of patients with DTC. This was based on the presumption that total thyroidectomy would not improve survival in low-risk patients, small contralateral lesions could be followed by ultrasound or were otherwise clinically insignificant, neck recurrences could be cured by reoperation, and total thyroidectomy had higher complication rates and worse quality of life.[19] Underlying cultural stigma of radiophobia due to the national nuclear disasters and strict regulations regarding RAI therapy was the likely impetus for these trends. Moreover, Japanese evidence shows that patients do not likely benefit from RAI in low-risk disease and therefore should be treated with less aggressive surgery.[20] Interestingly, European guidelines are less progressive compared to their American and Japanese counterparts. Although, British, German, Spanish and Dutch guidelines do agree on a hemithyroidectomy for low-risk PTC <1cm, there is a paucity of support for less than total thyroidectomy for low-risk PTC measuring 1-4cm.[15,16,21,22] For these patients, most countries in Europe currently recommend a total thyroidectomy except for the British Thyroid Association 2014 Guidelines that advices personalized decision-making.[15] There may be some explanations for differences in guidelines between countries, such as differences in case volumes and presentations of disease. In **chapter 2** we found that in the Dutch setting, 28% of patients treated for DTC with a total thyroidectomy, would be eligible for a hemithyroidectomy when applying the ATA guidelines. Therefore, a substantial number of future patients could potentially benefit from less aggressive surgical management, but when optimizing national guidelines different factors need to be taken into account. Outcomes of thyroid cancer patients has been shown to differ among high and low volume thyroid cancer centers.[23,24] This is clear both in the selection of patients for surgery as well as the surgical complication rates.[25,26] The former is dependent on good diagnostic tools such as ultrasound and pathology and the latter on the experience of the endocrine surgeon. Most published outcomes, especially those used in the 2015 ATA guidelines, are derived from high volume centers. In contrast the volume of malignant thyroid disease in Dutch health care facilities is relatively low, partly due to a comparatively lower incidence of DTC. The success of adopting ATA guidelines suggesting de-escalation of treatment paradigms involves the ability to identify aggressive disease. Standardisation of accurate identification techniques

and consensus on which patients fall into a low-risk category should be set on national level. Ultimately, agreement of guidelines across nations and professional organisations may provide better clinical recommendations and adherence to evidence-based quality of care for the increasing number of patients diagnosed with DTC.

Who to threat?

Only a 7-15% of thyroid nodules have malignant features on final pathology, and a subset are thought to be a normal variant representing a clinically insignificant disease reservoir.[27,28] Current guidelines select thyroid nodules for further diagnostic work up using fine needle aspiration cytology (FNAC) based on patient history, physical examination, biochemical markers and ultrasound characteristics.[14] If the clinician believes there is sufficient evidence to label the lesion as benign, still some patients are followed with ultrasounds and new FNACs indefinitely. To inform patients and clinicians on the follow-up of benign nodules, we describe in **chapter 3** the long-term malignancy risk of a presumed benign thyroid nodule. To diminish any loss to follow-up or selection bias we used the data of the entire population of Ontario, Canada. This region has a single-payer closed health care system with consolidated administrative databases derived from a legislated collection of clinical data that is over 95% complete for cancer diagnosis and procedures. We showed that the cumulative risk of developing thyroid cancer among patients with an initially negative thyroid biopsy followed up for 24 years was 7.5%. This is higher then the general population lifetime risk for thyroid cancer in the United States surveillance, epidemiology and end result (SEER) program of approximately 1.2%.[29] This confirms that patients with initial benign biopsies are a risk group with higher rates of thyroid malignancy in the future. The cumulative malignancy risk after a benign index biopsy in our population was also higher compared to other studies that evaluate outcome of patients with benign thyroid nodules, with recent studies showing a rate between 0.3% and 5%.[30,31] These studies, with more recent cohorts but substantially shorter follow-up, used a strict definition of benign nodules (Bethesda classification category II). This was not practical in our cohort as most patients had a thyroid biopsy before the Bethesda classification was widely implemented in 2009. What may explain the results of a higher rate of malignancy in this cohort is the idea that these patients are selected for more intensive follow-up. Considering that 38.3% of the patients had more than 1 biopsy and 16.3% had more that 2 biopsies the chance of finding a thyroid cancer is increased. Given data from autopsy studies as well as the microcarcinoma data from Japan, these thyroid cancers may not be clinically relevant.[18,27] To illustrate this point, the landmark study of Harach et al. showed occult PTC are found in up to 36% of autopsy specimens of healthy individuals and suggested that it may be a variant on ‘normal’ that never would have become clinically

apparent.[27] As the number of thyroid biopsies performed increased 4.1-fold between 1991-2010 in Ontario, Canada, our data does confirm the landscape of increased usage of diagnostics. To have further understanding in the malignancy risk in patients with initially benign thyroid nodules, future large administrative data studies should combine clinical information such as ultrasound characteristics of thyroid nodules, as well as surgical pathology excluding likely insignificant tumors, to improve selection of those nodules without malignant diagnosis that do need follow-up. Further, separating those with papillary microcarcinomas which may not be clinically relevant is important to determine which patients do develop clinically relevant thyroid cancer.

Considering a selection bias of groups of people who are more likely to undergo nodule investigation, the population of Multiple Endocrine Neoplasia type 1 (MEN1) may be a good example. MEN1 is caused by an inactivating germline mutation in the MEN1 gene, which encodes for the tumor suppressor protein menin.[32] It is characterized by the occurrence of different endocrine abnormalities including primary hyperparathyroidism. Lifelong screening starts at a young age and includes ultrasonography of the neck to visualize the parathyroids. Inevitably, the thyroid is seen and often, nodules are detected. Those patients, that already experience substantial uncertainty and anxiety due to their disease, are in need of clear advice regarding incidental findings in the thyroid and benefit from the avoidance of unnecessary medical interventions.[33] In **chapter 4**, we found no difference in prevalence of thyroid incidentalomas on a neck ultrasound in patients with MEN1 compared to a matched reference group without the germline mutation in the MEN1 gene. The presence of a positive nuclear menin stain in a subset of thyroid nodules from MEN1 patients, supports the epidemiologic findings and the hypothesis that the tumorigenesis of these thyroid incidentalomas is not MEN1 related. The results of this study may be useful to reassure MEN1 patients and inform physicians that once a thyroid incidentaloma is seen on cervical imaging they can be treated according to guidelines for thyroid nodules in the general population.[34] Hopefully this reduces uncertainty and overtreatment of benign thyroid lesions in MEN1 patients.

The increase in incidence of DTC is, in part, related to the diagnosis of a variant of PTC known as the follicular variant of PTC (FvPTC).[35] FvPTC is recognized as a tumor composed of neoplastic follicles rather than papillae, but with follicular cells showing nuclear features characteristic of PTC.[36] The encapsulated subtype of FvPTC (EFvPTC) is a challenging and controversial diagnosis, that lacks evidence of invasion beyond its capsule and rests exclusively on the findings of the nuclei. Under the premise that these tumors may not behave like cancer, specifically that they do not metastasize, Nikiforov et al. proposed that these indolent tumors were renamed ‘‘noninvasive follicular thyroid neoplasm with papillary-like nuclear features’’ or NIFTP, removing the word cancer from their description.[37] By doing so

many patients would no longer be considered to have cancer and may enjoy a significant reduction in the psychological burden, medical overtreatment and expense of care.[37] To rename a disease entity and reassure patients that they did not have cancer presumes the criteria will be rigid but also should be valid among centers and regions of the world. To verify this we described in **chapter 5** the amount of patients that would be renamed to NIFTP by reviewing a nine-year cohort of PTC cases and looked for signs of malignant behaviour in the follow-up. We found that only a 2.1% of PTC cases could be reclassified as NIFTP which was much lower than that published by the original description, and importantly, 6% of the cohort showed signs of invasive behaviour including both nodal and distant metastasis. A similar trend has been seen in a Korean cohort of patients which demonstrated a 3% rate of regional metastasis in NIFTP patients.[38] Explanations for the discrepancy between our work and that of Nikiforov et al. may be the low inter-observer agreement in patients with FvPTC and the lack of pathology practice guidelines addressing to the need of deeper and serial sections when dealing with a NIFTP.[39] To properly assess the criteria for NIFPT it requires examination of the complete tumor capsule which is, although diligently performed in our study, often not standard of practice. The practical implications of de-classification of these tumors are not inconsequential, since the approach may discourage follow-up and monitoring for recurrence or metastasis. Therefore caution is needed if renaming noninvasive EFvPTC as emphasized in the reply to a letter to the editor in **chapter 6**. Although we do encourage de-escalation of aggressive treatment of low-risk DTC, we believe that patients treated for NIFTP should stay in the follow-up protocol of very low-risk disease as they do have malignant potential.

Risk stratification

As most DTC has a low-risk of adverse outcomes, there is a possibility that thyroidologists fail to detect the small proportion of higher risk tumors which, if not treated adequately can cause recurrent disease or potentially death.[12] The 2015 ATA guidelines propose a three-tiered risk stratification system for DTC which is widely accepted.[14] Patients are categorized as having low-risk, intermediate-risk, or high-risk of recurrence based on an evidence-informed tool. Completeness of initial surgical resection is an important variable influencing prognosis regarding disease persistence or recurrence and important for accurate staging to guide additional therapies.[40] The use of computed tomography of the neck (CT) in preoperative staging of DTC is controversial, due to contradictory outcomes of studies comparing the performance of ultrasound of the neck (US) and CT.[41–43] The 2015 ATA guidelines advise to only perform a CT as adjunct to US in patients with clinical or ultrasound evidence of lymph node metastases or locally invasive tumors.[14] The guideline authors admit the inadequacy of

US in visualizing deep anatomic structures and the studies reliability on an experienced operator.[26,44] In **chapter 7** we looked the influence of adding a standard CT on the preoperative risk stratification and surgical plan in a prospective cohort of patients with clinical low-risk DTC. We showed that a standard preoperative CT changed surgical management in 22.5% of patients, leading to more extensive operations involving central and/or lateral neck dissections for clinically significant nodal disease. The risk of performing CT on all patients could lead to over-treatment given false positive or clinically insignificant lymph node metastasis. Although we did have 44.4% negative central neck dissections performed based on new CT findings, those all underwent a limited central neck dissection (also known as lymph node picking) based on mildly suspicious nodes seen on the CT, without post-operative complications. On the other hand 7 out of the 8 lateral neck dissections, performed based on CT findings, harboured macrometastatic disease. This finding may highlight the issue of ultrasound quality, especially outside tertiary care centers, however, this finding is often generalizable across the western world.[23,24,26,45] CT has other benefits such as reproducible results that can be reviewed remotely by a specialized thyroid radiologist and can be used for surgical mapping with detailed axial anatomic information that is familiar to most thyroid surgeons.[46] In our opinion, the study results of **chapter 7** may not provide an indication to include CT as part of the work-up for all low-risk thyroid cancer. Rather, this study may provide an incentive to further investigate whether staging based on preoperative CT will lead to improved disease-free survival and whether it has additional diagnostic value for staging in lower volume practices such as some centers in the Netherlands.

The continuous changes in thyroid cancer patients' risk stratification is calculated from information gathered post-operatively, such as the pathology report of the resection specimen.[14,47] An example of a poor prognostic factor for a thyroid cancer patient is the presence of aggressive histologic variants of papillary thyroid cancer (PTC). Different variants of PTC are recognized by characteristic histologic morphology, driven by genetic mutations and known to have a more aggressive disease course.[48] Therefore the ATA consider these tumors as intermediate-risk of recurrence recommending total thyroidectomy and consideration of RAI to minimize recurrence.[14] The tall cell variant, an example of higher risk pathology, is characterized by cells with a height that is at least two or three times its width, eosinophilic cytoplasm, basal nuclei and the classic nuclear features of PTC.[49] The most recent 4th edition of the WHO classification of Tumors of Endocrine Organs adopted the cut-off of that 30% of the tumor needs to be occupied with tall cells to be considered a true tall cell variant. A recent survey of expert thyroid pathologists showed that no consensus has been reached yet on diagnostic criteria for this variant proving that 30% may be arbitrary.[50] Consequently, depending on the pathologist, a given patient may be advised to undergo additional therapy if the final histology report determines the thyroid cancer to be a tall cell

variant. It implies that patients with tall cell change in the tumor which is less then the cut-off of 30% in the absence of other high-risk features are classified as low-risk disease and treated accordingly.[14] In **chapter 8** we highlighted the elevated risk profile of PTC with small percentages of tall cell change. Tumors with focal tall cell change (defined as <30% of the entire tumor volume) had worse outcomes then a control group of classical PTCs with no adverse cytomorphological features and resembled those of tall cell variants (>30% of entire volume). The results were in line with studies that found worse outcomes when only 10% tall cell change was seen in the sections examined.[51] We suggest re-classification to intermediatie risk for PTC with any amount of tall cell change over 10%, as it is a morphologic signature of underlying genetic mutations, such as enrichment of synchronous TERT-promoter mutations, leading to a more aggressive disease course.[52] To determine the exact extent of tall cell change within the entire tumor rather than the percentage in sampled slides, the thyroid specimen should be submitted in toto for microscopic examination. Although this was standard of practice in the hospital were this study was performed, it is a time-consuming process and there are currently no evidence-based guidelines addressing a generalizable framework for this. The inter-observer variability when pathology slides are re-reviewed is underlined by a recent study in which 39 cases including 17 tall cell variants were reviewed by 17 thyroid specialized pathologists.[53] Unanimous agreement for tall cell variants was reached in only two (5%) cases. This illustrates that high quality and standardized diagnostics are required to accurately select DTC in low and higher risk categories and imperative to minimize recurrence. Future studies will employ genetic testing which may allow clinicians to have indications on aggressive tumors potentially within a preoperative FNAC and to confirm an elevated risk profile in PTC with focal tall cell change.

Quality of life

One of the treatment goals for DTC is minimizing treatment-related morbidity and unnecessary therapy. As prognosis of low-risk DTC is generally excellent and as guidelines shift towards less extensive treatments to lower morbidity, the question arises; what are the specific details of the patient experience? Health related quality of life (HRQoL) deficiencies have been found in DTC patients in areas such as insomnia, fatigue, and limitations of daily functioning.[54,55] These may be rooted in the classic treatments for thyroid cancer, such as thyroid hormone replacement, radioactive iodine remnant ablation (RAI) and surgical complications, all negatively impacting psychological well-being and social functioning. Although research focusing on long-term HRQoL is scarce in the literature, one may hypothesize that less aggressive treatment may lead to long-term improvement in HRQoL. On the other hand, fear of persistence or recurrence of cancer may be experienced after less

extensive treatments that could have a negative impact on HRQoL.[56] The 2015 ATA guidelines highlight the importance of integrating long-term HRQoL outcomes into the treatment decision-making process for patients with thyroid cancer.[14] As a main recommendation for treating low-risk thyroid cancer suggests both total thyroidectomy and hemithyroidectomy of clinical equipoise, we described in **chapter 9** a comparison of long-term HRQoL in patients treated with each operation. In this cross-sectional questionnaire survey we found that the type of surgery performed for patients with low-risk DTC does not influence general domains of HRQoL in the long-term. Interestingly, after controlling for potential confounding factors, it appears that survivors that underwent a hemithyroidectomy experienced more worry about recurrence. This finding was part of an exploratory analysis that needs external confirmation. This study underlines that HRQoL and fear of recurrence are important when the clinician and patient with thyroid cancer are making decisions about treatment. The health provider may use these data to offer psychological support by introducing patients to a patient support group or by referring them to a psychologist.[57] We used a new thyroid cancer specific questionnaire of the European Organisation for Research and Treatment of Cancer.[58] After further validation using our data, we hope future studies will be able to benefit from a validated standardized questionnaire specific for thyroid cancer. This will improve generalizability within this area of research.

Conclusion

With the sharp rise in incidence of differentiated thyroid cancer, predominantly due to low-risk disease, there is a global trend towards less aggressive treatment. These include hemithyroidectomy or active surveillance where total thyroidectomy, RAI and thyroid suppression was commonplace. Worldwide, this change in management is currently at different stages as illustrated in **chapter 2**. To minimize treatment-related morbidity and unnecessary therapy, adequate risk stratification of DTC is needed. This is a complex and dynamic process which makes caring for patients with DTC exciting. In this book we give specific recommendations to further define thyroid malignancy risks for subgroups such as MEN1 patients in **chapter 4,** to those with entities not considered to be cancer in **chapter 5 & 6** and to those with tall cell variants of PTC in **chapter 8**. In **chapter 9** we show the influence of extent of surgery on the long-term quality of life of low-risk DTC. Next, we highlighted the need for further research on topics such as the follow-up of benign thyroid nodules in **chapter 3** and the influence of preoperative CT in **chapter 7.**

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CHAPTER 12

Nederlandse samenvatting (summary in Dutch)

Goed gedifferentieerde schildklierkanker

De schildklier is een vlindervormig orgaan aan de voorzijde van de hals dat bestaat uit twee helften. Middels de productie van de schildklierhormonen T3 en T4 zorgt het voor de regulatie van het energiemetabolisme in het lichaam. Wildgroei van schildkliercellen kan leiden tot goedaardige (benigne) of kwaadaardige (maligne) tumoren. Dit kan de patiënt soms bemerken als een knobbel in de hals, een schildkliernodus. Dit komt frequent voor bij volwassenen. Zo heeft 2-6% een voelbare afwijking in de hals, bij 19-35% worden noduli gezien met echografisch onderzoek van de hals, en wel 8-65% van de middels autopsie onderzochte mensen heeft schildklierafwijkingen. Slechts een klein deel van de schildklierafwijkingen is ook daadwerkelijk maligne. Ten behoeve van een adequate behandeling is het van belang een goede inschatting te maken van het risico op maligniteit. De diagnostiek van patiënten met een schildkliernodus bestaat uit het verhaal van de klachten (de anamnese), lichamelijk onderzoek van de hals, laboratoriumonderzoek (schildklierhormoonwaarden) en een echo van de hals. Op basis van risico verhogende kenmerken wordt besloten of ook een punctie van de schildkliernodus plaats moet vinden. Bij deze punctie, ofwel dunne naald aspiraat ('fine-needle aspiration cytology'), worden cellen van de afwijking verkregen en onder de microscoop beoordeeld op kenmerken van kanker. Helaas is de uitslag hiervan niet altijd onderscheidend tussen benigne of maligne, of is het aspiraat niet te beoordelen. Bij een onzeker resultaat kan de punctie herhaald worden, echter bij aanhoudende onzekerheid wordt geadviseerd de helft van de schildklier te verwijderen (diagnostische hemithyreoïdectomie) om uitsluitsel te krijgen over de aard van de tumor. Indien op basis van het weefselonderzoek van de hemithyreoïdetomie blijkt dat het een maligniteit betreft, kan deze bij schildklierkanker opgedeeld worden in verschillende groepen, op basis van het type cellen waar de maligniteit uit is ontstaan en de mate van gelijkheid die nog wordt vertoond met de oorspronkelijke cellen. Meer dan 90% van de schildkliermaligniteiten wordt gekwalificeerd als goed gedifferentieerd. Goed gedifferentieerde schildkliercarcinoom (in dit proefschrift 'well-differentiated' of 'differentiated thyroid carcinoma' genoemd) wordt verder onderverdeeld in papillair en folliculair schildkliercarcinoom; beide hebben een goede prognose, met een 10-jaars overleving van meer dan 95%. De overige groepen, waaronder het medullair en het anaplastisch schildkliercarcinoom, zijn zeldzamer, hebben een agressiever beloop en vereisen een andere behandeling. Zij worden niet verder besproken in dit proefschrift. Het aantal nieuwe diagnoses van goed gedifferentieerde schildklierkanker is de laatste decennia sterk gestegen. Zo is in de Verenigde Staten het jaarlijkse aantal diagnoses verviervoudigd in de periode 1975-2014. Eén van de oorzaken is de toename van beeldvormend onderzoek van de nek, vaak uitgevoerd voor andere redenen dan klachten van de schildklier. Hierbij wordt de schildklier ook afgebeeld en vaak afwijkingen ontdekt die geen klachten geven. Eén studie voorspelt dat in 2019 het goed gedifferentieerde schildklierkanker de derde meest

voorkomende maligniteit bij vrouwen in de Verenigde Staten zal zijn en met 2,4 miljard dollar bijna een verdubbeling van de jaarlijkse kosten voor de gezondheidszorg ten opzichte van 2010. Het aantal nieuwe diagnoses van schildklierkanker is in Nederland ook gestegen van 572 in 2010 naar 745 in 2017.

Verschillen tussen wereldwijde behandelrichtlijnen

Indien goed gedifferentieerde schildklierkanker gediagnosticeerd is bestaat de behandeling uit het verwijderen van de schildklier en vaak aanvullend radioactief jodium ablatie (RAI). Dit kan betekenen dat een patiënt na de eerdere diagnostische hemithyreoïdectomie nog een operatie ondergaat waarbij de resterende helft verwijderd wordt (totaliserende thyreoïdectomie) of indien uit het dunne naald aspiraat al bleek dat het kanker was wordt direct de hele schildklier verwijderd (totale thyreoïdectomie). Indien uitzaaiingen naar de halslymfeklieren worden deze verwijderd (lymfekliertoilet). Na de behandeling is de patiënt levenslang afhankelijk van schildklierhormoonvervangende medicijnen. De operaties hebben risico's die samenhangen met de omliggende structuren, zoals het meenemen van de bijschildklierhormoon producerende bijschildklieren of het beschadigen van de zenuwen die de stembanden aansturen. Over het algemeen zijn deze risico's hoger bij uitgebreidere of herhaalde operaties aan de schildklier. Dit gegeven, samen met de uitstekende prognose van goed gedifferentieerde schildklierkanker en een sterke toename van het aantal nieuwe diagnoses heeft ertoe geleid dat er een internationale trend gaande is richting een minder uitgebreide chirurgische behandeling. Volgens toonaangevende internationale richtlijnen, waaronder de *richtlijn voor goed gedifferentieerde schildklierkanker bij volwassenen van de American Thyroid Association* (ATA), volstaat nu een hemithyreoïdectomie bij schildklierkanker zonder hoogrisico kenmerken tot 4 cm in diameter. Dit is gestoeld op recente studies die geen verschil tonen in ziektevrije overleving tussen patiënten die een hemithyreoïdectomie of een totale thyreoïdectomie ondergingen als definitieve behandeling. Echter, in Nederland is het momenteel nog gangbaar om alle goed gedifferentieerde schildkliercarcinomen die groter zijn dan 1 cm te behandelen met een totale thyreoïdectomie gevolgd door RAI. Veranderingen in behandelrichtlijnen lopen dan wereldwijd ook niet synchroon en zijn deels afhankelijk van de landelijke epidemiologie en de inrichting van het zorgsysteem. In **hoofdstuk 2** beschrijven we wat in Nederland zou veranderen indien we de nieuwe ATA behandelrichtlijnen zouden overnemen. Het blijkt dat 28% van de patiënten met goed gedifferentieerde schildklierkanker uit een cohort van Nederlandse patiënten in aanmerking zou komen voor een hemithyreoïdectomie in plaats van de totale thyreoïdectomie die zij hebben ondergaan volgens de huidige Nederlandse richtlijn. We zijn van mening dat internationale richtlijnen niet simpelweg overgenomen kunnen worden, maar dat standaardisatie en hoge kwaliteit

van pre- en postoperatieve diagnostiek noodzakelijk zijn om internationale aanpassingen verantwoord te implementeren in de Nederlandse gezondheidszorg.

Wie te behandelen?

Omdat slechts een deel van de schildkliernoduli maligne ontaardt en veel afwijkingen als nevenbevinding op beeldvorming van de nek gevonden worden, is het belangrijk om de patiënten te selecteren die verdere diagnostiek en behandeling behoeven. In **hoofdstuk 3** onderzoeken we het risico dat een patiënt met een benigne nodus op basis van de schildklierpunctie in de toekomst toch gediagnosticeerd wordt met schildklierkanker. We hebben hiervoor naar de hele populatie van Ontario gekeken, een provincie met 17 miljoen inwoners in Canada. De database bevatte tot 95% van alle diagnoses van schildklierkanker in de provincie over een periode van 24 jaar. Het risico was 7,5% om gediagnosticeerd te worden met schildklierkanker in de follow-up na een eerdere schildklierpunctie waaruit geen diagnose kanker kwam. Dit is hoger dan het risico van de rest van de samenleving om gediagnosticeerd te worden met schildklierkanker. We vonden daarnaast dat het aantal schildklierpuncties in Ontario, gecorrigeerd voor bevolkingsgroei, verviervoudigd was tussen 1991-2010. Dit bevestigt de toename van het gebruik van deze diagnostische modaliteit.
Patiënten met het Multipele Endocriene Neoplasie Type 1 (MEN1) syndroom behoren tot een andere groep waarbij onduidelijkheid bestaat over de handelswijze bij het vinden van een schildkliernodus. Deze zeldzame aandoening (ongeveer 400 patiënten in Nederland) ontstaat door een genetische afwijking die leidt tot minder of niet functionerend menine eiwit. Als gevolg hiervan ontwikkelen deze patiënten tumoren in hormoonproducerende organen, waaronder de bijschildklieren. Om bijschildklierafwijkingen vroegtijdig te kunnen behandelen worden de bijschildklieren frequent echografisch gecontroleerd. Als gevolg van de nabijgelegen anatomische locatie wordt de schildklier hierbij ook in beeld gebracht. Schildkliernoduli die klein en niet palpabel zijn komen veel voor in de algemene bevolking en indien deze bij toeval worden gevonden, zoals vaak het geval bij MEN1 patiënten, worden deze schildklier incidentalomen genoemd. Het is voor de arts onduidelijk of deze een uiting van het MEN1 syndroom zijn en of ze een verhoogd risico met zich meebrengen om maligne te ontaarden. Om meer duidelijkheid hierover te geven hebben we in **hoofdstuk 4** deze patiëntengroep vergeleken met mensen zonder het MEN1 syndroom. De resultaten laten zien dat schildklier incidentalomen net zo vaak voorkomen in patiënten met het MEN1 syndroom als bij mensen die de genetische mutatie niet hebben. Dat er geen relatie is tot de genetische afwijking en het ontstaan van schildklier incidentalomen hebben we ondersteund met het doen van microscopie onderzoek (immunohistochemie) om de aanwezigheid van het menine eiwit te bepalen. De resultaten hiervan tonen aan dat het ontstaan van schildklier

incidentalomen op een andere manier verloopt. We concluderen dat schildklier incidentalomen bij MEN1 patiënten niet gerelateerd zijn aan het syndroom en daarom adviseren we hun behandelaars dezelfde richtlijnen te volgen als voor patiënten zonder het MEN1 syndroom. Dit kan geruststelling geven aan MEN1 patiënten en voorkomt overdiagnostiek en overbehandeling.
Een gevolg van overdiagnostiek bij schildkliernoduli is dat er maligniteiten worden gevonden die nooit zouden leiden tot klachten of ziek zijn van de patiënt. Dit fenomeen zien we ook veel bij andere vormen van kanker zoals prostaat- en borstkanker. Een bijzonder onschuldige vorm van goed gedifferentieerde schildklierkanker is het ingekapselde folliculair variant van het papillair schildkliercarcinoom, wat niet groeit uit het schildklierkapsel en geen potentie tot uitzaaiing lijkt te hebben. Met strenge pathologische criteria is deze variant recent door onderzoekers hernoemd tot 'niet-invasief schildklier neoplasme met papillaire cel structuren' (noninvasive follicular thyroid neoplasm with papillary-like nuclear features, ofwel NIFPT). Omdat ze geen tekenen van invasieve groei lijken te vertonen wordt geopperd dat NIFPT niet als maligniteit beschouwd moet worden. In **hoofdstuk 5** onderzochten wij hoeveel tumoren aan deze nieuwe NIFPT criteria voldoen en of ze daadwerkelijk niet maligne ontaarden. We vonden dat slechts 2,1% van de goed gedifferentieerde schildkliercarcinomen aan de NIFPT criteria voldeden. Dit is in tegenstelling tot de hogere percentages uit de studies die tot het voorstel van de naamswijziging hadden geleid. Daarnaast vertoonde 6% van de patiënten die in ons cohort aan de NIFPT criteria voldeden in de loop van de tijd wel kenmerken van invasieve groei zoals lymfeklieruitzaaiingen. Hieruit concluderen we dat NIFPT, ondanks een zeer goede prognose, niet als goedaardig moet worden beschouwd omdat dit kan leiden tot suboptimale controle en daarmee slechtere ziekte uitkomst. In **hoofdstuk 6,** in een reactie op een ingezonden brief, benadrukken wij dat we de-escalatie van de behandeling van laag risico goed gedifferentieerde schildklierkanker aanmoedigen, maar dat de huidige NIFPT-criteria invasieve groei niet volledig uitsluiten en goede nacontroles van belang zijn.

Risico inschatting

Het doel van de behandeling van goed gedifferentieerde schildklierkanker is om de overlevingskans te maximaliseren, de kans op terugkomen van ziekte (recidief) en het letsel als gevolg van de behandeling te verkleinen en tevens de kwaliteit van leven te optimaliseren. Omdat de overlevingskans van goed gedifferentieerde schildklierkanker zeer groot is, is de recidiefkans de meest gebruikte uitkomstmaat van de behandeling. Bij de risicostratificatie van de ATA richtlijnen worden patiënten ingedeeld in laag, midden en hoog risico op een recidief. Op basis van de kenmerken van de patiënt en tumor wordt een berekening van de kans op recidief gemaakt en een chirurgische behandeling geadviseerd. Patiënten met een laag risico op recidief kunnen volgens de recente literatuur volstaan met een

hemithyreoïdectomie wat minder kans heeft op letsels door de behandeling. Momenteel wordt geadviseerd aan patiënten met midden of hoog risico op recidief om een totale thyreoïdectomie te ondergaan met aanvullende RAI. De risicostratificatie is een complex proces waarbij zowel preoperatieve kenmerken van de patiënt, resultaten van echografie en schildklierpunctie worden meegenomen alsook de bevindingen van het weefselonderzoek na de operatie. Het preoperatief bepalen van de uitgebreidheid van de tumor, doorgroei in omliggend weefsel en lymfeklieruitzaaiingen, zijn belangrijk voor het kiezen van het type operatie en daarmee succesvolle behandeling. Dit wordt tumorstadiëring genoemd. Richtlijnen adviseren momenteel om hiervoor gebruiken te maken van een echo van de hals en alleen in specifieke gevallen andere beeldvorming te gebruiken zoals Computed Tomography scan (CT-scan) van de hals. Er is echter bewijs dat een CT-scan tumordoorgroei en lymfeklieruitzaaiingen in dieper gelegen structuren van de hals beter in kaar brengt dan een echo. Daarnaast heeft een CT-scan andere voordelen. Zo is, in tegenstelling tot bij echografie, de kwaliteit van een CT-scan niet afhankelijk van de expertise van de specialist die het onderzoek uitvoert en kunnen de beelden later beoordeeld worden door andere radiologen en chirurgen. In **hoofdstuk 7** hebben we onderzocht of het standaard toevoegen van een CT-scan aan de preoperatieve work-up bij patiënten met laag risico schildklierkanker leidt tot een ander beleid. Bij 22,5% van de patiënten werd door bevindingen op de CT-scans, die niet beschreven waren in het echoverslag, de operatie uitgebreid met een lymfekliertoilet van de hals. Het toevoegen van beeldvorming kan ook leiden tot onterechte verdenking op afwijkingen, ofwel fout-positieve bevindingen. Achteraf kan in zulke gevallen gesteld worden dat er een uitgebreidere operatie is verricht dan nodig. Ook in dit onderzoek vonden we dat een groot deel (44,4%) van de op CT-scan verdachte lymfeklieruitzaaiingen dichtbij de schildklier (het centrale compartiment) geen uitzaaiingen bleek te hebben bij het weefselonderzoek na de operatie. Echter zeven van de acht patiënten met verdachte lymfeklieruitzaaiingen welke verder van de schildklier af liggen (laterale compartiment) bleken wel klinisch relevante uitzaaiingen te hebben. Zij ondergingen terecht een uitgebreidere operatie, een lateraal lymfekliertoilet. Of het minimaliseren van de recidiefkans, een belangrijk doel van de behandeling van goed gedifferentieerde schildklierkanker, ook beïnvloed wordt door het toevoegen van de CT-scan aan de preoperatieve diagnostiek kunnen we uit dit onderzoek nu nog niet concluderen. Hiervoor moeten de patiënten langere tijd vervolgd worden en het aantal recidieven vergeleken worden met een groep die geen standaard CT-scan krijgen. Aangezien de kans op recidieven klein is en het jaren kan duren voordat ze gevonden worden, is een grote groep nodig die langdurig gevolgd wordt. Dit maakt het praktisch lastig uitvoerbaar. We zijn van mening dat het uitvoeren van een CT-scan in een medisch centrum waar relatief weinig patiënten met schildklierkanker behandeld worden zinvol kan zijn omdat de beelden door experts elders herbeoordeeld kunnen worden en de chirurg de beelden kan gebruiken om voor zichzelf de operatie voor te bereiden.

Het inschatten van het risico op recidief stopt niet na de eerste operatie. Bepaalde bevindingen van de patholoog, die het verwijderde weefsel verder onderzoekt, zijn gerelateerd aan een hogere recidiefkans. Zo weten we dat varianten van een papillair schildkliercarcinoom (PTC) welke herkend worden onder de microscoop, zich agressiever gedragen, een hoger risico op recidief hebben en daarom uitgebreidere chirurgie en nabehandeling met RAI behoeven. Een voorbeeld is de tall cell variant van het PTC. Deze variant wordt onder andere gekenmerkt door een uitgerekte vorm van de tumorcel en volgens de huidige criteria moet tenminste 30% van alle tumorcellen deze vorm hebben. In **hoofdstuk 8** beschrijven we een onderzoek waarbij we ons afvroegen wat de prognose was van de patiënten waarbij minder dan 30% van de tumorcellen de kenmerkende vorm hadden. Uit onze data blijkt dat patiënten met meer dan 10% van de tumorcellen met de karakteristieke vorm een hogere recidiefkans hebben dan patiënten met PTC zonder enige tall cell veranderingen. Op basis daarvan adviseren we dat alle patiënten met meer dan 10% tall cell veranderingen worden in de midden risico groep in plaats van de laag risico waaronder zij nu vallen. Dit heeft gevolgen voor de behandeling van deze patiënten, omdat volgens de huidige ATA richtlijnen nu nog een hemithyreoïdectomie en dan een totale thyreoïdectomie met RAI geadviseerd zou worden. Dit onderzoek onderstreept dat hoge kwaliteit weefselonderzoek en robuuste criteria belangrijk zijn om een betrouwbare risicostratificatie te kunnen maken en daarmee de optimale behandeling te kiezen.

Kwaliteit van leven

Eén van de doelen van de behandeling is optimalisatie van de kwaliteit van leven voor de patiënt. Dit is belangrijk omdat we weten dat ondanks de goede prognose van schildklierkanker de kwaliteit van leven die ervaren wordt vergelijkbaar is aan die van patiënten met agressievere vormen van kanker zoals darm- of hersenkanker. De oorzaak hiervan zou kunnen liggen in de klassieke behandelingen van schildklierkanker, zoals de RAI behandeling, levenslang afhankelijk zijn van schildklierhormoon vervangende medicijnen en morbiditeit van de chirurgische complicaties. De ATA richtlijn noemt zowel een hemi- als een totale thyreoïdectomie een geschikte behandeling voor laag risico goed gedifferentieerde schildklierkanker, dus is het interessant om te weten of deze keuze invloed heeft op de kwaliteit van leven. In **hoofdstuk 9** vergelijken we middels een enquête onderzoek patiënten jaren na hun operatie voor laag risico goed gedifferentieerde schildklierkanker. Globaal vonden we geen verschillen in kwaliteit van leven tussen patiënten die een hemithyreoïdectomie of totale thyreoïdectomie ondergaan hadden. In dit onderzoek keken we naar verschillende onderdelen van de kwaliteit van leven, zoals vermoeidheid, psychische klachten, functioneren op werk. Een van de onderdelen, angst voor een recidief, lijkt hoger

te zijn zelfs jaren na het ondergaan van een hemithyreoïdectomie. Een verklaring kan zijn dat het idee dat er nog steeds kanker kan ontstaan in de niet-verwijderde schildklierhelft onrust of angst geeft. Voor de behandelend arts is het belangrijk dit bespreekbaar te maken en het zou kunnen helpen om laagdrempelig te verwijzen voor psychologische hulp indien deze angst speelt. Het feit dat globaal de kwaliteit van leven niet verschilt tussen beide behandelstrategieën kan helpen in het gesprek tussen arts en patiënt in de spreekkamer om samen tot een behandelkeuze te komen.

Conclusie

De diagnose goed gedifferentieerde schildklierkanker wordt in toenemende mate gesteld. Dankzij een toename van kennis over de interpretatie van diagnostiek en voorspellende factoren voor een agressief beloop kan een betere risico inschatting gemaakt worden voor de individuele patiënt. Dit leidt tot minder uitgebreide behandeling bij geselecteerde laag risico patiënten. Dit proefschrift geeft de wereldwijde trend naar een minder aggressieve behandeling weer, verfijnt de risico inschatting, adviseert ter aanzien van de behandelstrategie bij schildkliernoduli en goed gedifferentieerde schildklierkanker en geeft inzicht in de kwaliteit van leven na de behandeling van deze maligniteit.

APPENDICES

List of abbreviations

ASC:	Assessment of Survivor Concerns
ATA guidelines:	2015 American Thyroid Association Management Guidelines for Adult Patients with Thyroid Nodules and Differentiated Thyroid Cancer
CND:	central neck dissection
CT:	Computed Tomography of the neck
DAB:	diaminobenzidine
DMSG:	Dutch MEN1 Study Group
DTC:	differentiated thyroid cancer
EFVPTC:	encapsulated follicular variant of papillary thyroid carcinoma
EORTC:	European Organisation for Research and Treatment of Cancer
ETE:	extrathyroidal extension
FFPE:	formalin-fixed paraffin-embedded
FNAC:	fine needle aspiration cytology
FTC:	follicular thyroid cancer
FvPTC:	follicular variant of papillary thyroid cancer
HRQoL:	health-related quality of life
HT:	hemithyroidectomy
IQR:	interquartile range
LND:	lateral neck dissection
LOH:	loss of heterozygosity
MEN1:	multiple endocrine neoplasia type 1
NET:	neuroendocrine tumor
NIFTP:	noninvasive follicular thyroid neoplasm with papillary-like nuclear features
pHPT:	primary hyperparathyroidism
PTC:	papillary thyroid cancer
PTMC:	papillary thyroid microcarcinoma
RAI:	radioactive iodine
SD:	standard deviation
SPSS:	Statistical Package for the Social Sciences
TG:	thyreoglobulin
TSH:	thyroid stimulating hormone
TT:	total thyroidectomy
UHN:	University Health Network
US:	ultrasound
95%CI:	95 percent confidence interval

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List of Publications

Bongers PJ, Verzijl R, Dzingala M, Vriens M, Yu E, Pasternak JD, Rotstein L. *Preoperative Computed Tomography changes surgical management in clinically low-risk well-differentiated thyroid cancer.* Annals of Surgical Oncology. 2019. (in press)

Bongers PJ, Greenberg CA, Hsiao R, Vermeer M, Vriens MR, Lutke Holzik MF, Goldstein DP, Devon K, Rotstein LE, Sawka A, Pasternak JD. *Differences in long-term quality of life between hemithyroidectomy and total thyroidectomy in patients treated for low-risk differentiated thyroid carcinoma.* Surgery. 2019. (in press)

Bongers PJ, Kluijfhout WP, Verzijl R, Lustgarten M, Vermeer M, Goldstein DP, Devon K, Rotstein LE, Asa SL, Brierley JD, Tsang RW, Ezzat S, Vriens MR, Mete O, Pasternak JD. *Papillary thyroid cancers with focal tall cell change are as aggressive as tall cell variants and should not be considered as low-risk disease.* Annals of Surgical Oncology. 2019;26(8):2533-2539.

Bongers PJ, Kluijfhout WP, Devon KM, Rotstein LE, Vriens MR, Urbach DR, Pasternak JD. *Long-term risk of thyroid cancer after initially negative thyroid biopsy results.* JAMA Otolaryngology Head Neck Surgery. 2019;145(6):579-580.

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Parente DN, **Bongers PJ**, Verzijl R, Kluijfhout WP, Devon KM, Rotstein LE, Goldstein DP, Asa SL, Mete O, Pasternak JD. *Noninvasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP): Trading six for a risky half dozen: Reply.* World Journal of Surgery. 2018;42(7):2279.

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Bongers PJ, Boogerd LSF, Handgraaf HJM, Burggraaf J, van de Velde CJH, Vahrmeijer AL. *Image guided surgery using fluorescence: Road to clinical translation of novel probes.* SPIE Conference Proceedings. Volume 9696, Molecular-Guided Surgery: Molecules, Devices, and Applications II. 2016;96960Z.

Bongers PJ, Lodewijk L, Kist JW, Conemans EB, de Laat JM, Pieterman CR, van der Horst-Schrivers AN, Jorna C, Hermus AR, Dekkers OM, de Herder WW, Drent ML, Bisschop PH, Havekes B, Rinkes IH, Vriens MR, Valk GD. *Thyroid incidentalomas in patients with multiple endocrine neoplasia type 1.* European Journal of Endocrinology. 2015;172(4):337-42.

Bongers PJ, van Hove DP, Stassen LP, Dankelman J, Schreuder HW. *A new virtual-reality training module for laparoscopic surgical skills and equipment handling: can multitasking be trained? A randomized controlled trial.* Journal of Surgical Education. 2015;72(2):184-91.