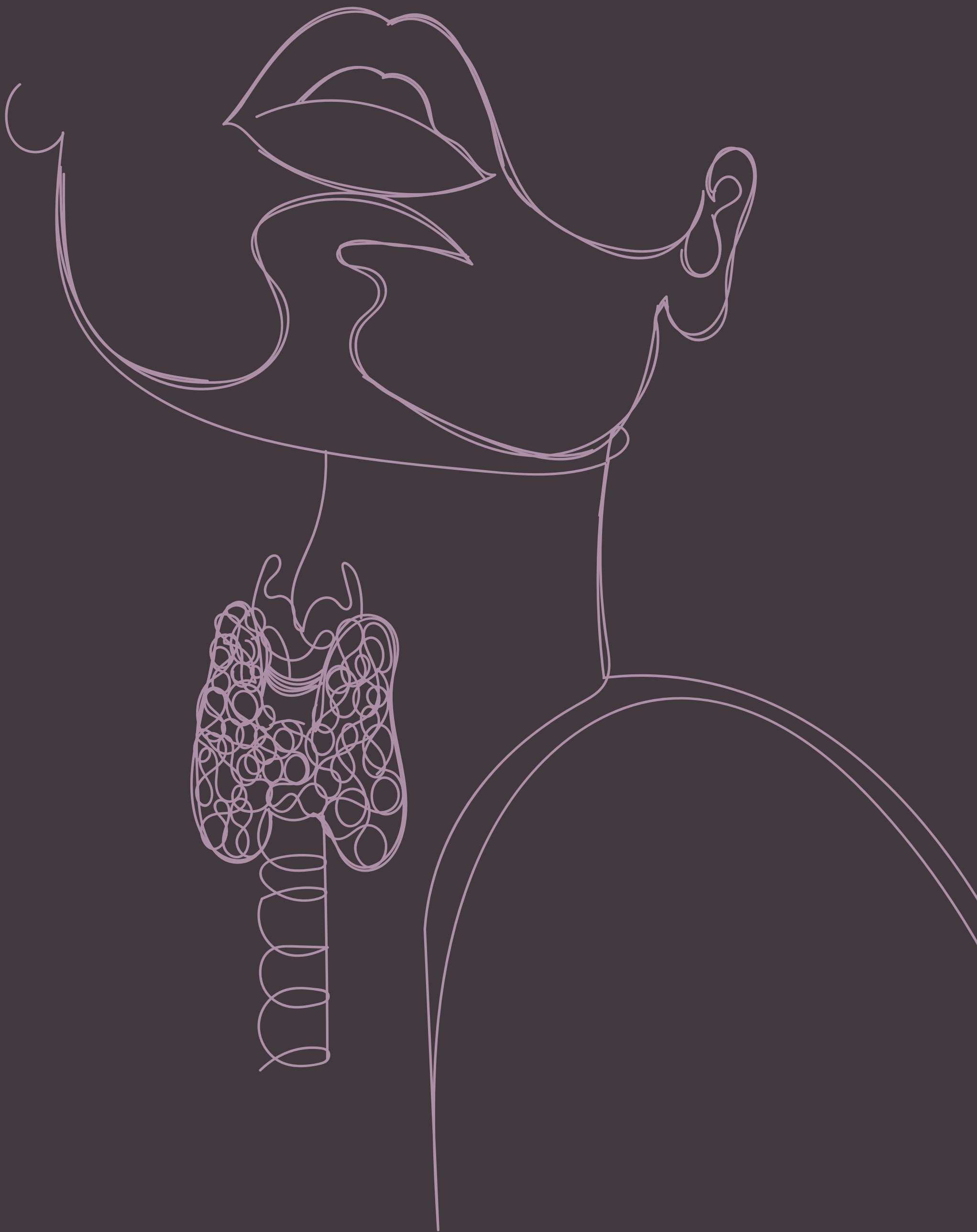
Refinement in Thyroid Surgery



Ivona Lončar

Refinement in Thyroid Surgery

Ivona Lončar

Financial support for the publication of this thesis was provided by the Deparment of Surgery Erasmus MC and the Erasmus University Rotterdam. Further financial support was kindly provided by:
ABN Amro
Chipsoft
Bayer B.V.
Eisai
Inomed Medizintechnik GmbH
Ipsen Farmaceutica B.V.

Cover design: Touch of Meraki | Mariska Germs | www.touchofmeraki.nl
Lay-out and printing: ProefschriftMaken | Vera van Beek | www.proefschriftmaken.nl
ISBN: 978-94-6469-202-0

Refinement in Thyroid Surgery

Verfijning van schildklierchirurgie

Proefschrift
ter verkrijging van de graad van doctor aan de
Erasmus Universiteit Rotterdam
op gezag van de rector magnificus
Prof.dr. A.L. Bredenoord

en volgens besluit van het College voor Promoties.

De openbare verdediging zal plaatsvinden op

woensdag 22 februari 2023 om 13:00 uur

door

Ivona Lončar

geboren te Ossendrecht

Erasmus University Rotterdam

Promotiecommissie

Promotoren	Prof.dr. C.H.J. van Eijck Prof.dr. R.P. Peeters
Overige leden	Prof.dr. E.J.M. Nieveen van Dijkum Prof.dr. W.W. de Herder Prof.dr. F.A. Verburg
Copromotor	Dr. T.M. van Ginhoven

TABLE OF CONTENTS

1

Chapter 1

General introduction and outline of this thesis

The Swiss professor of surgery Emil Theodor Kocher is known as the father of the modern thyroid surgery. In 1909 he received the Nobel prize for his work on the physiology, pathology and surgery of the thyroid gland. He managed to decrease the mortality rate of his patients to 0.5% as opposed to the 75% mortality rates before his days (1). His principles of thyroid surgery were the basis for the refinement of thyroid surgery as it is presently known. There are many indications for thyroid surgery in the current era, from symptomatic benign thyroid nodules and Graves' disease to (suspected) thyroid cancer. Although survival rates of patients with thyroid disease, including thyroid cancer, are mainly excellent, surgical treatment may cause complications and a serious burden for these patients. Therefore, the benefits of surgical treatment should always outweigh these risks. This thesis provides insights into further refinement possibilities of (non)surgical strategies in patients with different thyroid diseases.

Thyroid physiology and anatomy

The thyroid gland derives its name from the Greek word *thyreoiedes* meaning 'shield-shaped' gland (2). The main function of the thyroid is the production of the thyroid hormones (triiodothyronine and thyroxine), contributing to the regulation of normal development, growth and metabolism (3). The gland consists of two interconnected lobes and is located in the midline of the lower anterior neck, just below the thyroid cartilage. It is surrounded by several important structures (4). Lateral to the thyroid gland the left and right recurrent laryngeal nerves are located. These are branches of the vagus nerve and supply function to the intrinsic laryngeal muscles. The thyroid itself is extremely vascularized and is covered by a capsule. Usually, four small parathyroid glands are found in the vicinity (or in!) the thyroid gland. Their main function is the production of parathyroid hormone (PTH), which plays an important role in the calcium and phosphate homeostasis and opposes the effect of calcitonin.

Thyroid nodules

A thyroid nodule is an abnormal lump of thyroid cells in the thyroid gland. Thyroid nodules are more common in women and their frequency increases with age and with decreasing iodine intake (5). Most thyroid nodules are asymptomatic and are discovered incidentally with ultrasound, CT-, MRI- or ^{18}FDG-PET/CT scans done for other unrelated reasons, and are therefore called thyroid incidentalomas. In other cases, patients may present with a palpable thyroid nodule from which they experience symptoms due to mechanical compression. Ultrasound guided fine needle aspiration (FNA) is the cornerstone of thyroid nodule evaluation as treatment decisions rely on the cytological test results. To aid this process a uniform cytopathology reporting system was developed in 2007, known as the "Bethesda System for Reporting Thyroid Cytopathology". The Bethesda system consists of six categories, each associated with an implied risk of malignancy which is translated into a clinical management algorithm as can be seen in Table 1 (6). The management suggestions in Table 1 were proposed in 2009 and are still used in the 2015 Dutch national thyroid cancer guideline. The risk of malignancy and suggestions are a global guideline based on cytological results. However, clinical and radiological results should also be taken in consideration for a definitive treatment plan. Over the last years much has changed in the field of thyroid molecular cytopathology and the risk of malignancy and management suggestions have been updated (7). These will be highlighted in the next paragraphs.

Table 1. The Bethesda System for Reporting Thyroid Cytopathology: Implied Risk of Malignancy and Recommended Clinical Management (6)

Bethesda category		Risk of Malignancy (%)	Management
I.	Nondiagnostic or unsatisfactory	1-4	Repeat FNA with ultrasound guidance
II.	Benign	0-3	Clinical follow-up
III.	Atypia of undetermined significance or follicular lesion of undetermined significance	~5-15	Repeat FNA
IV.	Follicular neoplasm or suspicious for a follicular neoplasm	15-30	Diagnostic hemithyroidectomy
V.	Suspicious for malignancy	60-75	Diagnostic hemithyroidectomy/ total thyroidectomy
VI.	Malignant	97-99	Total thyroidectomy

Prior to initiating the diagnostic workup it is important to distinguish between incidentalomas and palpable thyroid nodules. Historically, the Netherlands has a conservative approach towards patients with thyroid nodules leading to a unique population with less incidentally discovered indolent tumors. Since 2007, the Dutch national thyroid cancer guideline advocates to only pursue further diagnostics in patients with a palpable thyroid nodule and to refrain from further diagnostics in incidentally found thyroid nodules (8), in contrast to various other guidelines from other countries (9-12). An exception is made for ^{18}FDG-PET/CT-positive incidentalomas due to the relatively higher risk of malignancy (13).

Benign thyroid nodules

Fortunately, after FNA most thyroid nodules are benign and do not require medical treatment. However, some cause symptoms by mechanical compression requiring intervention. Currently, a hemithyroidectomy is advised for these symptomatic benign thyroid nodules (SBTN). Unfortunately, thyroid surgery may lead to complications such as wound infection, hemorrhage, permanent laryngeal nerve paralysis and hypothyroidism and specifically to hypoparathyroidism after total thyroidectomy. Another drawback of surgery is that a scar is always visible often causing cosmetic problems leading to a psychosocial burden (14). To refine the treatment of SBTN alternatives are needed. One of the alternative procedures for treating SBTN is radiofrequency ablation (RFA), which was first described in South-Korea in 2006. The principle is based on localized heating of tissue with a high-frequency alternating current, which leads to necrosis and shrinkage of the thyroid nodule while sparing surrounding tissues (15). Reports from mainly South-Korea and Italy have shown promising results, with nodule volume reductions of 50-80% within the first year after treatment (16-20). Although RFA is considered to be safe, various complications may occur, including recurrent nerve damage, skins burns, and hematoma (21). Furthermore, data on health-related quality of life (QoL) after RFA are still limited, especially with regard to disease specific questionnaires. Based on the aforementioned reports, RFA was implemented in 2015 in three hospitals in the Thyroid Network (SchildklierNetwerk). In **chapter 3** we will describe the initial results regarding the nodule volume reduction and health-related QoL of patients undergoing RFA for SBTN in the Thyroid Network.

Indeterminate thyroid nodules

After FNA approximately 15 to 30% of the thyroid nodules are reported as cytologically indeterminate, including the Bethesda III (Atypia of Undetermined Significance or Follicular Lesion of Undetermined Significance), Bethesda IV (Follicular Neoplasm or Suspicious for a Follicular Neoplasm) and Bethesda V (Suspicious for malignancy) categories (6, 22). Following surgical resection, only one in three indeterminate nodules prove to be malignant, suggesting a large potential to avoid diagnostic surgical procedures (23). In order to refine the risk stratification and to reduce the diagnostic surgery rate several molecular tests have been developed in the past decade. Different approaches have been used, including microRNA based classifiers (Rosetta GX Reveal and ThyraMIR) and next-generation sequencing-based assays (Thyroseq v2 and v3) (24-27). In 2011 Veracyte's Afirma Gene Expression Classifier (GEC) became commercially available for patients with Bethesda III or Bethesda IV thyroid nodules. In this assay messenger RNA expression patterns of 167 genes are used to reclassify Bethesda III and Bethesda IV nodules as "benign" or "suspicious" (28). A GEC benign result has a malignancy risk of <5%, which is similar to the to the benign Bethesda II category. These data justify a wait and see policy based on a benign GEC result (29, 30) whereas in patients with a GEC suspicious result, the estimated malignancy rate of 37-38% often results in diagnostic surgery (28). Later, in 2017, Veracyte updated the GEC to Genomic Sequencing Classifier (GSC) and added the Xpression Atlas (XA) assay in 2019 which showed improved specificity and positive predictive value (31, 32). The GSC uses whole transcriptome RNA sequencing and machine learning algorithms to reclassify nodules, combined with the XA which uses RNA sequencing to detect genomic variants and fusions. Most clinical validation and utility studies of the GEC and GSC have been performed in the USA, with only one publication from Europe so far (33). As mentioned before the Netherlands historically has a conservative approach towards patients with thyroid nodules compared to many other countries, with a high threshold for neck ultrasound leading to relatively low number of incidental findings. The utility of the GEC in a population with longstanding restrictive workup protocols has not been assessed before and could provide insights for future implementations as de-escalating trends in diagnostics are upcoming. In **chapter 4** we will assess the clinical utility of the Afirma GEC in the Netherlands by describing the impact on surgical treatment and concordancy between GEC results and definitive histopathology. Post-hoc additional GSC testing will be performed on the same samples without influencing clinical decision making.

Malignant thyroid nodules

The incidence of malignancy in thyroid nodules varies between 7-15% (5, 34, 35). The risk of malignancy depends on factors such as age and sex, but also strongly depends on the threshold for using diagnostic imaging in a certain population (34). Thyroid cancer is generally categorized into papillary, follicular, medullary and anaplastic cancer. Papillary thyroid carcinoma (PTC), the most common type, and the more rare form follicular thyroid carcinoma (FTC) are considered differentiated thyroid cancers (DTC) and account for approximately 90% of all thyroid cancers (36). In this thesis we will focus on DTC.

Differentiated thyroid cancer

The worldwide incidence of DTC has increased over the last decades (37, 38). Based on data from the Dutch Cancer Registry (IKNL), DTC was diagnosed in 319 patients in 2000 and doubled to 726 patients in 2020 in the Netherlands (39). However, this two fold increase is much lower compared to the exponential rise that has been observed in the USA and South-Korea (40, 41). The rising incidence is most likely attributed to a significant increase in the use of diagnostic imaging modalities and the improvement of postoperative pathological examination, which leads to the discovery of mainly small low-risk PTC and incidentalomas (40, 42-45). The rising incidence alongside a stable 10-years survival rate of 96% is highly suggestive for overdiagnosis and overtreatment with traditional treatment strategies including surgery with or without cervical lymph node dissection, radioidine (RAI) ablation and TSH suppression (46-48). This treatment strategy comes with high morbidity rates and negatively impacts quality of life in thyroid cancer survivors (49-51). As a result the 2015 American Thyroid Association (ATA) guidelines shifted to a "less is more" approach, recommending de-escalation of treatment for patients with a low-risk DTC up to 4 cm (9). They recommend a hemithyroidectomy instead of total thyroidectomy followed by RAI ablation. These recommendations are based on large national USA registries and the question remains whether these recommendations can be extrapolated to low-risk DTC patients in the Netherlands (52). In **chapter 5** we assess whether the tumor stage of selected patients with low-risk DTC in the USA is similar to the low-risk DTC patients in the Netherlands using data from the Dutch Cancer Registry.

Another example of "less is more" is the trend to offer active surveillance instead of hemithyroidectomy for patients with a unifocal micropapillary thyroid carcinoma (mPTC, largest diameter is less than 1.0 cm) (9). Active surveillance for mPTC was first proposed at the Kuma hospital in Japan and entails monitoring the patient over time with neck ultrasounds and only operate when progressive disease is encountered (53). This strategy reduces the number of patients exposed to surgical morbidity and has comparable oncological outcomes to immediate surgery (54-56). However, again the question is whether we can extrapolate these results to the Dutch population. These studies have been performed in populations with a relatively high proportion of incidental mPTC encountered by the liberal use of ultrasonography of the neck. Active surveillance in a population with restrictive diagnostic workup may lead to other oncological outcomes due to patient selection and may not have a large additive value in the reduction of overtreatment. In the Netherlands it is currently stated in the guideline to refrain from FNA for thyroid nodules <1cm, unless high risk factors are present. The Netherlands has adopted this more restrictive diagnostic workup strategy in 2007. In **chapter 6** we will describe the proportion and characteristics of patients with mPTC from the Dutch Cancer Registry and describe the potential candidates for active surveillance in a situation with restrictive diagnostic protocols since 2007.

Multidisciplinary care

Since thyroid cancer is a rare disease, it is challenging to gain sufficient medical expertise by exposure to patients. For this reason guidelines recommend the use of a multidisciplinary approach and structured care pathways as the standard of care in thyroid cancer patients (9, 57). Through continuous re-assessment, care pathways aim to improve quality of clinical care, increase patient satisfaction and efficiency in the treatment of patients with thyroid cancer (58-60). In the South-Western part of the Netherlands, clinical care for patients with thyroid nodules and cancer was provided by one academic hospital, four large medical teaching hospitals and five general hospitals. This resulted in a lack of uniform protocols, absence of formal centralization rules for rare thyroid cancers and a need for second opinions. To achieve standardized regional care for patients with thyroid nodules and cancer, the Thyroid Network, a collaboration among ten hospitals, was initiated in January 2016. With the start of the Thyroid Network a biweekly regional multidisciplinary tumor board (MTBs) and a regional care pathway for patients with thyroid nodules and cancer were implemented. However, the impact of regional MTBs on patient referral patterns among regional hospitals concerning cancer care is unknown. In **chapter 2** a qualitative evaluation of the Thyroid Network, with a quantitative analysis of second opinion referrals for patients with thyroid nodules and cancer in the South-Western part of the Netherlands is described.

Hypoparathyroidism

Hypoparathyroidism is the most common iatrogenic complication after total or completion thyroidectomy and is caused by accidental resection or devascularization of the parathyroid glands, leading to absent or insufficient production of parathyroid hormone (PTH) (61, 62). Postoperative hypoparathyroidism results in hypocalcemia and may cause direct clinical symptoms such as perioral numbness, paraesthesia and muscle cramps, as well as severe seizures and cardiac arrhythmias in rare instances. Postoperative hypocalcaemia is treated with oral or intravenous calcium supplementation and, in some cases, additional active vitamin D supplementation (63). Fortunately, in most cases, parathyroid function will recover within weeks after surgery and calcium levels will normalize (64, 65). Yet, in a minority of patients parathyroid function will not restore and they will develop persistent hypoparathyroidism with the need for lifelong supplementation with calcium and active vitamin D analogues. In the long term, patients with hypoparathyroidism are at risk for various comorbidities and complications, such as chronic kidney disease and basal ganglia calcifications resulting in an impaired quality of life (66-68). A recent study even described higher mortality rates in this population (69). Altogether, hypoparathyroidism poses a significant disease burden on patients undergoing thyroid surgery and stresses the need for the refinement of surgical strategies. Despite being a common complication with a high burden of disease, uniformity in definition, diagnosis and treatment protocols are lacking. In order to diagnose, treat and prevent persistent hypoparathyroidism an international standardized definition for persistent hypoparathyroidism is needed. The definition of persistent hypoparathyroidism differs widely in medical literature varying from the need for calcium supplements six months after surgery to the need for calcium and/or active vitamin D analogues in combination with low PTH levels after 12 months (70). Multiple studies have shown that parathyroid function may recover within the first year after surgery. Therefore, defining persistent hypoparathyroidism as hypoparathyroidism at 6 months after surgery rather than 12 months may lead to inappropriate incidence rates (65, 71, 72). The same principle applies when persistent hypoparathyroidism is defined as the need for calcium supplements only, without the use of active vitamin D since active vitamin D with or without calcium is the conventional therapeutic approach for hypoparathyroidism (73-75). Furthermore, active weaning of supplementation must be attempted to prevent overtreatment and an incorrectly diagnosed hypoparathyroidism (75). However, to date active weaning has not been incorporated in definitions in literature. The current lack of this standardized definition, a uniform diagnosis and treatment guidelines impedes an unbiased comparison of studies. To overcome these limitations, we evaluated a new pragmatic definition of persistent hypoparathyroidism in a retrospective multi-center cohort study, as described in **chapter 7**. The reported rates of persistent hypoparathyroidism vary from 1.5% up to 16.7% (72, 76-81). It is hypothesized that the use of different definitions could influence the incidence of persistent hypoparathyroidism, which we will evaluate in **chapter 7.** Other explanations might be differences in case-mix and underreporting of this complication (70). As a result, the true incidence remains unknown. In **chapter 8** we evaluate the real-life incidence of postoperative, persistent hypoparathyroidism after total or completion thyroidectomy in a tertiary academic patient population in the Netherlands. At this moment it is not possible to reliably predict which patients will develop persistent hypoparathyroidism and in which patients parathyroid function will recover. Early identification of high-risk patients will allow clinicians not only to inform patients, but also to schedule tailored postoperative outpatient follow-up visits and reduce the burden for patients. Recent studies have described the value of serum PTH concentration to predict direct postoperative hypocalcaemia (79, 82). In **chapter 9** we determined if a decrease in PTH, measured at the first postoperative day, is able to identify patients with a high risk for persistent hypoparathyroidism one year after total or completion thyroidectomy. In **chapter 10** the results from the previous chapters are summarized and discussed and future perspectives will be outlined.

References

1. McGreevy PS, Miller FA. Biography of Theodor Kocher. Surgery. 1969;65(6):990-9.
2. Hoyes AD, Kershaw DR. Anatomy and development of the thyroid gland. Ear Nose Throat J. 1985;64(7):318-33.
3. Cheng SY, Leonard JL, Davis PJ. Molecular aspects of thyroid hormone actions. Endocr Rev. 2010;31(2):139-70.
4. Ozgur Z, Celik S, Govsa F, Ozgur T. Anatomical and surgical aspects of the lobes of the thyroid glands. Eur Arch Otorhinolaryngol. 2011;268(9):1357-63.
5. Alexander EK, Cibas ES. Diagnosis of thyroid nodules. Lancet Diabetes Endocrinol. 2022;10(7):533-9.
6. Cibas ES, Ali SZ, Conference NCITFSotS. The Bethesda System For Reporting Thyroid Cytopathology. Am J Clin Pathol. 2009;132(5):658-65.
7. Cibas ES, Ali SZ. The 2017 Bethesda System for Reporting Thyroid Cytopathology. Thyroid. 2017;27(11):1341-6.
8. Links T. Richtlijn voor de diagnostiek, behandeling en follow-up van patiënten met gedifferentieerd (niet-medullair) schildkliercarcinoom 2015 [updated 16-02-2015. Available from: https://richtlijnendatabase.nl/richtlijn/schildkliercarcinoom/algemeen.html.
9. Haugen BR, Alexander EK, Bible KC, Doherty GM, Mandel SJ, Nikiforov YE, et al. 2015 American Thyroid Association Management Guidelines for Adult Patients with Thyroid Nodules and Differentiated Thyroid Cancer: The American Thyroid Association Guidelines Task Force on Thyroid Nodules and Differentiated Thyroid Cancer. Thyroid. 2016;26(1):1-133.
10. Wémeau JL, Sadoul JL, d'Herbomez M, Monpeyssen H, Tramalloni J, Leteurtre E, et al. Guidelines of the French society of endocrinology for the management of thyroid nodules. Ann Endocrinol (Paris). 2011;72(4):251-81.
11. Pacini F, Basolo F, Bellantone R, Boni G, Cannizzaro MA, De Palma M, et al. Italian consensus on diagnosis and treatment of differentiated thyroid cancer: joint statements of six Italian societies. J Endocrinol Invest. 2018;41(7):849-76.
12. Yi KH. The Revised 2016 Korean Thyroid Association Guidelines for Thyroid Nodules and Cancers: Differences from the 2015 American Thyroid Association Guidelines. Endocrinol Metab (Seoul). 2016;31(3):373-8.
13. Bae JS, Chae BJ, Park WC, Kim JS, Kim SH, Jung SS, et al. Incidental thyroid lesions detected by FDG-PET/CT: prevalence and risk of thyroid cancer. World J Surg Oncol. 2009;7:63.
14. Balci DD, Inandi T, Dogramaci CA, Celik E. DLQI scores in patients with keloids and hypertrophic scars: a prospective case control study. J Dtsch Dermatol Ges. 2009;7(8):688-92.
15. Kim YS, Rhim H, Tae K, Park DW, Kim ST. Radiofrequency ablation of benign cold thyroid nodules: initial clinical experience. Thyroid. 2006;16(4):361-7.
16. Baek JH, Kim YS, Lee D, Huh JY, Lee JH. Benign predominantly solid thyroid nodules: prospective study of efficacy of sonographically guided radiofrequency ablation versus control condition. AJR Am J Roentgenol. 2010;194(4):1137-42.

17. Baek JH, Lee JH, Valcavi R, Pacella CM, Rhim H, Na DG. Thermal ablation for benign thyroid nodules: radiofrequency and laser. Korean J Radiol. 2011;12(5):525-40.
18. Baek JH, Lee JH, Sung JY, Bae JI, Kim KT, Sim J, et al. Complications encountered in the treatment of benign thyroid nodules with US-guided radiofrequency ablation: a multicenter study. Radiology. 2012;262(1):335-42.
19. Jeong WK, Baek JH, Rhim H, Kim YS, Kwak MS, Jeong HJ, et al. Radiofrequency ablation of benign thyroid nodules: safety and imaging follow-up in 236 patients. Eur Radiol. 2008;18(6):1244-50.
20. Deandrea M, Sung JY, Limone P, Mormile A, Garino F, Ragazzoni F, et al. Efficacy and Safety of Radiofrequency Ablation Versus Observation for Nonfunctioning Benign Thyroid Nodules: A Randomized Controlled International Collaborative Trial. Thyroid. 2015;25(8):890-6.
21. Chung SR, Suh CH, Baek JH, Park HS, Choi YJ, Lee JH. Safety of radiofrequency ablation of benign thyroid nodules and recurrent thyroid cancers: a systematic review and meta-analysis. Int J Hyperthermia. 2017;33(8):920-30.
22. American Thyroid Association Guidelines Taskforce on Thyroid N, Differentiated Thyroid C, Cooper DS, Doherty GM, Haugen BR, Kloos RT, et al. Revised American Thyroid Association management guidelines for patients with thyroid nodules and differentiated thyroid cancer. Thyroid. 2009;19(11):1167-214.
23. Wang CC, Friedman L, Kennedy GC, Wang H, Kebebew E, Steward DL, et al. A large multicenter correlation study of thyroid nodule cytopathology and histopathology. Thyroid. 2011;21(3):243-51.
24. Nikiforov YE, Carty SE, Chiosea SI, Coyne C, Duvvuri U, Ferris RL, et al. Highly accurate diagnosis of cancer in thyroid nodules with follicular neoplasm/suspicious for a follicular neoplasm cytology by ThyroSeq v2 next-generation sequencing assay. Cancer. 2014;120(23):3627-34.
25. Steward DL, Carty SE, Sippel RS, Yang SP, Sosa JA, Sipos JA, et al. Performance of a Multigene Genomic Classifier in Thyroid Nodules With Indeterminate Cytology: A Prospective Blinded Multicenter Study. JAMA Oncol. 2019;5(2):204-12.
26. Lupo MA, Walts AE, Sistrunk JW, Giordano TJ, Sadow PM, Massoll N, et al. Multiplatform molecular test performance in indeterminate thyroid nodules. Diagn Cytopathol. 2020;48(12):1254-64.
27. Benjamin H, Schnitzer-Perlman T, Shtabsky A, VandenBussche CJ, Ali SZ, Kolar Z, et al. Analytical validity of a microRNA-based assay for diagnosing indeterminate thyroid FNA smears from routinely prepared cytology slides. Cancer Cytopathol. 2016;124(10):711-21.
28. Alexander EK, Kennedy GC, Baloch ZW, Cibas ES, Chudova D, Diggans J, et al. Preoperative diagnosis of benign thyroid nodules with indeterminate cytology. N Engl J Med. 2012;367(8):705-15.
29. Chudova D, Wilde JI, Wang ET, Wang H, Rabbee N, Egidio CM, et al. Molecular classification of thyroid nodules using high-dimensionality genomic data. J Clin Endocrinol Metab. 2010;95(12):5296-304.
30. Duick DS, Klopper JP, Diggans JC, Friedman L, Kennedy GC, Lanman RB, et al. The impact of benign gene expression classifier test results on the endocrinologist-patient decision to operate on patients with thyroid nodules with indeterminate fine-needle aspiration cytopathology. Thyroid. 2012;22(10):996-1001.

31. Patel KN, Angell TE, Babiarz J, Barth NM, Blevins T, Duh QY, et al. Performance of a Genomic Sequencing Classifier for the Preoperative Diagnosis of Cytologically Indeterminate Thyroid Nodules. JAMA Surg. 2018;153(9):817-24.
32. Angell TE, Wirth LJ, Cabanillas ME, Shindo ML, Cibas ES, Babiarz JE, et al. Analytical and Clinical Validation of Expressed Variants and Fusions From the Whole Transcriptome of Thyroid FNA Samples. Front Endocrinol (Lausanne). 2019;10:612.
33. Andrioli M, Carocci S, Alessandrini S, Amini M, Van Doorne D, Pace D, et al. Testing for Afirma in Thyroid Nodules with High-Risk Indeterminate Cytology (TIR3B): First Italian Experience. Endocr Pathol. 2020;31(1):46-51.
34. Hegedus L. Clinical practice. The thyroid nodule. N Engl J Med. 2004;351(17):1764-71.
35. Frates MC, Benson CB, Doubilet PM, Kunreuther E, Contreras M, Cibas ES, et al. Prevalence and distribution of carcinoma in patients with solitary and multiple thyroid nodules on sonography. J Clin Endocrinol Metab. 2006;91(9):3411-7.
36. Fagin JA, Wells SA, Jr. Biologic and Clinical Perspectives on Thyroid Cancer. N Engl J Med. 2016;375(11):1054-67.
37. Davies L, Welch HG. Increasing incidence of thyroid cancer in the United States, 1973-2002. Jama. 2006;295(18):2164-7.
38. Vaccarella S, Franceschi S, Bray F, Wild CP, Plummer M, Dal Maso L. Worldwide Thyroid-Cancer Epidemic? The Increasing Impact of Overdiagnosis. N Engl J Med. 2016;375(7):614-7.
39. Kankerregistratie Nederland 2018 [Available from: www.iknl.nl/nkr-cijfers.
40. Hoang JK, Choudhury KR, Eastwood JD, Esclamado RM, Lyman GH, Shattuck TM, et al. An exponential growth in incidence of thyroid cancer: trends and impact of CT imaging. AJNR Am J Neuroradiol. 2014;35(4):778-83.
41. Ahn HS, Kim HJ, Welch HG. Korea's thyroid-cancer "epidemic"--screening and overdiagnosis. N Engl J Med. 2014;371(19):1765-7.
42. Park S, Oh CM, Cho H, Lee JY, Jung KW, Jun JK, et al. Association between screening and the thyroid cancer "epidemic" in South Korea: evidence from a nationwide study. Bmj. 2016;355:i5745.
43. Brito JP, Al Nofal A, Montori VM, Hay ID, Morris JC. The Impact of Subclinical Disease and Mechanism of Detection on the Rise in Thyroid Cancer Incidence: A Population-Based Study in Olmsted County, Minnesota During 1935 Through 2012. Thyroid. 2015;25(9):999-1007.
44. Vaccarella S, Dal Maso L, Laversanne M, Bray F, Plummer M, Franceschi S. The Impact of Diagnostic Changes on the Rise in Thyroid Cancer Incidence: A Population-Based Study in Selected High-Resource Countries. Thyroid. 2015;25(10):1127-36.
45. Grodski S, Brown T, Sidhu S, Gill A, Robinson B, Learoyd D, et al. Increasing incidence of thyroid cancer is due to increased pathologic detection. Surgery. 2008;144(6):1038-43; discussion 43.
46. Husson O, Haak HR, van Steenbergen LN, Nieuwlaat WA, van Dijk BA, Nieuwenhuijzen GA, et al. Rising incidence, no change in survival and decreasing mortality from thyroid cancer in The Netherlands since 1989. Endocr Relat Cancer. 2013;20(2):263-71.
47. La Vecchia C, Bosetti C, Lucchini F, Bertuccio P, Negri E, Boyle P, et al. Cancer mortality in Europe, 2000-2004, and an overview of trends since 1975. Ann Oncol. 2010;21(6):1323-60.

48. Davies L, Welch HG. Current thyroid cancer trends in the United States. JAMA Otolaryngol Head Neck Surg. 2014;140(4):317-22.
49. Sawant R, Hulse K, Sohrabi S, Yeo JCL, Pal K, Gibb FW, et al. The impact of completion thyroidectomy. Eur J Surg Oncol. 2019;45(7):1171-4.
50. van Velsen EFS, Massolt ET, Heersema H, Kam BLR, van Ginhoven TM, Visser WE, et al. Longitudinal analysis of quality of life in patients treated for differentiated thyroid cancer. Eur J Endocrinol. 2019;181(6):671-9.
51. Papaleontiou M, Reyes-Gastelum D, Gay BL, Ward KC, Hamilton AS, Hawley ST, et al. Worry in Thyroid Cancer Survivors with a Favorable Prognosis. Thyroid. 2019;29(8):1080-8.
52. Adam MA, Pura J, Gu L, Dinan MA, Tyler DS, Reed SD, et al. Extent of surgery for papillary thyroid cancer is not associated with survival: an analysis of 61,775 patients. Ann Surg. 2014;260(4):601-5; discussion 5-7.
53. Miyauchi A. Clinical Trials of Active Surveillance of Papillary Microcarcinoma of the Thyroid. World J Surg. 2016;40(3):516-22.
54. Tuttle RM, Fagin JA, Minkowitz G, Wong RJ, Roman B, Patel S, et al. Natural History and Tumor Volume Kinetics of Papillary Thyroid Cancers During Active Surveillance. JAMA Otolaryngol Head Neck Surg. 2017;143(10):1015-20.
55. Sugitani I, Toda K, Yamada K, Yamamoto N, Ikenaga M, Fujimoto Y. Three distinctly different kinds of papillary thyroid microcarcinoma should be recognized: our treatment strategies and outcomes. World J Surg. 2010;34(6):1222-31.
56. Ito Y, Miyauchi A, Kihara M, Higashiyama T, Kobayashi K, Miya A. Patient age is significantly related to the progression of papillary microcarcinoma of the thyroid under observation. Thyroid. 2014;24(1):27-34.
57. Perros P CS, Boelaert K, Evans C, Evans RM, Gerrard GE, Gilbert JA, Harrison B, Johnson SJ, Giles TE, Moss L, Lewington V, Newbold KL, Taylor J, Thakker RV, Watkinson J, Williams GR. British Thyroid Association Guidelines for the Management of Thyroid Cancer 2014 [Available from: https://onlinelibrary.wiley.com/doi/pdf/10.1111/cen.12515.
58. De Bleser L, Depreitere R, De Waele K, Vanhaecht K, Vlayen J, Sermeus W. Defining pathways. J Nurs Manag. 2006;14(7):553-63.
59. Castellnou S, Lifante JC, Polazzi S, Pascal L, Borson-Chazot F, Duclos A. Influence of Care Pathway on Thyroid Nodule Surgery Relevance: A Historical Cohort Study. J Clin Med. 2020;9(7).
60. Kwon H, Lee JH, Woo J, Lim W, Moon BI, Paik NS. Efficacy of a clinical pathway for patients with thyroid cancer. Head Neck. 2018;40(9):1909-16.
61. Rosato L, Avenia N, Bernante P, De Palma M, Gulino G, Nasi PG, et al. Complications of thyroid surgery: analysis of a multicentric study on 14,934 patients operated on in Italy over 5 years. World J Surg. 2004;28(3):271-6.
62. Bergenfelz A, Jansson S, Kristoffersson A, Mårtensson H, Reihnér E, Wallin G, et al. Complications to thyroid surgery: results as reported in a database from a multicenter audit comprising 3,660 patients. Langenbecks Arch Surg. 2008;393(5):667-73.

63. Bellantone R, Lombardi CP, Raffaelli M, Boscherini M, Alesina PF, De Crea C, et al. Is routine supplementation therapy (calcium and vitamin D) useful after total thyroidectomy? Surgery. 2002;132(6):1109-12; discussion 12-3.
64. Youngwirth L, Benavidez J, Sippel R, Chen H. Parathyroid hormone deficiency after total thyroidectomy: incidence and time. J Surg Res. 2010;163(1):69-71.
65. Sitges-Serra A, Ruiz S, Girvent M, Manjon H, Duenas JP, Sancho JJ. Outcome of protracted hypoparathyroidism after total thyroidectomy. Br J Surg. 2010;97(11):1687-95.
66. Astor MC, Lovas K, Debowska A, Eriksen EF, Evang JA, Fossum C, et al. Epidemiology and Health-Related Quality of Life in Hypoparathyroidism in Norway. J Clin Endocrinol Metab. 2016;101(8):3045-53.
67. David K, Moyson C, Vanderschueren D, Decallonne B. Long-term complications in patients with chronic hypoparathyroidism: a cross-sectional study. Eur J Endocrinol. 2018.
68. Underbjerg L, Sikjaer T, Mosekilde L, Rejnmark L. Cardiovascular and renal complications to postsurgical hypoparathyroidism: a Danish nationwide controlled historic follow-up study. J Bone Miner Res. 2013;28(11):2277-85.
69. Almquist M, Ivarsson K, Nordenstrom E, Bergenfelz A. Mortality in patients with permanent hypoparathyroidism after total thyroidectomy. Br J Surg. 2018;105(10):1313-8.
70. Harsløf T, Rolighed L, Rejnmark L. Huge variations in definition and reported incidence of postsurgical hypoparathyroidism: a systematic review. Endocrine. 2019;64(1):176-83.
71. Villarroya-Marquina I, Sancho J, Lorente-Poch L, Gallego-Otaegui L, Sitges-Serra A. Time to parathyroid function recovery in patients with protracted hypoparathyroidism after total thyroidectomy. Eur J Endocrinol. 2018;178(1):103-11.
72. Kim SM, Kim HK, Kim KJ, Chang HJ, Kim BW, Lee YS, et al. Recovery from Permanent Hypoparathyroidism After Total Thyroidectomy. Thyroid. 2015;25(7):830-3.
73. Brandi ML, Bilezikian JP, Shoback D, Bouillon R, Clarke BL, Thakker RV, et al. Management of Hypoparathyroidism: Summary Statement and Guidelines. The Journal of Clinical Endocrinology & Metabolism. 2016;101(6):2273-83.
74. Bollerslev J, Rejnmark L, Marcocci C, Shoback DM, Sitges-Serra A, van Biesen W, et al. European Society of Endocrinology Clinical Guideline: Treatment of chronic hypoparathyroidism in adults. Eur J Endocrinol. 2015;173(2):G1-20.
75. Perros P, Boelaert K, Colley S, Evans C, Evans RM, Gerrard Ba G, et al. Guidelines for the management of thyroid cancer. Clin Endocrinol (Oxf). 2014;81 Suppl 1:1-122.
76. Díez JJ, Anda E, Sastre J, Pérez Corral B, Álvarez-Escolá C, Manjón L, et al. Prevalence and risk factors for hypoparathyroidism following total thyroidectomy in Spain: a multicentric and nation-wide retrospective analysis. Endocrine. 2019;66(2):405-15.
77. Almquist M, Hallgrimsson P, Nordenstrom E, Bergenfelz A. Prediction of permanent hypoparathyroidism after total thyroidectomy. World J Surg. 2014;38(10):2613-20.
78. Banach R, Bartes B, Farnell K, Rimmele H, Shey J, Singer S, et al. Results of the Thyroid Cancer Alliance international patient/survivor survey: Psychosocial/informational support needs, treatment side effects and international differences in care. Hormones (Athens). 2013;12(3):428-38.

79. Asari R, Passler C, Kaczirek K, Scheuba C, Niederle B. Hypoparathyroidism after total thyroidectomy: a prospective study. Arch Surg. 2008;143(2):132-7; discussion 8.
80. Annebäck M, Hedberg J, Almquist M, Stålberg P, Norlén O. Risk of Permanent Hypoparathyroidism After Total Thyroidectomy for Benign Disease: A Nationwide Population-based Cohort Study From Sweden. Ann Surg. 2020.
81. Chadwick DR. Hypocalcaemia and permanent hypoparathyroidism after total/bilateral thyroidectomy in the BAETS Registry. Gland Surg. 2017;6(Suppl 1):S69-S74.
82. Cavicchi O, Piccin O, Caliceti U, Fernandez IJ, Bordonaro C, Saggese D, et al. Accuracy of PTH assay and corrected calcium in early prediction of hypoparathyroidism after thyroid surgery. Otolaryngol Head Neck Surg. 2008;138(5):594-600.

Part I

Refinement of surgical strategies

2

Chapter 2

Establishing a multi-center network for patients with thyroid nodules and cancer: effects on referral patterns

SPJ van Dijk, I Lončar, E van Veen-Berkx, WE Visser, RP Peeters, C van Noord, ET Massolt, M Castro Cabezas, M Schouten, EM von Meyenfeldt,TM van Ginhoven

Otolaryngol Head Neck Surg. 2022 Mar 15; online ahead of print.

Abstract

Objective

To perform a qualitative evaluation of the Thyroid Network, with a quantitative analysis of second opinion referrals for patients with thyroid nodules and cancer in the South-Western part of the Netherlands.

Methods

In this prospective observational study, all newly referred patients with thyroid nodules and cancer to the academic hospital from two years before and four years after the foundation of the Thyroid Network were registered. With the start of the Thyroid Network, we implemented (1) biweekly regional multidisciplinary tumor boards using video conference and (2) a regional patient care pathway for patients with thyroid nodules and cancer. For qualitative evaluation, interviews were conducted with a broad selection of stakeholders using maximum variation sampling. The primary outcome was the change in second opinions after the foundation of the Thyroid Network.

Results

Second opinions from Thyroid Network hospitals to the academic hospital decreased from 10 (30%) to 2 (7%) two years after start Thyroid Network ($p=0.001$), while patient referrals remained stable ($n=108$ to $n=106$). Qualitative evaluation indicated that both the uniform care pathway and the regional multidisciplinary tumor board were valued high.

Discussion

Establishing a regional network, including regional multi-disciplinary tumor boards and a care pathway for patients with thyroid nodules and cancer resulted in a decrease in second opinions within the Thyroid Network and high satisfaction of participating specialists.

Implications for Practice

The concept of the Thyroid Network could potentially spread to other regions as well as to other specialties in healthcare. Future steps would be to assess the effect of regional collaboration on quality of care and patient satisfaction.

Introduction

Problem description

In the South-Western part of The Netherlands (2.1 million habitants), clinical care for patients with thyroid nodules and cancer is provided by several hospitals i.e. one academic hospital (Erasmus University Medical Centre), four large medical teaching hospitals (1) and five general hospitals (~5.500 hospital beds), which is shown in Figure 1. Despite the close proximity of these ten hospitals to one another, no formal regional collaboration existed for the treatment of patients with thyroid nodules and cancer. This resulted in a lack of uniform protocols, absence of formal centralization rules for rare thyroid cancers, and a need for second opinions. Second opinions have the potential to make beneficial changes in treatment recommendations and prognosis in some patients (2). However, physical second opinions for advice that does not deviate from the initial advice are an example of inefficient care which can cause extra burden for patients entailing inconvenient patient travel, delays in care and higher costs. In addition, reducing unnecessary second opinions could be of benefit for the climate in general and infection prevention in terms of COVID-19 due to fewer travel needs.

Figure 1. The Thyroid Network hospitals in the South-Western region of the Netherlands.

Available knowledge

Thyroid cancer is a relatively rare disease (4.7 cases per 100.000 inhabitants in The Netherlands) requiring sufficient medical expertise. Guidelines recommend the use of a multidisciplinary approach and structured care pathways as the standard of care for patients with thyroid cancer (3, 4). Through continuous improvement, care pathways aim to improve the quality of clinical care, increase patient satisfaction and efficiency in the treatment of thyroid cancer (5-7).

Patients discussed at multidisciplinary tumor boards (MTBs) are more likely to receive more accurate and complete recommendations regarding diagnostics and treatments, especially in cancer care (8-11). Online MTBs attended by multiple regional hospitals are feasible to design and implement in a collaboration network with one academic medical hospital surrounded by multiple general hospitals (12-14). In the absence of regional MTB programs, hospitals are modifying variables affecting the chances of curative treatment and survival among patients with other malignancies (15-18). However, the impact of regional MTBs on patient referral patterns among regional hospitals concerning cancer care is unknown.

Rationale

We reasoned that implementation of a regional MTB and structured care pathway would reduce local practice variation and second opinions to the academic hospital. A uniform care pathway and biweekly MTBs have the potential to enhance the quality of care of patients with thyroid nodules and cancer as a whole at a regional level.

Specific aims

The aim of this study was to perform a qualitative evaluation of the Thyroid Network by means of structured interviews with participants. In addition a quantitative assessment was performed of the number of second opinions referred from Thyroid Network hospitals to the academic center regarding patients with thyroid nodules and/or cancer.

Methods

Context

Foundation of the Thyroid Network

To achieve standardized regional care for patients with thyroid nodules and cancer, the “SchildklierNetwerk” (English: Thyroid Network) was formed in January 2016. This collaboration among ten hospitals is managed by a daily board of five specialists. A scientific council was founded within the Thyroid Network to jointly review research initiatives and grant applications. Every two years, a regional symposium is organized at which updates on thyroid cancer are reviewed and scientific data are presented. Detailed information about the foundation of the Thyroid Network can be found in supplemental file 1.

Interventions

Intervention 1a:

A regional care pathway for patients with thyroid nodules and cancer was developed, which was adopted by all Thyroid Network hospitals (Supplemental file 2).

Intervention 1b:

Simultaneous with the start of the Thyroid Network, MTBs were implemented via video conference. Every two weeks, groups of 2 to 5 regional hospitals first conduct a local MTB, followed by one collective regional MTB with all participating hospitals. The local MTB existed prior to the initiation of the Thyroid Network. There are clear agreements in the regional care pathway for determining which patients will be discussed in the regional MTB.

Study of interventions

Data collection and patients for referral analysis

The analyzed cohort comprised all patients registered in the academic hospital from two years before to four years after the Thyroid Network foundation and all patients discussed at the regional MTB in the four years after the foundation. All newly referred patients with thyroid nodules (including multinodular goiter) and cancer to the academic hospital were prospectively registered. Referrals for Graves' disease, adjuvant radioactive iodine treatment and other thyroid diseases were registered separately and were therefore not included in this study. Baseline characteristics, diagnosis at presentation, way of entry in the academic hospital (second opinion, patient referral, or inter-collegial consultation from another specialty in the academic hospital (ICC)), treatment and patients vital status were collected. A patient referral was defined as a definite transfer of patient care (e.g. treatment or follow-up) from a general hospital to the academic hospital, while a second opinion was defined as a visit to a clinician in the academic hospital without transfer of care. Data were derived from the patient electronic health records (EHR) and referral letters. The regional MTB data from individual patients were registered following a structured protocol. The form contained the local EHR number of the patient, date of registration, and clinical characteristics such as TNM stage and the proposed treatment. TNM stage of patients were described using the 8th AJCC Cancer Staging Manual (19).

Interviews

The BeterKeten Foundation conducted a qualitative interview study with a broad selection of stakeholders. Interviewees were selected by purposive sampling, as well as maximum heterogeneity sampling (20). Purposive sampling involves the selection of interviewees with direct involvement to the research topic and aims to select information-rich cases for studying a topic in depth. Maximum heterogeneity sampling attempts to collect data from the most extensive range of perspectives possible about the topic of interest. In the current study, interviewees varied in age, medical specialty, hospital of employment, and duration of involvement with BeterKeten. The interviews were conducted by applying a realistic evaluation approach to identify context factors and underlying mechanisms that influence collaboration (21). In advance, two of the authors (EVB and MS) developed an interview guide with a list of open-ended questions to explore context factors, mechanisms and outcome patterns. A detailed description of these identified themes can be found in Supplemental file 3.

Measures

The primary outcome was the change in second opinions of in-Thyroid Network hospitals after the foundation of the Thyroid Network. Secondary outcomes were changes in second opinions from outside-network sources, patients referrals of in- and out-Thyroid Network sources, number of patients registered in the academic center and findings from the interviews.

For the quantitative analysis of referral patterns within the academic hospital, three cohorts were defined. The first cohort comprised patients who were referred to the academic hospital in the two years before the referring hospital joined the Thyroid Network and thus no regional MTB meeting available (pre-rMTB cohort). The second cohort consisted of all patients who were referred to the academic hospital or discussed in the regional MTB in the first two years after the referring hospital joined the Thyroid Network (early-rMTB cohort). Patients who were registered two to four years after the referring hospital joined the Thyroid Network were embedded in the continued cohort (cont-rMTB). A timeline regarding the foundation of the Thyroid Network and the cohorts are displayed in Figure 2.

The interviews were conducted face-to-face in the hospital or through video conferencing during COVID-19 pandemic. All semi-structured in-depth interviews were digitally audio recorded, anonymized and transcribed ad verbum. All respondents (n=24) gave permission to use the anonymous interview report for analysis.

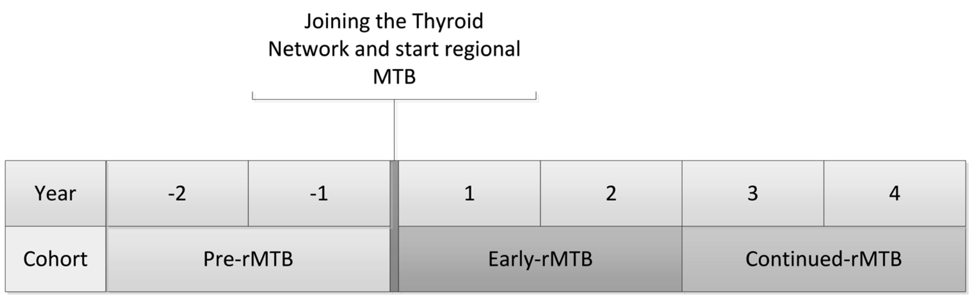


Figure 2. Timeline of the different cohorts.

Analysis

For the quantitative analysis, descriptive statistics were used to express continuous variables with normal distribution as mean with standard deviation or abnormal distribution as median with interquartile range. Distribution was assessed with the Shapiro-Wilk normality test. Categorical variables are described as count and percentage. Differences among the groups were analyzed with the Mood median test for continuous variables and the Pearson Chi-square test for nominal variables. SPSS Statistics version 25 (IBM Corp.) was used to perform all statistical analyses. P-values of <0.05 were considered significant.

For the qualitative data analysis of the interviews, ATLAS.ti version 8 software (ATLAS.ti Scientific Software Development GmbH) was used. At first, codes were assigned to the verbatim transcription of the recordings (open coding of raw data). Next, coded text fragments were sorted and grouped together into themes of context factors, mechanisms and outcomes/values. These fragments and themes were compared by means of axial and selective coding, which allowed for detecting patterns in responses. The most relevant and illustrative quotes were selected to invigorate the results of the qualitative data analysis. A concept version of these results was returned to participants to check for accuracy and resonance with their experiences. This is also known as 'member checking' or 'participant validation', a technique for exploring the credibility of results (22).

Ethical considerations

This study was approved by the Medical-Ethics Committee of Erasmus Medical Centre (MEC-2018-1195). The SQUIRE 2.0 guideline was used (Revised Standards for Quality Improvement Reporting Excellence) (23).

Results

Referral patterns

Trends in new patients with thyroid nodules or cancer referred to the academic hospital, without being discussed in a regional MTB

Within the six-year time frame (Figure 2), 908 new patients with thyroid nodules or cancer were registered at the thyroid center in the academic hospital, without previous discussion in the regional MTBs. Diagnoses at presentation included a suspicious thyroid nodule (n=460, 50.7%), thyroid cancer (n=243, 26.8%) and multinodular goiter (n=171, 18.8%). In total, 655 patients were referred from other hospitals (72.1%), 161 patients were referrals from other specialties within the academic hospital (17.7%) and 92 were referred for a second opinion (10.1%).

Analysis over the three cohorts (pre-, early-,cont-rMTB) shows that second opinions from general hospitals within the Thyroid Network significantly decreased from 30.3% (n=10) in the pre-rMTB cohort to 6.7% (n=2) in the cont-rMTB cohort (p=0.001). Second opinions from general practitioners decreased from 30.3% (n=10) to 3.3% (n=1) and second opinions from hospitals outside the region doubled. After the initiation of the Thyroid Network more referrals from hospitals outside the region were received. More details are given in Table 1.

Patients discussed in the regional MTBs

In total, 309 patients were discussed in the regional MTBs in a time range of 4 years. Thirty-nine patients were discussed for other thyroid diseases (e.g. parathyroid disease, auto-immune thyroiditis). These patients were excluded from the analysis, which resulted in a total of 270 discussed patients with thyroid nodules and/or cancer. In the early-rMTB cohort, 41.6% (n=62) of the patients discussed in the regional MTB were referred to the academic hospital, whereas this percentage was 47.9% (n=57) in the cont-rMTB cohort (Table 2).

Patients who were referred to the academic hospital after regional MTB discussion were more likely to have thyroid cancer (n = 90; 75.6% vs. n = 55; 36.9%, p<.001) and have a higher T-stage than patients that were recommended to stay at the local hospital (p=0.028). Also, 48% of patients with thyroid cancer referred to the academic hospital had lymph node metastases, as opposed to 7% who were recommended to stay at the local hospital (p<.001). Patients did not differ in M-stage and overall TNM stage (Table 3).

Table 1. Clinical characteristics of newly registered thyroid patients in the academic hospital[a]

	rMTB[b], No (%)				
Variable	**Pre -2 to 0 years**	**Early 0 to 2 years**	**Continued 2 to 4 years**	**p-value**	**Total**
Number of new registered patients	346 (38.1)	276 (30.4)	286 (31.5)		908
Age (years)	53 [40-64]	52 [44-65]	52 [41-62]	0.85	53 [42-64]
Sex				0.50	
Female	270 (78.0)	208 (75.4)	212 (74.1)		690 (76.0)
Male	76 (22.0)	68 (24.6)	74 (25.9)		218 (24.0)
Diagnosis at presentation				0.094	
Thyroid cancer	94 (27.2)	61 (22.1)	88 (30.8)		243 (26.8)
PTC	73 (21.1)	43 (15.6)	63 (20.0)		179 (19.7)
FTC	9 (2.6)	8 (2.9)	13 (4.5)		30 (3.3)
MTC	8 (2.3)	3 (1.1)	10 (3.5)		21 (2.3)
ATC	2 (0.6)	4 (1.4)	1 (0.3)		7 (0.8)
Other	2 (0.6)	3 (1.1)	1 (0.3)		6 (0.7)
Thyroid nodule	161 (46.5)	146 (56.5)	143 (50.0)		460 (50.7)
Multinodular Goiter	73 (21.1)	48 (17.4)	50 (17.5)		171 (18.8)
Other	18 (5.2)	11 (4.0)	5 (1.7)		34 (3.8)
Way of entry					
Referral	260 (75.1)	196 (71.0)	199 (69.6)	<0.001	655 (72.1)
TN-hospital	108 (41.5)	48 (24.5)	51 (25.6)		207 (31.6)
General practitioner	103 (39.6)	72 (36.7)	54 (27.1)		229 (35.0)
Hospitals outside the region	49 (18.8)	76 (38.8)	94 (47.2)		219 (33.4)
Second opinion	33 (9.5)	29 (10.5)	30 (10.5)	0.001	92 (10.1)
TN-hospital	10 (30.3)	2 (6.7)	2 (6.7)		14 (15.2)
General practitioner	10 (30.3)	12 (41.4)	1 (3.3)		23 (25.0)
Hospitals outside the region	13 (39.4)	15 (51.7)	27 (90.0)		55 (59.8)
Inter collegial consult (ICC)	53 (15.3)	51 (18.5)	57 (19.9)		161 (17.7)
Outpatient clinic endocrinology	342 (98.8)	254 (92.0)	275 (96.2)		871 (95.9)
Treatment				<0.001	
Medication, follow-up, no treatment	188 (54.3)	168 (60.9)	174 (60.8)		530 (58.4)
Surgery with or without RAI	122 (35.3)	71 (25.7)	67 (23.4)		260 (28.6)
RFA or sclerotherapy	7 (2.0)	17 (6.2)	36 (12.6)		60 (6.6)
Radioactive iodine	29 (8.4)	20 (7.2)	9 (3.1)		58 (6.4)
Current status of patients				<0.001	
Treated in the academic hospital	121 (35.0)	86 (31.2)	144 (50.3)		351 (38.7)
Out of treatment	208 (60.1)	178 (64.5)	136 (47.6)		522 (57.5)
Deceased	15 (4.3)	12 (4.3)	6 (2.1)		33 (3.6)
Unknown	2 (0.6)	0	0		2 (0.2)

Abbreviatons: ATC, anaplastic thyroid carcinoma; FTC, follicular thyroid carcinoma; MTC, medullary thyroid carcinoma; PTC, papillary thyroid carcinoma; RFA, radio frequency ablation; rMTB, regional multidisciplinary tumor board; TN, Thyroid Network.

[a] New patients with thyroid diseases referred to the academic hospital without being discussed in a rMTB b Pre: cohort of patients two years before joining the regional MTB. Early: cohort of patients two years after joining the rMTB. Continued:= cohort of patients two to four years after joining the rMTB. Data are expressed as numbers (percentage) or as median [IQR]

Table 2. Clinical characteristics of thyroid patients discussed in the rMTBs

	rMTB,[a]			
	Early 0 to 2 years	**Continued 2 to 4 years**	**p-value**	**Total**
Number of discussed patients	150	120		270
Age, y (n=7)	59 [49-73]	53 [41-69]	0.084	57 [46-73]
Sex			0.013	
Female	121 (80.7)	81 (67.5)		202 (74.8)
Male	29 (19.3)	39 (32.5)		68 (25.2)
Referrals (n=2)			0.303	
Treatment continuation in the academic center	62 (41.6)	57 (47.9)		119 (44.4)
Treatment continuation in local hospital after rMTB advice	87 (58.4)	62 (52.1)		149 (55.6)
rMTB advice			0.016	
Medication/follow-up/no treatment	51 (34.0)	39 (32.5)		90 (33.3)
Surgery with or without RAI	61 (40.7)	50 (41.7)		111 (41.1)
RFA or Sclerotherapy	1 (0.7)	9 (7.5)		10 (3.7)
RAI	25 (16.7)	19 (15.8)		44 (16.3)
Unknown	12 (8.0)	3 (2.5)		15 (5.6)

Abbreviations: RAI, radioactive iodine; RFA, radio frequency ablation; rMTB, regional multidisciplinary tumor board. a Early: cohort of patients 2 years after joining the rMTB. Continued: cohort of patients 2 to 4 years after joining the rMTB. Data are expressed as numbers (percentage) or as median [IQR]. Missing data is presented in parentheses behind variables

Table 3. Differences in clinical characteristics of patients discussed in the rMTBs

	Referred to the academic hospital	Recommended to stay at local hospital	p-value	Total
Number patients	119	149		268
Age in years (n=6)	55 [44-69]	58 [47-73]	0.198	57 [46-73]
Sex			0.629	
Female	88 (73.9)	114 (76.5)		202 (75.4)
Male	31 (26.1)	35 (23.5)		66 (24.6)
Diagnosis at presentation			<0.001	
Thyroid nodule	20 (16.8)	73 (49.0)		93 (34.7)
Multinodular Goiter	7 (5.9)	11 (7.4)		18 (6.7)
Other	2 (1.7)	10 (6.7)		12 (4.5)
Thyroid cancer	90 (75.6)	55 (36.9)		145 (54.1)
PTC	74	44		
FTC	10	8		
MTC	3	2		
ATC	1	0		
Other	2	1		
TNM staging[a]				
T (n=13)			0.028	
T1	22 (28.2)	22 (48.9)		44 (35.8)
T2	17 (21.8)	12 (26.7)		29 (23.6)
T3	30 (38.5)	10 (22.2)		40 (32.5)
T4	9 (11.5)	1 (2.2)		10 (8.1)
N (n=9)			<0.001	
N0/X	43 (51.8)	41 (93.2)		84 (66.1)
N1	40 (48.2)	3 (6.8)		43 (33.9)
M (n=7)			0.612	
M0/X	72 (88.9)	44 (91.7)		116 (89.9)
M1	9 (11.1)	4 (8.3)		13 (10.1)
Overall stage (n=9)			0.416	
Stage I	48 (60.0)	34 (72.3)		82 (64.6)
Stage II	19 (23.8)	9 (19.1)		28 (22.0)
Stage III	2 (2.5)	0		2 (1.6)
Stage IV	11 (13.8)	4 (8.5)		15 (11.8)
rMTB advice			<0.001	
Medication/follow-up/no treatment	16 (13.4)	74 (49.7)		90 (33.6)
Surgery with or without RAI	57 (47.9)	54 (36.2)		111 (41.4)
RFA or Sclerotherapy	7 (5.9)	3 (2.0)		10 (3.7)
RAI	39 (32.8)	4 (2.7)		43 (16.0)
Unknown	0	14 (9.4)		14 (5.2)

Abbreviations: ATC, anaplastic thyroid carcinoma; FTC, follicular thyroid carcinoma; MTC, medullary thyroid carcinoma; PTC, papillary thyroid carcinoma; RAI, radioactive iodine; rMTB, regional multidisciplinary tumor board. [a] For differentiated thyroid carcinomas (PTC and FTC)
Data are expressed as numbers (percentage) or as median [IQR]. Missing data is presented in parentheses behind variables

Patient flow in the three periods

The academic hospital was involved in 20% more patient treatment decisions after the implementation of the regional MTBs (n=346, pre-rMTB; n=426, early-rMTB ; n=406, cont-rMTB). Meanwhile, the number patients seen in the outpatient clinic remained stable (n=342, pre-rMTB; n=316, early-rMTB; n=332, cont-rMTB). The total number of referrals from the hospitals within the Thyroid Network also remained stable after the initiation of the regional MTB (n=108, pre-rMTB; n=108, early-rMTB; n=106, cont-rMTB; Figure 3).

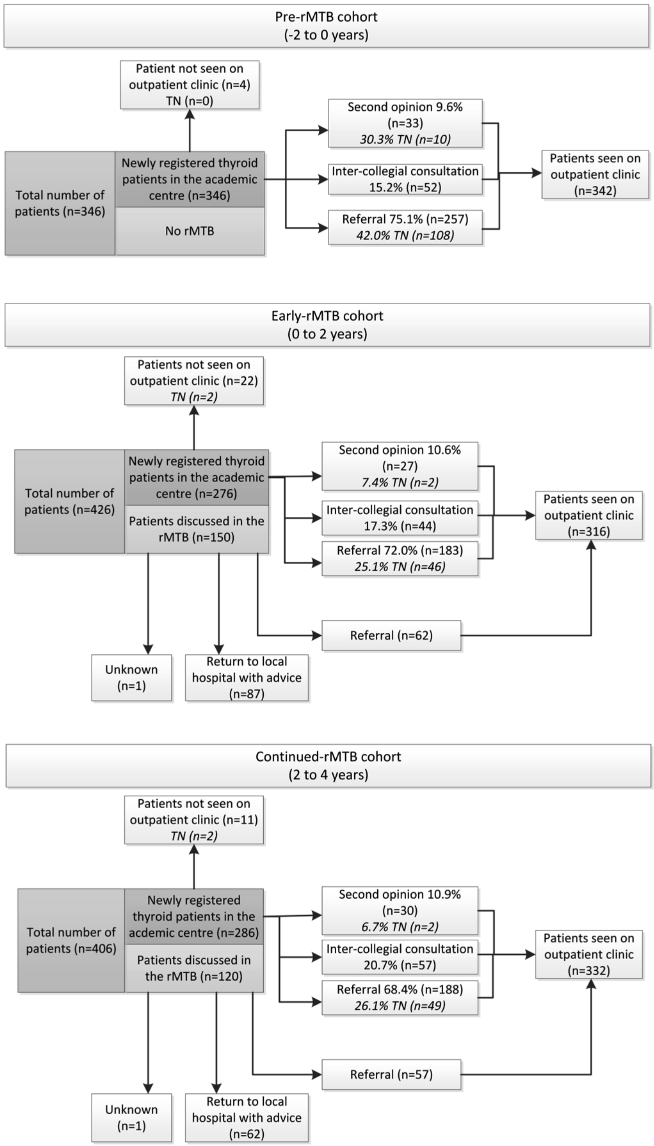


Figure 3. Patient flow in the different cohorts.

Interviews

The BeterKeten Foundation conducted a qualitative interview study with 24 stakeholders (24), including four board members of the Thyroid Network and 18 specialists from other regional networks of BeterKeten. The other regional networks each had their own regional MTB. The four board members of the Thyroid Network were from different hospitals and from two different specialties, surgery and endocrinology. A description of the selected participants is shown in Supplemental file 4.

Context factors and mechanisms

All respondents (24/24) acknowledged that by participating in a regional MTB, they learn from peers and enhance their knowledge and expertise. Written regional MTB evaluation shows that the majority of the respondents (22/24) found it desirable and/or interesting to join the regional MTB, even without presenting a case study of their own. One board member stated that the fact that the consulting academic hospital does not receive any compensation for patients who are discussed in the regional MTBs could be a restraining factor in the continuation of a regional network collaboration like the Thyroid Network.

Outcomes and values

The interview data showed that all four board members concordantly acknowledge and appreciate the added value in the cooperation within the Thyroid Network. The uniform care pathway for referral and treatment of patients and the associated biweekly structured joint regional MTB were indicated as most important for a successful collaboration by all board members.

"The most important aspect of BeterKeten, is that I am learning from others; I am expanding my knowledge as well as my professional network."[Respondent 8].

Another respondent emphasized the benefit of the regional MTB when it comes to saving travel time and providing a full professional opinion.

"When a patient, living outside the region of Rotterdam, says to me 'Doctor, I would like to be referred to the Erasmus MC, I can answer: 'I will provide even more: the university hospital and nine other hospitals'. The patient does not have to travel to Rotterdam, because his case is discussed in the regional MTB and the patient is provided with a professional opinion supported by ten different hospitals. Thus, care is provided close to home and it saves the patient a ride to Rotterdam and back." [Respondent 9].

Discussion

Summary

This prospective study evaluates the impact of a multicenter network on referral patterns within ten hospitals in the south-western region of the Netherlands. There were fewer second opinions from the hospitals within the Thyroid Network after the start of the regional MTBs while maintaining a stable amount of referrals for tertiary care. In addition, the academic hospital was involved in 20% more patient cases than before the start of the collaboration. The Thyroid Network can be indicated as a "professional learning network" in which the learning capacity is large and effective due to the continuity of the biweekly regional MTB.

Interpretation

Collaborating networks like the Thyroid Network often grow organically (25), leaving no opportunity to observe and analyze improvements in, for example, quality of care, hospitalization costs, referral patterns, or quality of life. By prospectively registering all newly referred patients with thyroid nodules and cancer, we were able to analyze and evaluate how the interventions influenced referral patterns in one of the largest academic hospitals in the Netherlands concerning thyroid care.

The implementation of the structured regional care pathway was intended to decrease regional practice variation and standardize referral patterns, thereby reducing second opinions. This is in line with the 2014 British Thyroid Association guideline on thyroid cancer (4), which recommends that hospitals providing secondary care for thyroid cancer patients should develop well-defined and streamlined pathways of referral and care for general practitioners. Several cancer guidelines for malignancies other than thyroid cancer recommend the initiation of regional MTBs to ensure that all relevant disciplines are involved, provide relevant educational opportunities for medical specialists, and reduce practice variation and individual physician biases (26, 27). In addition, the initiation of a structured care pathway and regional MTB is in line with the Dutch government promoting care close to the patient, where different healthcare providers cooperate and digital channels are increasingly used.

By conducting an online regional MTB, all patients with thyroid nodules/cancer in the south-western region of the Netherlands, regardless of the hospital in which the diagnosis is made, are offered the same optimal treatment. The regional MTB made it possible for general hospitals to instantly discuss and review patients, instead of referring them for second opinions. This leads to a more efficient and structured way of decision making and selective referral of patients necessitating academic expertise. This is reflected by the relatively lower number of patients needing to attend the outpatient clinic of the academic hospital. Patients do not have to travel for a second opinion, and due to the high number of participating hospitals in the regional MTB, patients are provided with a widely supported professional opinion. This is in accordance with a study from the United States on the implementation of online regional MTBs and the reduced burden of travel needs for patients with hepatocellular carcinoma (28).

Second opinions and referrals from hospitals outside the region doubled after the implementation of the Thyroid Network and the two intervention. Presumably, the structured collaborative approach implemented by the Thyroid Network is considered as best practice by these hospitals, which could be a reason for the increase in second opinions and referrals. Literature shows that interhospital collaboration facilitates the accessibility of hospitals with higher quality of care, resulting in improved outcomes for individual patients as well as for regional health care systems (29, 30). In addition, organizational centrality in a collaborating referral network is associated with fewer readmissions and lower hospitalization cost (31-33). This substantiates the assumption that an interhospital collaboration such as the Thyroid Network is the preferred approach in patients with thyroid nodules and cancer.

All board members of the Thyroid Network emphasized that the uniformly structured care pathway among general practitioners, general hospitals, and the academic hospital is a key ingredient for a successful interhospital collaboration of physicians concerning thyroid care. The close cooperation within the Thyroid Network ensures mutual trust to learn from one another and to share knowledge in formal as well as informal settings. Therefore, the Thyroid Network can be indicated as a "professional learning network".

There is one major negative consequence following the establishment of the Thyroid Network. In the Netherlands, costs concerning local MTBs can be charged by all hospitals. However, hospitals attending regional MTBs can claim their expenses only if they are the primary care provider for the discussed patient. Currently, the consulting academic hospital does not receive any compensation for patients who are discussed in the regional MTBs. All costs concerning the regional MTB patients (e.g. pathological specimen revisions) are covered from the academic hospitals' own resources. To create a sustainable, structured implementation of regional MTBs in the Netherlands, a regional MTB should come with a financial compensation.

Limitations

We were unable to assess changes in quality of care since we did not implement quality assessment tools yet. To assess the effect on quality of care after initiation of the Thyroid Network, qualitative analysis regarding treatment strategies, quality of life and treatment complications before and after the initiation of the Thyroid Network should be performed.

The interview study did not include any patients. This study was conducted within the Netherland's healthcare system; therefore, the results and implementation barriers may not extrapolate to other systems. Occasionally, there was insufficient documentation of patients who were discussed in the regional MTB. Although the number of unregistered patients is estimated to be low, the exact incidence is unknown and could not retrospectively be determined.

Conclusions

The interhospital collaboration of ten hospitals in the south-western region of the Netherlands and the initiation of the regional MTB have resulted in a decrease in second opinions from the Thyroid Network hospitals to the academic hospital while maintaining referrals for tertiary care. The regional MTB led to a 20% increase in patient cases wherein the academic hospital was involved. The concept of the Thyroid Network could spread to other regions as well as to other specialties in healthcare. The next step would be to integrate primary healthcare within the Thyroid Network and to assess the effect of the Thyroid Network on quality of care and patient satisfaction.

References

1. Samenwerkende Topklinische opleidingsZiekenhuizen (STZ) 2021 [updated 10-03-2021. Available from: https://www.stz.nl/.
2. Ruetters D, Keinki C, Schroth S, Liebl P, Huebner J. Is there evidence for a better health care for cancer patients after a second opinion? A systematic review. J Cancer Res Clin Oncol. 2016;142(7):1521-8.
3. Haugen BR, Alexander EK, Bible KC, Doherty GM, Mandel SJ, Nikiforov YE, et al. 2015 American Thyroid Association Management Guidelines for Adult Patients with Thyroid Nodules and Differentiated Thyroid Cancer: The American Thyroid Association Guidelines Task Force on Thyroid Nodules and Differentiated Thyroid Cancer. Thyroid. 2016;26(1):1-133.
4. Perros P CS, Boelaert K, Evans C, Evans RM, Gerrard GE, Gilbert JA, Harrison B, Johnson SJ, Giles TE, Moss L, Lewington V, Newbold KL, Taylor J, Thakker RV, Watkinson J, Williams GR. British Thyroid Association Guidelines for the Management of Thyroid Cancer 2014 [Available from: https://onlinelibrary.wiley.com/doi/pdf/10.1111/cen.12515.
5. De Bleser L, Depreitere R, De Waele K, Vanhaecht K, Vlayen J, Sermeus W. Defining pathways. J Nurs Manag. 2006;14(7):553-63.
6. Castellnou S, Lifante JC, Polazzi S, Pascal L, Borson-Chazot F, Duclos A. Influence of Care Pathway on Thyroid Nodule Surgery Relevance: A Historical Cohort Study. J Clin Med. 2020;9(7).
7. Kwon H, Lee JH, Woo J, Lim W, Moon BI, Paik NS. Efficacy of a clinical pathway for patients with thyroid cancer. Head Neck. 2018;40(9):1909-16.
8. Basta YL, Bolle S, Fockens P, Tytgat K. The Value of Multidisciplinary Team Meetings for Patients with Gastrointestinal Malignancies: A Systematic Review. Ann Surg Oncol. 2017;24(9):2669-78.
9. Pillay B, Wootten AC, Crowe H, Corcoran N, Tran B, Bowden P, et al. The impact of multidisciplinary team meetings on patient assessment, management and outcomes in oncology settings: A systematic review of the literature. Cancer Treat Rev. 2016;42:56-72.
10. Ung KA, Campbell BA, Duplan D, Ball D, David S. Impact of the lung oncology multidisciplinary team meetings on the management of patients with cancer. Asia-Pacific Journal of Clinical Oncology. 2016;12(2):e298-e304.
11. Specchia ML, Frisicale EM, Carini E, Di Pilla A, Cappa D, Barbara A, et al. The impact of tumor board on cancer care: evidence from an umbrella review. BMC Health Services Research. 2020;20(1):73.
12. Dharmarajan H, Anderson JL, Kim S, Sridharan S, Duvvuri U, Ferris RL, et al. Transition to a virtual multidisciplinary tumor board during the COVID-19 pandemic: University of Pittsburgh experience. Head Neck. 2020;42(6):1310-6.
13. Stevenson MM, Irwin T, Lowry T, Ahmed MZ, Walden TL, Watson M, et al. Development of a Virtual Multidisciplinary Lung Cancer Tumor Board in a Community Setting. Journal of Oncology Practice. 2013;9(3):e77-e80.
14. Lesslie M, Parikh JR. Implementing a Multidisciplinary Tumor Board in the Community Practice Setting. Diagnostics (Basel). 2017;7(4).

15. Ung KA, Campbell BA, Duplan D, Ball D, David S. Impact of the lung oncology multidisciplinary team meetings on the management of patients with cancer. Asia Pac J Clin Oncol. 2016;12(2):e298-304.
16. Rovers KP, Simkens GA, Vissers PA, Lemmens VE, Verwaal VJ, Bremers AJ, et al. Survival of patients with colorectal peritoneal metastases is affected by treatment disparities among hospitals of diagnosis: A nationwide population-based study. Eur J Cancer. 2017;75:132-40.
17. van Putten M, Verhoeven RH, van Sandick JW, Plukker JT, Lemmens VE, Wijnhoven BP, et al. Hospital of diagnosis and probability of having surgical treatment for resectable gastric cancer. Br J Surg. 2016;103(3):233-41.
18. van Putten M, Koëter M, van Laarhoven HWM, Lemmens V, Siersema PD, Hulshof M, et al. Hospital of Diagnosis Influences the Probability of Receiving Curative Treatment for Esophageal Cancer. Ann Surg. 2018;267(2):303-10.
19. Amin MB, Greene FL, Edge SB, Compton CC, Gershenwald JE, Brookland RK, et al. The Eighth Edition AJCC Cancer Staging Manual: Continuing to build a bridge from a population-based to a more "personalized" approach to cancer staging. CA: A Cancer Journal for Clinicians. 2017;67(2):93-9.
20. Green JTN. Qualitative methods for health research2014.
21. Pawson R, Tilley N. Realistic Evaluation: SAGE Publications; 1997.
22. Birt L, Scott S, Cavers D, Campbell C, Walter F. Member Checking: A Tool to Enhance Trustworthiness or Merely a Nod to Validation? Qual Health Res. 2016;26(13):1802-11.
23. Ogrinc G, Davies L, Goodman D, Batalden P, Davidoff F, Stevens D. SQUIRE 2.0 (Standards for QUality Improvement Reporting Excellence): revised publication guidelines from a detailed consensus process. BMJ Quality & Safety. 2016;25(12):986.
24. van Veen-Berkx E, Schouten MS, van der Woerd O. BeterKeten: Samen voor betere zorg. 2021.
25. Robinson TE, Rankin N, Janssen A, McGregor D, Grieve S, Shaw T. Collaborative research networks in health: a pragmatic scoping study for the development of an imaging network. Health Research Policy and Systems. 2015;13(1):76.
26. D'cruz A, Lin T, Anand AK, Atmakusuma D, Calaguas MJ, Chitapanarux I, et al. Consensus recommendations for management of head and neck cancer in Asian countries: A review of international guidelines. Oral Oncology. 2013;49(9):872-7.
27. Anderson BO, Yip C-H, Smith RA, Shyyan R, Sener SF, Eniu A, et al. Guideline implementation for breast healthcare in low-income and middle-income countries. Cancer. 2008;113(S8):2221-43.
28. Salami AC, Barden GM, Castillo DL, Hanna M, Petersen NJ, Davila JA, et al. Establishment of a Regional Virtual Tumor Board Program to Improve the Process of Care for Patients With Hepatocellular Carcinoma. J Oncol Pract. 2015;11(1):e66-74.
29. Lomi A, Mascia D, Vu DQ, Pallotti F, Conaldi G, Iwashyna TJ. Quality of care and interhospital collaboration: a study of patient transfers in Italy. Med Care. 2014;52(5):407-14.
30. Gaies M, Pasquali SK, Banerjee M, Dimick JB, Birkmeyer JD, Zhang W, et al. Improvement in Pediatric Cardiac Surgical Outcomes Through Interhospital Collaboration. J Am Coll Cardiol. 2019;74(22):2786-95.

31. Mascia D, Angeli F, Di Vincenzo F. Effect of hospital referral networks on patient readmissions. Soc Sci Med. 2015;132:113-21.
32. Spear SE. Reducing readmissions to detoxification: an interorganizational network perspective. Drug Alcohol Depend. 2014;137:76-82.
33. Uddin S, Hossain L, Kelaher M. Effect of physician collaboration network on hospitalization cost and readmission rate. Eur J Public Health. 2012;22(5):629-33.

Supplemental data chapter 2

Supplemental file 1: Detailed information of the foundation of the Thyroid Network and interventions

To achieve standardized regional care for patients with thyroid nodules and cancer, the "SchildklierNetwerk" (English: Thyroid Network) was formed in January 2016. This collaboration initially started with seven hospitals in January 2016 and in June 2017 three regional hospitals consecutively joined the Thyroid Network. The collaboration between the ten hospitals in the South-West region of the Netherlands was supported by the "BeterKeten Foundation", an organization initially established by Erasmus University Medical Centre and several hospitals in the Rotterdam region to support collaborations between healthcare institutions in patient care and scientific research. After iterative bottom-up procedures to define the care pathway, the Thyroid Network was formed and approved by all boards of directors of the participating hospitals. A board with five specialists was formed to manage the Thyroid Network. The Thyroid Network-board communicates with every hospital through a dedicated specialist functioning as a network representative. The Thyroid Network representatives disseminate the dedicated vision for inter-hospital partnership in their own hospital and beyond, supported by hospital management and local tumor boards.

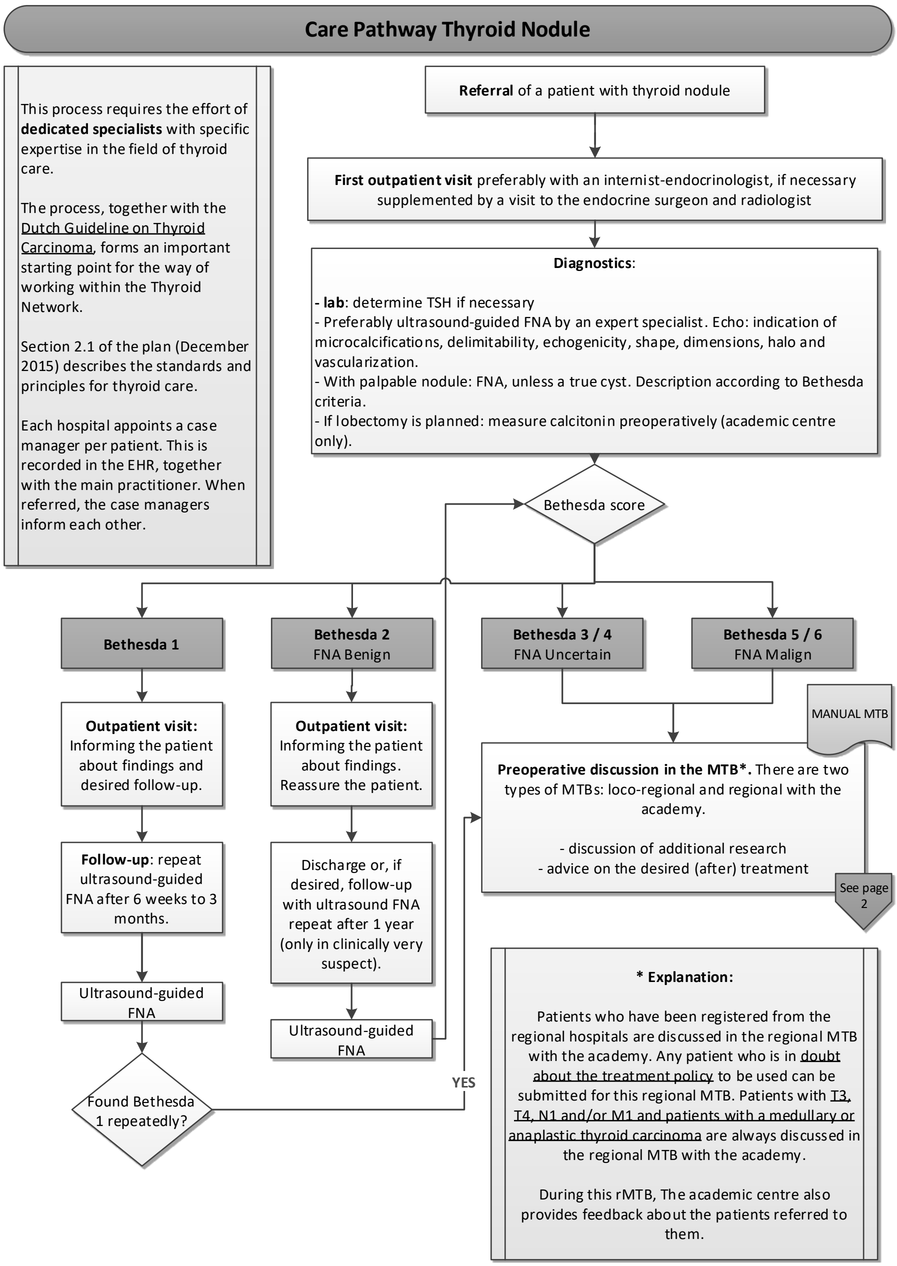
A scientific council was founded within the Thyroid Network to stimulate research initiatives and grant applications. Once every two years, a regional symposium is organized wherein researchers can present data and new research ideas regarding thyroid care. The Thyroid Network is also involved in the creation of patient information materials, including brochures and a website, for Thyroid Network-hospitals in the region. Clear communication with patient associations regarding research, expectations of patients, extension of collaborations, and innovation plans is aspired and established. Patient association SON (Thyroid Organisation Netherlands) is closely involved in the foundation and expansion of the Thyroid Network. The main purpose of the initiation of the Thyroid Network was to reduce practice variation and improve regional thyroid care. In order to do so, all participating hospitals agreed on a common regional care pathway. In order to achieve a homogeneous interpretation of these guidelines and to discuss complex or rare cases, a regional MTB was formed.

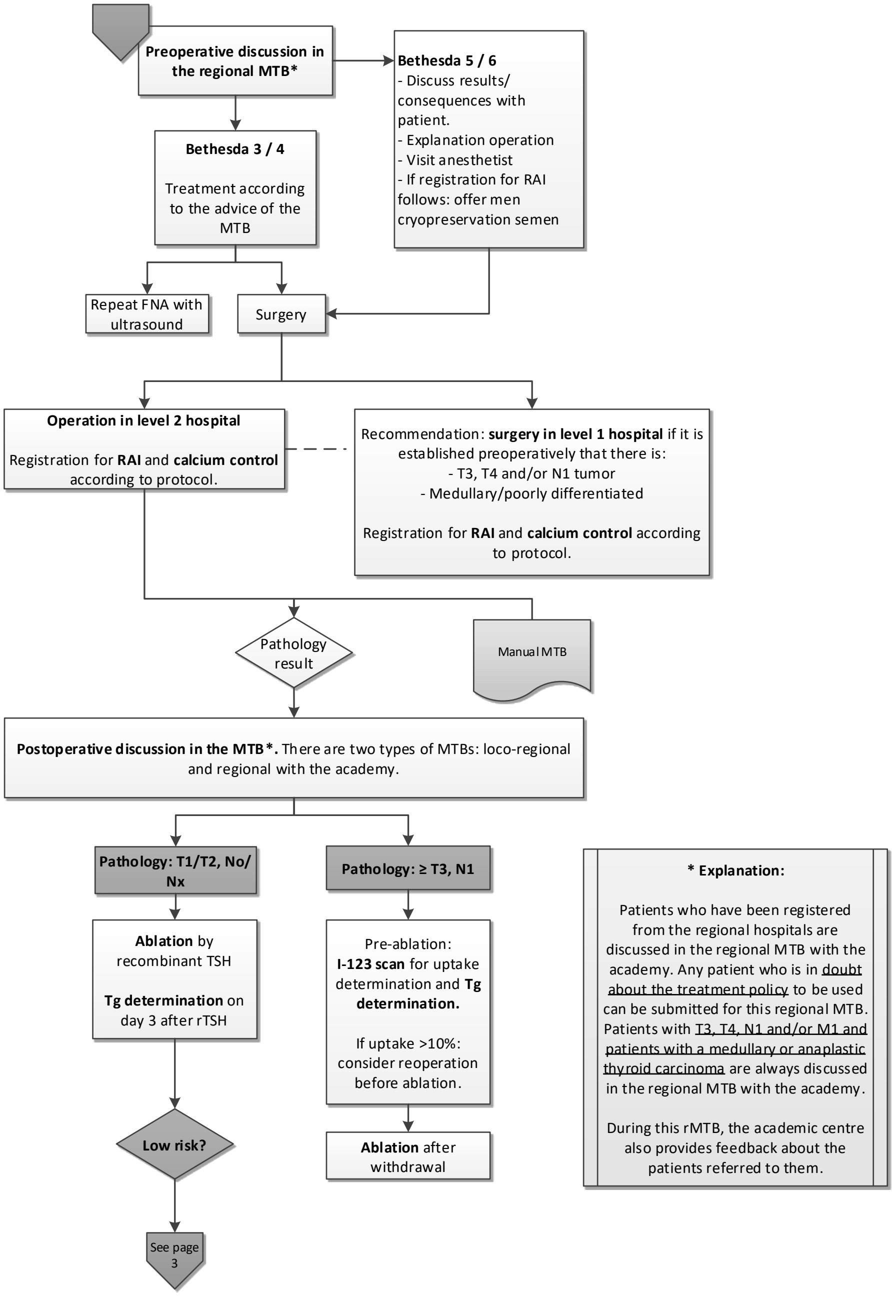
Regional MTBs

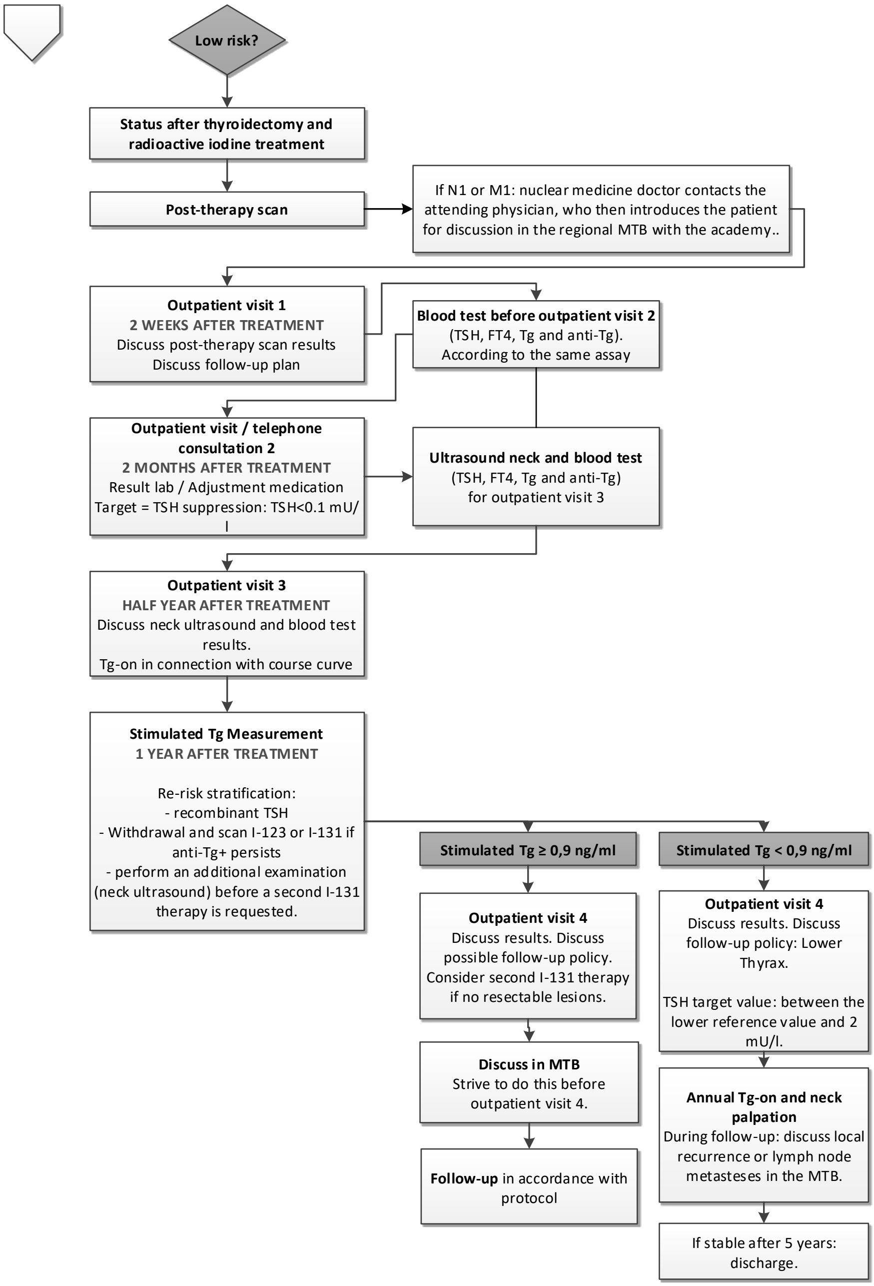
The regional MTBs were implemented using video conference. Every two weeks, groups of 2-5 regional hospitals conduct a local MTB, followed by one collective regional MTB with all participating hospitals. The local MTB already existed prior to the initiation of the Thyroid Network. There are clear agreements which patients will be discussed in the regional MTB. In accordance with the care pathway (Supplemental file 2), patients with T3, T4, N1 and/or M1 papillary or follicular carcinoma and medullary or anaplastic thyroid carcinoma are standardly discussed in the rMTB. Also, if there is any doubt about a treatment to be used or a second opinion is desired by the local team, the patient will be discussed. Physicians can register the patients for the regional MTB centrally with the coordinator at the academic hospital. The academic hospital will share the patient cases to all participating hospitals prior to the regional MTB so that the attending physicians can prepare. The sharing of patient data is done in accordance with Dutch privacy laws. The regional MTBs are conducted using a secured video conference connection. After each regional MTB, there is time for feedback and questions regarding the Thyroid Network.

Care pathway

With the national guideline as a basis, meetings were organized with representatives from each hospital wherein a conceptual care pathway was created. This concept was reviewed and discussed by physicians of all the hospitals in the Thyroid Network. Eventually, the board of the Thyroid Network approved the regional care pathway as it stands today.


Care Pathway Thyroid Nodule
This process requires the effort of dedicated specialists with specific expertise in the field of thyroid care.
The process, together with the Dutch Guideline on Thyroid Carcinoma, forms an important starting point for the way of working within the Thyroid Network.
Section 2.1 of the plan (December 2015) describes the standards and principles for thyroid care.
Each hospital appoints a case manager per patient. This is recorded in the EHR, together with the main practitioner. When referred, the case managers inform each other.
Referral of a patient with thyroid nodule
First outpatient visit preferably with an internist-endocrinologist, if necessary supplemented by a visit to the endocrine surgeon and radiologist
Diagnostics:
- lab: determine TSH if necessary
- Preferably ultrasound-guided FNA by an expert specialist. Echo: indication of microcalcifications, delimitability, echogenicity, shape, dimensions, halo and vascularization.
- With palpable nodule: FNA, unless a true cyst. Description according to Bethesda criteria.
- If lobectomy is planned: measure calcitonin preoperatively (academic centre only).
Bethesda score
Bethesda 1
Bethesda 2
FNA Benign
Bethesda 3 / 4
FNA Uncertain
Bethesda 5 / 6
FNA Malign
Outpatient visit: Informing the patient about findings and desired follow-up.
Outpatient visit: Informing the patient about findings. Reassure the patient.
MANUAL MTB
Preoperative discussion in the MTB*. There are two types of MTBs: loco-regional and regional with the academy.
- discussion of additional research
- advice on the desired (after) treatment
See page 2
Follow-up: repeat ultrasound-guided FNA after 6 weeks to 3 months.
Discharge or, if desired, follow-up with ultrasound FNA repeat after 1 year (only in clinically very suspect).
Ultrasound-guided FNA
Ultrasound-guided FNA
YES
Found Bethesda 1 repeatedly?
* Explanation:
Patients who have been registered from the regional hospitals are discussed in the regional MTB with the academy. Any patient who is in doubt about the treatment policy to be used can be submitted for this regional MTB. Patients with T3, T4, N1 and/or M1 and patients with a medullary or anaplastic thyroid carcinoma are always discussed in the regional MTB with the academy.
During this rMTB, The academic centre also provides feedback about the patients referred to them.


Preoperative discussion in the regional MTB*
Bethesda 5 / 6
- Discuss results/ consequences with patient.
- Explanation operation
- Visit anesthetist
- If registration for RAI follows: offer men cryopreservation semen
Bethesda 3 / 4
Treatment according to the advice of the MTB
Repeat FNA with ultrasound
Surgery
Operation in level 2 hospital
Registration for RAI and calcium control according to protocol.
Recommendation: surgery in level 1 hospital if it is established preoperatively that there is:
- T3, T4 and/or N1 tumor
- Medullary/poorly differentiated
Registration for RAI and calcium control according to protocol.
Pathology result
Manual MTB
Postoperative discussion in the MTB*. There are two types of MTBs: loco-regional and regional with the academy.
Pathology: T1/T2, No/ Nx
Pathology: ≥ T3, N1
Ablation by recombinant TSH
Tg determination on day 3 after rTSH
Pre-ablation:
I-123 scan for uptake determination and Tg determination.
If uptake >10%: consider reoperation before ablation.
Ablation after withdrawal
Low risk?
See page 3
* Explanation:
Patients who have been registered from the regional hospitals are discussed in the regional MTB with the academy. Any patient who is in doubt about the treatment policy to be used can be submitted for this regional MTB. Patients with T3, T4, N1 and/or M1 and patients with a medullary or anaplastic thyroid carcinoma are always discussed in the regional MTB with the academy.
During this rMTB, the academic centre also provides feedback about the patients referred to them.



Supplemental file 2: Regional Care Pathway for Patients with Thyroid Nodules

Disclaimer

This care path originates from the Thyroid Network in the Southwest Netherlands region. Each hospital is itself responsible for the quality and efficiency of the thyroid care as provided by their professionals to the patient. Although the professionals involved in the Thyroid Network do their best to provide all information, including this care path, as good and error-free to third parties for information, they cannot be held responsible for any errors or for keeping the care pathway 'up-to-date'. The Thyroid Network therefore waives any liability whatsoever, within the limits of Dutch law.

Supplemental file 3: Detailed description of the identified themes of 'context factors, mechanisms and outcomes' of regional collaboration

QUALITATIVE DATA ANALYSIS	
CONTEXT FACTORS	*Enabling regional network collaboration*
	Volume and quality standards defined by medical associations
	Collaborative approach in specialization and concentration of healthcare
	Professional and personal network
	Collaborative strategy and support from hospital board
	Restraining regional network collaboration
	The cost of collaboration: extra time and effort causing extra challenges for managing a healthy work/life-balance of doctors
	Financial-economic context: incentive to increase the quantity of provided services ('production incentive') and not necessarily the quality with which service are provided
MECHANISMS	Trust and respect for each other's professional skills and competencies
	Professional identity formation, professional pride and ambition, the presence of a respected 'expert' clinical leader
	Character traits of clinical leaders: vulnerability, openness, transparency, honest, approachable, conducive and respectful attitude
	The ability to share and learn from and with each other
	The balancing act between investing in and profiting from a collaborative learning network
	The personal ability to connect with other professionals
OUTCOMES/VALUE	Professional collaborative learning network or 'professional community': share knowledge and learn from and with each other on medical professional level as well as on organizational level (e.g. process improvement)
	Close network with easy and fast access to peers in other hospitals
	Complete continuum of care/health services available for patients
	Standardized methods and uniform quality information for patients
	Clearly defined referral patterns between health care providers/hospitals
	A 'professional opinion' widely supported by several doctors from different hospitals, extending beyond the well-known 'second opinion'
	Multicenter scientific research and PhD positions
	Collaborative networking accomplishes 'the right care in the right place' for patients

Supplemental file 4: Description of all 24 interviewed stakeholders of BeterKeten

The interviewees were medical specialists from the:
• Thyroid Network (n=4; two surgeons and two specialists in internal medicine, one with special emphasis on endocrine diseases)
• Pediatric Rheumatology Network (n=2; one rheumatologist and one pediatric rheumatologist)
• Partners for Gynecology Obstetrics and Reproductive Medicine (n=3; three gynecologists, one with special emphasis on reproductive medicine)
• Healthy Weight Center / The Obesity Clinic (n=3; one pediatrician and two specialists in internal medicine with special emphasis on endocrine diseases)

Follow-up reflection interviews were conducted with:
• Directors of the hospitals boards and chairmen of the medical board of all hospitals involved (BeterKeten board, n=8)
• Consultants of the project office of BeterKeten (n=2)
• Researchers from the Erasmus School of Health Policy & Management with expertise in health policy, network governance and regionalizing in The Netherlands (n=2)

3

Chapter 3

Radiofrequency ablation for benign symptomatic thyroid nodules in the Netherlands: successful introduction of a minimally-invasive treatment option improving quality of life

I Lončar, SPJ van Dijk, EFS van Velsen, SE Buijk, ND Niemeijer, CJ Veeken, EM von Meyenfeldt, W Dinkelaar, GJH Franssen, RP Peeters, ET Massolt, A Moelker, TM van Ginhoven

J Vasc Interv Radiol. 2022 May;33(5):530-537.e1

Abstract

Purpose
To determine whether adoption of radiofrequency ablation (RFA) in patients with symptomatic benign thyroid nodules (SBTNs) in a Dutch regional thyroid network resulted in clinical success and improvement in health-related and thyroid-related quality of life (QoL).

Materials and methods
The eligibility criteria for RFA were as follows: (a) nodule size between 2.0 and 5.0 cm, (b) solid component >20%; (c) benign cytology in 2 separate cytological assessments, and (d) symptoms unequivocally related to mechanical compression. The primary end point of this study was volume reduction 1 year after ablation. The secondary outcomes were health-related and thyroid-related QoL, measured using the short form health survey questionnaire (SF-36) and thyroid-specific patient-reported outcome questionnaire (ThyPRO-39), respectively, as well as adverse event rates.

Results
A total of 72 SBTNs in 67 patients were included. Median age was 50.0 (interquartile range, 41.0–56.0) years, and 91.0% were women. The median volume reduction at 6 weeks, 6 months, 1 year, 2 years, and 3 years was 51.0%, 63.9%, 65.2%, 81.3%, and 90.3%, respectively. The patients showed a significant improvement on the SF-36 physical component scale and ThyPRO-39 overall QoL-impact scale. An absolute improvement was seen in goiter and cosmetic complaints, determined using ThyPRO-39. The overall adverse event rate was 9.0%, of which 4.5% were considered major.

Conclusions
RFA is an effective treatment option for SBTNs, with a significant volume reduction and improvement in health-related and thyroid-related QoL.

Introduction

Epidemiologic studies show that about 5% of the adult population has a palpable thyroid nodule (1, 2). Although most thyroid nodules are benign and do not require medical treatment, some cause symptoms due to mechanical compression and mass effect, thus requiring an intervention. For a symptomatic benign thyroid nodule (SBTN), a hemithyroidectomy is the standard treatment. However, surgery may lead to complications such as wound infection in 0%-2%, haemorrhage up to 4.4%, and permanent laryngeal nerve paralysis ranging from 0%-11% (3-6). Furthermore, a scar is almost always visible, and 20-30% of the patients are at the risk of hypothyroidism, which may result in an impaired quality of life (QoL) despite adequate hormone supplementation (7, 8). As a result of these outcomes, non-surgical minimally invasive alternatives have been explored. One of the alternative procedures for treating SBTN is radiofrequency ablation (RFA). The principle is based on localized heating of tissue with a high-frequency alternating current, which leads to necrosis and shrinkage of the thyroid nodule without damaging the surrounding tissues (9). Nodule volume reductions of 50-80% within the first year after treatment were reported (10-14). Although RFA is considered safe, various adverse events may occur. A recent systematic review showed a major and minor complication rate of 2.4%, including recurrent nerve damage, skins burns, and haematomas (15). Additionally, data on health-related QoL after RFA are still limited, especially with regard to disease-specific questionnaires such as the thyroid-specific patient-reported outcome questionnaire (ThyPRO-39) (16). In 2015, the Dutch Thyroid Network (www.schildkliernetwerk.nl) was the first in the Netherlands to implement this technique based on promising reports from South-Korea and Italy (9, 17). In this study, step-wise implementation and the initial results of patients with a SBTN undergoing RFA in the Dutch Thyroid Network are described. The primary aim of this study was to analyze the nodule volume reduction. Because data on health-related QoL are scarce, a secondary aim of this study was to assess the health-related QoL and thyroid specific QoL using the short form health survey questionnaire (SF-36) and ThyPRO-39 questionnaire.

Materials and Methods

Patient selection and patient characteristics

Patients undergoing RFA treatment for an SBTN were prospectively evaluated in three centers offering dedicated RFA from the Dutch thyroid network: 1 was the University Medical Center (Erasmus MC in Rotterdam; EMC) and 2 were general hospitals (Albert Schweitzer hospital in Dordrecht; ASZ and Ijsselland hospital in Capelle aan den Ijssel; YSL). The Dutch thyroid network is a regional interhospital network collaboration of 10 hospitals in the southwest region of the Netherlands and aims to improve clinical thyroid care in the Netherlands. According to the regional care pathway, patients were eligible if the following criteria were fulfilled: ≥18 years of age; nodule size between 2.0 and 5.0 cm; solid component > 20%, and benign cytology (Bethesda II) in two separate cytological assessments (18). The upper limit of 5.0 cm was an extra measure of precaution in the initial phase. After some experience was gained, a slightly larger size could be accepted for an individual patient. Finally, mechanical mass effect complaints had to be severe enough that patients would be willing to undergo a different therapy (eg, surgery or radioiodine therapy). Mechanical mass effect complaints were defined as dysphagia, compression symptoms, a foreign body sensation, pain, or discomfort. None of the patients in this study were treated for cosmetic reasons. The exclusion criteria for RFA were as follows: contralateral vocal cord paralysis, anticoagulant therapy that could not be suspended, or unresolvable coagulation disorders. Patients with two or more nodules were not eligible for RFA primarily. However, deviation from the protocol was possible on an individual basis. For statistical analyses, 87 SBTNs treated in 80 patients between November 2015 and August 2020, enabling at least 6 months of follow-up, were included. Autonomously functioning thyroid hormone-secreting nodules, patients without informed consent, and patients without complete measurements were excluded (Fig 1). The baseline characteristics of the cohort are summarized in Table 1. The median age of the final study cohort was 50.0 (interquartile range [IQR], 41.0–56.0) years, and 91.0% were women. All the patients were euthyroid before the procedure. At the baseline, the largest median nodule diameter was 3.8 (IQR, 3.2–4.9) cm, and the median nodule volume was 15.5 (IQR, 8.4–32.0) mL. The treated nodules were mainly solid (90%; range, 80–100). Approval was obtained from the medical ethics committee of the Erasmus MC, and all the included patients gave informed consent. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement guidelines for reporting observational studies were used.

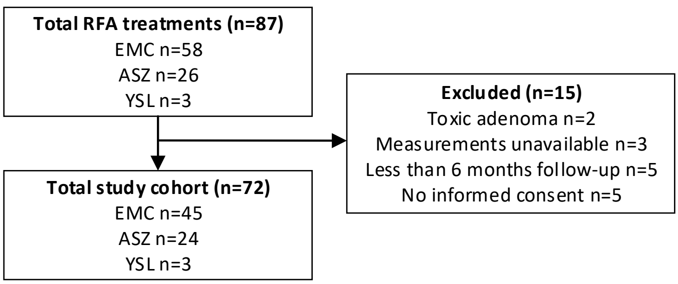


Figure 1. – Study flow chart

Pre-procedural assessment

The patients were informed about possible adverse events and were evaluated using clinical, laboratory, cytological, and ultrasound examinations before the RFA procedure. Three orthogonal diameters of the nodules were measured using ultrasound. The volume of the nodules was calculated using the ellipsoid formula:

$$V = \frac{\pi abc}{6}$$

V = Volume (mL)
a = Largest nodule diameter (cm)
b and c = Other two perpendicular diameters

The laboratory examinations included the measurement of serum thyroid-stimulating hormone (TSH; normal range 0.4–4.3 mU/L), free thyroxine (FT4; normal range 11.0–25.0 pmol/L), and erythrocyte sedimentation rate (normal range 0–20 mm/h); complete blood count; and blood coagulation tests (prothrombin time, activated partial thromboplastin time, international normalized ratio, and thrombocyte count)

Radiofrequency ablation procedure and implementation

Patients in the EMC and YSL hospitals were treated at the outpatient clinic under local anesthesia (10 mL of 2% lidocaine) and conscious sedation with analgesia or conscious sedation with propofol and fentanyl. In the ASZ hospital, patients were treated at the outpatient clinic under local anesthesia with 7.5 mg of midazolam. Under ultrasound guidance, the symptomatic benign thyroid nodule was accessed for ablation using a transisthmic approach and "moving-shot" technique, as described by Baek et al (1). We used an RF generator (HS Amica, Rome, Italy) and a VIVA RF system (MML Medical, Silvolde, The Netherlands) with a hand-sized 18-gauge electrode and an internally cooled 0.7- or 1.0-cm active tip. Ablation was initiated at 30 W and increased by 10 W if the desired effect was not observed within 30 seconds. Cystic components were aspirated at the discretion of the interventional radiologist performing the procedure. However, in most cases, the interventional radiologist would proceed to ablation primarily and not aspirate the cystic component first. Nodules with large cystic components could have been treated with aspiration and sclerosis in the first place. If a sharp increase in impedance above 300 Ω was observed, the needle was moved to an untreated area within the nodule. All treatments were performed or supervised by 1 interventional radiologist (A.M.). The first 20 patients were treated at the EMC hospital and admitted overnight. Subsequent patients were offered treatment in an outpatient setting. Thereafter, the same diagnostic workup and treatment protocol was implemented in YSL and ASZ hospitals.

Follow-up

Follow-up was performed using laboratory and ultrasound examinations; no other imaging modalities were used. Ultrasound examinations were performed at 6 weeks, 6 months, and 12 months and annually for at least 5 years thereafter. The thyroid function was biochemically assessed at 12 months. The percentage of volume reduction (VR) was calculated using the following formula:

$$VR = \frac{(IV - FV) \cdot 100}{IV}$$

VR = Volume reduction (%)
IV = Initial volume (mL)
FV = Final volume (mL)

A nodule size smaller than 10 mL was considered small, medium-sized nodules were defined as 10–20 mL, and large nodules were larger than 20 mL. Additional treatment was allowed if the VR after 1 year was insufficient and if the mechanical mass effect complaints persisted and were related to the thyroid nodule. All nodules showing signs of growth were evaluated cytologically prior to the second RFA treatment. The adverse events were defined based on the Society of Interventional Radiology classification system (19). Major adverse events were defined as those requiring therapy or hospitalization, those with permanent adverse sequelae, and death. Other adverse events were considered minor.

QoL assessment

Health-related QoL was assessed since 2019 by means of the validated Dutch version of the Short Form Health Survey (SF-36) before RFA treatment and at 3, 6 and months follow-up. The SF-36 is a validated and standardized instrument for the measurement of the health-related QoL (20). It is composed of 36 questions and standardized response choices in eight different dimensions: physical functioning, bodily pain, role limitations because of physical problems (physical component), general health, vitality, social functioning, role limitations because of emotional problems (emotional component), and mental health. All scores are linearly transformed to a 0 to 100 scale, with higher scores associated with better QoL. The scale scores were aggregated into two summary scores: a physical component summary (PCS) and a mental component summary (MCS). The component summary scores are standardized using normative data from the US general population with a mean score of 50 and a standard deviation of 10 (21). The thyroid specific QoL was measured at the same time points as the SF-36 using the Dutch translated Thyroid-specific Patient Reported Outcome short-form (ThyPRO-39) questionnaire, which is a validated questionnaire for thyroid diseases (16). The ThyPRO-39 is composed of 13 scales: goiter symptoms, hyperthyroid symptoms, hypothyroid symptoms, eye symptoms, tiredness, cognitive complaints, anxiety, depression, emotional susceptibility, impaired social life, impaired daily life, cosmetic complaints/appearance, and overall QoL-impact scale. Each item is rated on a 0-4 Likert scale from "no symptoms or problems" to "severe symptoms or problems". The ThyPRO-39 composite scale is based on the 22 items from the scales of tiredness, cognition, anxiety, depression, emotional susceptibility, impaired social life, impaired daily life, and overall QoL-impact scale. Scores are transformed to a 0 to 100 scale, with higher scores indicating a worsened QoL. Greater scores in the scales, overall QoL-impact, and Composite Scale indicate a worsened HRQOL. The ThyPro-39 composite scale and overall QoL-impact score were calculated.

End points

The primary end point of this study was the VR of the nodules 1 year after the RFA treatment. The secondary end points were health-related QoL, thyroid-specific QoL, and adverse event rate

Statistical analysis

The data were assessed for normality using the Shapiro-Wilk normality test. Continuous variables were expressed as medians with interquartile ranges as appropriate. Categorical variables were described as count and percentages. The Wilcoxon signed rank test was used to compare changes in largest nodule diameter, volume changes and changes in QoL between baseline and each follow-up moment. Two-tailed $p < 0.05$ values were considered statistically significant. For the QoL data, superiority testing was only performed for the SF-36 component scores (PCS and MCS) and the ThyPro-39 overall QoL-impact scale and composite scale due to the low number of cases. Statistical analyses were performed with IBM SPSS version 24.0 (Armonk, NY: IBM Corp).

Table 1. Baseline characteristics

Clinical values	No. (%)
Age (y)	50.0 [41.0 – 56.0]
Sex	
Male	6 (9.0%)
Female	61 (91.0%)
TSH (mU/L)	1.27 [0.82 – 1.66]
FT4 (pmol/L)	14.00 [12.30 – 16.40]
Diameter (cm)	3.8 [3.2 – 4.9]
Volume (mL)	15.5 [8.4 – 32.0]
Solidity (%)	90.0 [80.0 – 10.00]
Follow-up time (m)	11.3 [9.3 – 23.0]

Data are expressed as a percentage or as median [IQR]

Results

Follow-up after RFA regarding nodule diameter and volume

The largest nodule volume and median volume changes are depicted in Figure 2. The nodule volume decreased significantly from 15.5 (IQR, 8.4–32.0) mL to 5.4 (IQR,1.5–13.1) mL 1 year after the RFA treatment and 1.5 (IQR, 0.3–6.6) mL after 3 years, corresponding to a VR of 65.2% ($P < .001$) and 90.3% ($P = .012$), respectively. Initially, smaller and medium-sized nodules showed a greater VR at 1 year (71.4% and 76.7%, respectively) than larger nodules (60.1%) (Table 2). However, the VR was similar for small, medium, and large nodules after 2 years of follow-up (79.6%, 75.3%, and 75.5%, respectively). All the patients remained euthyroid at 1 year of follow-up. The median follow-up time was 11.3 (IQR, 9.3–23.0) months. Figure 3 shows the results of a case at 1 year of follow-up.

Necessity of re-treatment

Four (5.6%) patients underwent a second RFA session. One patient underwent 2 ablations, with no VR after either procedure and no change in the symptoms. The patient is considering alternative therapies. The remaining 3 patients underwent the second ablation session 1 year after the initial procedure because of persistent symptoms of mechanical compression despite a VR of 33.3%, 20%, and 42.5% in their SBTN. Of the 3 patients, 2 remained symptomatic despite achieving further VR (86.7% and 58.0%). The results of the third patient are forthcoming. A fifth patient experienced recurrence 4 years after RFA, with Bethesda IV histology in a cytological assessment, for which a hemithyroidectomy was performed (1.5% recurrence). The thyroid nodule was proven to be an adenoma on histopathology. Lastly, a sixth patient received radioiodine treatment for a multinodular goiter.

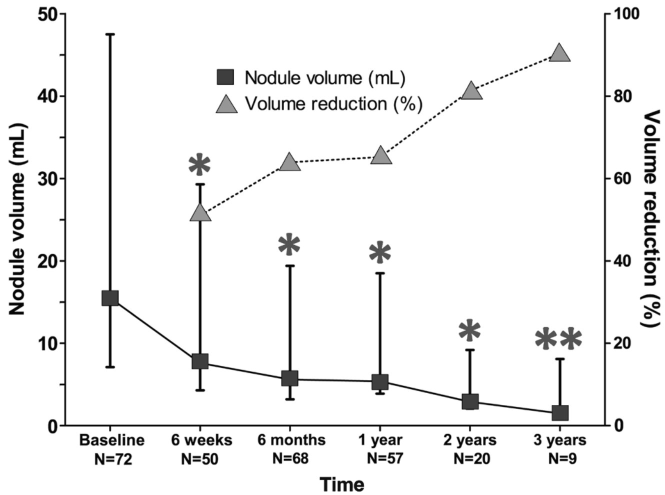


Figure 2. – Median nodule volume changes over time and volume reduction (VR). VR is reduction as compared to baseline. * p-value <0.001 ** p-value = 0.012. P-values for differences in volume are between baseline and each follow-up moment.

Table 2. Changes in thyroid nodule volume in smaller and larger nodules

	<10 mL			10-20 mL			>20 mL		
	No.	Volume (mL)	VR (%)	No.	Volume (mL)	VR (%)	No.	Volume (mL)	VR (%)
Baseline	23	4.9 [3.9-8.0]		24	14.6 [13.0-17.2]		25	44.1 [30.1-54.6]	
6 weeks	16	3.3 [2.1-5.9]	32.7	16	5.8 [4.5-8.9]	60.2	17	23.3 [20.8-25.4]	47.2
6 months	21	2.2 [1.1-3.1]	55.1	23	4.7 [2.9-8.1]	67.8	24	16.1 [10.5-25.8]	63.5
1 year	18	1.4 [1.0-2.7]	71.4	17	3.4 [1.4-7.1]	76.7	19	17.6 [10.5-25.8]	60.1
2 years	9	1.0 [0.1-2.2]	79.6	6	3.6 [0.9-5.1]	75.3	5	10.8 [6.8-16.9]	75.5
3 years	6	0.4 [0.1-2.2]	91.8	2			1		

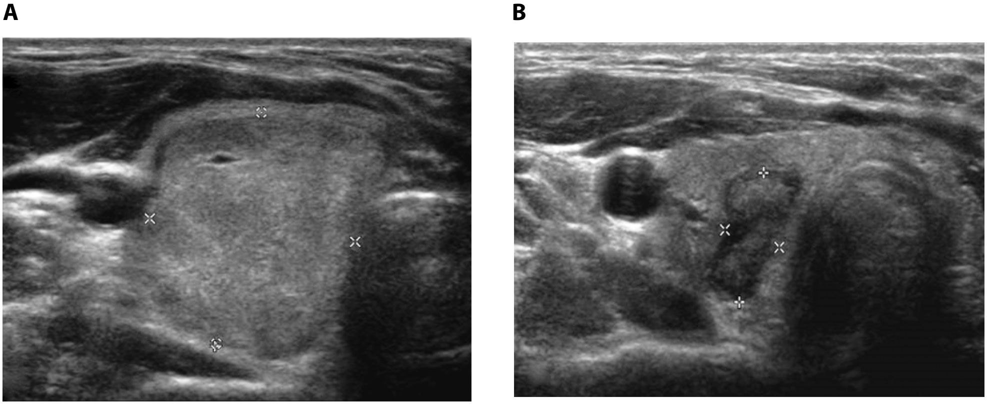


Figure 3. – (a) Transverse ultrasound image of a SBTN before RFA treatment measuring 3.3 x 2.0 x 2.1 cm (b) and 1 year after RFA treatment reduced in size to 1.5 x 1.0 x 0.6 cm.

Adverse events

The overall adverse event rate was 9.0 % (6/67), of which 3 (4.5%) were major and 3 (4.5%) were minor adverse events. One patient had a hematoma, which resolved spontaneously within weeks. Three patients complained of vocal changes, 2 of whom recovered within months without any intervention. Of the 3 major adverse events, one (1.5%) patient had a superior laryngeal nerve injury requiring speech therapy. The other 2 major adverse events were pain and swelling several days after the RFA treatment, both of which were deemed as sterile inflammation due to nodule rupture, as described by Shin et al (22).

QoL outcomes

In total, 19 patients were asked to respond to the question naires, of which 2 declined participation and 3 never responded. Therefore, the SF-36 and ThyPRO-39 questionnaires were completed by 14 patients before and after 3, 6, and 12 months. In this subgroup, the median age was 51.0 (IQR,46.0–55.5) years, 100% of the patients were women, and the baseline nodule volume was 19.4 (IQR, 13.7–37.8) mL, which is comparable with that in the total cohort. The median VR in this subgroup was 30.4%, 47.4%, and 53.1% at 6 weeks, 6 months, and 12 months, respectively. The QoL scores at the baseline and during follow-up for SF-36 and ThyPRO-39 are shown in Figures 4 and 5. The SF-36 PCS significantly improved after 3 months but was not significant at 6 and 12 months compared with that at the baseline. The ThyPRO-39 overall QoL-impact scale improved significantly after 3 months and remained significant during the next follow-up time points. A significant improvement was also seen in the composite scale after 3 months. The ThyPRO-39 score showed improvement in goiter symptoms, cosmetic complaints, and tiredness at 3, 6, and 12 months compared with those at the baseline. However, superiority was not statistically tested because of the small sample size.

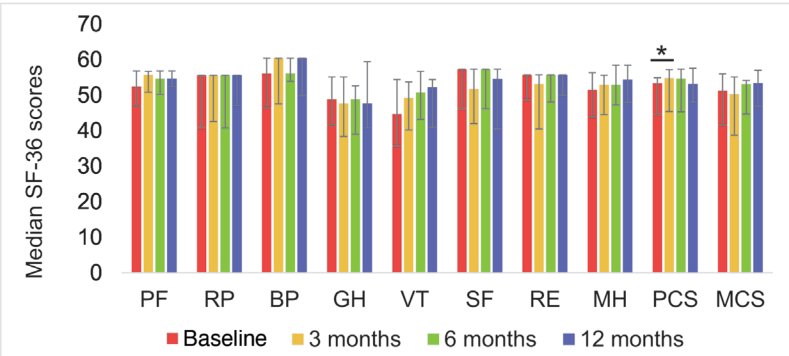


Figure 4. - Bar chart shows median Short Form Health Survey-36 dimension scores in patients before RFA treatment and 3, 6 and 12 months after RFA treatment. * p-value < 0.05, with Wilcoxon Signed ranks test. Data are presented as median [25-75].

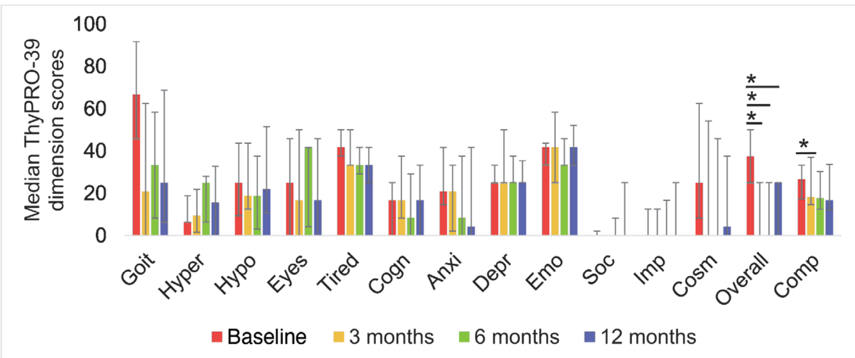


Figure 5. - Bar chart shows the median Short Form ThyPRO-39 dimension scores in patients before RFA treatment and 3, 6 and 12 months after RFA treatment. * p-value < 0.05, with Wilcoxon Signed ranks test. Data are presented as median [25-75].

Discussion

In 2015, the Thyroid Network in the South-West region of the Netherlands implemented RFA as a treatment modality for SBTN. This study reports the outcomes of introducing this technique and assessing the QoL using two questionnaires. RFA induced a significant VR of 70% at 1 year and approximately 80% at 2 years. These results are comparable with the published literature (23-26). A recent multicenter study demonstrated that the best response (a VR of 82% after 1 year) was achieved in small nodules with an initial volume of <10 mL (25). This study confirmed the occurrence of improved results of RFA for small SBTN at 1 year; however, the results were not maintained at two years of follow-up. Additionally, Rabuffi *et al.* did not find any relationship between nodule size and VR after 1 year (27). In this study, serum thyroid-stimulating hormone and free thyroxine levels remained within the normal range during the first year after RFA, which is consistent with the literature (10, 27).

The recurrence rate in this study was lower than that described in the literature (5.0% to 24.1%) (28, 29). Moreover, the number of patients requiring repeat treatment sessions (5.6%) was lower compared with that in the literature. Lim *et al.* showed that nearly 60% of patients required two or more sessions, and Spiezia *et al.* described repeat sessions in more than 34% of patients (24, 28). Furthermore, other studies have shown that a single treatment session is sufficient for the treatment of smaller SBTN but that multiple sessions may be required for large nodules, because of their higher recurrence risk (25, 30). However, a consensus or guidelines regarding the indication and timing repeat treatment sessions is still lacking.

Several studies have compared RFA with surgery in terms of efficacy and safety. Che *et al.* reported a higher rate of adverse events and longer hospitalization duration in patients who underwent surgery (31). However, the cost difference was not significant. Another study by Bernardi *et al.* showed that RFA costs 2.6 times less than surgery, without including social costs (32). In addition, surgery poses a higher risk of iatrogenic hypothyroidism and recurrent nerve paralysis (4, 7, 8). In the present study, the overall complication rate was 9.0%, which is higher than previously reported by Baek *et al* (12). They reported an adverse event rate rate as low as 3.3% in 1459 patients. These differences could be explained by the lower sample size and difference in procedural experience. The same study reported that major adverse event rates were significantly higher in patients treated by less-experienced operators (<50 ablations performed) than in patients treated by experienced operators (>100 ablations performed). It should be noted that all adverse events in this cohort occurred in the first 50 patients, and it is expected that the overall complication rate will be lower when more procedures are performed. Because of the interhospital collaboration of the Thyroid Network, RFA can be offered in dedicated hospitals which enables more rapid development and maintenance of expertise. Although, the complication rate was higher, only one patient had permanent vocal changes. Nevertheless, this highlights the fact that, similar to surgical interventions, patients complaints must be weighed against the disadvantages of the intervention and patients should be informed thoroughly regarding the risks.

The health-related QoL, measured using SF-36, of patients treated with RFA has been reported to be better than that of patients who undergo surgery for SBTN (33). The current study showed that patients undergoing RFA have a significant increase in the PCS score, measured using the SF-36 questionnaire, after 3 months. A previous study that measured the PCS score in a cohort in the Netherlands that underwent surgery for a SBTN did not show significant differences compared with the QoL at the baseline (34). Moreover, the patients in this cohort showed higher PCS scores at the measured time points, which suggests a benefit of RFA compared with surgery. The MCS scores showed similar results at every time point. A study by Valcavi *et al.* assessed the health-related QoL using the SF-12 health survey, which is a reduced form of the SF-36 questionnaire and can also be summarized using PCS and MCS score (35). They showed a significant improvement in both MCS and PCS 1 year after RFA treatment, which was maintained for more than two years. More recently a randomized controlled trial showed that thermal ablation for an SBTN was superior to surgery in terms of patient satisfaction and thyroid-related QoL (36). However, thyroid thermal ablation was defined as RFA and microwave ablation, and the effect of RFA alone was not evaluated. The thyroid-related QoL was measured using the thyroid-specific QoL questionnaire scale, which is a disease specific questionnaire for thyroid cancer survivors. This study showed that patients undergoing thermal ablation scored better in terms of physical, psychological and social well-being. A thyroid specific questionnaire, such as the ThyPRO-39 questionnaire, which has been validated for benign thyroid diseases, is expected to be more sensitive than a general health survey or a questionnaire for thyroid cancer survivors. In the ideal world, a randomized controlled trial would be performed to compare RFA with surgery, with a primary outcome of QoL, measured using thyroid specific questionnaires such as the ThyPRO-39. Currently, data on thyroid specific QoL measured using the ThyPRO-39 questionnaire in patients with an SBTN treated with RFA are scarce. A recent study showed a significant improvement of the thyroid-specific QoL 6 months after RFA (37). Unfortunately, no data on the specific domains were reported and longest follow-up duration was 6 months. On the contrary, in a study by Oddo *et al.,* improved QoL scores, measured using ThyPRO-39, were not observed within the first three years after RFA (38). It should be noted that their mean VR was only 27% after 1 year and 45% after three years, which is lower than that reported in the current and previous studies. This study showed a significant improvement in the ThyPRO-39 overall QoL-impact scale and composite scale. Furthermore, the ThyPRO-39 score showed improvement in goiter symptoms and cosmetic complaints, which corresponds to the adequate VR rates. However, superiority was not tested because of the small sample size. Other minimally invasive techniques, such as laser ablation, are being introduced for the treatment of SBTN. Laser ablation has shown promising results with significant improvement in thyroid-specific QoL, measured using the ThyPRO-39 (39, 40). Future studies will show which technique should be used for which patient, enabling patient tailored medicine.

This study has several limitations. First, it is a non-randomized study, without a direct comparison group. Second, the sample size was relatively small with a median follow up of 12 months. Therefore, limited conclusions regarding possible regrowth can be drawn (28, 29). Long-term follow-up data must be used to assess regrowth rates and concomitant cytology results. Third, the QoL assessment was performed only starting in 2019, resulting in only 14 patients with data. Because of the small number of patients, superiority testing was only performed for the SF-36 PCS and MCS as well as the ThyPRO-39 overall QoL-impact scale and composite scale. Moreover, some degree of bias could not be ruled out because the patients were asked to fill in questionnaires starting from 2019. Therefore, it is a reflection of the period in which more experience was gained with the RFA technique.

Conclusion

In conclusion, the current study showed that RFA is an effective treatment option for SBTNs, with significant VR and improvement in health-related and thyroid-related QoL. Although the major adverse event rates are relatively low, patient complaints must be weighed against the disadvantages of the intervention and patients should be informed thoroughly regarding the risks. RFA is a suitable alternative to the surgical treatment of SBTNs and can be offered to patients qualifying for treatment based on the severity of symptoms.

References

1. Mazzaferri EL. Management of a solitary thyroid nodule. N Engl J Med. 1993;328(8):553-9.
2. Vander JB, Gaston EA, Dawber TR. The significance of nontoxic thyroid nodules. Final report of a 15-year study of the incidence of thyroid malignancy. Ann Intern Med. 1968;69(3):537-40.
3. Liu J, Sun W, Dong W, Wang Z, Zhang P, Zhang T, et al. Risk factors for post-thyroidectomy haemorrhage: a meta-analysis. Eur J Endocrinol. 2017;176(5):591-602.
4. Bergenfelz A, Jansson S, Kristoffersson A, Mårtensson H, Reihnér E, Wallin G, et al. Complications to thyroid surgery: results as reported in a database from a multicenter audit comprising 3,660 patients. Langenbecks Arch Surg. 2008;393(5):667-73.
5. Dralle H, Sekulla C, Lorenz K, Brauckhoff M, Machens A, German ISG. Intraoperative monitoring of the recurrent laryngeal nerve in thyroid surgery. World J Surg. 2008;32(7):1358-66.
6. Medas F, Canu GL, Cappellacci F, Romano G, Amato G, Erdas E, et al. Antibiotic Prophylaxis for Thyroid and Parathyroid Surgery: A Systematic Review and Meta-analysis. Otolaryngol Head Neck Surg. 2021;164(3):482-8.
7. Verloop H, Louwerens M, Schoones JW, Kievit J, Smit JW, Dekkers OM. Risk of hypothyroidism following hemithyroidectomy: systematic review and meta-analysis of prognostic studies. J Clin Endocrinol Metab. 2012;97(7):2243-55.
8. Wekking EM, Appelhof BC, Fliers E, Schene AH, Huyser J, Tijssen JG, et al. Cognitive functioning and well-being in euthyroid patients on thyroxine replacement therapy for primary hypothyroidism. Eur J Endocrinol. 2005;153(6):747-53.
9. Kim YS, Rhim H, Tae K, Park DW, Kim ST. Radiofrequency ablation of benign cold thyroid nodules: initial clinical experience. Thyroid. 2006;16(4):361-7.
10. Baek JH, Kim YS, Lee D, Huh JY, Lee JH. Benign predominantly solid thyroid nodules: prospective study of efficacy of sonographically guided radiofrequency ablation versus control condition. AJR Am J Roentgenol. 2010;194(4):1137-42.
11. Baek JH, Lee JH, Valcavi R, Pacella CM, Rhim H, Na DG. Thermal ablation for benign thyroid nodules: radiofrequency and laser. Korean J Radiol. 2011;12(5):525-40.
12. Baek JH, Lee JH, Sung JY, Bae JI, Kim KT, Sim J, et al. Complications encountered in the treatment of benign thyroid nodules with US-guided radiofrequency ablation: a multicenter study. Radiology. 2012;262(1):335-42.
13. Jeong WK, Baek JH, Rhim H, Kim YS, Kwak MS, Jeong HJ, et al. Radiofrequency ablation of benign thyroid nodules: safety and imaging follow-up in 236 patients. Eur Radiol. 2008;18(6):1244-50.
14. Deandrea M, Sung JY, Limone P, Mormile A, Garino F, Ragazzoni F, et al. Efficacy and Safety of Radiofrequency Ablation Versus Observation for Nonfunctioning Benign Thyroid Nodules: A Randomized Controlled International Collaborative Trial. Thyroid. 2015;25(8):890-6.
15. Chung SR, Suh CH, Baek JH, Park HS, Choi YJ, Lee JH. Safety of radiofrequency ablation of benign thyroid nodules and recurrent thyroid cancers: a systematic review and meta-analysis. Int J Hyperthermia. 2017;33(8):920-30.

16. Watt T, Bjorner JB, Groenvold M, Cramon P, Winther KH, Hegedüs L, et al. Development of a Short Version of the Thyroid-Related Patient-Reported Outcome ThyPRO. Thyroid. 2015;25(10):1069-79.
17. Deandrea M, Limone P, Basso E, Mormile A, Ragazzoni F, Gamarra E, et al. US-guided percutaneous radiofrequency thermal ablation for the treatment of solid benign hyperfunctioning or compressive thyroid nodules. Ultrasound Med Biol. 2008;34(5):784-91.
18. Na DG, Lee JH, Jung SL, Kim JH, Sung JY, Shin JH, et al. Radiofrequency ablation of benign thyroid nodules and recurrent thyroid cancers: consensus statement and recommendations. Korean J Radiol. 2012;13(2):117-25.
19. Sacks D, McClenny TE, Cardella JF, Lewis CA. Society of Interventional Radiology Clinical Practice Guidelines. Journal of Vascular and Interventional Radiology. 2003;14(9, Part 2):S199-S202.
20. Aaronson NK, Muller M, Cohen PD, Essink-Bot ML, Fekkes M, Sanderman R, et al. Translation, validation, and norming of the Dutch language version of the SF-36 Health Survey in community and chronic disease populations. J Clin Epidemiol. 1998;51(11):1055-68.
21. Ware JE, Kosinski, M., Bayliss, M. S., McHorney, C. A., et al. Comparison of methods for the scoring and statistical analysis of SF-36 health profile and summary measures: Summary of results from the medical outcomes study. Medical Care. 1995;33(4):264-79.
22. Shin JH, Jung SL, Baek JH, Kim JH. Rupture of benign thyroid tumors after radio-frequency ablation. AJNR Am J Neuroradiol. 2011;32(11):2165-9.
23. Cesareo R, Palermo A, Pasqualini V, Simeoni C, Casini A, Pelle G, et al. Efficacy and safety of a single radiofrequency ablation of solid benign non-functioning thyroid nodules. Arch Endocrinol Metab. 2017;61(2):173-9.
24. Spiezia S, Garberoglio R, Milone F, Ramundo V, Caiazzo C, Assanti AP, et al. Thyroid nodules and related symptoms are stably controlled two years after radiofrequency thermal ablation. Thyroid. 2009;19(3):219-25.
25. Deandrea M, Trimboli P, Garino F, Mormile A, Magliona G, Ramunni MJ, et al. Long-Term Efficacy of a Single Session of RFA for Benign Thyroid Nodules: A Longitudinal 5-Year Observational Study. J Clin Endocrinol Metab. 2019;104(9):3751-6.
26. Trimboli P, Castellana M, Sconfienza LM, Virili C, Pescatori LC, Cesareo R, et al. Efficacy of thermal ablation in benign non-functioning solid thyroid nodule: A systematic review and meta-analysis. Endocrine. 2020;67(1):35-43.
27. Rabuffi P, Spada A, Bosco D, Bruni A, Vagnarelli S, Ambrogi C, et al. Treatment of thyroid nodules with radiofrequency: a 1-year follow-up experience. J Ultrasound. 2019;22(2):193-9.
28. Lim HK, Lee JH, Ha EJ, Sung JY, Kim JK, Baek JH. Radiofrequency ablation of benign non-functioning thyroid nodules: 4-year follow-up results for 111 patients. Eur Radiol. 2013;23(4):1044-9.
29. Sim JS, Baek JH, Lee J, Cho W, Jung SI. Radiofrequency ablation of benign thyroid nodules: depicting early sign of regrowth by calculating vital volume. Int J Hyperthermia. 2017;33(8):905-10.
30. Huh JY, Baek JH, Choi H, Kim JK, Lee JH. Symptomatic benign thyroid nodules: efficacy of additional radiofrequency ablation treatment session--prospective randomized study. Radiology. 2012;263(3):909-16.

31. Che Y, Jin S, Shi C, Wang L, Zhang X, Li Y, et al. Treatment of Benign Thyroid Nodules: Comparison of Surgery with Radiofrequency Ablation. AJNR Am J Neuroradiol. 2015;36(7):1321-5.
32. Bernardi S, Dobrinja C, Fabris B, Bazzocchi G, Sabato N, Ulcigrai V, et al. Radiofrequency ablation compared to surgery for the treatment of benign thyroid nodules. Int J Endocrinol. 2014;2014:934595.
33. Yue WW, Wang SR, Li XL, Xu HX, Lu F, Sun LP, et al. Quality of Life and Cost-Effectiveness of Radiofrequency Ablation versus Open Surgery for Benign Thyroid Nodules: a retrospective cohort study. Sci Rep. 2016;6:37838.
34. Dulfer R, Geilvoet W, Morks A, van Lieshout EM, Smit CP, Nieveen van Dijkum EJ, et al. Impact of parathyroidectomy for primary hyperparathyroidism on quality of life: A case-control study using Short Form Health Survey 36. Head Neck. 2016;38(8):1213-20.
35. Valcavi R, Tsamatropoulos P. Health-Related Quality of Life after Percutaneous Radiofrequency Ablation of Cold, Solid, Benign Thyroid Nodules: A 2-Year Follow-up Study in 40 Patients. Endocr Pract. 2015;21(8):887-96.
36. Jin H, Lin W, Lu L, Cui M. Conventional thyroidectomy vs thyroid thermal ablation on postoperative quality of life and satisfaction for patients with benign thyroid nodules. Eur J Endocrinol. 2021;184(1):131-41.
37. Jawad S, Morley S, Otero S, Beale T, Bandula S. Ultrasound-guided radiofrequency ablation (RFA) of benign symptomatic thyroid nodules - initial UK experience. Br J Radiol. 2019;92(1098):20190026.
38. Oddo S FE, Repetto AM, Mussap M and Giusti M. Quality of life in patients treated with radiofrequency ablation for thyroid nodules. Res J Endocrinol Metab. 2016;4(1).
39. Oddo S, Felix E, Mussap M, Giusti M. Quality of Life in Patients Treated with Percutaneous Laser Ablation for Non-Functioning Benign Thyroid Nodules: A Prospective Single-Center Study. Korean J Radiol. 2018;19(1):175-84.
40. Bernardi S, Giudici F, Cesareo R, Antonelli G, Cavallaro M, Deandrea M, et al. Five-Year Results of Radiofrequency and Laser Ablation of Benign Thyroid Nodules: A Multicenter Study from the Italian Minimally Invasive Treatments of the Thyroid Group. Thyroid. 2020;30(12):1759-70.

5

Chapter 5

Is less always more in a national well-differentiated thyroid cancer population?

MJH Metman, I Lončar, S Kruijff, AF Engelsman, TM van Ginhoven

Eur J Surg Oncol. 2020;46(4 Pt A):709-11.

Letter to the editor

With great interest, we have read the manuscript of Sawant and Nixon et al. in the European Journal of Surgical Oncology (1) and the subsequent comments of Shaha and Tuttle (2). Both highlight the need for understanding the biology for well-differentiated thyroid cancer and the philosophy of "less is more" in this population. Whether or not to perform a total thyroidectomy followed by radioactive iodine for low-risk well-differentiated thyroid cancer is a daily subject of debate in the Netherlands, but also worldwide.

In this letter to the editor we want to discuss the following; although the guideline of the American Thyroid Association (ATA) is very clear about the option of de-escalating treatment with a hemithyroidectomy, we would like to caution for extrapolating this practice worldwide. Each nation has its own pathway in which the patients are referred to the hospital and diagnosed with papillary thyroid cancer (PTC) or follicular thyroid cancer, also known as well-differentiated thyroid cancer (DTC). This nation specific form of selection greatly affects the biological behaviour of DTC the local treating physicians are confronted with. Therefore, we envision that prior to implementing ATA guidelines one must assess the comparability of the patient population.

It is known that the incidence of thyroid cancer is rising due to increased use of imaging modalities such as ultrasonography, MRI and PET/CT scan, which mainly leads to the identification of small well-differentiated papillary thyroid carcinomas and thyroid incidentalomas without improving survival rate of the disease (3,4). DTC has an excellent 10-year overall survival rate of 96% (5) and the stable overall survival rate suggests widespread overtreatment following current treatment strategy (4). Therefore, changing treatment strategies for low-risk DTC patients is of great importance. This is reflected by the 2015 ATA guidelines stating that hemithyroidectomy is sufficient for patients with low-risk DTC (6) based on large national USA registration database studies (7). However, the main question is: "Is the patient selected with low-risk DTC in the USA similar to the low-risk DTC patient in the Netherlands or any other country?.

Here we explain our doubt regarding the comparability of the USA and Dutch patient selection. The ATA guideline (recommendation 6) states: "Diagnostic ultrasound should be performed in all patients with a suspected radiographic abnormality suggesting a thyroid nodule incidentally detected on another imaging study." (6) The decision to perform FNA is thereafter based on the sonographic characteristics and size of the nodule. In contrast, our 2015 Dutch guideline states to fully refrain from further diagnostic workup of the thyroid incidentalomas (TI). TI's are defined as an unexpected, asymptomatic thyroid nodule discovered during the investigation of an unrelated condition by means of any imaging modality, such as ultrasound, CT-scan or MRI. (For clarity, FDG avid TI discovered by means of PET/CT scanning are subsequently analysed by ultrasound and FNA) (8). These differences in guideline result in a completely different population by selection, whereas in the Netherlands probably small TI's mainly comprising of DTC are not diagnosed.

The USA following the ATA 2015 guideline results that in the practice more patients are diagnosed with cancer after which treatment is de-escalated, whereas the Dutch guidelines make sure these patients are not selected and subsequently not diagnosed at all. Survival rates of patients with thyroid cancer in the Netherlands are excellent and comparable to international literature (9). This supports our belief that early diagnosis and treatment of low-risk DTC patients does not lead to better outcomes in terms of oncological benefit. This was illustrated a decade ago in an almost shocking way when the South Koreans started a screening program which resulted in an explosion of small PTC rates in the general population without a change in mortality pathognomonic for overdiagnosis (3).

Table 1. Comparison of DTC populations. In column A data of Sawant et al. (1) and in column B the Dutch DTC population based on data of the Netherlands Cancer Registry.

	A: Sawant et al.		B: Dutch DTC population	
Disease	**Number of cases**	**Percentage (%)**	**Number of cases**	**Percentage (%)**
pT stage				
T0/Tx	na	na	45	1.5
T1	44	27	1273	43.5
T2	73	45	691	23.6
T3	40	25	728	24.9
T4	4	3	66	2.3
T missing	na	na	121	4.1
pN Stage				
N0/Nx	151	94	2120	72.5
N+	10	6	683	23.4
N missing	na	na	121	4.1
pM Stage				
M0/Mx	na	na	2865	98
M1	na	na	55	1.9
M missing	na	na	4	0.1
Histology				
FTC	73	45	452	15.5
PMC	87	54	2472	84.5
FTC/PMC	1	0.6	na	na

na: not available

The answer to the question "Is the population of patients selected with low-risk DTC in the USA similar to the low-risk DTC patient in the Netherlands?" seems therefore be answered with "No". We compared the population of Sawant et al. used to support their conclusion to only perform completion thyroidectomy for patients who will benefit from surgery with our Dutch DTC population, refer to Table 1. We collected data from the Netherlands Cancer Registry from 2010 to 2015. Median age at diagnosis was higher in the Netherlands compared to Sawant et al. which will affect mortality. Additionally, we identified an important difference in TNM stage in the data In the Netherlands, a higher percentage of pT1 tumor, N+ and PTCs was observed.

A sub-analysis of our DTC population between 2005 and 2015, also showed a different population low risk PTCs compared to Adam et al. (7), which is based on the National Cancer Database in the United states of America. As expected Fig. 1 shows a higher percentage of PTCs ranging from 2 to 4 cm found during histopathological examination in the Dutch population, which is considered a prognostic factor. However, we do observe a lower percentage of nodal and distant metastasis in our population. All mentioned differences in our DTC and PTC subpopulation are still leading to an excellent survival rate (9) and do not indicate any undertreatment in the Netherlands as a consequence of a significantly different diagnostic workup and therefore selection of patients.

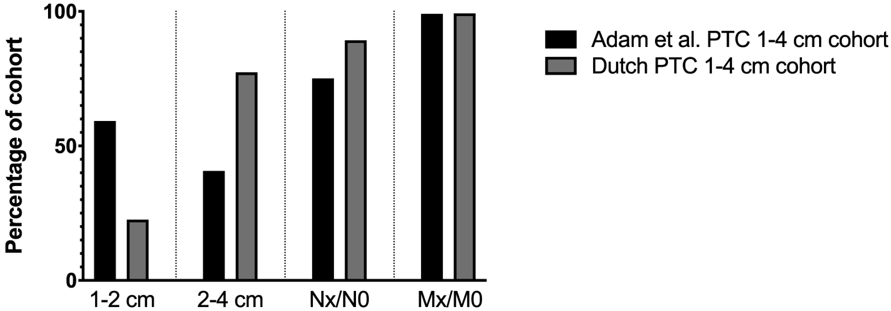


Figure 1. Comparison of PTCs ranging from 1 to 4 cm cohorts of Adam et al. (black bars) and the Netherlands (grey bars). This figure shows the differences in tumor size 1-2 cm (59.3% vs 22.6%) and tumor size 2-4 cm (40.7% vs 77.4%) between cohorts. Differences in percentages of absent nodal metastasis (75.1% vs 89.3%) and absent distant metastasis (99.1 % vs 99.3%) are displayed.

We postulate that the Dutch population harbours less incidentally discovered indolent tumors and consequently question the safety of implementing a de-escalated treatment following the 2015 ATA guideline in the Netherlands without the thorough analysis of our own data.

Therefore, to assess the safety and impact of de-escalation of treatment in the already selected Dutch population with low risk PTCs ranging from 1 to 4 cm a national randomized controlled trial is currently designed comparing total thyroidectomy followed by radioactive iodine treatment with hemithyroidectomy followed by active surveillance.

In this comment, we explained our concerns about implementing a de-escalated treatment without thorough data analysis and we showed the differences in the Dutch DTC population as a consequence of differences in diagnostic workup. We still believe in "less is more" and look forward to conduction the national trial. It is our ambition to combine both reduced diagnostics with reduced treatments while maintaining safe oncological care and higher quality of life.

References

1. Sawant R, et al. The impact of completion thyroidectomy. Eur J Surg Oncol 2019;45:1171e4.
2. Shaha AR, Michael Tuttle R. Completion thyroidectomy-indications and complications. Eur J Surg Oncol 2019;45:1129e31.
3. Ahn HS, et al. Korea's thyroid-cancer "epidemic"–screening and overdiagnosis. N Engl J Med 2014;371:1765e7.
4. Vaccarella S, et al. Worldwide thyroid-cancer epidemic? The increasing impact of overdiagnosis. N Engl J Med 2016;375:614e7.
5. Ganly I, et al. Survival from differentiated thyroid cancer: what has age got to do with it? Thyroid 2015;25:1106e14.
6. Haugen BR, et al. American thyroid association management guidelines for adult patients with thyroid nodules and differentiated thyroid cancer: the American thyroid association guidelines task force on thyroid nodules and differentiated thyroid cancer. Thyroid 2015;26:1e133. 2016.
7. Adam MA, et al. Extent of surgery for papillary thyroid cancer is not associated with survival: an analysis of 61,775 patients. Ann Surg 2014;260:601e5. Discussion 5-7.
8. Werkgroepleden. Richtlijn Schildkliercarcinoom. 2015. 2.0.
9. La Vecchia C, et al. Thyroid cancer mortality and incidence: a global overview.

6

Chapter 6

Active surveillance for papillary thyroid microcarcinoma in a population with restrictive diagnostic workup strategies

I Lončar *, SPJ van Dijk *, MJH Metman, JF Lin, S Kruijff, RP Peeters, AF Engelsman, TM van Ginhoven
* Both authors contributed equally

Thyroid. 2021 Aug;31(8):1219-1225.

Abstract

Background

The worldwide incidence of papillary thyroid carcinoma (PTC) has increased. Efforts to reduce overtreatment follow two approaches: limiting diagnostic workup of low-risk thyroid nodules and pursuing active surveillance (AS) after diagnosis of microscopic PTC (mPTC). However, most studies on AS have been performed in countries with a relatively high proportion of overdiagnosis and thus incidental mPTC. The role of AS in a population with a restrictive diagnostic workup protocol for imaging and fine-needle aspiration remains unknown. Therefore, the aim of this study was to describe the proportion and characteristics of patients with mPTC in the Netherlands and to describe the potential candidates for AS in a situation with restrictive diagnostic protocols since 2007.

Methods

All operated patients with an mPTC in the Netherlands between 2005 and 2015 were identified from the Netherlands Cancer Registry database. Three groups were defined: (Group 1) mPTC with preoperative distant or lymph node metastases, (Group 2) mPTC in pathology report after thyroid surgery for another indication, and (Group 3) patients with a preoperative high suspicious thyroid nodule or proven mPTC (Bethesda 5 or 6). Only patients in Group 3 were considered potential candidates for AS.

Results

A total of 1018 mPTC patients were identified. Group 1 consisted of 152 patients with preoperatively discovered metastases. Group 2 consisted of 667 patients, of whom 16 (2.4%) had lymph node metastases. There were 199 patients in Group 3, of whom 27 (13.6%) had lymph node metastases. After initial treatment in Group 3, 3.5% (7/199) of the patients had recurrence.

Conclusions

Restrictive diagnostic workup strategies of patients with small thyroid nodules lead to limited patients eligible for AS and a higher incidence of lymph node metastases. We believe that there is limited additive value for AS in countries with restrictive diagnostic workup guidelines such as in the Netherlands. However, if an mPTC is encountered, AS can be offered on an individual basis

Introduction

The worldwide incidence of papillary thyroid carcinoma (PTC) has increased (1-3). This rising incidence is due to a significant increase in the use of diagnostic imaging modalities (e.g. ultrasonography, computed tomography [CT] and magnetic resonance imaging [MRI]) (4-7) and the improvement of quality of the postoperative pathological examination (8) as prevalence rates of PTC in autopsies over the last 45 years remain stable (9). The rising incidence of PTC alongside a stable or even declining mortality rate (1, 10, 11) combined with the stable prevalence in autopsies is highly suggestive for overdiagnosis and overtreatment of PTC (12, 13). The latter is in line with the observation that particularly the incidence of microscopic PTC (mPTC, PTC with the largest dimension of 1.0 cm or less) is rising. Where in 1990 only 25% of detected thyroid cancers in the United States was an mPTC, this number increased to 40% in 2008 (13). The clinical significance of mPTC still remains unclear. Some suggest that mPTC are indolent tumors and have no impact on survival and morbidity (1). However, a study by Mehanna et al. suggested the existence of at least two different entities of mPTC (14). They found that incidental mPTC had a lower incidence of lymph node metastases and a lower risk of recurrence than non-incidental mPTC, and they, therefore, propose less aggressive treatment in patients with incidentally found mPTC.

Currently, worldwide efforts have been made to reduce overtreatment using a parallel approach, in which a limited workup of incidentally found thyroid nodules is combined with active surveillance (AS) after diagnosis of mPTC. Most international guidelines are shifting to a less aggressive treatment approach in order to reduce overtreatment mostly by advocating the use of AS instead of immediate surgery for patients with unifocal mPTC without lymph node metastasis. AS entails monitoring the patient over time with neck ultrasounds and only operate when progressive disease is encountered. This strategy reduces the number of patients exposed to surgical morbidity and has comparable oncological outcomes to immediate surgery (15-17). However, most studies on AS have been performed in countries with a relatively high proportion of overdiagnosis and thus incidental mPTC (18).

The 2015 American Thyroid Association (ATA) guidelines recommend AS as an alternative treatment option for patients with low-risk mPTC and also adopted a more restrictive diagnostic workup for thyroid nodules, advocating not to perform fine-needle aspiration (FNA) in non-palpable nodules (< 1.0 cm) (19). However, if no FNA is performed in the vast majority of nodules <1cm, AS may not have a large additive value in the reduction of overtreatment. Since 2007, Dutch national guidelines advocated, in contrast to various other earlier guidelines (4, 20-22), to only perform FNA in palpable (assuming larger than 1 cm) nodules (23). In addition, thyroid incidentalomas found on ultrasound, CT and MRI have no strict indication for further follow-up. Only [18F]2-fluoro-2-deoxy-D-glucose (FDG) positron emission tomography (18FDG-PET)(/CT)-positive incidentalomas are evaluated by means of FNA cytology due to the relatively higher risk of malignancy (24). Currently, the role of AS in a population with a highly restrictive diagnostic workup protocol for imaging and performing FNA remains unclear.

Therefore, the aim of this study was to describe the proportion and characteristics of patients with mPTC in the Netherlands. The potential candidates for AS are described in a situation where more restrictive diagnostic protocols have been implemented since 2007.

Methods

Data collection

Data was obtained from the Netherlands Cancer Registry managed by the Netherlands Comprehensive Cancer Organization (IKNL) and from the Dutch registry of histo- and cytopathology reports (PALGA). Adult patients diagnosed and treated for mPTC in the Netherlands from January 2005 to December 2015 were included. They were identified by means of pathology reports in which the tumor had to be ≤ 1.0 cm in the largest dimension, using the Eight Edition of the American Joint Committee on Cancer TNM classification (25). Patients with unknown tumor diameter were also included if the report explicitly stated that a microcarcinoma was found in the specimen. All reports that were identified by IKNL as T1a and T1 were reviewed. Baseline characteristics (age, sex and follow-up time), findings from the pathology reports (tumor diameter, number of localizations, type of mPTC, co-existence of thyroiditis, vascular/capsular invasion, multifocality, bilaterality, extrathyroidal extension, lymph node involvement, BRAF-mutation, encapsulating tumor and complete [R0] or less than complete [R1 and R2] resection), follow-up and recurrence data were collected. Recurrence was defined as local recurrence of disease, the occurrence of lymph node metastases and distant metastases after initial treatment. This study was approved by the Medical Ethics committee of the Erasmus Medical Center (MEC-2018-1195). The STROBE guideline for reporting observational studies was used.

Patients

Three patient groups were defined: (Group 1) patients with preoperative pathologically proven lymph node or distant metastases of mPTC, (Group 2) patients with mPTC in a pathological specimen after thyroid surgery for another indication (e.g., Graves' disease, Bethesda 3 or 4 nodules, multinodular goiter), and (Group 3) patients with a preoperative high suspicious thyroidal nodule or proven mPTC (Bethesda 5 or 6). Patients in Group 1 are not candidates for AS due to lymph node or distant metastases. As patients in Group 2 underwent surgery for another indication, they are not candidates for AS for mPTC (incidentally) found in the specimen. Patients in Group 3 were classified as potential candidates for AS.

Statistical analysis

Descriptive statistics were used to express continuous variables with normal distribution as mean with standard deviation or abnormal distribution as median with interquartile range (IQR). Distribution was assessed using the Shapiro-Wilk normality test. Categorical variables are described as count (n) and percentage (%). Differences between the groups were analyzed using the Mood's median test for continuous variables and the Pearson Chi-square or Fisher's exact test for nominal variables. The Kaplan Meier method was used to estimate recurrence-free survival, and the log-rank test was used to evaluate statistical differences in recurrence between the different groups. IBM SPSS Statistics 25 (IBM Corp., Armonk, NY) and R 3.6.3 were used to perform all statistical analyses. p-values of <0.05 were considered significant. No data imputation was used for missing data.

Results

Patient and treatment characteristics

From January 2005 until December 2015 a total of 6,477 patients were diagnosed with thyroid cancer in the Netherlands (26). A total of 1459 patients were identified as T1a or T1. After review of the pathology reports, 441 patients were excluded (Fig. 1). In 1018 patients, an mPTC diagnosis was confirmed, representing 15.7% of the total number of thyroid cancer cases in the study period in the Netherlands. Patients had a median follow-up time of 68.7 [IQR: 42.8–102.6] months. The median age at time of diagnosis was 50.0 [IQR: 41.0–60.0] years and 75.8% were female. The median tumor diameter in the pathological specimen was 6.0 [IQR: 3.0–8.0] mm. In total, 368 (36.1%) patients underwent a total thyroidectomy, 240 (23.6%) underwent a completion thyroidectomy, and 401 (39.4%) patients underwent a hemithyroidectomy. In total, 397 (39.0%) patients received radioiodine ablation (RAI) treatment after total or completion thyroidectomy, and therapeutic cervical lymph node dissection was performed in 170 (16.7%) patients. Prophylactic cervical lymph node dissections were not performed. Additional baseline characteristics are summarized in Table 1.

Active surveillance candidates

Group 1 consisted of 152 patients (14.9%) who were diagnosed with an mPTC and preoperative cytology or pathology-proven lymph node or distant metastases. Group 2 consisted of 667 patients (65.6%) who were incidentally diagnosed after thyroid surgery for another indication. The remaining 199 (19.5%) mPTC patients were treated because of a preoperative Bethesda 5 or 6 result after FNA cytology and categorized into Group 3. Figure 2 shows the yearly distribution of these groups. At highest, 30 patients annually would have been suitable for AS.

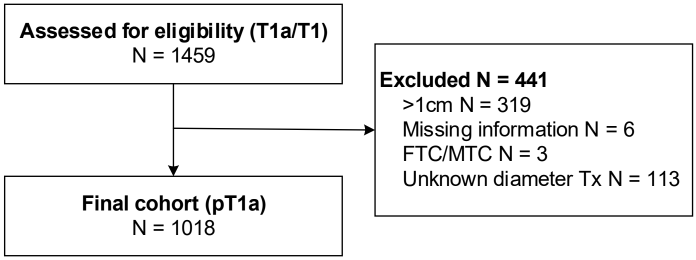


Figure 1. Flowchart of patient enrollment. FTC, follicular thyroid carcinoma; MTC, medullary thyroid carcinoma.

Follow-up

Overall, lymph node metastases were found in 19.0% of the total cohort while the percentage of distant metastases was 0.4%. Group 1 showed a lymph node metastases percentage of 98.7% (150/152) preoperatively. Lymph node metastases were found in the surgical specimen in 2.4% (16/667) in Group 2 and in 13.6% (27/199) of the patients in Group 3. The overall recurrence rate in patients was 3.8% (including local recurrence, lymph node metastases, and distant metastases after initial treatment). Recurrence rate was significantly higher in Group 1 compared with Group 2 and Group 3 (19.1% vs. 0.4% vs. 3.5%, $p < 0.001$) (Fig. 3; Table 2). Tumor diameter in the potential AS group was larger than that in Group 1 and Group 2 (8.0 [IQR: 6.0–9.0] mm vs. 6.0 [IQR: 3.4–8.0] mm and 5.0 [IQR: 2.0–7.0] mm, $p < 0.001$). Table 2 summarizes additional characteristics.

Discussion

mPTC of the thyroid accounted for 15.7% of the total amount of thyroid cancers diagnosed in the Netherlands from 2005 – 2015 (26). In this time frame of 11 years, 199 patients were identified as potentially eligible for AS (± 3.1% of all thyroid cancers). The burden of mPTC in the Netherlands is strikingly lower than in other countries. In the USA, nearly half of all identified thyroid cancers were <1.0 cm in 2008 (13). In France, the proportion of mPTC among all operated thyroid cancers was 43.1% (1998 to 2001) (27). Another study that included data from eight Chinese cancer registries showed that 32.1% of the thyroid cancers between 2000 and 2014 were mPTC (28). The lower incidence of mPTC in the Netherlands is a direct result from a decade long, more restrictive diagnostic workup strategy aiming to reduce the detection of small, indolent tumors with no need for treatment at all (23). expected more restrictive diagnostic protocol will lead to a population with less frequently diagnosed mPTC and less patients who would be eligible for AS.

Table 1 Clinical and histopathological characteristics of microscopic papillary thyroid carcinoma patients in the Netherlands (N=1018)

Age (years)	50 [41.0-60.0]
Sex	
Female	772 (75.8%)
Male	246 (24.2%)
Presentation of mPTC	
Group 1: Pre-operative lymph node/distant metastases	152 (14.9%)
Group 2: Resection for other indication	667 (65.6%)
Group 3: AS candidates	199 (19.5%)
Follow-up (months)	68.7 [42.8-102.6]
Surgical treatment	
Hemithyroidectomy and follow-up	401 (39.4%)
Total thyroidectomy with RAI	236 (23.2%)
Completion thyroidectomy with RAI	160 (15.7%)
Total thyroidectomy without RAI	132 (13.0%)
Completion thyroidectomy without RAI	80 (7.9%)
Thyroglossal-duct resection	6 (0.6%)
Isthmus resection	2 (0.2%)
Lateral neck cyst resection	1 (0.1%)
CLND	170 (16.7%)
CCLND	109 (64.1%)
LCLND	114 (67.1%)
Location unknown	24 (14.1%)
Non-surgical treatment	
Radioactive Iodine treatment	397 (39.0%)
Pathology report	
Diameter (mm) (n=19)[a]	6.0 [3.0-8.0]
Diameter ≥ 5.0 mm (n=19)	616 (61.7%)
Vascular invasion	32 (3.1%)
Bilaterality	131 (12.9%)
Less than complete resection (R1 and R2)	75 (7.4%)
Capsular invasion	30 (2.9%)
Multifocality	275 (27.0%)
Extrathyroidal extension	13 (1.3%)
Encapsulated tumor	29 (2.8%)
Invasion through capsule	11 (1.1%)
Metastases	
Lymph node	193 (19.0%)
Distant	4 (0.4%)
Recurrence	
Overall recurrence	39 (3.8%)
Lymph node	37 (3.6%)
Distant	2 (0.2%)
Local	1 (0.1%)

Data are expressed as numbers (percentage) or as median [IQR]; Missing data are presented in parentheses behind variables. [a] Certain mPTC but precise diameter unknown. AS, active surveillance; CLND, Concomitant cervical lymph node dissection; CCLND, Central CLND (level VI); LCLND, Lateral CLND (level II-IV) (total number of dissections); mPTC, microscopic papillary thyroid carcinoma; RAI, radioidine ablation

Although, the burden of mPTC in the Netherlands is lower than that in other countries, the incidence of mPTC after surgery for another indication has increased over time, which can be attributed to the improved quality of the postoperative pathological examination and reporting (8). Also, an increase in potential candidates for AS can be seen, which could be explained by the increased use of 18FDG-PET(/CT) for the staging and diagnosis of malignancies other than thyroid cancer (29, 30). Patients that could be eligible for AS (Group 3) in the Netherlands, have a higher incidence of lymph node metastases (13.6%) when compared with other AS studies. Ito et al. demonstrated that lymph node metastases appeared in only 3.8% of mPTC patients at 10-year follow-up when applying an AS strategy (17). These results are supported by a study from Tuttle et al (15), in which they closely observed 291 patients with PTC <1.5 cm as an alternative to immediate surgery. They observed tumor growth in 3.8% of the patients and no regional or distant metastases developed during AS. It needs to be noted that median follow-up time was relatively short (25 months, range; 6-166 months) and that they included PTC <1.5 cm (15). More importantly, these studies were performed in a setting where no restrictive diagnostic protocols were applied. The differences in mPTC incidence and the occurrence of lymph node metastases underline the fact that different diagnostic protocols will result in different populations by selection and thereby likely affect the biological behavior of mPTCs in a population. In other words, if a more restrictive diagnostic protocol is being used, less mPTC incidentalomas with indolent behavior are found. This will lead to fewer patients eligible for AS, and when eligible, they may tend to have relatively more lymph node metastases representing a more aggressive selected biological population.

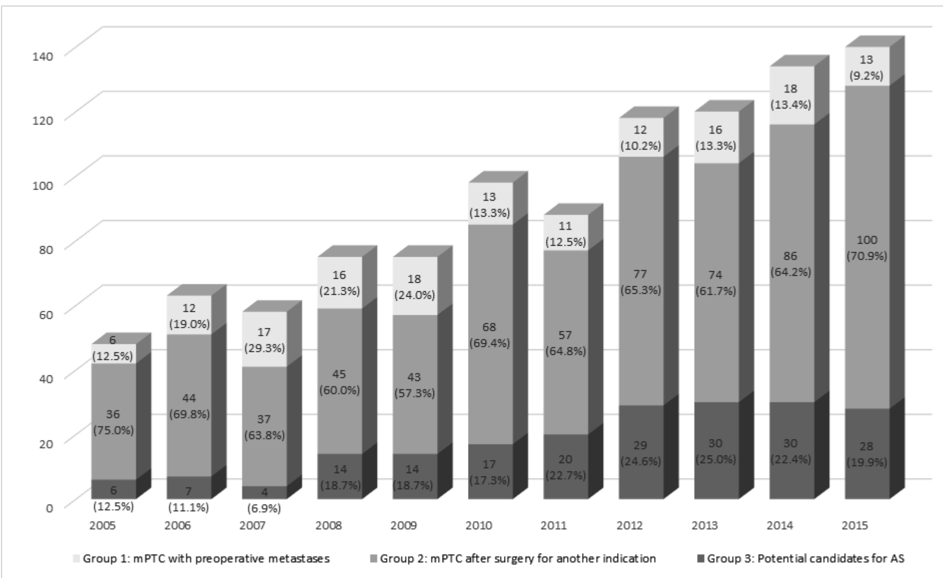


Figure 2. mPTC over the period 2005–2015 in the Netherlands. mPTC, microscopic papillary thyroid carcinoma.

Table 2 Differences in clinical and histopathological characteristics between the three groups

	Group 1: Pre-operative lymph node/ distant metastases	Group 2: Resection for other indication	Group 3: AS candidates	p-value
Number of patients	152 (14.9%)	667 (65.6%)	199 (19.5%)	
Age	46.0[37.0-56.8]	51.0 [41.0-61.0]	51.0 [41.0-59.0]	0.001
Sex				<0.001
Male	78 (51.3%)	117 (17.5%)	51 (25.6%)	
Female	74 (48.7%)	550 (82.5%)	148 (74.4%)	
Pathology report				
Diameter (mm)	6.0 [3.4-8.0]	5.0 [2.0-7.0]	8.0 [6.0-9.0]	<0.001
Diameter ≥ 5.0 mm	94 (64.4%)	342 (52.3%)	180 (90.5%)	<0.001
Vascular invasion	20 (13.2%)	5 (0.7%)	7 (3.5%)	<0.001
Bilaterality	49 (34.0%)	54 (8.1%)	28 (14.3%)	<0.001
Less than complete resection (R1 and R2)	27 (17.8%)	31 (4.7%)	17 (8.6%)	<0.001
Capsular invasion	14 (9.2%)	10 (1.5%)	6 (3.0%)	<0.001
Multifocality	90 (59.6%)	134 (20.1%)	51 (25.6%)	<0.001
Extrathyroidal extension	5 (3.3%)	8 (1.2%)	0 (0.0%)	0.024
Encapsulated tumor	2 (1.3%)	18 (2.7%)	9 (4.5%)	0.186
Invasion through capsule	1 (0.7%)	5 (0.7%)	5 (2.5%)	0.350
Metastases				
Lymph node	150 (98.7%)	16 (2.4%)	27 (13.6%)	<0.001
Distant	4 (2.6%)	0 (0.0%)	0 (0.0%)	<0.001
Recurrence				
Overall recurrence	29 (19.1%)	3 (0.4%)	7 (3.5%)	<0.001
Lymph node	28 (18.4%)	2 (0.3%)	7 (3.5%)	<0.001
Local	0 (0.0%)	1 (0.1%)	0 (0.0%)	0.768
Distant	2 (1.3%)	0 (0.0%)	0 (0.0%)	0.003

Data are expressed as numbers (percentage) or as median [IQR]
AS, active surveillance

Despite the higher incidence of lymph node metastases in the Dutch population, the Dutch thyroid cancer survival rates were excellent and comparable or even higher than the international survival rates regardless of the more restrictive diagnostic workup. The Dutch age-standardized death rates for men and women are 0.23 and 0.33 per 100,000, respectively. This is lower or comparable to the European and American average death rate for men and women (10, 31). The equal survival rates demonstrate that the Dutch workup protocol is an excellent treatment strategy to prevent overdiagnosis and overtreatment of PTC. However, because of the limited number of patients who would be eligible for AS and a higher incidence of lymph node metastases due to patient selection, we believe that a national AS standardized protocol has limited additive value in preventing the overtreatment of PTC. Since the 2015 ATA guideline adopted a more restrictive diagnostic workup strategy, it is expected that if the guideline is followed, AS will not have large additive value in the management of mPTC. However, when a mPTC is incidentally found, despite the restrictive protocol (e.g. by 18FDG-PET(/CT) scan), AS can be offered on an individual basis after discussing the risks and benefits of surgery versus AS with patients. The ideal candidate for AS would be an older patient (>60 years) with a unifocal mPTC without evidence of lymph node metastases, as proposed by the Memorial Sloan Kettering Cancer Center (32). It still remains unclear at which frequency and for how long patients should be followed in an AS protocol. Additional studies are needed to asses these issues, but also the impact on quality of life should be monitored.

This study has several limitations. First, it is a non-randomized retrospective study. Despite the care of data collection and the use of clear inclusion criteria, some degree of observation bias cannot be ruled out. Second, it should be noted that this study's data is based on histopathological reports and patients that actually underwent AS are therefore not included in this study. However, according to the Dutch guideline, AS was not a treatment option in the study period and we, therefore, assume that there were few to no patients undergoing AS in this study period. Third, ultrasound data were not available, and therefore, it was not possible to distinguish between Bethesda 5 with or without highly suspicious ultrasound. For this reason all Bethesda 5 nodules were included in the AS group. Furthermore, the database did not specify the date of RAI treatment. It was therefore not possible to determine the exact number of patients who had cancer-specific RAI treatment or, for example, RAI for Graves' disease preoperatively. Finally, 29 patients with an encapsulated tumor were included. These tumors could potentially be noninvasive follicular tumors with papillary features (NIFTP) tumors, which are considered benign in the current era. Unfortunately, it was not possible to reclassify the pathology reports with the present data. However, the number of encapsulated tumors did not differ between the different groups.

Restrictive diagnostic workup strategies of patients with small thyroid nodules results in a low proportion of mPTC and as a consequence a limited number of patients eligible for AS. Furthermore, patients that are eligible for AS in the Netherlands have a higher incidence of lymph node metastasis than in other populations due to patient selection. Based on these data, it can be concluded that in countries with restrictive diagnostic guidelines there is a limited additive value of AS in order to prevent overtreatment of mPTC. However, if an mPTC is encountered, AS can be offered on an individual basis. We would encourage the collection of follow-up data of patients in AS in national prospective databases.

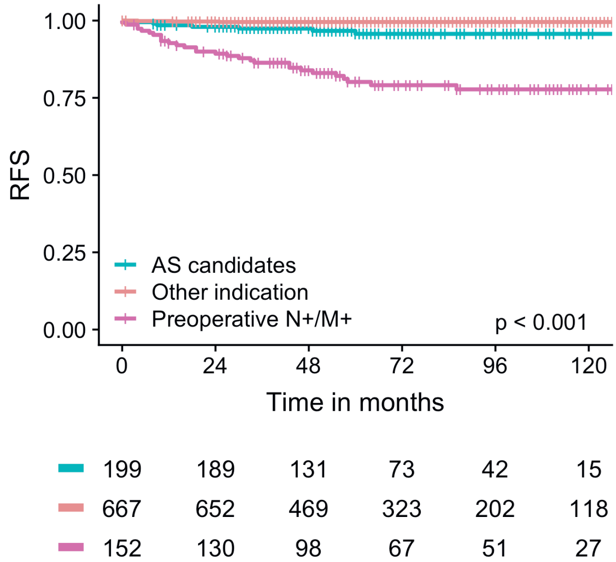


Figure 3. RFS in the different groups. AS, active surveillance; RFS, recurrence free survival.

References

1. Davies L, Welch HG. Increasing incidence of thyroid cancer in the United States, 1973-2002. Jama. 2006;295(18):2164-7.
2. Kent WDT, Hall SF, Isotalo PA, et al. Increased incidence of differentiated thyroid carcinoma and detection of subclinical disease. CMAJ. 2007;177(11):1357-61.
3. Colonna M, Grosclaude P, Remontet L, et al. Incidence of thyroid cancer in adults recorded by French cancer registries (1978–1997). European Journal of Cancer. 2002;38(13):1762-8.
4. Park S, Oh C-M, Cho H, et al. Association between screening and the thyroid cancer "epidemic" in South Korea: evidence from a nationwide study. Bmj. 2016;355:i5745.
5. Brito JP, Al Nofal A, Montori VM, et al. The Impact of Subclinical Disease and Mechanism of Detection on the Rise in Thyroid Cancer Incidence: A Population-Based Study in Olmsted County, Minnesota During 1935 Through 2012. Thyroid. 2015;25(9):999-1007.
6. Hoang JK, Choudhury KR, Eastwood JD, et al. An Exponential Growth in Incidence of Thyroid Cancer: Trends and Impact of CT Imaging. American Journal of Neuroradiology. 2014;35(4):778-83.
7. Vaccarella S, Dal Maso L, Laversanne M, et al. The Impact of Diagnostic Changes on the Rise in Thyroid Cancer Incidence: A Population-Based Study in Selected High-Resource Countries. Thyroid. 2015;25(10):1127-36.
8. Grodski S, Brown T, Sidhu S, et al. Increasing incidence of thyroid cancer is due to increased pathologic detection. Surgery. 2008;144(6):1038-43.
9. Luis F-K, Katy JLB, Justin C, et al. Prevalence of Differentiated Thyroid Cancer in Autopsy Studies Over Six Decades: A Meta-Analysis. Journal of Clinical Oncology. 2016;34(30):3672-9.
10. Husson O, Haak HR, van Steenbergen LN, et al. Rising incidence, no change in survival and decreasing mortality from thyroid cancer in The Netherlands since 1989. Endocr Relat Cancer. 2013;20(2):263-71.
11. La Vecchia C, Bosetti C, Lucchini F, et al. Cancer mortality in Europe, 2000-2004, and an overview of trends since 1975. Ann Oncol. 2010;21(6):1323-60.
12. Vaccarella S, Franceschi S, Bray F, et al. Worldwide Thyroid-Cancer Epidemic? The Increasing Impact of Overdiagnosis. New England Journal of Medicine. 2016;375(7):614-7.
13. Davies L, Welch HG. Current Thyroid Cancer Trends in the United States. JAMA Otolaryngology–Head & Neck Surgery. 2014;140(4):317-22.
14. Mehanna H, Al-Maqbili T, Carter B, et al. Differences in the recurrence and mortality outcomes rates of incidental and nonincidental papillary thyroid microcarcinoma: a systematic review and meta-analysis of 21 329 person-years of follow-up. J Clin Endocrinol Metab. 2014;99(8):2834-43.
15. Tuttle RM, Fagin JA, Minkowitz G, et al. Natural History and Tumor Volume Kinetics of Papillary Thyroid Cancers During Active Surveillance. JAMA Otolaryngol Head Neck Surg. 2017;143(10):1015-20.
16. Sugitani I, Toda K, Yamada K, et al. Three Distinctly Different Kinds of Papillary Thyroid Microcarcinoma should be Recognized: Our Treatment Strategies and Outcomes. World Journal of Surgery. 2010;34(6):1222-31.

17. Ito Y, Miyauchi A, Kihara M, et al. Patient age is significantly related to the progression of papillary microcarcinoma of the thyroid under observation. Thyroid. 2014;24(1):27-34.
18. Ahn HS, Kim HJ, Welch HG. Korea's thyroid-cancer "epidemic"--screening and overdiagnosis. N Engl J Med. 2014;371(19):1765-7.
19. Haugen BR, Alexander EK, Bible KC, et al. 2015 American Thyroid Association Management Guidelines for Adult Patients with Thyroid Nodules and Differentiated Thyroid Cancer: The American Thyroid Association Guidelines Task Force on Thyroid Nodules and Differentiated Thyroid Cancer. Thyroid. 2016;26(1):1-133.
20. Wémeau JL, Sadoul JL, d'Herbomez M, et al. Guidelines of the French society of endocrinology for the management of thyroid nodules. Annales d'Endocrinologie. 2011;72(4):251-81.
21. Pacini F, Basolo F, Bellantone R, et al. Italian consensus on diagnosis and treatment of differentiated thyroid cancer: joint statements of six Italian societies. J Endocrinol Invest. 2018;41(7):849-76.
22. Yi KH, Park YJ, Koong SS, et al. Revised Korean Thyroid Association Management Guidelines for Patients with Thyroid Nodules and Thyroid Cancer. Endocrinol Metab. 2010;25(4):270-97.
23. Links T. Richtlijn voor de diagnostiek, behandeling en follow-up van patiënten met gedifferentieerd (niet-medullair) schildkliercarcinoom [pdf]. 2015 [updated 16-02-2015. 188]. Available from: https://richtlijnendatabase.nl/richtlijn/schildkliercarcinoom/algemeen.html
24. Bae JS, Chae BJ, Park WC, et al. Incidental thyroid lesions detected by FDG-PET/CT: prevalence and risk of thyroid cancer. World J Surg Oncol. 2009;7:63-.
25. Edge SB, Byrd DR, Carducci MA, et al. AJCC cancer staging manual: Springer New York; 2010.
26. Nederlandse Kankerregistratie (NKR) I. [Available from: iknl.nl/nkr-cijfers.
27. Leenhardt L, Grosclaude P, Chérié-Challine L, et al. Increased incidence of thyroid carcinoma in france: a true epidemic or thyroid nodule management effects? Report from the French Thyroid Cancer Committee. Thyroid. 2004;14(12):1056-60.
28. Du L, Wang Y, Sun X, et al. Thyroid cancer: trends in incidence, mortality and clinical-pathological patterns in Zhejiang Province, Southeast China. BMC Cancer. 2018;18(1):291.
29. Zhuang H, Codreanu I. Growing applications of FDG PET-CT imaging in non-oncologic conditions. J Biomed Res. 2015;29(3):189-202.
30. Barrio M, Czernin J, Yeh MW, et al. The incidence of thyroid cancer in focal hypermetabolic thyroid lesions: an 18F-FDG PET/CT study in more than 6000 patients. Nucl Med Commun. 2016;37(12):1290-6.
31. La Vecchia C, Malvezzi M, Bosetti C, et al. Thyroid cancer mortality and incidence: a global overview. Int J Cancer. 2015;136(9):2187-95.
32. Brito JP, Ito Y, Miyauchi A, et al. A Clinical Framework to Facilitate Risk Stratification When Considering an Active Surveillance Alternative to Immediate Biopsy and Surgery in Papillary Microcarcinoma. Thyroid. 2016;26(1):144-9.

Part II

Hypoparathyroidism

7

Chapter 7

Persistent post-thyroidectomy hypoparathyroidism: a multicenter retrospective cohort study

I Lončar *, CMJ van Kinschot *, SPJ van Dijk, GJH Franssen, WE Visser, RP Peeters, CJH van Eijck, C van Noord, TM van Ginhoven
* Both authors contributed equally

Scand J Surg. Apr-Jun 2022;111(2):14574969221107282.

Abstract

Background and aims
The reported incidence of persistent hypoparathyroidism varies widely and consensus on a definition is lacking. The objective was to evaluate the real-life incidence of persistent hypoparathyroidism by investigating a new pragmatic definition.

Methods
This retrospective multi-center cohort study evaluated the effect of different definitions for persistent hypoparathyroidism on the incidence of hypoparathyroidism. Additionally, risk factors for hypoparathyroidism were analyzed.

Results
In total 749 patients were included. Using the new pragmatic definition we report an incidence of 7.9% of persistent hypoparathyroidism. When applying other commonly used definitions, incidence varied between 11.8% and 22.1%. Risk factors were parathyroid auto transplantation, presence of another surgical complication and low postoperative serum calcium.

Conclusion
Our data show that the incidence of persistent hypoparathyroidism in literature may vary through the use of different definitions. This study indicates that a new pragmatic definition of persistent hypoparathyroidism, has the potential to enable unbiased comparison between studies.

Introduction

Hypoparathyroidism is the most common iatrogenic complication after total or completion thyroidectomy and is caused by inadvertent resection or devascularization of the parathyroid glands, leading to the absence or insufficient production of parathyroid hormone (PTH) (1). Postoperative hypoparathyroidism results in hypocalcemia and may cause direct clinical symptoms such as paraesthesia and muscle cramps. On the long term, patients with hypoparathyroidism are at risk for various comorbidities and complications, such as chronic kidney disease, basal ganglia calcifications, and hospitalization due to seizures resulting in an impaired quality of life (2-4). A recent study even described higher mortality rates in this population (5).

In most cases, parathyroid function will recover within the first year after surgery and calcium levels will normalize (6, 7). Although the majority of single center studies have shown an incidence of persistent hypoparathyroidism of less than 5%, more recent national registries and multicenter studies have published much higher incidence rates up to 16.7% (8-13). Incidence rates are affected by the populations case-mix, as patients with Graves' disease and patients undergoing lymph node dissection have an increased risk of hypoparathyroidism (14, 15). Besides case-mix, incidence rates are greatly influenced by the definition being used, as demonstrated by the study of Mehanna et al. (16). Definitions vary from the need for calcium supplements after six months to the need for calcium and/or active vitamin D analogues, and low PTH levels after 12 months (17). Multiple studies have shown that parathyroid function may recover within the first year after surgery and by diagnosing patients with persistent hypoparathyroidism before 12 months may lead to inappropriate incidence rates (6-8). The same principle applies when persistent hypoparathyroidism is defined as the need for calcium supplements only, without the use of active vitamin D since active vitamin D with or without calcium is the conventional therapeutic approach for hypoparathyroidism (18-20). Furthermore, active weaning off supplementation must be attempted to prevent overtreatment and an incorrectly diagnosed hypoparathyroidism (20). Currently, there is no international consensus on the definition of persistent hypoparathyroidism, which impedes an unbiased comparison of studies. To overcome these limitations, we evaluated a new pragmatic definition of persistent hypoparathyroidism (the need for active vitamin D analogues with or without calcium supplements 12 months after surgery with an attempt to actively wean off supplementation) in a retrospective multi-center cohort study and compared it with commonly used other definitions In addition, we tried to identify risk factors for persistent hypoparathyroidism

Materials and methods

Study design and setting

This is a retrospective multi-center cohort study performed in ten hospitals in the Southwestern region of the Netherlands who participate in the Thyroid Network. This collaboration entails one university hospital and nine non-university hospitals, and was formed to implement uniform and structured regional care pathways. Approval was obtained from the Medical Ethical committee of Erasmus MC (MEC-2018-1195). The requirement for written informed consent was waived, given the retrospective character of this study. The STROBE guidelines for reporting observational studies were used.

Patients and data

All adult patients (≥18 years) undergoing a total or completion thyroidectomy between January 2010 and December 2016 in the Thyroid Network were included. Exclusion criteria included preoperative parathyroid dysfunction, the use of active vitamin D for any cause, reoperation in the central neck compartment within one year after total or completion thyroidectomy or missing 1-year follow-up data. For clarity the use of preoperative calcium supplementation is not an exclusion criteria as de novo calcium supplementation after surgery was assessed. Data on calcium and/or active vitamin D treatment at discharge and 12 months after surgery were retrieved directly from the medical charts. Other data that were retrospectively collected from electronic medical charts were: baseline characteristics (age, gender, BMI, indication for surgery), perioperative data (type of surgery, extent of surgery, parathyroid gland identification), postoperative data (length of hospital stay, hospital readmission and emergency department (ED) visits for hypocalcemic symptoms, serum calcium at first postoperative day), histopathological data (histopathological diagnosis, presence of parathyroid tissue)and data on adjuvant treatment. Hospital readmission is defined as a hypocalcemia event in which the patient could have been admitted from both the ED or outpatient clinic. ED visits are defined as a hypocalcemia related visit to the ED, without the need for hospital readmission. ED visits prior to hospital readmission are counted as an hospital readmission and not as an ED visit separately. Data on other complications were collected. Temporary laryngeal nerve paralysis was defined as laryngeal nerve paralysis confirmed by fibroscopy that resolved within the first year after surgery. Permanent laryngeal nerve paralysis was defined as laryngeal nerve paralysis one year or more after surgery confirmed by fibroscopy.

Surgical procedure

Total or completion thyroidectomy was performed by endocrine surgeons via a Kocher incision. Thyroidectomy procedures were performed in the same standardized manner by ligating the superior vessels, mobilizing the upper pole, followed by the capsular dissection technique with respect to the parathyroid glands. Inferior vessel ligation was performed after identification of the recurrent laryngeal nerve. Inadvertently resected parathyroid glands were auto-transplanted into the sternocleidomastoid muscle. A central (CLND) or lateral (LLND) lymph node dissection was performed when indicated (preoperative suspicion of lymph node metastasis or proven lymph node metastasis). Prophylactic cervical lymph node dissections were not performed.

Definitions and management

To assess the impact of definition on the rate of hypoparathyroidism we applied the following three definitions. For the first definition, patients were considered to have persistent hypoparathyroidism (1) if they used de novo prescribed active vitamin D analogues with or without calcium supplements 12 months after surgery, irrespective of the dosage and (2) if they had an unsuccessful attempt of active weaning off in supplementation. Patient medical records were searched for attempts of weaning. Both treating physician notes and pharmacy prescriptions were checked. If no information was available, data were assumed as missing. The second definition included all patients that at least used a de novo active vitamin D analogue, whether or not in combination with de novo calcium supplements, 12 months post-surgery. This definition did not take into account active weaning off. The third definition included all patients that used de novo calcium and/or active vitamin D analogues, 12 months post-surgery without any confirmed attempt to decrease and stop this medication. Every hospital had their own calcium supplementation protocol and weaning off medication was according to the discretion of the treating physician. Direct postoperative hypocalcemia was treated with calcium carbonate and active vitamin D analogues. Serum calcium levels were adjusted for albumin levels according to the formula: adjusted total calcium (mmol/L) = measured calcium (mmol/L) + (0.025 × (40 – albumin (g/L).

7

Statistical analysis

Continuous variables were expressed as mean and S.D. or median with interquartile ranges (IQR) as appropriate. Categorical variables were described as counts (n) and percentages (%). Normality was assessed using the Shapiro-Wilk normality test. Means and medians were compared with a Mann-Whitney U test and Chi-square or Fishers exact test, where appropriate. Missing data are presented in parentheses behind variables. Univariate and multivariable logistic regression analysis was performed to evaluate risk factors for persistent hypoparathyroidism, by using the first definition. Statistically significant variables in univariate analysis and those judged to be clinically relevant were included in the multivariable logistic regression analysis, considering the restricted number of variables of 1 variable per 10 cases. P-values of <0.05 were considered significant. IBM SPSS Statistics 25 (IBM Corp., Armonk, NY, USA) was used to perform all statistical analyses.

Results

Total study cohort

In total, 780 adult patients underwent a total or completion thyroidectomy between January 2010 and December 2016, of which 749 were included in the present study (Figure 1). Baseline characteristics of the total study cohort are summarized in Table 1. In total 470 (62.8%) patients underwent a one stage total thyroidectomy, 279 (37.2%) patients underwent a completion thyroidectomy. CLND+/-LLND was performed in 153 (20.4%) patients, of which 61 (8.1%) CLND only and 92 (12.3%) had both CLND + LLND surgery. A parathyroid auto transplantation was performed in 52 (6.9%) patients and in 183 (24.4%) patients' parathyroid tissue was found at histology. Other complications than hypoparathyroidism were wound infection in 9 (1.2%) patients, chyle leakage in 11 (1.5%) patients, reoperation for bleeding in 27 (3.6%) patients, temporary laryngeal nerve paralysis in 21 (2.8%) patients and permanent laryngeal nerve paralysis 43 (5.7%) patients.

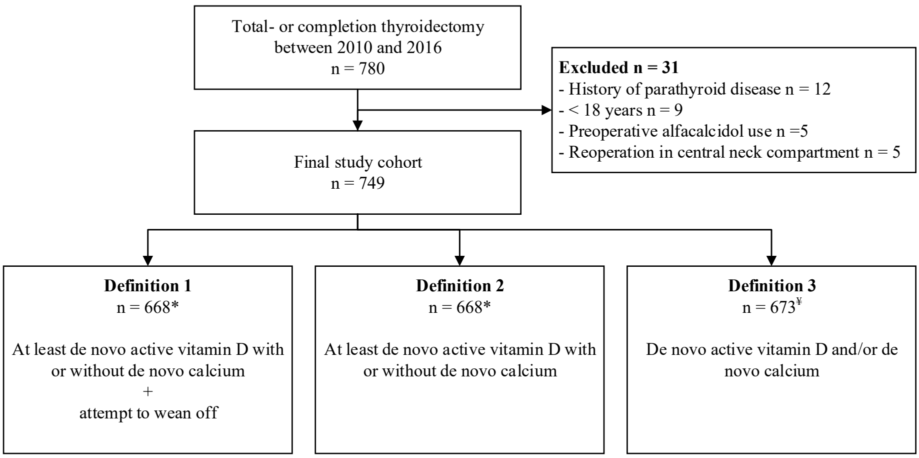


Figure 1. Flowchart of patient enrollment. * 81 patients were excluded due to missing data on active vitamin D one year after surgery. ¥ 76 patients were excluded due to missing data on calcium and/or active vitamin D one year after surgery.

Incidence of hypoparathyroidism using different definitions

Three different definitions were used to assess the incidence of persistent hypoparathyroidism. Due to the use of different definitions three different cohorts were created (Figure 1). For the first and second definition 81 patients were excluded due to missing data on active vitamin D one year after surgery. For the third definition 76 patients were excluded due to missing data on calcium and/or active vitamin D one year after surgery. When applying the first definition, 53 out of 668 (7.9%) patients were considered to have persistent hypoparathyroidism (Table 2). The incidence of persistent hypoparathyroidism was 11.8% (79/668) when using the second definition and 22.1% (149/673) when using the third definition. Subgroup analysis of patients with benign versus malignant disease and whether a CLND+/-LLND was performed showed a similar trend for to the three definitions (Table 2).

Post-operative outcomes and risk factors for persistent hypoparathyroidism

The post-operative outcomes of patients with or without persistent hypoparathyroidism are depicted in Table 3. Patients with persistent hypoparathyroidism had a longer hospital stay than patients without persistent hypoparathyroidism (4.00 [IQR: 2.24 – 6.75] days vs 2.0 [IQR: 1.0 – 3.00] days; $p < 0.001$). Patients with persistent hypoparathyroidism were readmitted to the hospital more often and visited the emergency department more often for hypocalcemia (15.1% vs 2.1%; $p < 0.001$ and 9.4% vs 0.7%; $p < 0.001$ respectively). Univariate analysis showed that a malignancy, 1-stage thyroidectomy, CLND +/- LLND and CLND + LLND, parathyroid autotransplantation, parathyroid tissue at histology, lower postoperative serum calcium and the occurrence of a surgical complication were significantly associated with persistent hypoparathyroidism (Table 3). Multivariable analysis showed that a lower postoperative serum calcium, parathyroid gland auto transplantation and presence of another surgical complication were significantly associated with persistent hypoparathyroidism (Table 4).

7

Table 1. Clinicopathological, procedural and postoperative outcomes for the total study cohort

	Total cohort (n=749)	
Baseline		
Gender, female	566	75.6%
Age (y)	50.0	[38.0 - 62.0]
BMI (kg/m^2)	26.2	[23.2 – 29.8]
Baseline medication		
Thyroid hormone supplementation	107	14.3%
Colecalciferol supplementation	61	8.1%
Calcium supplementation	35	4.7%
Hospital		
Academic centre	339	45.3%
Regional hospital	410	54.7%
Indication for surgery		
Malignancy	183	24.4%
Indeterminate or suspicious nodule	220	29.4%
Multinodular goiter	179	23.9%
Graves	95	12.7%
Bethesda I nodule	26	3.5%
Symptomatic benign nodule	25	3.5%
Surgical characteristics		749
1-stage thyroidectomy	470	62.8%
2-stage thyroidectomy	279	37.2%

Table 1. Clinicopathological, procedural and postoperative outcomes for the total study cohort (continue)

CLND+/-LLND	153	20.4%
CLND	61	8.1%
CLND + LLND	92	12.3%
Parathyroid gland reimplanted	52	6.9%
Histological characteristics		
Malignant	445	59.4%
Multinodular goitre	160	21.4%
Graves	78	10.4%
Parathyroid tissue at histology	183	24.4%
Postoperative outcomes		
Serum calcium corrected (POD1) (n=532)	2.15 [2.04 - 2.25]	
Surgical complication		
Reoperation for bleeding	27	3.6%
Woundinfection	9	1.2%
Reoperation for woundinfection	6	0.8%
Chyle leake	11	1.5%
Temporary RLNP	21	2.8%
Permanent RLNP	43	5.7%
Hospital stay (days)	2.00 [1.00 - 3.00]	
Readmission for hypocalcemia	21	2.8%
ED visit for hypocalcemia	9	1.2%
Supplementation at discharge (de novo)		
Calcium only	206	27.5%
Active vitamin D only	4	0.5%
Calcium + active vitamin D	157	21.0%
No supplementation	353	47.1%
Unknown	11	1.5%
Supplementation after 1 year (de novo)		
Calcium only	67	8.9%
Active vitamin D only	4	0.5%
Calcium + active vitamin D	79	10.5%
No supplementation	523	68.2%
Unkown	76	10.1%

Data are expressed as a percentage or as median with interquartile range; CLND = central lymph node dissection; LLND = lateral lymph node dissection; POD1 = first postoperative day; RLNP = recurrent laryngeal nerve paralysis; ED = emergency department

Table 2. Subgroup analysis on the incidence of hypoparathyroidism using the three different definitions

	Total		Benign		Malignant		CLND +/- LLND +		CLND +/- LLND -	
Definition 1	53/668	7.9%	13/250	4.9%	40/418	9.6%	23/139	16.5%	30/529	5.7%
Definition 2	79/668	11.8%	22/250	8.8%	57/418	13.6%	30/139	21.6%	49/529	9.3%
Definition 3	149/673	22.1%	50/252	19.8%	99/421	23.5%	52/140	37.1%	97/533	18.2%

Definition 1 = At least de novo active vitamin D with or without de novo calcium + attempt to wean off
Definition 2 = At least de novo active vitamin D with or without de novo calcium
Definition 3 = De novo active vitamin D and/or de novo calcium
CLND+/-LLND + = central lymph node dissection with or without lateral lymphnode dissection performed
CLND+/-LLND - = central lymph node dissection with or without lateral lymphnode dissection not performed

Table 3. Clinicopathological, procedural and postoperative outcomes stratified by hypoparathyroidism for the first definition (n=670)

	Hypoparathyroidism+ (n=53)		Hypoparathyroidism- (n=615)		p-value
Baseline					
Gender, female	37	69,8%	469	76,3%	0.293
Age (y)	45.0	[37.5 - 69.0]	50.0	[37.0 - 60.0]	0.337
BMI (kg/m^2)	26.3	[23.5 – 28.7]	26.3	[23.0 – 29.9]	0.802
Baseline medication					
Thyroid hormone supplementation	6	11,3%	86	14,1%	0.638
Colecalciferol	4	7,5%	50	8,1%	0.904
Hospital					
Academic centre	30	56,6%	257	41,8%	0.037
Regional hospital	23	43,4%	358	58,2%	
Indication for surgery					
Malignancy	24	45.3%	143	23.3%	0.000
Indeterminate or suspicious nodule	12	22.6%	189	30.7%	0.218
Multinodular goiter	12	22.6%	136	22.1%	0.929
Graves	2	3.8%	84	13.7%	0.051
Bethesda I nodule	0	0.0%	24	3.9%	0.143
Symptomatic benign nodule	1	1.9%	23	3.7%	0.487
Surgical characteristics		749		749	
1-stage thyroidectomy	39	73,6%	367	59,7%	0.047
2-stage thyroidectomy	14	26,4%	248	40,3%	
CLND +/- LLND	23	43,4%	116	18.9%	0.000
CLND	8	15,1%	47	7,6%	0.058
CLND + LLND	15	28,3%	69	11,2%	0.000
Parathyroid gland reimplanted	10	18,9%	38	6,2%	0.001
Histological characteristics					
Malignant	40	75,5%	378	61,5%	0.043
Graves	2	3.8%	67	10.9%	0.102
Multinodular goitre	9	17.0%	119	19.3%	0.674
Parathyroid tissue at histology	24	45,3%	141	22.9%	0.000
Postoperative outcomes					
Serum calcium corrected (POD1) (n=472)	2.00	[1.93 - 2.11]	2.16	[2.07 - 2.25]	0.000
Surgical complication	13	24,5%	79	12,8%	0.000
Hospital stay (days)	4.00	[2.24 - 6.75]	2.00	[1.00 - 3.00]	0.000
Readmission for hypocalcemia	8	15.1%	13	2,1%	0.000
ED visit for hypocalcemia	5	9.4%	4	0.7%	0.000

Data are expressed as a percentage or as median with interquartile range
Hypoparathyroidism + = hypoparathyroidism; hypoparathyroidism - = no hypoparathyroidism; CLND = central lymph node dissection; LLND = lateral lymph node dissection; POD1= first postoperative day; ED= emergency department.

Table 4. Multivariable analysis of variables affecting the development of hypoparathyroidism using the first definition

	OR	(95% CI)	p-value
CLND +/- LLND	1.579	(0.728 - 3.426)	0.247
Postoperative calcium	0.004	(0.000 - 0.054)	0.000
PTG pathology report	1.712	(0.811 - 3.615)	0.159
PTG auto transplantation	2.851	(1.057 - 7.687)	0.038
Surgical complication	2.410	(1.032 - 5.629)	0.042

CLND = central lymph node dissection; LLND = lateral lymph node dissection; PTG = parathyroid gland

Discussion

Utilizing a new pragmatic definition we report in this multicenter study an incidence of 7.9% of persistent hypoparathyroidism. This new definition incorporates both the use of an active vitamin D analogue with or without calcium supplementation with an attempt to actively wean off supplementation. When applying other commonly used definitions, incidence of hypoparathyroidism in our study varied between 11.8% and 22.1% (17). These differences further underline the need for international consensus on the definition of hypoparathyroidism. Active vitamin D has been the conventional therapeutic approach for many years (18-20) in patients with persistent hypoparathyroidism after surgery. However, active weaning off vitamin D and calcium supplementation in these patients is often overlooked and leads to often, life-long overtreatment (20). We therefore propose to use this new definition, which gives a fair picture of the true incidence of postoperative hypoparathyroidism. This definition is underlined by the recently published expert consensus statement regarding the management of parathyroid disorders in which they state that persistent hypoparathyroidism should be diagnosed if active vitamin D analogues are still necessary to maintain calcium concentrations low normal. They also recommend to confirm the chronicity by carefully tapering active treatment (21]. When utilizing our definition of hypoparathyroidism lower postoperative serum calcium, parathyroid gland auto transplantation and the occurrence of surgical complications were found to be independent risk factors for persistent hypoparathyroidism.

The herein reported rate of persistent hypoparathyroidism is high compared to single center studies applying the definition of using active vitamin D analogue only. For example, a single center study by Almquist et al. (22] reported an incidence rate of 1.9%, while we found an incidence of 11.8% when applying the same definition. Furthermore, nationwide and multi-center studies reported higher incidence rates up to 5.2%, using this definition, yet this is not as high as in the present study (5, 23). Studies that used the definition of calcium and/or active vitamin D analogues use, 12 months post-surgery without any confirmed attempt stop this medication reported higher incidence rates. A nationwide population-based cohort study from Sweden reported an incidence rate of 12.5%, however only patients with benign disease were included (12). Differences in incidence rates might not only be explained by the definitions used for hypoparathyroidism but also by the included population. In the present study, more than half of the patients underwent surgery for malignant disease of whom 20.4% underwent lymph node surgery. This might explain the relatively high incidence of hypoparathyroidism, which is about equal to the finding by Diez et al who reported an incidence of hypoparathyroidism of 16.7% in a population comparable to ours (10).

Influence of definition on incidence of hypoparathyroidism

Previous studies have investigated the influence of the use of different definitions on the incidence of hypoparathyroidism. Mehanna et al. (16) described that the incidence of persistent hypoparathyroidism varied from 0.9% to 4.4% when different definitions were applied. On the contrary, a study by Harsløf et al. (17) did not find an association between the incidence rate and the use of different definitions. However, they did express their concern regarding the wide variety of definitions that are used across studies which might be linked to confounding factors affecting the reported incidence of hypoparathyroidism. All definitions for hypoparathyroidism that were applied in our study were defined solely by a clinical parameter; the use of active vitamin D analogues with or without calcium supplements one-year post-surgery. Serum calcium and PTH levels were not part of the definitions, which makes this definition pragmatic to use and enhance the comparability of hypoparathyroidism rates between different centers.

The discrepancy in incidence between the groups with and without any attempt to wean off supplementation (a difference of 16.0%) implies that a significant proportion of our patients might use unnecessary supplementation one year after surgery. This highlights the importance of the implementation of a standardized and uniform protocol for weaning off medication, especially if only calcium supplements are prescribed. Unfortunately, to date there is no worldwide consensus on such a treatment algorithm and it is to be expected that overtreatment is not solely a problem in the Netherlands. However, data on this topic is lacking. Furthermore, by including only the use of calcium in the definition, patients receiving supplementation for another indication are defined as having hypoparathyroidism which increases the incidence rate. To our knowledge, this is the first study including patients with an inability to wean off vitamin D and calcium supplementation which is different from most studies including patients based on serum PTH levels in their definition of hypoparathyroidism (24-26). Nevertheless, a normal PTH level does not preclude the occurrence of hypocalcemic symptoms necessitating supplementation (25, 27, 28).

As discussed previously by Lorente-Poch et al. (28), hypoparathyroidism could be sub classified in aparathyroidism (undetectable PTH levels), hypoparathyroidism (detectable but subnormal PTH levels) and relative parathyroid insufficiency (normal PTH levels but insufficient to maintain calcium levels). This is highly suggestive for heterogeneity of persistent hypoparathyroidism, which makes it all the more difficult to reach consensus regarding the definition. Also, this could partly explain why some patients will never be tapered off medication. Furthermore, PTH levels are not measured routinely in the participating centers of this study. Also, national investigation shows that PTH levels are not measured in standard protocols (29). We therefore propose the use of our pragmatic and clinical definition without the use of serum PTH levels, to enable worldwide and unbiased comparison of incidence rates. Yet, it should include the effort of the clinician to wean off supplementation, which should also be standardized.

Risk factors of persistent hypoparathyroidism

In this study we found that lower serum calcium level on the first postoperative day is an independent risk factor for persistent hypoparathyroidism, which confirmed a previous finding in a meta-analysis (14). Moreover, parathyroid auto transplantation was found to be an independent risk factor for persistent hypoparathyroidism. However, the influence of auto transplantation on persistent hypoparathyroidism is still debated. Some studies have found that it may prevent hypoparathyroidism on the long term or found no association at all (6, 22, 30). On the other hand others reported auto transplantation as a risk factor of persistent hypoparathyroidism, which is in line with our results (12, 31). Parathyroid tissue on pathology report was not found to be an independent risk factor for persistent hypoparathyroidism. However, in nearly one quarter of the patients, parathyroid tissue was found on histology, which is comparable to the 22.7% found by Diez et al. and the 29.0% incidence of inadvertent parathyroid gland resection found by Paek et al. (10, 31). Although, comparable to the literature, the incidence of inadvertent parathyroid gland resection in our cohort is substantial and future research should focus on developing new techniques for the surgical preservation of parathyroid glands. It is hypothesized that lymph node surgery increases the risk of inadvertent parathyroid gland removal or damaging the parathyroid gland and therefore increases the risk for persistent hypoparathyroidism (10, 15). In this study there was no statistically significant association between CLND and persistent hypoparathyroidism on univariate analysis, while there was an association for CLND +/- LLND and CLND+LLND. This could be explained by insufficient power for CLND, but also by the higher risk for parathyroid gland damage when a LLND is performed. However, on multivariable analysis no association was found for any type of lymph node dissection. The occurrence of surgical complications was an independent risk factor for persistent hypoparathyroidism which could partially be explained by reoperation for bleeding, as described previously (30).

Limitations

This study is a non-randomized, retrospective study and despite the care of data collection and the use of clear inclusion criteria, observation bias cannot be ruled out. Second, the number of cases precluded an extensive multivariable analysis. Lastly, serum PTH levels were not available and therefore the use of PTH in a definition could not be compared to our pragmatic definition.

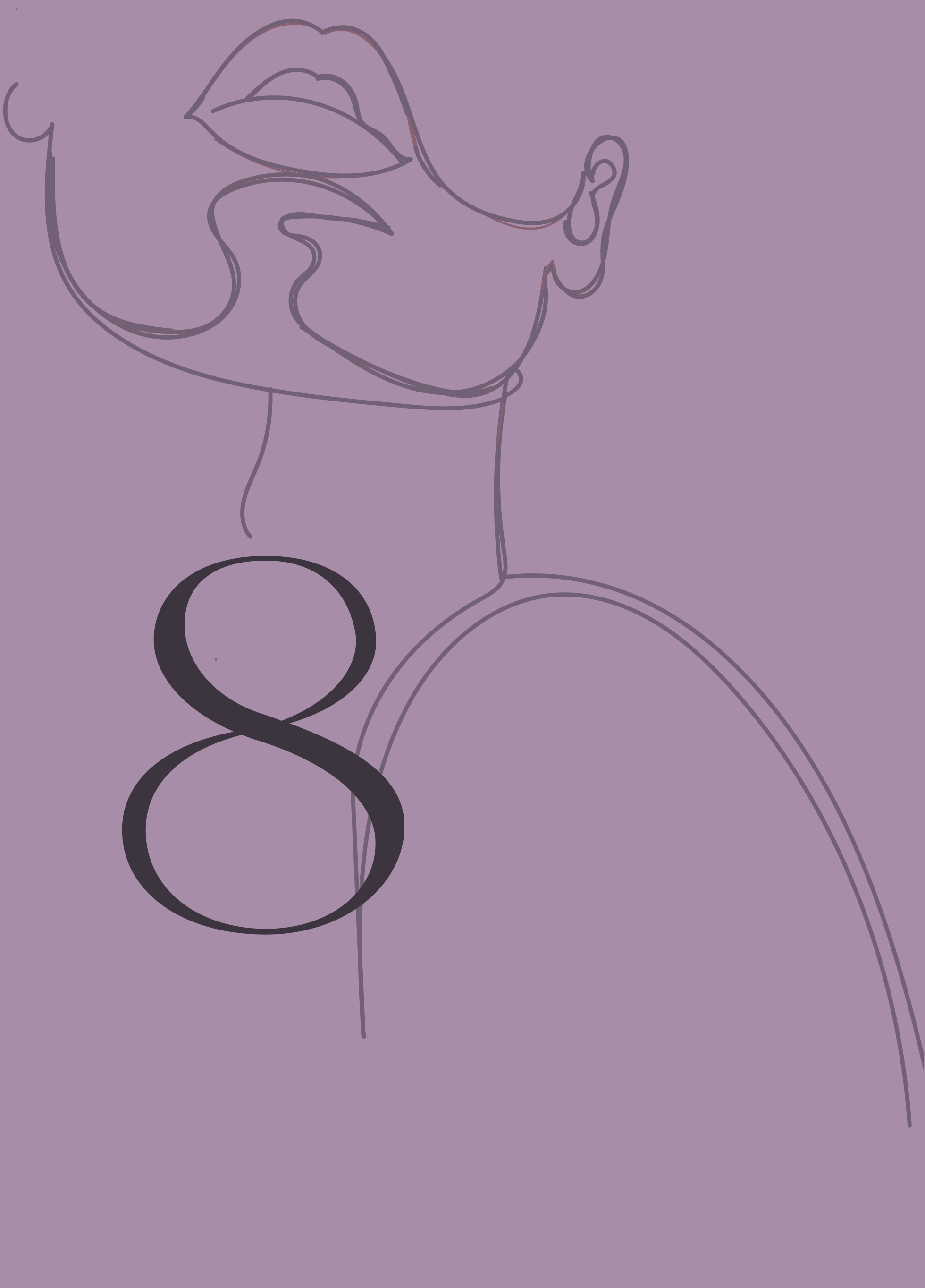
Conclusions

Our data show that the incidence of persistent hypoparathyroidism in literature may vary through the use of different definitions. Our study indicates that a new pragmatic definition of persistent hypoparathyroidism, solely based on clinical parameters and in alignment with all current guidelines for hypoparathyroidism management, has the potential to enable unbiased and universal comparison between studies.

References

1. Rosato L, Avenia N, Bernante P et al. Complications of thyroid surgery: analysis of a multicentric study on 14,934 patients operated on in Italy over 5 years. World J Surg. 2004;28(3):271-6.
2. Astor MC, Lovas K, Debowska A et al. Epidemiology and Health-Related Quality of Life in Hypoparathyroidism in Norway. J Clin Endocrinol Metab. 2016;101(8):3045-53.
3. David K, Moyson C, Vanderschueren D, Decallonne B. Long-term complications in patients with chronic hypoparathyroidism: a cross-sectional study. Eur J Endocrinol. 2018.
4. Underbjerg L, Sikjaer T, Mosekilde L, Rejnmark L. Cardiovascular and renal complications to postsurgical hypoparathyroidism: a Danish nationwide controlled historic follow-up study. J Bone Miner Res. 2013;28(11):2277-85.
5. Almquist M, Ivarsson K, Nordenstrom E, Bergenfelz A. Mortality in patients with permanent hypoparathyroidism after total thyroidectomy. Br J Surg. 2018;105(10):1313-8.
6. Sitges-Serra A, Ruiz S, Girvent M, Manjon H, Duenas JP, Sancho JJ. Outcome of protracted hypoparathyroidism after total thyroidectomy. Br J Surg. 2010;97(11):1687-95.
7. Villarroya-Marquina I, Sancho J, Lorente-Poch L, Gallego-Otaegui L, Sitges-Serra A. Time to parathyroid function recovery in patients with protracted hypoparathyroidism after total thyroidectomy. Eur J Endocrinol. 2018;178(1):103-11.
8. Kim SM, Kim HK, Kim KJ et al. Recovery from Permanent Hypoparathyroidism After Total Thyroidectomy. Thyroid. 2015;25(7):830-3.
9. Asari R, Passler C, Kaczirek K, Scheuba C, Niederle B. Hypoparathyroidism after total thyroidectomy: a prospective study. Arch Surg. 2008;143(2):132-7; discussion 8.
10. Díez JJ, Anda E, Sastre J et al. Prevalence and risk factors for hypoparathyroidism following total thyroidectomy in Spain: a multicentric and nation-wide retrospective analysis. Endocrine. 2019;66(2):405-15.
11. Chadwick DR. Hypocalcaemia and permanent hypoparathyroidism after total/bilateral thyroidectomy in the BAETS Registry. Gland Surg. 2017;6(Suppl 1):S69-S74.
12. Annebäck M, Hedberg J, Almquist M, Stålberg P, Norlén O. Risk of Permanent Hypoparathyroidism After Total Thyroidectomy for Benign Disease: A Nationwide Population-based Cohort Study From Sweden. Ann Surg. 2020.
13. Jørgensen CU, Homøe P, Dahl M, Hitz MF. High incidence of chronic hypoparathyroidism secondary to total thyroidectomy. Dan Med J. 2020;67(5).
14. Edafe O, Antakia R, Laskar N, Uttley L, Balasubramanian SP. Systematic review and meta-analysis of predictors of post-thyroidectomy hypocalcaemia. Br J Surg. 2014;101(4):307-20.
15. Giordano D, Valcavi R, Thompson GB et al. Complications of central neck dissection in patients with papillary thyroid carcinoma: results of a study on 1087 patients and review of the literature. Thyroid. 2012;22(9):911-7.
16. Mehanna HM, Jain A, Randeva H, Watkinson J, Shaha A. Postoperative hypocalcemia--the difference a definition makes. Head Neck. 2010;32(3):279-83.

17. Harsløf T, Rolighed L, Rejnmark L. Huge variations in definition and reported incidence of postsurgical hypoparathyroidism: a systematic review. Endocrine. 2019;64(1):176-83.
18. Brandi ML, Bilezikian JP, Shoback D et al. Management of Hypoparathyroidism: Summary Statement and Guidelines. The Journal of Clinical Endocrinology & Metabolism. 2016;101(6):2273-83.
19. Bollerslev J, Rejnmark L, Marcocci C et al. European Society of Endocrinology Clinical Guideline: Treatment of chronic hypoparathyroidism in adults. Eur J Endocrinol. 2015;173(2):G1-20.
20. Perros P, Boelaert K, Colley S et al. Guidelines for the management of thyroid cancer. Clin Endocrinol (Oxf). 2014;81 Suppl 1:1-122.
21. Bollerslev J, Rejnmark L, Zahn A et al. European Expert Consensus on Practical Management of Specific Aspects of Parathyroid Disorders in Adults and in Pregnancy: Recommendations of the ESE Educational Program of Parathyroid Disorders. Eur J Endocrinol. 2021;186(2):R33-63.
22. Almquist M, Hallgrimsson P, Nordenstrom E, Bergenfelz A. Prediction of permanent hypoparathyroidism after total thyroidectomy. World J Surg. 2014;38(10):2613-20.
23. Bergenfelz A, Nordenström E, Almquist M. Morbidity in patients with permanent hypoparathyroidism after total thyroidectomy. Surgery. 2020;167(1):124-8.
24. Lorente-Poch L, Sancho JJ, Ruiz S, Sitges-Serra A. Importance of in situ preservation of parathyroid glands during total thyroidectomy. Br J Surg. 2015;102(4):359-67.
25. Ritter K, Elfenbein D, Schneider DF, Chen H, Sippel RS. Hypoparathyroidism after total thyroidectomy: incidence and resolution. J Surg Res. 2015;197(2):348-53.
26. Julián MT, Balibrea JM, Granada ML et al. Intact parathyroid hormone measurement at 24 hours after thyroid surgery as predictor of parathyroid function at long term. Am J Surg. 2013;206(5):783-9.
27. Lončar I, Dulfer RR, Massolt ET et al. Postoperative parathyroid hormone levels as a predictor for persistent hypoparathyroidism. Eur J Endocrinol. 2020;183(2):149-59.
28. Lorente-Poch L, Sancho JJ, Muñoz-Nova JL, Sánchez-Velázquez P, Sitges-Serra A. Defining the syndromes of parathyroid failure after total thyroidectomy. Gland Surg. 2015;4(1):82-90.
29. Loncar I, Noltes ME, Dickhoff C et al. Persistent Postthyroidectomy Hypoparathyroidism in the Netherlands. JAMA Otolaryngol Head Neck Surg. 2021.
30. Hallgrimsson P, Nordenström E, Almquist M, Bergenfelz AO. Risk factors for medically treated hypocalcemia after surgery for Graves' disease: a Swedish multicenter study of 1,157 patients. World J Surg. 2012;36(8):1933-42.
31. Paek SH, Lee YM, Min SY, Kim SW, Chung KW, Youn YK. Risk factors of hypoparathyroidism following total thyroidectomy for thyroid cancer. World J Surg. 2013;37(1):94-101.



8

Chapter 8

Persistent postthyroidectomy hypoparathyroidism in the Netherlands

I Lončar *, ME Noltes *, C Dickhoff, AF Engelsman, A Schepers, MR Vriens, ND Bouvy, S Kruijff ¥, TM van Ginhoven ¥
* ¥ Both authors contributed equally

JAMA Otolaryngol Head Neck Surg. 2021 Nov 1;147(11):959-965

Abstract

Importance

Hypoparathyroidism is one of the most common complications after total or completion thyroidectomy. The reported incidence rate of hypoparathyroidism in the literature is highly variable. Data that provide a better understanding of the magnitude of this postoperative complication are warranted and can provide a stepping stone for further collaborations that aim to reduce complication rates and establish uniform treatment protocols.

Objective

To evaluate the incidence of postoperative, persistent hypoparathyroidism after total or completion thyroidectomy in patients who were referred to university hospital centers and assess the association of different definitions with the incidence of hypoparathyroidism.

Design, Setting, and Participants

This retrospective multicenter cohort study conducted throughout 2016 in 7 Dutch university hospital centers included 200 patients who were undergoing a total or completion thyroidectomy. Data analysis was conducted in January 2021.

Main outcomes and Measures

We report on the incidence of persistent hypoparathyroidism, defined as the need for active vitamin D with or without calcium supplementation longer than 1 year after surgery.

Results

A total of 200 patients (143 women [71.5%]; mean [IQR] age, 49.0 [37.0-62.0] years) were included and 30 patients (15.0%) developed persistent hypoparathyroidism. The incidence of persistent hypoparathyroidism varied between 14.5% (calcium and active vitamin D 1 year postsurgery) to 28.5% (calcium and/or active vitamin D 6 months postsurgery) depending on the definition used.

Conclusions and Relevance

In this cohort study, the risk of persistent hypoparathyroidism after total or completion thyroidectomy was 15%in patients who were referred to university hospital centers. The high rate of persistent hypoparathyroidism warrants efforts to reduce this complication rate. There is discrepancy in the definition and treatment of persistent hypoparathyroidism, and use of uniform evidence-based treatment guidelines enables comparison of interventions.

Introduction

The parathyroid glands are usually 4 delicate structures 3 to 4mmin size and located close to the thyroid gland. Their function is to maintain calcium (Ca) homeostasis by producing the parathyroid hormone (PTH). Unfortunately, these organs are at risk of damage during thyroid surgery, potentially resulting in postoperative hypoparathyroidism. Hypoparathyroidism is one of the most common complications after total or completion thyroidectomy and is in most patients caused by accidental damage or resection of parathyroid glands or impaired blood supply.(1,2) Immediate clinical signs of hypoparathyroidism due to hypocalcemia are perioral numbness, muscle cramps, and paresthesia, as well as severe seizures and cardiac arrhythmias in rare instances. In the case of persistent hypoparathyroidism, patients are at risk for kidney complications, impaired quality of life, and increased mortality rates. (3-5) Transient hypoparathyroidism (parathyroid function restores within the first year after surgery) occurs in up to 19% to 38% of patients after total or completion thyroidectomy. (6) Patients with hypoparathyroidism beyond this period are usually classified as having persistent hypoparathyroidism. (7-9) Data from high-volume single centers show frequencies of persistent hypoparathyroidism less than 5%. A single-center study from Sweden and a Korean case series published a 1.9% and 1.5% incidence rate, respectively. (8,10) Another single-center study from Austria and a French multicenter study showed even lower incidences of 1.2% and 1.0%, respectively. (11,12) However, recent registries and nationwide multicentric studies reported much higher incidence rates. A Swedish population-based study reported a persisting hypoparathyroidism rate of 14.5%, and a Spanish multicenter nationwide study reported an even higher incidence rate of 16.7%.7,13 The British Association of Endocrine and Thyroid Surgeons (BAETS) reported a 7.3% rate in their fifth national audit, and a survey from the Thyroid Cancer Alliance yielded a 13.8% rate. (9,14) This variety in reported incidence rates might be partially explained by the absence of an international standardized definition for persistent hypoparathyroidism, (15) differences in case mix, and underreporting of this complication. Despite the fact that there is substantial literature on the incidence of hypoparathyroidism, uniform diagnosis and treatment guidelines are still lacking. We hypothesized that the incidence of hypoparathyroidism in the literature is underreported because there are no diagnostic guidelines, and national registries and multicenter studies demonstrate substantially different outcomes compared with single-center studies. In the Netherlands, nearly a decade ago, centralization of complex health care and (oncological) thyroid care was introduced. Centralization is defined as the reorganization of health care services into fewer specialized units. (16) Correspondingly, surgical procedures for high-risk thyroid cancer, large goiters, and repeated thyroid surgery, for example, are predominantly conducted in academic centers. Within this framework, and because most studies, to our knowledge, include single-center studies or national registries, this study evaluates the real-life incidence of postoperative, persistent hypoparathyroidism after total or completion thyroidectomy in a tertiary academic patient population. In addition, the effect of different definitions regarding hypoparathyroidism is assessed. The outcome of this study has the potential to refine the informed consent procedure in specialized centers and provide a stepping stone for further collaborations that aim to reduce complication rates and establish uniform treatment protocols.

Methods

Study Design and Study Participants

This is a retrospective, 1-year, multicenter cohort study of patients undergoing a total or completion thyroidectomy in 7 university hospitals (of 8) in the Netherlands during 2016. All 8 university hospitals were invited to participate in this study, of which 7 responded to the invitation. Oncological thyroid care in the Netherlands is centralized, and patients who require extensive thyroid surgery, such as for advanced cancer or large goiters, mainly undergo their procedures in university hospitals. Patients eligible for inclusion were 18 years or older and underwent a total or completion thyroidectomy for any diagnosis. Patients were excluded if (1) they were known to have preoperative parathyroid disease (eg, hyperparathyroidism) or used active vitamin D (Dv) for another indication, (2) follow-up data were unavailable, or (3) the patient underwent reoperation in the central neck compartment within 1 year after total or completion thyroidectomy.

Ethics

Data obtained from patient records were anonymously stored using study-specific patient codes in a password-protected database. The protocol had been approved by the Medical Ethics Committee Rotterdam, and informed consent was waived. The study used the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline.

Data Collection and Definition

Medical health records were reviewed to determine the patient's age and sex, the indication, extent and outcome of surgery, the length of hospital stay, and additional postoperative treatment. Data on Ca and Dv supplementation at discharge, 6 months after surgery, and 1 year after surgery were collected. We chose a clinical and pragmatic definition of persistent hypoparathyroidism as requiring Dv with or without Ca longer than 1 year after surgery.We believe that this definition reflects those patients who have a markedly low amount or lack of PTH levels because it is well known that patients with hypoparathyroidism require active Dv suppletion (with or without Ca) to absorb Ca because of the markedly low amount or lack of PTH levels. Therefore, this definition approximates the true incidence of persistent hypoparathyroidism. Parathyroid hormone levels are not routinely assessed in participating hospitals and are therefore not included in this article.

Surgical Procedure

Total or completion thyroidectomy was performed by endocrine surgeons in university hospitals in the Netherlands. One hospital performed robot-assisted transaxillary thyroidectomies in 2016. All other hospitals performed the surgery via a Kocher incision over the thyroid parallel to the skin folds. Thyroidectomy procedures were performed in the same standardized manner by ligation of the superior vessels and mobilization of the upper pole followed by the capsular dissection technique with respect to the parathyroid glands. The inferior vessels were ligated after identifying the recurrent laryngeal nerve. Incidentally resected parathyroid glands were autotransplanted into the sternocleidomastoid muscle. A central (level VI) or lateral (levels IIa, III, IV, and Vb) lymph node dissection (cervical lymph node dissection [CLND] and lateral lymph node dissection [LLND]) was performed when indicated (eg, preoperative suspicion of lymph node metastasis).

Postoperative Hypocalcemia Supplementation Protocols

Each hospital had its own Ca supplementation protocol (Supplemental Table 1). In one of the participating hospitals, a prophylactic Ca supplementation protocol was used during 2016. However, as stated in this center's Ca protocol, Ca supplementation was discontinued 2 weeks postoperatively, if possible (eTable in the Supplement). Two hospitals initiated Ca supplementation when serum Ca levels were lower than 8.4 mg/dL (to convert to mmol/L, multiply by 0.25) and all other hospitals when the serum Ca levels were less than 8.8 mg/dL. The initial daily dose of calcium carbonate varied between 1500 mg and 3000 mg. In 4 hospitals, active Dv analogues were administered when serum Ca levels were less than8 mg/dL and in 1 hospital when serum Ca levels were less than 8.4 mg/dL. Another hospital administered Dv with Ca supplements, and another if persisting hypocalcemia (Ca <8.8 mg/dL) was seen during the first postoperative day. All hospitals adjusted the dosage based on serum Ca levels. Target serum Ca levels were within the lower normal range in all hospitals (Table 1). Three hospitals explicitly stated that weaning could be initiated when normocalcemia or Ca levels greater than 8.8 mg/dL were reached. In the case of severe hypocalcemia, an endocrinologist was consulted. All hospitals left weaning of supplementation at the discretion of the endocrinologist at the outpatient clinic.

Statistical Analysis

Data were analyzed using descriptive statistics. Categorical variables are displayed as count and percentage. Continuous variables with normal distribution or abnormal distribution are displayed by mean (SD) or median (IQR), respectively. Differences between groups were evaluated with an effect size metric of absolute difference, and the precision of the effect size metric was measured with 95% CI.17 Statistical analyses were performed using IBM SPSS, version 25.0.

Results

Study Population and Baseline Characteristics

Of the 224 adult patients who underwent a total or completion thyroidectomy, 200 (89.3%) were included in this study. Demographic characteristics and clinical data of the final study cohort are summarized in Table 1. The median age of our final study cohort was 49.0 (IQR 37.0-62.0) years, and 143 (71.5%) were women. The reason for surgery was carcinoma for 138 (69.2%), Graves' disease for 33 (16.5%), and multinodular goiter for 17 patients (8.5%), and 12 (6.0%) had other indications.

Table 1. Baseline characteristics

Characteristic	Study population (n=200)	HPT + (n=30)	HPT – (n=170)
Sex			
Men	57 (28.5)	9 (15.8)	48 (84.2)
Women	143 (71.5)	21 (14.7)	122 (85.3)
Age (years)	49.0 [37.0 – 62.0]	49.5 [41.75 – 62.0] (n=30)	49.0 [36.75 – 62.0] (n=170)
BMI	25.9 [22.3 – 30.7] (n=192)	25.4 [23.1 – 30.7] (n=30)	26.0 [22.3 – 31.2] (n=162)
Diagnosis			
Carcinoma	138 (69.0)	19 (13.8)	119 (86.2)
Papillary	102 (51.0)	13 (12.7)	89 (87.3)
Follicular	20 (10.0)	0 (0.0)	20 (100.0)
Medullary	16 (8.0)	6 (37.5)	10 (62.5)
Graves	33 (16.5)	7 (21.2)	26 (78.8)
MNG	17 (8.5)	3 (17.6)	14 (82.4)
Other	12 (6.0)	1 (8.3)	11 (91.7)

Data are expressed as numbers (percentage) or as median [IQR]; Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); MNG, multi nodular goiter; HPT, postoperative hypoparathyroidism.

Surgery and Additional Postoperative Treatment

In total, 135 patients (67.5%) underwent a total thyroidectomy (TTx) and 65 patients (32.5%) a completion thyroidectomy; 4 patients (2.0%) underwent robot-assisted transaxillary thyroidectomy. Of the 135 patients who underwent a TTx, 128 patients (94.8%) underwent a TTx alone without a CLND or LLND. A CLND alone was performed in 34 patients (17.0%), and a CLND and LLND was performed in 38 patients (19.0%). In patients who underwent a TTx (n = 135), 27 (20.0%) developed postoperative persistent hypoparathyroidism, while the rate was 4.6% for the 65 patients who underwent a completion thyroidectomy (difference, 15.4%; 95% CI, 7.0%-23.9%). Among the 38 patients who underwent a CLND and LLND, the rate of postoperative hypoparathyroidism was 26.3%, while the rate was 12.4% for the 162 patients who did not (difference, 14.0%; 95% CI, –0.9% to 28.9%). The mean (SD) length of hospital stay in patients with a diagnosis of postoperative persistent hypoparathyroidism was 6.7 (3.7) days; this was 3.5 days (95% CI, 2.2-4.8 days) longer than in patients without hypoparathyroidism (Table 2). In total, 119 patients (59.7%) received postoperative radioiodine (RAI) therapy. In these patients, the rate of persistent hypoparathyroidism was 10.1%, and the rate among the 81 who did not receive RAI was 22.2% (difference, 12.1%; 95% CI, –22.7% to –1.6%). Postoperative radiotherapy of the neck was performed in 6 patients (3.0%), of whom 0 developed persistent hypoparathyroidism vs a hypoparathyroidism rate of 15.5% in the 194 patients who did not receive radiotherapy (difference, 15.5%; 95% CI, –20.6% to –10.4%). Reoperation for postoperative bleeding was performed for 12 patients, of whom 2 (16.7%) developed persistent hypoparathyroidism; in patients who did not undergo a reoperation, 28 (14.9%) developed persistent hypoparathyroidism (difference, 1.8%, 95% CI, –19.9% to 23.5%) (Table 2).

Table 2. Procedural characteristics and outcomes, stratified by the presence of persistent hypoparathyroidism.

Characteristic	Study population (n=200)	HPT + (n=30)	HPT – (n=170)	Difference (95% CI)
Thyroidectomy				
Total	135 (67.5%)	27 (20.0%)	108 (80.0%)	15.4%
Completion	65 (32.5%)	3 (4.6%)	62 (95.4%)	(7.0% to 23.9%)
CLND				
Positive	34 (17.0%)	7 (20.6%)	27 (79.4%)	6.7%
Negative	166 (83.0%)	23 (13.9%)	143 (86.1%)	(-7.9% to 21.3%)
CLND and LLND				
Positive	38 (19.0%)	10 (26.3%)	28 (73.7%)	14.0%
Negative	162 (81.0%)	20 (12.3%)	142 (87.7%)	(-0.9 to 28.9%)
Days of hospitalization	3.7 (±3.6)	6.7 (±3.7)	3.2 (±3.3)	3.5[a] (2.2 to 4.8)
RAI				
Positive	119 (59.5%)	12 (10.1%)	107 (89.9%)	-12.1%
Negative	81 (40.5%)	18 (22.2%)	63 (77.8%)	(-22.7% to -1.6%)
RT neck				
Positive	6 (3.0%)	0 (0.0%)	6 (100.0%)	-15.5%
Negative	194 (97.0%)	30 (15.5%)	164 (84.5%)	(-20.6% to -10.4%)
Reoperation for bleeding				
Positive	12 (6.0%)	2 (16.7%)	10 (83.3%)	1.8%
Negative	188 (94.0%)	28 (14.9%)	160 (85.1%)	(-19.9% to 23.5%)

Abbreviations: CLND, central lymph node dissection; HPT, hypoparathyroidism; LLND, lateral lymph node dissection; NA, not applicable; RAI, postoperative radioiodine therapy; RT, postoperative radiotherapy. [a] Difference calculated from 3.2 days of hospitalization for patients without hypoparathyroidism.

Postoperative Ca and Dv Supplementation

The rate of persistent hypoparathyroidism in this cohort was 15.0% (30 patients). The range of incidence of persistent hypoparathyroidism across the 7 participating hospitals was 5.6% to 26.9%, and there was no meaningful difference in the incidence of persistent hypoparathyroidism between the hospitals. At discharge, 78 patients (39.0%) received postoperative Ca supplementation only (of whom 31 patients [39.7%] received a prophylactic), 1 patient (0.5%) Dv supplementation only, and 55 patients (27.5%) Ca and Dv (CaDv) supplementation (Table 3). One year after surgery, 13 patients (6.5%) received Ca supplementation only, 1 (0.5%) Dv only, and 29 (14.5%) CaDv supplementation (Table 3).

Table 3. Postoperative Ca and Dv supplementation.

Treatment	At discharge	Six months post-surgery	One-year post-surgery
Ca only	78 (39.0%)[a]	21 (10.5%)	13 (6.5%)
Dv only	1 (0.5%)	4 (2.0%)	1 (0.5%)
CaDv	55 (27.5%)	32 (16.0%)	29 (14.5%)
Dv or CaDv	56 (28.0%)	36 (18.0%)	30 (15.0%)
Ca and/or Dv	134 (67.0%)	57 (28.5%)	43 (21.5%)

Data are expressed as numbers (percentage); Abbreviations: Ca, calcium supplementation; CaDv, calcium and active vitamin D supplementation; Dv, active vitamin D supplementation. [a] Thirty-one patients (39.7%) received prophylactic supplementation.

Discussion

This study assessed the real-life incidence of postoperative persistent hypoparathyroidism in patients who were referred to university hospital centers in the Netherlands and found that persistent hypoparathyroidism, defined as the need for Dv with or without Ca supplementation that persists at least 1 year after surgery, occurred in 15.0% of the participants after total or completion thyroidectomy. This number compares unfavorably with data from high-volume single centers that reported incidences of less than 5% (the definition of hypoparathyroidism ranged from Dv or CaDv supplementation 6 months postsurgery to serum levels of intact PTH <15 pg/mL [to convert to ng/L, multiply by 1] for at least 1 year) (8,10,11) and is considerably higher than reported by the BAETS fifth national audit (7.3%, with a definition of hypoparathyroidism as the need for treatment with CaDv supplementation 6 months postoperatively). (14) However, it is similar to data from a multicenter study (16.7%, with a definition of hypoparathyroidism as the need for treatment with Ca or Dv 12months after surgery) (7) and a survey from the Thyroid Cancer Alliance (13.8%, with a definition of hypoparathyroidism as low blood Ca levels 1 year after surgery). (9) More recently, a Swedish nationwide study reported a 12.5% risk of persistent hypoparathyroidism after TTx (definition of hypoparathyroidism as the need for Ca and/

or Dv more than 12 months after surgery). (13) These numbers reflect the discrepancy in incidence rates between single-center studies and national registries, which can partially be explained by the use of different definitions for hypoparathyroidism. Mehanna et al (18) demonstrated that the rate of persistent hypoparathyroidism varied between 0% to 4.4% depending on the definition. This finding was confirmed in our study cohort, with a persistent hypoparathyroidism incidence varying from 14.5% (CaDv 1 year postsurgery) to 28.5% (Ca and/or active Dv 6 months postsurgery) depending on the definition used. (18)

The incidence of persistent hypoparathyroidism in this cohort warrants a closer look. In this study, only university hospital centers participated, where oncological thyroid care is centralized and mainly extensive thyroid surgeries are performed, as they serve as referral centers in the Netherlands for advanced cancers and large goiters. This challenging case mix could be 1 reason for the high incidence of persistent hypoparathyroidism, a possible explanation that is supported by the literature in which higher rates of persistent hypoparathyroidism were seen after more extensive surgery and lymph node dissections. (7,19,20) Moreover, thyroid malignancy and Graves' disease are risk factors for persistent hypoparathyroidism. (21,22) Because 77.0% of TTx performed in this cohort were to treat thyroid cancer or Graves' disease and for 17.0% a CLND alone and 19.0% a CLND and LLND were performed, this might explain the high incidence of persistent hypoparathyroidism. This contrasts with the Swedish study from Almquist et al (8) in which 19.3% of TTx were performed for thyroid cancer and a study from Bergenfelz et al (23) in which all cancers were excluded. Both studies reported a persistent hypoparathyroidism incidence rate below 5%. (8,23) Other studies have also reported higher rates of persistent hypoparathyroidism after more extensive surgery and lymph node dissections. (12,18,19) When excluding patients who underwent CLND or LLND, the incidence rate of postoperative persistent hypoparathyroidism decreased to 10.2%. This suggests that hypoparathyroidism reflects extensive disease. The number of cases overall that qualified for inclusion was not large. However, we assume this had a limited effect because all centers also perform many hemithyroidectomies, redo surgeries, neck dissections, and parathyroidectomies (>100-150 neck surgeries per hospital), rendering the necessary expertise to save parathyroid glands during thyroid surgery.

Reported hypoparathyroidism incidence rates in the literature may be inaccurate because of loss to follow-up. In line with this assertion, 25% of patients do not have long-term data on CaDv replacement in the BAETS audit; therefore, the hypoparathyroidism rate may be underrated. (14) The BAETS study focuses on a national audit in which nonacademic centers also participated, probably reflecting less complex surgical cases. Our definition assumes that physicians have attempted to decrease Dv supplementation doses within 1 year after surgery. It is hypothesized that oncologic trajectories are intensive because of thyroid hormone withdrawal and RAI therapy, leading to maintaining the initial supplementation regimen to protect patients from new interventions. Therefore, patients may use unnecessary supplementation, which may be followed by a higher incidence of persistent hypoparathyroidism. However, we do not have data to support this assumption.

Despite persistent hypoparathyroidism being such a common complication, we lacked uniformity in definition and treatment. With this study, we intended to emphasize the problem of high incidence rates and large variations among guidelines and local hospital protocols. However, there was no meaningful difference in the incidence of hypoparathyroidism between the hospitals. Efforts should be made to reduce this complication rate and use national uniform diagnostic and treatment guidelines to enable comparison of interventions. An international consensus for the definition of persistent hypoparathyroidism after thyroid surgery and the development of reliable registration systems can serve national and international benchmarking purposes that aim for improved quality for patients who are treated with total or completion thyroidectomy. Furthermore, new techniques that aim to decrease hypoparathyroidism after thyroid surgery should be investigated and implemented. Recently, Benmiloud et al (12) showed that the use of near-infrared auto fluorescence during TTx lowered the temporary postoperative hypocalcemia rate from 22% to 9%. However, it did not aid in decreasing the rate of persistent hypoparathyroidism (corrected Ca level <8.0 mg/dL 6 months after surgery), which was only 1%. Intraoperative parathyroid gland angiography with indocyanine green (ICG) has also been proposed to prevent postoperative hypoparathyroidism. Vidal Fortuny et al (24) showed that ICG angiography obviates the need for Ca supplementation and postoperative measurement of Ca and PTH 10 days after surgery in patients with at least 1 well perfused parathyroid gland on ICG angiography. (24) Although promising, the clinical value of ICG angiography in preventing persistent hypoparathyroidism is undetermined. Other ways to decrease the incidence of hypoparathyroidism could be centralization of thyroid surgery to high-volume centers (25) and hesitancy in performing a TTx. (26-29) Patients should be informed realistically regarding the complication rate of total or completion thyroidectomy in the context of the gain in the oncological outcome and should be informed about alternative treatments. Lastly, we should focus on refining surgical techniques and continuously incorporating these in surgical training programs.

Limitations

This study is a nonrandomized, retrospective study, and despite the care of data collection and the use of clear inclusion criteria, some degree of observation bias cannot be ruled out. Although this study was performed in university hospitals in the Netherlands, we believe the results of this study are generalizable to institutions who also perform fewer than 100 to 150 specialized and complex head and neck surgeries per year, comprising an average of 30 total and completion thyroidectomies. The heterogeneity in surgical techniques, such as sealing devices within the different centers, is a limitation of this study. The definition of persistent hypoparathyroidism was based on the use of Dv supplementation, and serum Ca or PTH levels were not considered. However, PTH levels may not be the optimal criterium to define hypoparathyroidism because Lončar et al (30) showed that in 6 of 14 patients who could not discontinue Ca supplementation 1 year after surgery, PTH levels were within the normal range. Additionally, a recent study showed that the incidence of persistent hypoparathyroidism was 18.7%, with a definition of PTH concentrations less than the normal range for more than 12 months. (31) This may indicate that the definition based on CaDv supplementation does not necessarily result in a higher incidence of persistent hypoparathyroidism compared with a definition based on PTH values. (32,33) A recent systematic review found 20 different definitions in 89 articles, emphasizing the need for uniform diagnosis and treatment guidelines. (15) Only if measurements are used universally can we study the incidence of postoperative hypoparathyroidism and identify which practices need to improve and how to do so. Furthermore, serum magnesium, phosphate, and Dv levels were not collected. Therefore, the severity of parathyroid deficiency could not be quantified. However, this was not the goal of our study, and we believe that if hypomagnesaemia was the cause of hypocalcemia, it would have been corrected by the experienced endocrinologists during the first year after surgery and not have any association with the incidence of persistent hypoparathyroidism. However, this is an assumption and a possible limitation of this study. Also, no data on discontinuing medication were collected, as this is not routinely described in medical health records and not standardized in local protocols. Lastly, data on parathyroid glands in situ and autotransplantation were not available, which are shown to be significantly associated with persistent hypoparathyroidism. (34)

Conclusions

This cohort study describes the real-life incidence of hypoparathyroidism after total or completion thyroidectomy in the setting of centralized thyroid care in a highly selected population undergoing extensive thyroid surgery. These data provide a better understanding of the magnitude of this postoperative complication and enable more realistic information for patients who are undergoing extensive and complex thyroid surgery. Efforts should be made to reduce this complication rate and use national uniform treatment guidelines to enable comparison of interventions.

References

1. Rosato L, Avenia N, Bernante P, et al. Complications of thyroid surgery: analysis of a multicentric study on 14,934 patients operated on in Italy over 5 years. World J Surg. 2004;28(3):271-276.
2. Bergenfelz A, Jansson S, Kristoffersson A, et al. Complications to thyroid surgery: results as reported in a database from a multicenter audit comprising 3,660 patients. Langenbecks Arch Surg. 2008;393(5):667-673.
3. Astor MC, Løvås K, Debowska A, et al. Epidemiology and Health-Related Quality of Life in Hypoparathyroidism in Norway. J Clin Endocrinol Metab. 2016;101(8):3045-3053.
4. Mitchell DM, Regan S, Cooley MR, et al. Long-term follow-up of patients with hypoparathyroidism. J Clin Endocrinol Metab. 2012;97(12):4507-4514.
5. Almquist M, Ivarsson K, Nordenström E, Bergenfelz A. Mortality in patients with permanent hypoparathyroidism after total thyroidectomy. Br J Surg. 2018;105(10):1313-1318.
6. Edafe O, Antakia R, Laskar N, Uttley L, Balasubramanian SP. Systematic review and meta-analysis of predictors of post-thyroidectomy hypocalcaemia. Br J Surg. 2014;101(4):307-320.
7. Díez JJ, Anda E, Sastre J, et al. Prevalence and risk factors for hypoparathyroidism following total thyroidectomy in Spain: a multicentric and nation-wide retrospective analysis. Endocrine. 2019;66(2):405-415.
8. Almquist M, Hallgrimsson P, Nordenström E, Bergenfelz A. Prediction of permanent hypoparathyroidism after total thyroidectomy. World J Surg. 2014;38(10):2613-2620.
9. Banach R, Bartes B, Farnell K, et al. Results of the Thyroid Cancer Alliance international patient/survivor survey: Psychosocial/informational support needs, treatment side effects and international differences in care. Hormones (Athens). 2013;12(3):428-438.
10. Kim SM, Kim HK, Kim KJ, et al. Recovery from Permanent Hypoparathyroidism After Total Thyroidectomy. Thyroid. 2015;25(7):830-833.
11. Asari R, Passler C, Kaczirek K, Scheuba C, Niederle B. Hypoparathyroidism after total thyroidectomy: a prospective study. Arch Surg. 2008;143(2):132-137; discussion 138.
12. Benmiloud F, Godiris-Petit G, Gras R, et al. Association of Autofluorescence-Based Detection of the Parathyroid Glands During Total Thyroidectomy With Postoperative Hypocalcemia Risk: Results of the PARAFLUO Multicenter Randomized Clinical Trial. JAMA Surg. 2020;155(2):106-112.
13. Annebäck M, Hedberg J, Almquist M, Stålberg P, Norlén O. Risk of Permanent Hypoparathyroidism After Total Thyroidectomy for Benign Disease: A Nationwide Population-based Cohort Study From Sweden. Ann Surg. 2020.
14. Chadwick DR. Hypocalcaemia and permanent hypoparathyroidism after total/bilateral thyroidectomy in the BAETS Registry. Gland Surg. 2017;6(Suppl 1):S69-S74.
15. Harsløf T, Rolighed L, Rejnmark L. Huge variations in definition and reported incidence of postsurgical hypoparathyroidism: a systematic review. Endocrine. 2019;64(1):176-183.
16. Ostermann M, Vincent J-L. How much centralization of critical care services in the era of telemedicine? Critical Care. 2019;23(1):423.

17. Gardner MJ, Altman DG. Confidence intervals rather than P values: estimation rather than hypothesis testing. Br Med J (Clin Res Ed). 1986;292(6522):746-750.
18. Mehanna HM, Jain A, Randeva H, Watkinson J, Shaha A. Postoperative hypocalcemia--the difference a definition makes. Head Neck. 2010;32(3):279-283.
19. Giordano D, Valcavi R, Thompson GB, et al. Complications of central neck dissection in patients with papillary thyroid carcinoma: results of a study on 1087 patients and review of the literature. Thyroid. 2012;22(9):911-917.
20. Ywata de Carvalho A, Chulam TC, Kowalski LP. Long-term Results of Observation vs Prophylactic Selective Level VI Neck Dissection for Papillary Thyroid Carcinoma at a Cancer Center. JAMA Otolaryngol Head Neck Surg. 2015;141(7):599-606.
21. Karamanakos SN, Markou KB, Panagopoulos K, et al. Complications and risk factors related to the extent of surgery in thyroidectomy. Results from 2,043 procedures. Hormones (Athens). 2010;9(4):318-325.
22. Puzziello A, Rosato L, Innaro N, et al. Hypocalcemia following thyroid surgery: incidence and risk factors. A longitudinal multicenter study comprising 2,631 patients. Endocrine. 2014;47(2):537-542.
23. Bergenfelz A, Nordenström E, Almquist M. Morbidity in patients with permanent hypoparathyroidism after total thyroidectomy. Surgery. 2020;167(1):124-128.
24. Vidal Fortuny J, Sadowski SM, Belfontali V, et al. Randomized clinical trial of intraoperative parathyroid gland angiography with indocyanine green fluorescence predicting parathyroid function after thyroid surgery. Br J Surg. 2018;105(4):350-357.
25. Meltzer C, Hull M, Sundang A, Adams JL. Association Between Annual Surgeon Total Thyroidectomy Volume and Transient and Permanent Complications. JAMA Otolaryngology–Head & Neck Surgery. 2019;145(9):830-837.
26. Haugen BR, Alexander EK, Bible KC, et al. 2015 American Thyroid Association Management Guidelines for Adult Patients with Thyroid Nodules and Differentiated Thyroid Cancer: The American Thyroid Association Guidelines Task Force on Thyroid Nodules and Differentiated Thyroid Cancer. Thyroid. 2016;26(1):1-133.
27. Adam MA, Pura J, Gu L, et al. Extent of surgery for papillary thyroid cancer is not associated with survival: an analysis of 61,775 patients. Ann Surg. 2014;260(4):601-605; discussion 605-607.
28. Sawant R, Hulse K, Sohrabi S, et al. The impact of completion thyroidectomy. Eur J Surg Oncol. 2019;45(7):1171-1174.
29. Rodriguez Schaap PM, Botti M, Otten RHJ, et al. Hemithyroidectomy versus total thyroidectomy for well differentiated T1-2 N0 thyroid cancer: systematic review and meta-analysis. BJS Open. 2020.
30. Lončar I, Dulfer RR, Massolt ET, et al. Postoperative parathyroid hormone levels as a predictor for persistent hypoparathyroidism. Eur J Endocrinol. 2020;183(2):149-159.
31. Canu GL, Medas F, Longheu A, et al. Correlation between iPTH Levels on the First Postoperative Day After Total Thyroidectomy and Permanent Hypoparathyroidism: Our Experience. Open Med (Wars). 2019;14:437-442.

32. Gupta S, Chaudhary P, Durga CK, Naskar D. Validation of intra-operative parathyroid hormone and its decline as early predictors of hypoparathyroidism after total thyroidectomy: A prospective cohort study. Int J Surg. 2015;18:150-153.
33. Sonne-Holm E, Holst Hahn C. Prolonged Duration of Surgery Predicts Postoperative Hypoparathyroidism among Patients Undergoing Total Thyroidectomy in a Tertiary Referral Centre. Eur Thyroid J. 2017;6(5):255-262.
34. Sitges-Serra A. The PGRIS and parathyroid splinting concepts for the analysis and prognosis of protracted hypoparathyroidism. Gland Surg. 2017;6(Suppl 1):S86-S93.

Supplemental data chapter 8

Supplemental Table 1. Overview of the calcium supplementation protocol per hospital.

Hospital	Calcium treatment initiated *	Calcium supplements and dosage	Active vitamin D treatment initiated **	Active vitamin D dosage ***	IV treatment initiated ****	IV treatment dosage	Weaning initiated	Target serum calcium
1	Ca <2.1 / symptoms	3 times daily 1g calciumcarbonate	POD 1 Ca <2.2	Start 1 time daily 0.5ug	Ca <2.0	Bolus 1g	Ca >2.2	Ca 2.2
2	Ca <2.2	2 times daily 1g calciumcarbonate	Ca <2.0	Start 1 time daily 1ug	Ca <1.9 or severe symptomatology	Bolus 1g	NA	Ca 2.1-2.2
3	Prophylactic	2 times daily 1g calcium/ 400IE D3	Prophylactic	1 time daily 1ug (stopped at discharge)	Ca <1.8 or severe symptomatology	Bolus 1g	Normocalcemia	Lower normal range
4	Ca <2.2	3 times daily 500mg calciumcarbonate	Ca <2.0	Start 1 time daily 1ug	Ca <1.9	3 times daily 1g	NA	NA
5	Ca <2.1	2-3 times daily 1g calciumcarbonate	Ca <2.1	Start 2-3 times daily 0.5ug	Ca <1.9	Bolus 1-2g	Ca >2.2	Ca 2.1-2.2
6	Ca <2.2	3 times daily1g calciumcarbonate	Ca <2.0	Start 1 times daily 1ug	Ca <1.9	3 times daily 1g	NA	Ca >2.0
7	Ca <2.2	3 times daily1g carbonate	Ca <2.0	Start 1 time daily 1ug	Ca <1.9	3 times daily 1g	NA	Ca >2.0

*Serum calcium in mmol/L adjusted for albumin; ** active vitamin D or active vitamin D analogues; *** Starting dosage of active vitamin D
**** Intravenous (IV) treatment with calciumgluconate POD = postoperative day

9

Chapter 9

Postoperative parathyroid hormone levels as a predictor for persistent hypoparathyroidism

I Lončar, RR Dulfer, ET Massolt, R Timman, YB de Rijke, GJH Franssen, JWA Burger, PC Smit, FAL van der Horst, RP Peeters, CHJ van Eijck, TM van Ginhoven

Eur J Endocrinol. 2020 Aug;183(2):149-159.

Abstract

Objective

Hypoparathyroidism is a common complication after thyroidectomy. It is not yet possible to predict in which patients hypoparathyroidism will persist. We aim to determine whether a decrease in PTH levels, measured at the first postoperative day, can identify patients with a high risk for persistent hypoparathyroidism one year after thyroidectomy.

Design

Prospective multi-center cohort study.

Methods

Patients undergoing total or completion thyroidectomy were included. We measured PTH levels preoperatively and on the first postoperative day. Primary outcome is the proportion of patients with persistent hypoparathyroidism, defined as the need for calcium supplementation one year after surgery.

Results

We included 110 patients of which 81 were used for analysis of the primary outcome. At discharge 72.8% of patients were treated with calcium supplementation. Persistent hypoparathyroidism was present in 14 patients (17.3%) at one-year follow-up, all of them had a decrease in PTH >70% at the first postoperative day. These 14 were 43.8% of the 32 patients who had such a decrease. In the group of 49 patients (59.8%) without a PTH >70% decrease, none had persistent hypoparathyroidism one year after surgery (P-value <0.001). A decrease of >70% in PTH levels had a sensitivity of 100.0% (95% CI: 85.8–100.0%), a specificity of 73.1% (95% CI: 62.5–83.7%) and an area under the curve of 0.87 (95% CI: 0.79–0.94) to predict the risk for persistent hypoparathyroidism.

Conclusion

In our study a decrease in PTH levels of >70% after total or completion thyroidectomy is a reliable predictor for persistent hypoparathyroidism, and this should be confirmed in larger cohorts.

Introduction

Surgical treatment of both benign and malignant thyroid diseases often necessitates total thyroidectomy. This procedure is considered safe, but has specific postoperative complications such as hoarseness due to damage of the recurrent nerves and hypoparathyroidism because of surgery-related factors such as inadvertent devascularization, bruising or accidental removal of parathyroid glands. Clinical signs of hypocalcaemia are perioral numbness, paraesthesia and muscle cramps. Severe hypocalcaemia can cause seizures, spasms and cardiac arrhythmias. Patients are therefore routinely monitored for clinical signs and symptoms of hypocalcaemia and serum calcium levels are measured at set times. Postoperative hypocalcaemia is treated with oral or intravenous calcium supplementation and, in some cases, additional vitamin D supplementation (1). In most cases, parathyroid function will recover within weeks after surgery and calcium levels will normalize (2, 3). However, most studies show that less than 5% of the patients will develop persistent hypoparathyroidism (defined as the persistent need for calcium supplementation 1 year after surgery) (4, 5, 6, 7). But higher rates of up to 14% have been reported (8). Given the rates of patients with permanent voice problems and other postoperative complications, the surgical risk of a total thyroidectomy may be higher than what surgeons anticipate. Persistent hypoparathyroidism impairs quality of life (9) of an otherwise relatively healthy population and poses a burden of disease (10). It may even be associated with an increased risk of death (11). Therefore, early identification of high-risk patients allows clinicians not only to inform patients, but also to schedule tailored postoperative outpatient follow-up visits. Patients with a low risk for persistent hypoparathyroidism can be offered less visits and blood withdrawals and an early reduction of calcium supplementation, being favorable from both patient and cost-effective perspectives. Current predictive factors for post-surgical hypoparathyroidism include perioperative calcium and parathyroid hormone (PTH) levels as well as surgical factors (12, 13). Serum PTH concentration obtained between 4 and 24 h postoperatively is currently the best parameter to predict postoperative hypocalcaemia (4, 14, 15, 16, 17). In this multicenter prospective cohort study our primary aim is to determine if a decrease in PTH levels, measured at the first postoperative day, is able to identify patients with a high risk for persistent hypoparathyroidism 1 year after thyroidectomy.

Methods

Patients and data collection

Patients were recruited between March 2014 and March 2016 at one university medical center (Erasmus MC, Rotterdam, the Netherlands) and one local hospital (Reinier de Graaf Gasthuis, Delft, the Netherlands). All adult patients undergoing a total thyroidectomy or a completion thyroidectomy were included. Exclusion criteria were inability to provide informed consent or suffering from disorders in calcium homeostasis. Patients who underwent a second head and neck surgery (e.g. central cervical lymph node dissection) or patients who underwent external beam radiation therapy of the neck (18) within one year of the index procedure were excluded from the study. Baseline characteristics such as gender, age, preoperative diagnosis, medical history and blood values were obtained at the outpatient clinic. Preoperative calcium, albumin, PTH and vitamin D serum levels were measured. All patients were admitted overnight, according to standard postoperative care in both hospitals. Following surgery, blood samples were drawn on the day of surgery (6 hours postoperatively) and on the first postoperative day (within 24 hours postoperatively). Postoperative calcium, albumin and PTH levels were assessed. Primary measurement for the analysis is the PTH level on the first postoperative day. This enables easy implementation in daily practice and is shown to accurately predict direct postoperative hypocalcaemia. Standard study follow-up including laboratory screening is performed at two weeks and one year postoperatively. Other outpatient visits were scheduled according to the discretion of the treating medical specialist. Approval was obtained from the Medical Ethical committee of Erasmus MC (MEC-2013-233). The STROBE guidelines for reporting observational studies were used.

Laboratory findings and treatment of hypocalcaemia

Serum calcium levels were adjusted for albumin levels according to the formula: adjusted total calcium (mmol/L) = measured calcium (mmol/L) + (0.025 * 40 – [albumin (g/L)]). The reference value for calcium is 2.20 – 2.65 mmol/L. The reference value for PTH is 1.4 – 7.3 pmol/L. Hypocalcaemia was treated according to the local calcium supplementation protocol with calcium carbonate and vitamin D. According to the hospitals protocol, a corrected calcium level lower than 2.20 mmol/L warrants calcium supplementation. If calcium levels remain beneath 2.20 mmol/L for two consecutive days, supplementation with active vitamin D is started.

Reference change value

The reference change value (RCV) is an objective tool for the assessment of the significance of differences in serial results from an individual, based on intra-individual biological and analytical coefficient of variation. To assess the within-subject biological variation, we used the most recent database on biological variation by Ricos et al.(19). The RCV for PTH is calculated with the following formula (20):

$$RCV = \sqrt{2} \cdot Z_{\alpha} \cdot \sqrt{{CV_A}^2 + {CV_I}^2}$$

Where:

Zα is the normal probability distribution function at the desired p-value;
CVA is the analytical variation;
CVI is the within biological variation.

For α=0.05 the normal probability distribution function is 1.96. The analytical variation in our lab is 2.2%, the within biological variation for PTH is 25.3% (19), which is an assumption obtained from the table of Ricos et al. This resulted in a RCV of 70%. In this article we define patients with a PTH level change of more than the RCV (70%) as patients with a "significant PTH change". This is referred to as a decrease in PTH>70% in the text. The change in PTH levels was calculated using the following formula: PTH-change = ([pre-operative PTH – post-operative PTH] / pre-operative PTH) * 100%.

Outcome measurements

Primary outcome of the study was the proportion of patients with persistent hypoparathyroidism one year after surgery, when comparing the group with a decreased in PTH>70% versus the group without this decrease in PTH levels on the first postoperative day. Persistent hypoparathyroidism was defined as the persisting need for calcium supplementation one year after thyroid surgery and inability to be tapered off supplementation. Tapering was protocolized, yet the initiation and time frame was left to the discretion of the treating physician. The one year moment was chosen as in daily practice not all patients are tapered off calcium supplementation by their physician within the first six months after surgery and because of expected restoration of parathyroid function within the first year after surgery. Secondary outcomes were postoperative outcomes such as histologic diagnosis, hospital stay and follow-up data regarding the serum calcium, PTH levels, calcium- and active vitamin D supplementation and the diagnostic accuracy of the RCV.

Statistical analysis

Data were assessed for normality using the Shapiro-Wilk normality test. Continuous variables were expressed as means and standard deviations or medians with interquartile ranges as appropriate. Categorical variables were described as count and percentages. Differences between groups were analyzed with independent samples t-test or the Mann-Whitney U for continuous variables and Pearson Chi-square with continuity correction for categorical variables. To determine the diagnostic accuracy of a change in postoperative PTH levels we calculated the area under the curve (AUC). The sensitivity, specificity, and overall accuracy of PTH change in predicting persistent hypoparathyroidism were calculated. We performed a sample size calculation, based on a sensitivity of 100%, because it is undesirable to miss potential cases, a specificity of 80%, a maximum acceptable clinical width of the 95% confidence interval of 10%. Assuming a prevalence in our study group of 5%, we would need to include 65 patients, in case of a prevalence of 10%: 69 cases and with 20%: 77 cases (21) Therefore our sample of 81 cases can be considered sufficient. Two-tailed $p < 0.05$ values were considered statistically significant. Statistical analyses were performed with IBM SPSS version 24.0 (Armonk, NY: IBM Corp).

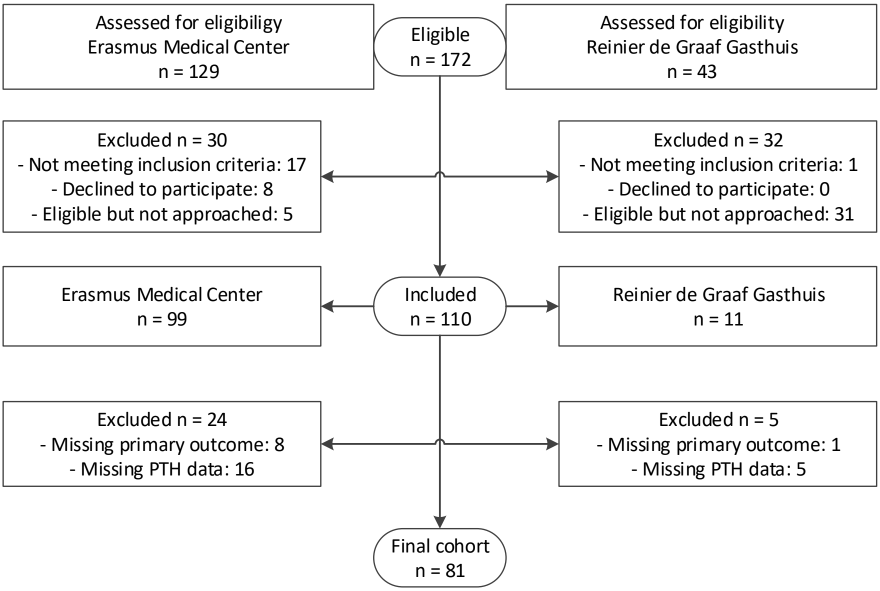


Figure 1. Flowchart of patient enrollment.

Results

Study population and baseline characteristics

We included 110 patients in this study between April 2014 and April 2016 out of 172 patients assessed for eligibility (Figure 1). For the analysis of the primary outcome, a total of 20 patients were excluded from the study due to missing data on PTH decrease at the first postoperative day and another 9 because of missing data on the primary outcome, leading to a final study cohort of 81 patients. Demographic, clinical and laboratory data of the final study cohort are summarized in Table 1. The median age of our final study cohort was 53.0 [41.0 – 65.0] years and 72.8% was female. Most patients had a total thyroidectomy (79.0%), a completion thyroidectomy was performed in 21.0% of the patients and 33.3% underwent a concomitant cervical lymph node dissection. The indication for surgery was carcinoma in 59.8%, multi-nodular goiter in 18.5%, Graves' disease in 16.0% of patients and 6.2% for other indications.

Table 1. Demographic, clinical and laboratory data of the total study cohort (n=81).

Clinical values	No. (%)
Sex	
Male	22 (27.2%)
Female	59 (72.8%)
Age (y)	53.0 [41.0 – 65.0]
ASA-classification	
I	21 (25.9%)
II	54 (66.7%)
III	6 (7.4%)
Preoperative serum calcium	2.24 [2.19 – 2.30]
Preoperative serum vitamin D	48.0 [30.3 – 66.0]
Preoperative serum PTH	4.7 [3.5 – 5.7]
Indication for surgery[a]	
Papillary carcinoma	40 (49.9%)
Multi nodular goiter	15 (18.5%)
Graves	13 (16.0%)
Follicular carcinoma	4 (4.9%)
Medullary carcinoma	2 (2.5%)
Hürthlecell carcinoma	2 (2.5%)
Other	5 (6.2%)
Surgery	
Total	64 (79.0%)
Completion	17 (21.0%)
CLND[b]	27 (33.3%)
CCLND	26 (32.1%)
LCLND	22 (27.2%)

Serum calcium in mmol/L; serum PTH in pmol/L; serum vitamin D in nmol/L; [a] Indication for surgery as diagnosed pre-operatively; [b] Concomitant cervical lymph node dissection (CLND) ; CCLND = Central CLND (level VI) ; LCLND = Lateral CLND (level II-IV)

Decline of postoperative PTH levels and risk of persistent hypoparathyroidism

In Table 2, patient characteristics are summarized and stratified by decrease in PTH>70%. A total of 32 patients (39.5%) had a decrease in PTH>70% on the first postoperative day. Besides age, there were no statistically significant differences at baseline in patients with this decrease in PTH versus patients without this PTH decrease (48.0 [34.5 – 62.0] vs 59.0 [49.5-66.3] years of age, p-value = 0.045). Persistent hypoparathyroidism was present in 14 patients (17.3%) at one-year follow-up, all of them had a decrease in PTH>70% at the first postoperative day. These 14 were 43.8% of the 32 patients who had such a decrease (Table 3). In the group of 49 patients (59.8%) without a PTH>70% decrease, none had persistent hypoparathyroidism one year after surgery (p-value < 0.001). A decrease of >70% in PTH levels had a sensitivity of 100.0% (95% CI 85.8-100.0%), a specificity of 73.1% (95% CI 62.5 – 83.7%) and an area under the curve of 0.87 (95% CI 0.79 – 0.94) to predict the risk for persistent hypoparathyroidism.

Table 2. Demographic, clinical and laboratory data of the total study cohort according to PTH change

Clinical values	No decrease PTH>70% (n=49)	Decrease PTH>70% (n=32)	p-value
Sex			
Male	10 (20.4%)	12 (37.5%)	0.091
Female	39 (79.6%)	20 (62.5%)	
Age (y)	48.0 [34.5 – 62.0]	59.0 [49.5 – 66.3]	0.045
ASA-classification			
I	13 (26.5%)	8 (25.0%)	
II	33 (67.3%)	21 (66.6%)	0.860
III	3 (6.2%)	3 (9.4%)	
Preoperative serum calcium	2.24 [2.18 – 2.31]	2.23 [2.19 – 2.32]	0.877
Preoperative serum vitamin D	50.0 [30.8 – 67.5]	44.0 [28.8 – 64.5]	0.718
Preoperative serum PTH	4.6 [3.5 – 5.4]	4.8 [3.5 – 6.0]	0.292
Indication for surgery[a]			
Papillary carcinoma	23 (46.9%)	17 (53.1%)	
Multi nodular goiter	9 (18.4%)	6 (18.8%)	
Graves	7 (14.3%)	6 (18.8%)	
Follicular carcinoma	3 (6.1%)	1 (3.1%)	0.650
Medullary carcinoma	1 (2.0%)	1 (3.1%)	
Hürthlecell carcinoma	1 (2.0%)	1 (3.1%)	
Other	5 (10.2%)	0 (0.0%)	
Surgery			
Total	37 (75.5%)	27 (84.4%)	0.338
Completion	12 (24.5%)	5 (15.6%)	
CLND[b]	14 (28.6%)	13 (40.6%)	0.261
CCLND	13 (26.5%)	13 (40.6%)	0.184
LCLND	10 (20.4%)	12 (37.5%)	0.091

Serum calcium in mmol/L; serum PTH in pmol/L; serum vitamin D in nmol/L [a] Indication for surgery as diagnosed pre-operatively; [b] Concomitant cervical lymph node dissection (CLND) ; CCLND = Central CLND (level VI) ; LCLND = Lateral CLND (level II-IV)

Table 3. Postoperative outcomes and follow-up data according to PTH decrease

Clinical values	Total cohort (n=81)	No decrease PTH>70% (n=49)	Decrease PTH>70% (n=32)	p-value
Day of surgery				
Serum calcium	2.16 [2.09 – 2.23]	2.16 [2.10 – 2.24]	2.11 [2.08 – 2.22]	0.046
Serum PTH (9 missing)	1.5 [0.6 – 2.7]	2.5 [1.5 – 3.8]	0.5 [0.3 – 0.8]	< 0.001
Oral calcium supplementation	17 (21.0%)	8 (16.3%)	9 (28.1%)	0.202
IV calcium supplementation	16 (19.8%)	7 (14.3%)	9 (28.1%)	0.126
First postoperative day				
Serum calcium	2.12 [2.05 – 2.21]	2.14 [2.08 – 2.22]	2.06 [1.93 – 2.17]	< 0.001
Serum PTH	1.6 [0.7 – 2.8]	2.4 [1.7 – 3.2]	0.6 [0.3 – 0.9]	< 0.001
Oral calcium supplementation	59 (71.6%)	29 (59.2%)	29 (90.6%)	0.002
IV calcium supplementation	16 (19.8%)	3 (6.1%)	13 (40.6%)	< 0.001
Vitamin D supplementation	8 (9.9%)	4 (8.2%)	4 (12.5%)	0.522
Discharge				
Calcium supplementation	59 (72.8%)	30 (61.2%)	29 (90.9%)	0.004
Vitamin D supplementation	30 (37.0%)	12 (24.5%)	19 (56.3%)	0.004
Histologic diagnosis[a]				0.868
Benign	32 (39.5%)	19 (38.8%)	13 (40.6%)	
Malignant	50 (61.0%)	30 (61.2%)	20 (60.6%)	
Hospital stay (days)	3.0 [3.0 - 4.0]	3.0 [3.0 – 3.0]	4.0 [3.0 – 6.5]	0.001
2 weeks postoperative				
Serum calcium (1 missing)	2.28 [2.17 – 2.33]	2.27 [2.19 – 2.33]	2.29 [2.15 – 2.31]	0.562
Serum PTH (10 missing)	1.9 [0.9 – 3.8]	2.9 [1.7 – 4.6]	0.9 [0.5 – 1.9]	< 0.001
Calcium supplementation	50 (61.7%)	21 (42.9%)	29 (90.6%)	< 0.001
Vitamin D supplementation	27 (33.3%)	7 (14.3%)	20 (62.5%)	< 0.001
1 year postoperative				
Persistent hypoparathyroidism	14 (17.3%)	0 (0.0%)	14 (43.8%)	< 0.001
Serum calcium (12 missing)	2.22 [2.13 – 2.27]	2.25 [2.16 – 2.29]	2.17 [2.06 – 2.25]	0.001
Serum PTH (12 missing)	2.8 [2.0 – 4.5]	3.1 [2.0 – 4.9]	2.5 [1.4 – 2.9]	< 0.001

Table 3. Postoperative outcomes and follow-up data according to PTH decrease

Clinical values	Total cohort (n=81)	No decrease PTH>70% (n=49)	Decrease PTH>70% (n=32)	p-value
Calcium supplementation	14 (17.3%)	0 (0.0%)	14 (43.8%)	< 0.001
Vitamin D supplementation	10 (12.3%)	0 (0.0%)	10 (31.3%)	< 0.001
Number of lab visits	4.0 [3.0 – 7.0]	3.5 [2.0 – 5.0]	7.0 [4.0 – 8.0]	< 0.001

Data are expressed as a percentage or as median [IQR]
Serum calcium in mmol/L; serum PTH in pmol/L; serum vitamin D in nmol/L
Oral calcium supplementation with calciumcarbonate; Oral vitamin D supplementation with alfacalcidol
[a] Diagnosis after histopathological examination

Postoperative outcomes and follow-up

Postoperative outcomes and follow-up data regarding the serum calcium, PTH levels and calcium and vitamin D supplementation are summarized in Table 3. At discharge 59 patients (72.8%) used calcium supplementation and 30 patients (37.0%) used vitamin D supplementation in addition to calcium supplementation. Both calcium and vitamin D supplementation was more frequent in patients with a decrease in PTH>70% (respectively 61.2% vs 90.9%, p-value = 0.004 and 24.5% vs 56.3%, p-value = 0.004). This difference remained present over time up till 1 year of follow-up.

Patients with this PTH decrease tended to have lower serum calcium levels at the day of surgery, the first postoperative day and 1 year postoperatively. This difference was not present at two weeks after surgery. A difference in PTH serum levels was seen at each time point. We also demonstrated that patients with this PTH decrease had a more prolonged hospital stay (3.0 [3.0 – 3.0] vs 4.0 [3.0 – 6.5], p-value = 0.001) and had more laboratory visits in the first year after surgery (3.5 [2.0 – 5.0] vs 7.0 [4.0 – 8.0], p-value = <0.001). Patients with a decrease in PTH>70% but without persisting hypoparathyroidism needed a median time of 3.0 [1.0 – 8.0] months to taper off their calcium and/or vitamin D medication.

Data regarding patients with persistent hypoparathyroidism are summarized in Table 4. All cases had a PTH level at the first postoperative day below the reference value of 1.4 pmol/L. At discharge, all patients with persistent hypoparathyroidism were prescribed oral calcium supplementation and 10 patients were prescribed vitamin D in addition to the oral calcium supplementation. At two weeks follow-up, another two patients were prescribed vitamin D because of persisting low serum calcium levels. One patient was readmitted because of a symptomatic hypocalcaemia at the 17th postoperative day, and was prescribed vitamin D in addition to his oral calcium. At 1 year follow-up all patients with persistent hypoparathyroidism used oral calcium supplementation, dosage varying from 500mg to 4000mg daily and 10 patients used vitamin D with dosage varying from 0.25µg to 2.5µg daily. In six patients with persistent hypoparathyroidism, PTH levels were within the normal range after one year.

The graphs in Figure 2 show this relation between PTH levels, corrected calcium levels and whether calcium supplementation was provided at the first postoperative day, two weeks postoperatively and 1 year postoperatively. It shows the normalization of the serum PTH levels and corrected calcium levels over time. However, patients with persistent hypoparathyroidism, defined as the patients with a persisting need of calcium supplementation, tend to stay below the limit of normal or in the low normal range of serum calcium and PTH levels after one year.

Table 4. Demographic, clinical and laboratory data of 14 patients with persistent hypoparathyroidism

Clinical value	1	2	3	4	5	6	7	8	9	10	11	12	13	14
Age (y)	56	62	70	45	71	60	41	29	47	69	48	74	66	73
Sex	Male	Male	Male	Female	Female	Female	Female	Female	Male	Male	Male	Female	Female	Female
Diagnosis[a]	PTC	PTC	MTC	MNG	PTC	MNG	PTC	FTC	PTC	PTC	PTC	MNG	PTC	MNG
Surgery[b]	CT	TT	TT	TT	TT	CT	TT	TT	TT	CT	TT	TT	TT	TT
CLND[c]	CCLND + LCLND	CCLND	CCLND + LCLND		CCLND + LCLND		CCLND + LCLND		CCLND + LCLND		CCLND + LCLND		CCLND + LCLND	
Preoperative serum calcium	2.26	2.18	2.13	2.19	2.20	2.24	2.22	2.30	2.23	2.14	2.22	2.19	2.09	2.43
Preoperative serum PTH	3.9	5.2	5.9	5.5	4.9	3.9	5.6	3.2	6.6	4.2	5.1	10.1	9.5	3.4
6 hours postoperative serum calcium	2.07	2.08	2.15	1.95	2.00	2.09	2.08	2.31	2.16	2.07	1.98	2.05	2.08	2.32
6 hours postoperative serum PTH	0.7	0.3	0.4	0.6	1.6	0.3	0.4			0.5	0.3	0.3	0.6	0.3
24 hours postoperative serum calcium	1.92	2.17	2.19	1.93	2.20	2.08	1.94	2.09	1.95	2.16	1.92	2.02	1.82	2.16
24 hours postoperative serum PTH	0.7	0.3	0.3	0.4	1.2	0.3	0.6	0.6	0.3	0.4	0.3	0.4	0.6	0.3
Calcium dosage at discharge (mg)	3000	4000	3000	4000	3000	4000	4000	3000	3000	3000	4000	3000	4000	3000
Vitamin D dosage at discharge (µg)	2	2	0.5	3			2	0.5		0.5	1.25	2	2	
Symptoms during admission	-	-	+	+	-	-	+	+	-	-	+	+	+	Unknown

Table 4. Demographic, clinical and laboratory data of 14 patients with persistent hypoparathyroidism (continued)

Clinical value	1	2	3	4	5	6	7	8	9	10	11	12	13	14
2 weeks postoperative serum calcium	2.29	2.54	1.83	2.06	2.20	1.83	2.01	2.21	2.00	2.43	2.13	2.50	2.45	2.16
2 weeks postoperative serum PTH	0.5	0.3	0.3	2.0		0.7		1.1	0.7	0.4	0.9	0.6	0.3	0.6
Calcium dosage at 2 weeks (mg)	3000	4000	3000	4000	2000	4000	2000	1500	3000	2000	3000	2000	4000	3000
Vitamin D dosage at 2 weeks (µg)	1	2	1	3		1	1	0.5		0.5	1.25	2	2	0.5
1 year postoperative serum calcium	2.17	2.04	2.00	2.05	2.05	1.98	1.90	2.20	2.20	2.10	1.95	2.25	1.94	2.28
1 year postoperative serum PTH	2.0	0.8	0.3	1.2	5.1	0.9	2.4	1.1	0.9	2.7	3.4	1.6	1.0	0.6
Calcium dosage at 1 year (mg)	2000	2000	3000	4000	2000	1000	1500	1000	1500	1500	500	500	2000	4000
Vitamin D dosage at 1 year (µg)	1	0.75	1.25	2.5			0.5	0.5	2		0.25		1	0.5

PTC = papillary thyroid carcinoma; FTC = follicular thyroid carcinoma; MTC = medullary thyroid carcinoma; MNG = multinodular goiter
Serum calcium in mmol/L; serum PTH in pmol/L; Oral calcium supplementation with calciumcarbonate; Oral vitamin D supplementation with alfacalcidol
[a] Diagnosis after histopathological examination; [b] Type of surgery performed; CT = completion thyroidectomy; TT = total thyroidectomy
[c] Concomitant cervical lymph node dissection (CLND) ; CCLND = Central CLND (level VI) ; LCLND = Lateral CLND (level II-IV)

9

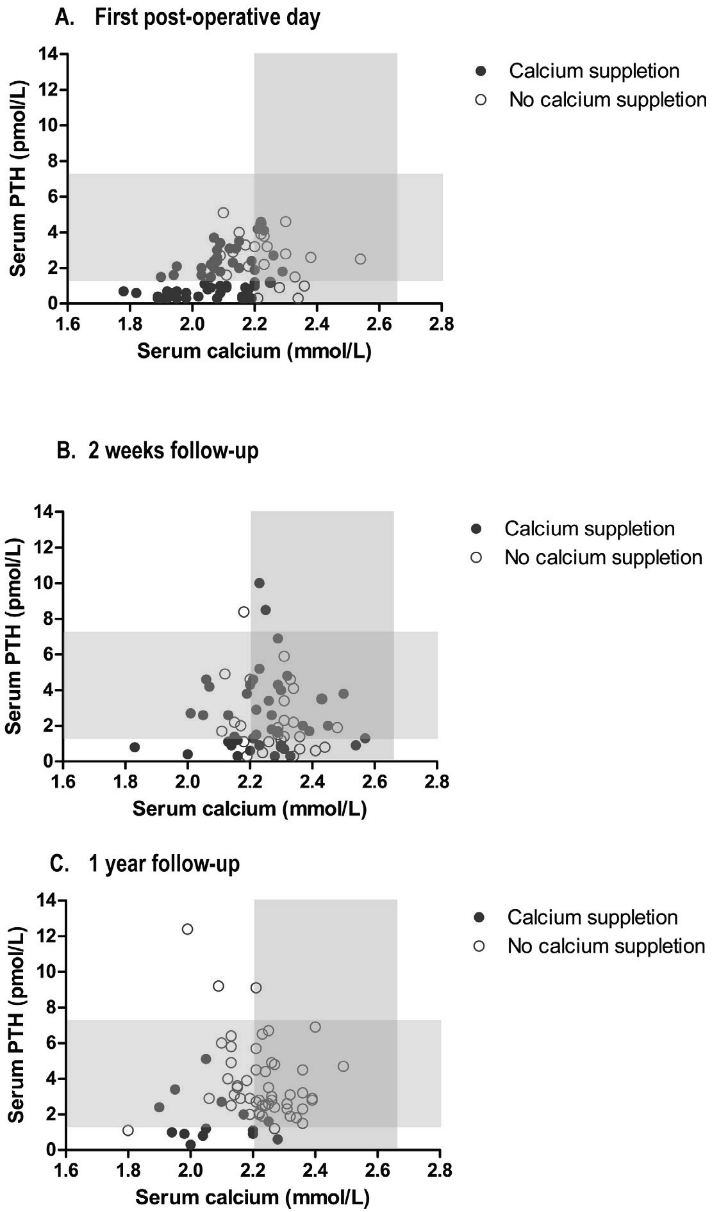


Figure 2. Relation between serum PTH levels, corrected serum calcium levels and calcium supplementation at the first postoperative day (a), two weeks post-operative (b) and 1 year post-operative (c). Reference values of serum PTH levels and corrected serum calcium levels are shown in the shaded areas.

Discussion

This study evaluates the predictive value of PTH levels obtained at the first postoperative day after total or completion thyroidectomy in predicting the risk for persistent hypoparathyroidism one year after surgery. It shows that a decrease in PTH>70%, measured at the first postoperative day after total or completion thyroidectomy, predicts persistent hypoparathyroidism. Also, the absence of this PTH change excludes the development of persistent hypoparathyroidism. This is, to the best of our knowledge, the first study that uses the RCV to asses a change (and not just a biological variation) of PTH levels in predicting persistent hypoparathyroidism after thyroidectomy. Calculation of the reference change value takes the biological- and analytical variation into account when interpreting the change in PTH levels. Our results are supported by other studies showing that a decrease in PTH levels is likely to predict persistent hypoparathyroidism. Wang et al. evaluated the postoperative 24 hour PTH decline in 110 patients undergoing a total or completion thyroidectomy (22). They showed that a 24 hour PTH level decline of more than 88.4% is an accurate predictor of persistent hypoparathyroidism with a sensitivity of 100%, specificity of 83% and a AUC of 0.965 (95% CI 0.925–1.000). In another study, Suwannasarn et al. even suggested that a 72% decline in PTH levels 4 hours after surgery could identify patients with a high risk for persistent hypoparathyroidism with a 100% sensitivity and 80.4% specificity (23) . This study included 65 patients and the 72% threshold, enabling prediction of persistent hypoparathyroidism, was obtained by ROC analyses. A recent study by Calvo Espino et al. found that a single postoperative PTH measurement can serve as a predictor of persistent hypoparathyroidism because of its high negative predictive value (AUC 0.87, 95% CI 0.84–0.91) (24). A study by Al-Dhahri et al. evaluated PTH recovery by repeated PTH measurements in 53 patients until normalization of PTH levels or up to 6 months (25). They showed that if PTH levels after surgery dropped by more than 88% compared with baseline measurements, the patient only had a chance of 10% of recovery of PTH levels within 6 months. However, the use of calcium supplementation was not reported in that study, so the clinical implication remains unknown.

One of the strengths of our study is the use of the RCV to calculate a predetermined cut-off value for the PTH change. Another strength is the use of one hypocalcaemia treatment algorithm. Our study is limited by the patient selection, as extrapolation of the results to non-tertiary thyroid surgeries could be debatable. This study was initially set up as a multicentre study. Unfortunately, logistics did not allow us to fully use the inclusion potential of our participating peripheral hospital, as can be seen in Figure 1. The vast majority of patients were included at the Erasmus university medical center and therefore these data should be interpreted as a mono-center study. Another limitation of this study is the high percentage of missing endpoint data, for which 26.4% subjects were excluded from the analysis. However, clinical characteristics did not differ between the included and excluded population as can be seen in the Supplemental data Table 1. Although this study was powered to answer the primary research question in this cohort, it should be confirmed in larger cohorts.

Second, it would have been interesting to be able to provide details about parathyroid glands preserved during surgery or found during pathology. However, these data were not complete and thus this study led to the implementation of a more standardized operation reporting protocol including detailed information regarding parathyroid glands. As it seems that the number of parathyroid glands remaining in situ (PGRIS) is critical in preventing persistent hypoparathyroidism (26). Therefore, it is of paramount importance to optimize and validate promising novel techniques, such as the use of methylene blue and indocyanine green fluorescence angiography, to facilitate the in situ preservation of parathyroid glands and reducing the risk of persistent hypoparathyroidism (27-29).

According to most studies, less than 5% of the patients develop persistent hypoparathyroidism (4-7). We would like to provide a framework in which our above average persistent hypoparathyroidism rate (17.3%) could be interpreted. First, we used a clinical definition of persistent hypoparathyroidism, namely the use of calcium supplementation one year after surgery and inability to be tapered off supplementation. Daily calcium supplementation dosages one year after surgery varied from 500mg to 4000mg per patient per day. There is currently no international standardized definition for persistent hypoparathyroidism, which results in many definitions described in the literature (30, 31). The British Association of Endocrine and Thyroid Surgeons (BAETS) for example defines persistent hypoparathyroidism as the need of calcium and/or active vitamin D supplements to maintain normocalcaemia at 6 months or more following surgery (32). Almost the same definition is used by the American Association of Clinical Endocrinologists and American College of Endocrinology (AACE/ACE), however they define persistent hypoparathyroidism as the requirement for medical regimen for longer than 12 months (33). The European Society of Endocrinology considers persistent hypoparathyroidism in patients with a low calcium and inappropriately low intact parathyroid hormone (iPTH) at more than 6 months (34). When adjusting our case definition to calcium and vitamin D supplementation one year after surgery instead of calcium supplementation alone, our rate of persistent hypoparathyroidism would be 12.3%. In addition, if those same patients with PTH levels within the normal range are excluded, the rate of persistent hypoparathyroidism would be 7.9%. This demonstrates the impact of different definitions on the persistent hypoparathyroidism rate as shown previously by Mehanna et al. (35) , and stresses the need for an international consensus on the definition of persistent hypoparathyroidism.

Second, the hospitals hypocalcaemia treatment protocol was quite cautious and warrants calcium supplementation when calcium levels are below the lower limit of normal (<2.20

mmol/L). A lower serum calcium threshold would presumably result in a lower amount of patients with calcium supplementation and therefore a lower number of patients with persistent hypoparathyroidism. Third, we perceive our patient population as a selected group of patients with higher risk for postoperative hypoparathyroidism as the majority of the patients are tertiary referrals. Lastly, it is not certain whether the true incidence of persistent hypoparathyroidism is known. Most articles report persistent hypoparathyroidism rates below 5%. However, in striking contrast, in a survey from the Thyroid Cancer Alliance(8), the rate of persistent hypoparathyroidism was reported to be around 14%. The BAETS reported a percentage of 12.1% in their fourth national audit(36). This is clearly discordant with other studies (4-7). Differences can be explained by publication bias, differences in case mix, definitions or data registration of persistent hypoparathyroidism.

Since PTH measurements on the first postoperative day are able to select patients with a high risk of persistent hypoparathyroidism, we therefore propose the following use in clinical practice (Figure 3). Every hospital should calculate its own RCV, as it is influenced by the laboratory's specific analytical imprecision. We recommend a preoperative PTH level blood test and a PTH level blood test on the first postoperative day to determine the change in PTH levels. If the percentage change in PTH levels is lower than the calculated RCV, than there is no significant change in PTH levels. These patients can be informed about their very low risk (0.0%) of persistent hypoparathyroidism and can start tapering off their calcium and vitamin D supplementation in the first week after surgery. If the percentage change in PTH levels is higher than the calculated RCV, than the risk of persistent hypoparathyroidism is high (43.8%). Patients should be informed about their high risk of persistent hypoparathyroidism and a longer hospital stay can be expected. In this study we had two standard follow-up laboratory visit, the first at two weeks after surgery and the second after one year. However, we showed that in practice patients are subjected to vena punctures more often. Patients with a high risk of persistent hypoparathyroidism even more frequently if compared to the low risk patients. We showed that these patients needed a median time of 3.0 months to taper off their calcium and/or vitamin D medication. Therefore, we suggest tapering off their calcium and vitamin D supplementation should not be initiated in the first three months. This would improve efficiency in patient care as well as cost effectiveness.

In conclusion, we show that a decrease of PTH>70% on the first postoperative day after total or completion thyroidectomy is a predictive factor for persistent hypoparathyroidism and can be used to improve efficiency of postoperative follow-up and provide patients with tailored information regarding the future.

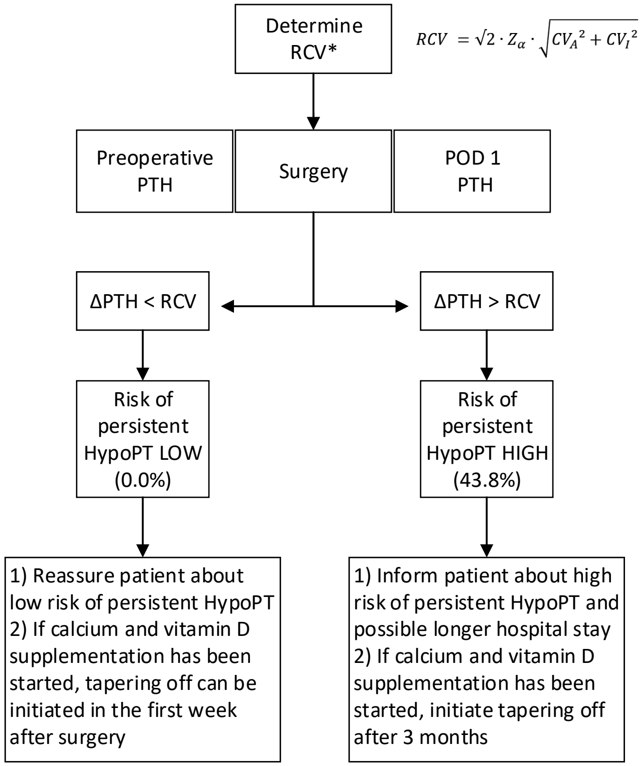


Figure 3. Proposed use of the RCV in clinical practice.

References

1. Bellantone R, Lombardi CP, Raffaelli M, Boscherini M, Alesina PF, De Crea C, Traini E, Princi P. Is routine supplementation therapy (calcium and vitamin D) useful after total thyroidectomy? Surgery. 2002;132(6):1109-12; discussion 12-3.
2. Youngwirth L, Benavidez J, Sippel R, Chen H. Parathyroid hormone deficiency after total thyroidectomy: incidence and time. J Surg Res. 2010;163(1):69-71.
3. Sitges-Serra A, Ruiz S, Girvent M, Manjon H, Duenas JP, Sancho JJ. Outcome of protracted hypoparathyroidism after total thyroidectomy. Br J Surg. 2010;97(11):1687-95.
4. Asari R, Passler C, Kaczirek K, Scheuba C, Niederle B. Hypoparathyroidism after total thyroidectomy: a prospective study. Arch Surg. 2008;143(2):132-7; discussion 8.
5. Raffaelli M, De Crea C, D'Amato G, Moscato U, Bellantone C, Carrozza C, Lombardi CP. Post-thyroidectomy hypocalcemia is related to parathyroid dysfunction even in patients with normal parathyroid hormone concentrations early after surgery. Surgery. 2016;159(1):78-84.
6. Kim SM, Kim HK, Kim KJ, Chang HJ, Kim BW, Lee YS, Chang HS, Park CS. Recovery from Permanent Hypoparathyroidism After Total Thyroidectomy. Thyroid. 2015;25(7):830-3.
7. Almquist M, Hallgrimsson P, Nordenstrom E, Bergenfelz A. Prediction of permanent hypoparathyroidism after total thyroidectomy. World J Surg. 2014;38(10):2613-20.
8. Banach R, Bartes B, Farnell K, Rimmele H, Shey J, Singer S, Verburg FA, Luster M. Results of the Thyroid Cancer Alliance international patient/survivor survey: Psychosocial/informational support needs, treatment side effects and international differences in care. Hormones (Athens). 2013;12(3):428-38.
9. Astor MC, Lovas K, Debowska A, Eriksen EF, Evang JA, Fossum C, Fougner KJ, Holte SE, Lima K, Moe RB, et al. Epidemiology and Health-Related Quality of Life in Hypoparathyroidism in Norway. J Clin Endocrinol Metab. 2016;101(8):3045-53.
10. Mitchell DM, Regan S, Cooley MR, Lauter KB, Vrla MC, Becker CB, Burnett-Bowie SA, Mannstadt M. Long-term follow-up of patients with hypoparathyroidism. J Clin Endocrinol Metab. 2012;97(12):4507-14.
11. Almquist M, Ivarsson K, Nordenstrom E, Bergenfelz A. Mortality in patients with permanent hypoparathyroidism after total thyroidectomy. Br J Surg. 2018;105(10):1313-8.
12. Kakava K, Tournis S, Papadakis G, Karelas I, Stampouloglou P, Kassi E, Triantafillopoulos I, Villiotou V, Karatzas T. Postsurgical Hypoparathyroidism: A Systematic Review. In Vivo. 2016;30(3):171-9.
13. Edafe O, Antakia R, Laskar N, Uttley L, Balasubramanian SP. Systematic review and meta-analysis of predictors of post-thyroidectomy hypocalcaemia. Br J Surg. 2014;101(4):307-20.
14. Selberherr A, Scheuba C, Riss P, Niederle B. Postoperative hypoparathyroidism after thyroidectomy: efficient and cost-effective diagnosis and treatment. Surgery. 2015;157(2):349-53.
15. Barczynski M, Cichon S, Konturek A, Cichon W. Applicability of intraoperative parathyroid hormone assay during total thyroidectomy as a guide for the surgeon to selective parathyroid tissue autotransplantation. World J Surg. 2008;32(5):822-8.

16. Cavicchi O, Piccin O, Caliceti U, Fernandez IJ, Bordonaro C, Saggese D, Ceroni AR. Accuracy of PTH assay and corrected calcium in early prediction of hypoparathyroidism after thyroid surgery. Otolaryngol Head Neck Surg. 2008;138(5):594-600.
17. Landry CS, Grubbs EG, Hernandez M, Hu MI, Hansen MO, Lee JE, Perrier ND. Predictable criteria for selective, rather than routine, calcium supplementation following thyroidectomy. Arch Surg. 2012;147(4):338-44.
18. Sarkar S, Mondal M, Das K, Shrimal A. Mucocutaneous manifestations of acquired hypoparathyroidism: An observational study. Indian J Endocrinol Metab. 2012;16(5):819-20.
19. Ricos C, Alvarez V, Cava F, Garcia-Lario JV, Hernandez A, Jimenez CV, Minchinela J, Perich C, Simon M. Current databases on biological variation: pros, cons and progress. Scand J Clin Lab Invest. 1999;59(7):491-500.
20. Fraser CG. Reference change values. Clin Chem Lab Med. 2011;50(5):807-12.
21. Buderer NM. Statistical methodology: I. Incorporating the prevalence of disease into the sample size calculation for sensitivity and specificity. Acad Emerg Med. 1996;3(9):895-900.
22. Wang W, Xia F, Meng C, Zhang Z, Bai N, Li X. Prediction of permanent hypoparathyroidism by parathyroid hormone and serum calcium 24h after thyroidectomy. Am J Otolaryngol. 2018;39(6):746-50.
23. Suwannasarn M, Jongjaroenprasert W, Chayangsu P, Suvikapakornkul R, Sriphrapradang C. Single measurement of intact parathyroid hormone after thyroidectomy can predict transient and permanent hypoparathyroidism: a prospective study. Asian J Surg. 2017;40(5):350-6.
24. Calvo Espino P, Rivera Bautista JA, Artes Caselles M, Serrano Gonzalez J, Garcia Pavia A, Garcia-Oria MJ, Caravaca-Fontan F, Lucena de la Poza JL, Sanchez Turrion V. Serum levels of intact parathyroid hormone on the first day after total thyroidectomy as predictor of permanent hypoparathyroidism Endocrinol Diabetes Nutr. 2019;66(3):195-201.
25. Al-Dhahri SF, Mubasher M, Mufarji K, Allam OS, Terkawi AS. Factors predicting post-thyroidectomy hypoparathyroidism recovery. World J Surg. 2014;38(9):2304-10.
26. Lorente-Poch L, Sancho JJ, Ruiz S, Sitges-Serra A. Importance of in situ preservation of parathyroid glands during total thyroidectomy. Br J Surg. 2015;102(4):359-67.
27. Lang BH, Wong CK, Hung HT, Wong KP, Mak KL, Au KB. Indocyanine green fluorescence angiography for quantitative evaluation of in situ parathyroid gland perfusion and function after total thyroidectomy. Surgery. 2017;161(1):87-95.
28. Hillary SL, Guillermet S, Brown NJ, Balasubramanian SP. Use of methylene blue and near-infrared fluorescence in thyroid and parathyroid surgery. Langenbecks Arch Surg. 2018;403(1):111-8.
29. Vidal Fortuny J, Sadowski SM, Belfontali V, Guigard S, Poncet A, Ris F, Karenovics W, Triponez F. Randomized clinical trial of intraoperative parathyroid gland angiography with indocyanine green fluorescence predicting parathyroid function after thyroid surgery. Br J Surg. 2018;105(4):350-7.
30. Wu J HB. Hypocalcemia after Thyroidectomy: The Need for Improved Definitions. World J End Surg. 2010;2(1):17-20.

31. Harslof T, Rolighed L, Rejnmark L. Huge variations in definition and reported incidence of postsurgical hypoparathyroidism: a systematic review. Endocrine. 2019;64(1):176-83.
32. Chadwick DR. Hypocalcaemia and permanent hypoparathyroidism after total/bilateral thyroidectomy in the BAETS Registry. Gland surgery. 2017;6(Suppl 1):S69.
33. Stack BC, Jr., Bimston DN, Bodenner DL, Brett EM, Dralle H, Orloff LA, Pallota J, Snyder SK, Wong RJ, Randolph GW. American Association of Clinical Endocrinologists and American College of Endocrinology Disease State Clinical Review: Postoperative Hypoparathyroidism--Definitions and Management. Endocr Pract. 2015;21(6):674-85.
34. Bollerslev J, Rejnmark L, Marcocci C, Shoback DM, Sitges-Serra A, van Biesen W, Dekkers OM, European Society of E. European Society of Endocrinology Clinical Guideline: Treatment of chronic hypoparathyroidism in adults. Eur J Endocrinol. 2015;173(2):G1-20.
35. Mehanna HM, Jain A, Randeva H, Watkinson J, Shaha A. Postoperative hypocalcemia--the difference a definition makes. Head Neck. 2010;32(3):279-83.
36. Chadwick D KR, Walton P, Systems DC. The British Association of Endocrine and Thyroid Surgeon Fourth National Audit. Dendrite Clinical Systems Ltd: Henley-on-Thames; 2012.

Supplemental data chapter 9

Supplemental Table 1. Baseline characteristics of included and excluded cases

Clinical values	Included cases (n=81)	Excluded cases (n=29)	p-value
Sex			0.691
Male	22 (27.2%)	9 (31.0%)	
Female	59 (72.8%)	20 (69.0%)	
Age (y)	53.00 [41.00 – 65.00]	64.00 [34.00 – 70.00]	0.889
ASA-classification			0.786
I	21 (25.9%)	6 (20.7%)	
II	54 (66.7%)	20 (27.0%)	
III	6 (7.4%)	3 (33.3%)	
Preoperative serum calcium	2.24 [2.19 – 2.30]	2.26 [2.25 -2.30]	0.051
Preoperative serum vitamin D	48.0 [30.3 – 66.0]	52.0 [41.0 – 72.0]	0.279
Preoperative serum PTH	4.7 [3.5 – 5.7]	4.2 [3.6 – 5.2]	0.439
Indication for surgery[a]			0.136
Papillary carcinoma	40 (49.9%)	11 (37.9%)	
Multi nodular goiter	15 (18.5%)	9 (31.0%)	
Graves	13 (16.0%)	2 (6.9%)	
Follicular carcinoma	4 (4.9%)	0 (0.0%)	
Medullary carcinoma	2 (2.5%)	2 (6.9%)	
Hürthlecell carcinoma	2 (2.5%)	0 (0.0%)	
Other	5 (6.2%)	5 (17.2%	
Surgery			0.724
Total	64 (79.0%)	22 (75.9%)	
Completion	17 (21.0%)	7 (29.2%)	
CLND[b]	27 (33.3%)	9 (31.0%)	0.821
CCLND	26 (32.1%)	9 (31.0%)	0.916
LCLND	22 (27.2%)	6 (20.7%)	0.492

Data are expressed as a percentage or as median [IQR]; Serum calcium in mmol/L; serum PTH in pmol/L; serum vitamin D in nmol/L; [a] Indication for surgery as diagnosed pre-operatively [b] Concomitant cervical lymph node dissection (CLND) ; CCLND = Central CLND (level VI) ; LCLND = Lateral CLND (level II-IV)

10

Chapter 10

Summary, general discussion and future perspectives

Benign thyroid nodules

Historically, the Netherlands has a conservative approach towards diagnosing patients with thyroid nodules. In general, diagnostics are limited to patients with a palpable and/or symptomatic thyroid nodule and not in incidentally found thyroid nodules (1), in contrast to various other guidelines from other countries (2-5). Fortunately, most thyroid nodules are benign after workup and do not require medical or surgical intervention unless they cause symptoms by mechanical compression. Especially in these patients, considering the benign nature of disease, treatment strategies should aim to be minimally invasive. In **chapter 3** we therefore reported the results of radiofrequency ablation (RFA) in patients with symptomatic benign thyroid nodules (SBTN) and evaluated their health-related and thyroid-related quality of life (QoL). We found that RFA is an effective treatment option with thyroid nodule volume reductions up to 70% after one year and 80% after two years, which is in line with the current known literature (6-9). Moreover, patients showed significant improvement in physical wellbeing and overall thyroid-related QoL after RFA treatment and an absolute improvement was seen in goiter and cosmetic complaints. The overall complication rate was 9.0%, of which 3 (4.5%) were minor including one hematoma and spontaneously resolved vocal changes in two patients. The other 3 (4.5%) were considered major adverse events, of which one superior laryngeal nerve injury requiring speech therapy and two nodule ruptures. The overall complication rate of 9.0% in our cohort is higher than the previously reported 3.3% in a cohort of 1459 patients (10). Differences might be explained by the lower sample size and differences in procedural experience, as this study was started in the initiation phase of RFA. Although, the complication rate was higher, only one patient had permanent vocal changes. Nevertheless, this highlights that, similar to surgical interventions, patients complaints must be weighed against the disadvantages of the intervention and patients should be informed thoroughly regarding the risks. A recent randomized controlled trial showed that thermal ablation for SBTN was superior to surgery in terms of patient satisfaction and thyroid-related QoL (11). Thyroid thermal ablation was defined as both RFA and microwave ablation and the effect of RFA alone was not evaluated. Another key question which should be addressed is the cost-effectiveness of RFA. To date only one Chinese retrospective cohort study has reported a higher direct cost for RFA when compared to thyroidectomy (12). However, increased availability and use of RFA could potentially lower the costs. Moreover, it is expected that long-term follow-up studies could show that regular ultrasound guided follow-up examinations may not be necessary in the future. Nevertheless, taking into account these factors, we conclude that RFA is a suitable alternative to surgical treatment of SBTN and could be offered to patients qualifying for treatment due to severity of symptoms. This conclusion is also reflected by the 2020 European Thyroid Association practice guideline for the use of image-guided ablation in benign thyroid nodules, recommending RFA as an alternative option to surgical treatment or observation alone (13).

Indeterminate thyroid nodules

Approximately 15 to 30% of the thyroid nodules are classified as indeterminate after FNA and diagnostic surgery is often recommended in these patients (14). Postoperatively two-thirds are found to be benign, which suggests the need for refinement of risk stratification in order to reduce the number of diagnostic surgeries. In **chapter 4** we assessed the clinical utility of the Afirma GEC in the Netherlands by describing the impact on surgical treatment and concordance between the GEC results and definitive histopathology. In addition, we retrospectively evaluated the possible impact of using the newer GSC/XA in this cohort. This study assessed the clinical utility of the Afirma GEC for the first time in a European country with a restrictive diagnostic workup protocol for thyroid nodules. Our results show that incorporating the GEC in diagnostic workup did not influence the overall surgical rate of patients with an indeterminate thyroid nodule as 72% was classified as GEC suspicious warranting diagnostic interventions. The first GEC clinical validation study achieved 52% specificity (15). These results were confirmed in a multicenter clinical utility study reporting a GEC benign call rate of 51%, meaning that half of all indeterminate thyroid nodules were reclassified as benign and thereby potentially reducing the number of diagnostic surgeries (16). Later, a large meta-analysis of 19 studies reported a pooled GEC benign call rate of 45% in 2568 indeterminate thyroid nodules, ranging between 26% and 61% (17). In the current Dutch study population, the GEC benign call rate was among the lowest with 26%. As a consequence, the 72.1% surgical rate did not differ from the historical cohort and the literature (18). We are not the first to report that institutional rates of surgery did not change after the implementation of the GEC (19). The lower benign call rate in the Dutch population might be explained by several factors. First, the restrictive diagnostic workup protocol for thyroid nodules could have resulted in different patient populations by selection, and thereby affecting the ratio of different histological types of thyroid nodules between populations (1, 20, 21). This again underlines the need for more clinical data from different populations. Second, the relatively lower benign call rate might be explained by our study design. Some degree of bias could have occurred as most GEC tests have been performed on repeat FNA unlike the first validation study which performed the GEC on first FNA passes (15). This could have led to the exclusion of more non-Hürthle cell and Bethesda III lesions and therefore the concentration of Hürthle cell dominant cytology and histologically follicular thyroid cancers and Hürthle adenomas in the prospective cohort. Third, multiple studies have demonstrated that the GEC categorizes nodules with Hürthle cell dominant morphology as GEC suspicious more often, which leads to higher surgical rates in these populations (22-26). A sensitivity analysis showed that the exclusion of Hürthle cell dominant nodules decreased the surgical rate in the GEC cohort to 50.0%, which is significantly lower than the historical surgical rate. Altogether, these results in general increase the concern of the usefulness of the Afirma GEC in Hürthle cell lesions and show that the GEC should not be used in these nodules. In response to this, the GSC has been developed and was claimed to have a higher specificity while maintaining a high negative predictive value resulting in a decreased surgical rate (27, 28). The post-hoc analysis of the GSC in **chapter 4** suggests that more patients with benign diseases could have been identified, possibly reducing the number of diagnostic surgeries. However, the GSC would have misdiagnosed six cases of cancer as benign. This clinical utility study currently does not support widespread implementation of the Afirma GEC and/or GSC test in the management of indeterminate thyroid nodules in a European country with restrictive diagnostic workup. These results show limitations of both the GEC and GSC test in nodules with Hurthle cell morphology. These data should encourage other (European) countries to assess the clinical utility of the Afirma GEC and/or GSC test in the management of indeterminate thyroid nodules in their specific populations prior to widespread implementation. As the field of molecular biology is rapidly evolving, new markers are sought and could possibly improve the risk stratification of indeterminate nodules. Other assays, such as the ThyroSeq v3 have shown promising results with a benign call rate of 61%, indicating that up to 61% of surgeries may be avoided for patients with indeterminate thyroid nodules (29). However, real world long term results are awaited and especially European data would be of interest. Meanwhile research also focusses on other diagnostic modalities to refine the risk stratification of indeterminate nodules. The EfFECTS trial studied the implementation of FDG-PET/CT as a rule out test in the diagnostic workup of indeterminate thyroid nodules. The results have shown that an FDG-PET/CT driven diagnostic workup of indeterminate thyroid nodules reduces the number of diagnostic surgeries by 40% (30). Unfortunately, FDG-PET/CT visual assessment did not contribute to any reduction of futile surgeries in patients with Hürthle cell nodules. Once again underlining the challenge of molecular tests in Hürthle cell lesions. Another promising area of research is the use of deep learning-based artificial intelligence models to differentiate between benign and malignant nodules. These models can be designed to detect abnormalities in thyroid nodules that move beyond human vision and could be used on both fine needle aspirates and ultrasound images. Previous studies have shown that these models have the potential to further improve the evaluation of FNA specimens and diagnostic accuracy of radiologists (31, 32). Yet, more studies are needed to evaluate the role of artificial intelligence for patients with thyroid nodules in clinical practice.

Differentiated thyroid cancer

In **chapter 5** and **6** we have found that diagnostic workup plays an important role in differentiated thyroid cancer (DTC) as well. In order to prevent over diagnosis and overtreatment of DTC, the 2015 American Thyroid Association (ATA) formulated several recommendations (2). Herein, a limited workup of (incidental) thyroid nodules is combined with the de-escalation of treatment. Prior to implementing de-escalated treatment options the similarity of patient populations should be assessed. In **chapter 5** we assessed whether a patient selected with low-risk DTC in the USA is similar to the low-risk DTC patient in the Netherlands using data from the Dutch Cancer Registry, and if de-escalation of treatment can be extrapolated to the Dutch population as well. In **chapter 5** we express our doubt regarding the similarity of the USA and Dutch population. The 2015 ATA guidelines recommend to perform a diagnostic ultrasound in all patients with a suspected thyroid nodule incidentally detected on another imaging study. As stated earlier, the Dutch national thyroid cancer guideline advocates to only pursue further diagnostics in patients with a palpable thyroid nodule and to refrain from further diagnostics in incidentally found thyroid nodules, except for FDG-PET/CT avid thyroid nodules (1). These differences in guidelines result in different populations which we confirmed by comparing the nationwide data from the Netherlands Cancer Registry to data from the National Cancer Database in the USA, on which the 2015 ATA guideline has based its recommendations. When analyzing the 1-4 cm cohort (T1b and T2), we found that the Dutch population has a higher proportion of 2-4 cm PTCs than the USA population, which is a known prognostic factor. Not only a lower proportion of 1-2 cm PTCs has been observed in the Dutch population but also a lower percentage of nodal and distant metastases. Therefore, we postulate that the Dutch population harbors less incidentally discovered indolent tumors and consequently question the safety of implementing a de-escalated treatment following the 2015 ATA guideline in the Netherlands. Before implementing de-escalation of treatment, there is a need for data from the Dutch population in which total thyroidectomy followed by radioiodine ablation is being compared to hemithyroidectomy followed by active surveillance.

The abovementioned principles also hold for the extrapolation of active surveillance instead of immediate surgery for patients with unifocal mPTC without lymph node metastases. In **chapter 6** we have evaluated the role of active surveillance in the Dutch population, which has a highly restrictive diagnostic workup protocol for imaging and performing FNA. We found that 15.7% of the total amount of thyroid cancer diagnoses were mPTCs. Only 3.1% of all thyroid cancer patients and 19.5% of all mPTCs would have been potentially eligible for active surveillance in a timeframe of 11 years. This contrasts with a recent study in the USA that states that 25% of all thyroid cancers would be potential candidates for active surveillance (33). This once again confirms the lower proportion of low-risk thyroid cancer compared to other countries (~50% of all thyroid cancers in the USA is an mPTC), which is the result from a decade long more restrictive diagnostic workup strategy aiming to reduce the detection of small, indolent tumors with no need for treatment at all (34). As a result patients that could be eligible for active surveillance in the Netherlands, have a higher incidence of lymph node metastases (13.6%) when compared to an active surveillance study by Ito *et al.* (3.8%) (35). However, this study was performed in a setting where no restrictive diagnostic protocols were applied, and shows that differences in diagnostic protocols will result in different populations by selection and thereby likely affect the biological behavior of mPTCs in a population. Stated otherwise, if a more restrictive diagnostic protocol is being used, less mPTC incidentalomas with indolent behavior are found. This will lead to fewer patients eligible for active surveillance, and when eligible, they may tend to have relatively more lymph node metastases possibly representing a more aggressive selected biological population. However, more data is needed to confirm this hypothesis. Despite this higher incidence of lymph node metastases in the Dutch mPTC population, the Dutch thyroid cancer survival rates are excellent and similar or even higher than the international survival rates regardless of the more restrictive diagnostic workup (36). The equal survival rates demonstrate that the Dutch workup protocol is an excellent treatment strategy to prevent over diagnosis and overtreatment of PTC. Because of the limited number of patients who would be eligible for active surveillance and a higher incidence of lymph node metastases due to patient selection, we believe that a national active surveillance standardized protocol has limited additive value in preventing the overtreatment of PTC. However, when an mPTC is incidentally found, despite the restrictive protocol (e.g. by 18FDG-PET(/CT) scan), active surveillance can be offered on an individual basis after discussing the risks and benefits of surgery versus active surveillance with patients. If such a strategy would be adopted we would advise to collect follow-up data of patients in active surveillance in a national prospective databases. However, it still remains unclear at which frequency and for how long patients should be followed in an active surveillance protocol. Additional studies are needed to assess these issues, but also the impact on quality of life should be monitored. Nevertheless, we believe the main goal should be to prevent over diagnosis by adjusting diagnostic workup protocols instead of focusing on improving active surveillance protocols. Lastly, a recent meta-analysis has suggested that RFA is a safe and efficient method to treat selected low-risk mPTCs. This study reported a pooled complete disappearance rate of 79% and a 1.5% overall tumor progression rate (37). However, most data are derived from small case series in mainly Asian countries and long-term follow-up data is lacking. Before implementation, future research should determine the role of, and indication for RFA in the treatment of mPTC by randomized controlled trials or prospective registries, especially in countries with restrictive diagnostic workup strategies such as the Netherlands.

Multidisciplinary care

Guidelines recommend the use of a multidisciplinary approach and structured care pathways as the standard of care in thyroid cancer patients (2, 38). To achieve standardized regional care for patients with thyroid nodules and cancer, the Thyroid Network, a collaboration among ten hospitals, was initiated in January 2016. In **chapter 2** we have performed a qualitative evaluation of the Thyroid Network, with a quantitative analysis of second opinion referrals for patients with thyroid nodules and cancer in the South-Western part of the Netherlands. We found that the inter-hospital collaboration of ten hospitals in the South-West region of the Netherlands and the initiation of the regional multidisciplinary tumor board (MTB) has resulted in a significant decrease of 23% in second opinions from the Thyroid Network hospitals to the academic hospital while maintaining referrals for tertiary care. Additionally, the academic hospital was involved in 20% more patient cases than before the start of the collaboration. Qualitative evaluation indicated that both the uniform care pathway and the regional multidisciplinary tumor board were valued high. The next step would be to integrate primary healthcare within the Thyroid Network and to assess the effect of the Thyroid Network on quality of care and patient satisfaction.

Hypoparathyroidism

Despite being a common complication with a high burden of disease, uniformity in definition, diagnosis and treatment protocols for persistent hypoparathyroidism are lacking. In order to diagnose, treat and prevent persistent hypoparathyroidism an international standardized definition for persistent hypoparathyroidism is needed. In **chapter 7** we have we evaluated a new pragmatic definition of persistent hypoparathyroidism in a retrospective multi-center cohort study. Utilizing this definition we reported an incidence of 7.9% of persistent hypoparathyroidism. This new definition incorporates both the use of an active vitamin D analogue with or without calcium supplementation with an attempt to actively wean supplementation. Active weaning of vitamin D and calcium supplementation in patients with hypoparathyroidism is often overlooked and leads to often, life-long overtreatment (39). We therefore propose the use of this new definition, which gives a fair picture of the true incidence of persisting hypoparathyroidism. The 2021 European expert consensus statement on parathyroid disorders stresses the need to check for chronicity by tapering off, which is incorporated in the definition we proposed in **chapter 7** (40). Moreover, it is hypothesized that the use of different definitions could influence the incidence of persistent hypoparathyroidism (41). In **chapter 7** we have shown that depending on the definition being used the incidence of persistent hypoparathyroidism varied between 11.8% and 23.9%. This variation is reflected by the rate of persistent hypoparathyroidism in literature, as it varies widely from 1.5% to 16.7% and therefore the true incidence remains unknown (42-47). The study in **chapter 8** was undertaken to evaluate the real-life incidence of postoperative, persistent hypoparathyroidism after total or completion thyroidectomy in patients referred to university hospital centers in the Netherlands. We found that persistent hypoparathyroidism, defined as the need for active vitamin D with or without calcium supplementation that persists at least 1 year after surgery, occurred in 15.0% of the participants after total or completion thyroidectomy. It compares unfavorably to data from high-volume single centers reporting incidences of less than 5%, but similar to data from other multicenter studies reporting higher incidence rates. Our higher incidence rate could be explained by our challenging university hospital case-mix, a possible explanation that is supported by the literature in which higher rates of persistent hypoparathyroidism were seen after more extensive surgery and lymph node dissections (44, 48). Also, the attempt to actively wean supplementation was not evaluated in this study, which could have influence the incidence. These data provide a better understanding of the magnitude of this postoperative complication and enable more realistic information for patients who are undergoing extensive and complex thyroid surgery. In **chapter 9**, we have shown that PTH levels can be used to identify patients with a high risk for persistent hypoparathyroidism. We have demonstrated that a decrease in postoperative PTH levels of >70% on the first day after surgery is a reliable predictor for persistent hypoparathyroidism. The strength of our study is that we have used the reference change value (RCV) to calculate this significant PTH change of more than 70%, which is based on intra-individual biological variation for PTH and our laboratory's analytical variation. For clinical practice we would recommend a serum PTH measurement preoperatively and on the first day after surgery, to calculate the change in PTH. If the percentage change is lower than the hospital specific RCV for PTH, then there is a very low risk of persistent hypoparathyroidism and vice versa. This is underlined by the earlier mentioned 2021 European expert consensus statement on parathyroid disorders, in which PTH measurements before and the day following surgery are recommended to predict the risk for persistent hypoparathyroidism (40). We have also shown serum PTH could be used to anticipate on longer hospitalization and it could possibly be used as a tool for patient tailored calcium supplementation and tapering schedules in order to reduce the burden on patients. Not only should we de-escalate treatment to prevent complications and morbidity, we should also focus on techniques that preserve the parathyroid glands and their function. Literature shows that the number of parathyroid glands remaining in situ (PGRIS) is critical in preventing persistent hypoparathyroidism (49). The auto-transplantation of accidentally resected parathyroid glands into the sternocleidomastoid muscle has been recommended for decades in order to prevent postoperative hypoparathyroidism (50). Some have even recommended the routine auto-transplantation of one gland (51). On the other hand, some studies have shown that auto-transplantation does not decrease and could even promote the risk of persistent hypoparathyroidism (43, 49). Although recommended for decades, the auto-transplantation of parathyroid glands remains controversial and it has been suggested that leaving the parathyroid glands well vascularized in situ has more benefits (52). In order to prevent the accidental removal or devascularisation of the parathyroid glands, techniques that facilitate the identification and in situ preservation should be investigated and implemented. Recent and much promising advances are the use of near-infrared auto fluorescence during thyroid surgery and the use of parathyroid gland angiography with indocyanine green (ICG). Near-infrared auto fluorescence can be used to accurately identify parathyroid glands during thyroid and parathyroid surgery (53). It has shown to lower the rate of direct postoperative hypocalcemia (54, 55). However, the effect on permanent hypoparathyroidism is still debatable and is an area of interest for future research. The same applies to ICG, which can reliably predict the vascularization of the parathyroid gland, but the clinical application in preventing persistent hypoparathyroidism remains unknown (56). Moreover, the treatment of persisting hypoparathyroidism should be scrutinized, as it is the only major endocrine deficiency that is not treated routinely by hormone replacement therapy. In 2015 the FDA and in 2017 the EMA approved the use of recombinant human parathyroid hormone (1-84) (rhPTH(1-84)) for persisting hypoparathyroidism. Studies have shown that patients who received rhPTH (1-84) were able to reduce more than 50% of their calcium and active vitamin D supplements, with stable renal function and subjective improvement in quality of life using the SF-36 questionnaire (57-59). Questions remain regarding ideal dosing and administration regimens for rhPTH(1–84) and its long-term effects on calcium homeostasis and safety.

Conclusions

The aim of this thesis was to refine surgical strategies of benign, indeterminate and malignant thyroid nodules and to provide novel insights in the management of postoperative hypoparathyroidism. We showed that symptomatic benign thyroid nodules can effectively be treated with RFA. Thereafter, the routine implementation of the Afirma GEC and GSC for the risk stratification of indeterminate thyroid nodules in a country with restrictive workup protocols is currently not supported. Subsequently, de-escalating treatment with a hemithyroidectomy for 1-4 cm DTC and active surveillance for mPTC should not be extrapolated to the Dutch population without nation specific data. Moreover, PTH levels can be used to identify patients with a high risk for persistent hypoparathyroidism. The incidence of persistent hypoparathyroidism depends on the used definition, and active vitamin D use and the weaning of supplementation should be incorporated in the definition for persistent hypoparathyroidism. Finally, the care for patients with thyroid nodules and cancer should be performed multidisciplinary and if possible regionally in an inter-hospital collaboration. In conclusion, there are many indications for thyroid surgery and survival rates for the majority of thyroid disorders are excellent. Therefore, the refinement of treatment should take place in every step of the patient's journey, in such a way that they have the best prognosis using the least invasive treatment option resulting in minimal complications and morbidity.

References

1. Links T. Richtlijn voor de diagnostiek, behandeling en follow-up van patiënten met gedifferentieerd (niet-medullair) schildkliercarcinoom 2015 [updated 16-02-2015. Available from: https://richtlijnendatabase.nl/richtlijn/schildkliercarcinoom/algemeen.html.
2. Haugen BR, Alexander EK, Bible KC, Doherty GM, Mandel SJ, Nikiforov YE, et al. 2015 American Thyroid Association Management Guidelines for Adult Patients with Thyroid Nodules and Differentiated Thyroid Cancer: The American Thyroid Association Guidelines Task Force on Thyroid Nodules and Differentiated Thyroid Cancer. Thyroid. 2016;26(1):1-133.
3. Wémeau JL, Sadoul JL, d'Herbomez M, Monpeyssen H, Tramalloni J, Leteurtre E, et al. Guidelines of the French society of endocrinology for the management of thyroid nodules. Ann Endocrinol (Paris). 2011;72(4):251-81.
4. Pacini F, Basolo F, Bellantone R, Boni G, Cannizzaro MA, De Palma M, et al. Italian consensus on diagnosis and treatment of differentiated thyroid cancer: joint statements of six Italian societies. J Endocrinol Invest. 2018;41(7):849-76.
5. Yi KH. The Revised 2016 Korean Thyroid Association Guidelines for Thyroid Nodules and Cancers: Differences from the 2015 American Thyroid Association Guidelines. Endocrinol Metab (Seoul). 2016;31(3):373-8.
6. Cesareo R, Palermo A, Pasqualini V, Simeoni C, Casini A, Pelle G, et al. Efficacy and safety of a single radiofrequency ablation of solid benign non-functioning thyroid nodules. Arch Endocrinol Metab. 2017;61(2):173-9.
7. Spiezia S, Garberoglio R, Milone F, Ramundo V, Caiazzo C, Assanti AP, et al. Thyroid nodules and related symptoms are stably controlled two years after radiofrequency thermal ablation. Thyroid. 2009;19(3):219-25.
8. Deandrea M, Trimboli P, Garino F, Mormile A, Magliona G, Ramunni MJ, et al. Long-Term Efficacy of a Single Session of RFA for Benign Thyroid Nodules: A Longitudinal 5-Year Observational Study. J Clin Endocrinol Metab. 2019;104(9):3751-6.
9. Trimboli P, Castellana M, Sconfienza LM, Virili C, Pescatori LC, Cesareo R, et al. Efficacy of thermal ablation in benign non-functioning solid thyroid nodule: A systematic review and meta-analysis. Endocrine. 2020;67(1):35-43.
10. Baek JH, Lee JH, Sung JY, Bae JI, Kim KT, Sim J, et al. Complications encountered in the treatment of benign thyroid nodules with US-guided radiofrequency ablation: a multicenter study. Radiology. 2012;262(1):335-42.
11. Jin H, Lin W, Lu L, Cui M. Conventional thyroidectomy vs thyroid thermal ablation on postoperative quality of life and satisfaction for patients with benign thyroid nodules. Eur J Endocrinol. 2021;184(1):131-41.
12. Yue WW, Wang SR, Li XL, Xu HX, Lu F, Sun LP, et al. Quality of Life and Cost-Effectiveness of Radiofrequency Ablation versus Open Surgery for Benign Thyroid Nodules: a retrospective cohort study. Sci Rep. 2016;6:37838.

13. Papini E, Monpeyssen H, Frasoldati A, Hegedüs L. 2020 European Thyroid Association Clinical Practice Guideline for the Use of Image-Guided Ablation in Benign Thyroid Nodules. Eur Thyroid J. 2020;9(4):172-85.
14. Hegedus L. Clinical practice. The thyroid nodule. N Engl J Med. 2004;351(17):1764-71.
15. Alexander EK, Kennedy GC, Baloch ZW, Cibas ES, Chudova D, Diggans J, et al. Preoperative diagnosis of benign thyroid nodules with indeterminate cytology. N Engl J Med. 2012;367(8):705-15.
16. Alexander EK, Schorr M, Klopper J, Kim C, Sipos J, Nabhan F, et al. Multicenter clinical experience with the Afirma gene expression classifier. J Clin Endocrinol Metab. 2014;99(1):119-25.
17. Valderrabano P, Hallanger-Johnson JE, Thapa R, Wang X, McIver B. Comparison of Postmarketing Findings vs the Initial Clinical Validation Findings of a Thyroid Nodule Gene Expression Classifier: A Systematic Review and Meta-analysis. JAMA Otolaryngol Head Neck Surg. 2019;145(9):783-92.
18. Wang CC, Friedman L, Kennedy GC, Wang H, Kebebew E, Steward DL, et al. A large multicenter correlation study of thyroid nodule cytopathology and histopathology. Thyroid. 2011;21(3):243-51.
19. Sacks WL, Bose S, Zumsteg ZS, Wong R, Shiao SL, Braunstein GD, et al. Impact of Afirma gene expression classifier on cytopathology diagnosis and rate of thyroidectomy. Cancer Cytopathol. 2016;124(10):722-8.
20. Lončar I, van Dijk SPJ, Metman MJH, Lin JF, Kruijff S, Peeters RP, et al. Active Surveillance for Papillary Thyroid Microcarcinoma in a Population with Restrictive Diagnostic Workup Strategies. Thyroid. 2021;31(8):1219-25.
21. Metman MJH, Lončar I, Kruijff S, Engelsman AF, van Ginhoven TM. Is less always more in a national well-differentiated thyroid cancer population? Eur J Surg Oncol. 2020;46(4 Pt A):709-11.
22. Brauner E, Holmes BJ, Krane JF, Nishino M, Zurakowski D, Hennessey JV, et al. Performance of the Afirma Gene Expression Classifier in Hurthle Cell Thyroid Nodules Differs from Other Indeterminate Thyroid Nodules. Thyroid. 2015;25(7):789-96.
23. Parajuli S, Jug R, Ahmadi S, Jiang XS. Hurthle cell predominance impacts results of Afirma gene expression classifier and ThyroSeq molecular panel performance in indeterminate thyroid nodules. Diagn Cytopathol. 2019;47(11):1177-83.
24. Harrell RM, Bimston DN. Surgical utility of Afirma: effects of high cancer prevalence and oncocytic cell types in patients with indeterminate thyroid cytology. Endocr Pract. 2014;20(4):364-9.
25. Lastra RR, Pramick MR, Crammer CJ, LiVolsi VA, Baloch ZW. Implications of a suspicious afirma test result in thyroid fine-needle aspiration cytology: an institutional experience. Cancer Cytopathol. 2014;122(10):737-44.
26. McIver B, Castro MR, Morris JC, Bernet V, Smallridge R, Henry M, et al. An independent study of a gene expression classifier (Afirma) in the evaluation of cytologically indeterminate thyroid nodules. J Clin Endocrinol Metab. 2014;99(11):4069-77.
27. Patel KN, Angell TE, Babiarz J, Barth NM, Blevins T, Duh QY, et al. Performance of a Genomic Sequencing Classifier for the Preoperative Diagnosis of Cytologically Indeterminate Thyroid Nodules. JAMA Surg. 2018;153(9):817-24.

28. San Martin VT, Lawrence L, Bena J, Madhun NZ, Berber E, Elsheikh TM, et al. Real-world Comparison of Afirma GEC and GSC for the Assessment of Cytologically Indeterminate Thyroid Nodules. J Clin Endocrinol Metab. 2020;105(3).
29. Steward DL, Carty SE, Sippel RS, Yang SP, Sosa JA, Sipos JA, et al. Performance of a Multigene Genomic Classifier in Thyroid Nodules With Indeterminate Cytology: A Prospective Blinded Multicenter Study. JAMA Oncol. 2019;5(2):204-12.
30. de Koster EJ, de Geus-Oei LF, Brouwers AH, van Dam E, Dijkhorst-Oei LT, van Engen-van Grunsven ACH, et al. [(18)F]FDG-PET/CT to prevent futile surgery in indeterminate thyroid nodules: a blinded, randomised controlled multicentre trial. Eur J Nucl Med Mol Imaging. 2022.
31. Peng S, Liu Y, Lv W, Liu L, Zhou Q, Yang H, et al. Deep learning-based artificial intelligence model to assist thyroid nodule diagnosis and management: a multicentre diagnostic study. Lancet Digit Health. 2021;3(4):e250-e9.
32. Kezlarian B, Lin O. Artificial Intelligence in Thyroid Fine Needle Aspiration Biopsies. Acta Cytol. 2021;65(4):324-9.
33. Roman BR, Gupta P, Tuttle RM, Morris LGT, Lohia S. Assessing the Number of Candidates There Are for Active Surveillance of Low-risk Papillary Thyroid Cancers in the US. JAMA Otolaryngol Head Neck Surg. 2020;146(6):585-6.
34. Davies L, Welch HG. Current thyroid cancer trends in the United States. JAMA Otolaryngol Head Neck Surg. 2014;140(4):317-22.
35. Ito Y, Miyauchi A, Kihara M, Higashiyama T, Kobayashi K, Miya A. Patient age is significantly related to the progression of papillary microcarcinoma of the thyroid under observation. Thyroid. 2014;24(1):27-34.
36. Husson O, Haak HR, van Steenbergen LN, Nieuwlaat WA, van Dijk BA, Nieuwenhuijzen GA, et al. Rising incidence, no change in survival and decreasing mortality from thyroid cancer in The Netherlands since 1989. Endocr Relat Cancer. 2013;20(2):263-71.
37. van Dijk SPJ, Coerts HI, Gunput STG, van Velsen EFS, Medici M, Moelker A, et al. Assessment of Radiofrequency Ablation for Papillary Microcarcinoma of the Thyroid: A Systematic Review and Meta-analysis. JAMA Otolaryngol Head Neck Surg. 2022.
38. Perros P CS, Boelaert K, Evans C, Evans RM, Gerrard GE, Gilbert JA, Harrison B, Johnson SJ, Giles TE, Moss L, Lewington V, Newbold KL, Taylor J, Thakker RV, Watkinson J, Williams GR. British Thyroid Association Guidelines for the Management of Thyroid Cancer 2014 [Available from: https://onlinelibrary.wiley.com/doi/pdf/10.1111/cen.12515.
39. Perros P, Boelaert K, Colley S, Evans C, Evans RM, Gerrard Ba G, et al. Guidelines for the management of thyroid cancer. Clin Endocrinol (Oxf). 2014;81 Suppl 1:1-122.
40. Bollerslev J, Rejnmark L, Zahn A, Heck A, Appelman-Dijkstra NM, Cardoso L, et al. European Expert Consensus on Practical Management of Specific Aspects of Parathyroid Disorders in Adults and in Pregnancy: Recommendations of the ESE Educational Program of Parathyroid Disorders. Eur J Endocrinol. 2021;186(2):R33-63.
41. Mehanna HM, Jain A, Randeva H, Watkinson J, Shaha A. Postoperative hypocalcemia--the difference a definition makes. Head Neck. 2010;32(3):279-83.

42. Kim SM, Kim HK, Kim KJ, Chang HJ, Kim BW, Lee YS, et al. Recovery from Permanent Hypoparathyroidism After Total Thyroidectomy. Thyroid. 2015;25(7):830-3.
43. Asari R, Passler C, Kaczirek K, Scheuba C, Niederle B. Hypoparathyroidism after total thyroidectomy: a prospective study. Arch Surg. 2008;143(2):132-7; discussion 8.
44. Díez JJ, Anda E, Sastre J, Pérez Corral B, Álvarez-Escolá C, Manjón L, et al. Prevalence and risk factors for hypoparathyroidism following total thyroidectomy in Spain: a multicentric and nation-wide retrospective analysis. Endocrine. 2019;66(2):405-15.
45. Chadwick DR. Hypocalcaemia and permanent hypoparathyroidism after total/bilateral thyroidectomy in the BAETS Registry. Gland Surg. 2017;6(Suppl 1):S69-S74.
46. Annebäck M, Hedberg J, Almquist M, Stålberg P, Norlén O. Risk of Permanent Hypoparathyroidism After Total Thyroidectomy for Benign Disease: A Nationwide Population-based Cohort Study From Sweden. Ann Surg. 2020.
47. Jørgensen CU, Homøe P, Dahl M, Hitz MF. High incidence of chronic hypoparathyroidism secondary to total thyroidectomy. Dan Med J. 2020;67(5).
48. Giordano D, Valcavi R, Thompson GB, Pedroni C, Renna L, Gradoni P, et al. Complications of central neck dissection in patients with papillary thyroid carcinoma: results of a study on 1087 patients and review of the literature. Thyroid. 2012;22(9):911-7.
49. Lorente-Poch L, Sancho JJ, Ruiz S, Sitges-Serra A. Importance of in situ preservation of parathyroid glands during total thyroidectomy. Br J Surg. 2015;102(4):359-67.
50. Lo CY, Lam KY. Routine parathyroid autotransplantation during thyroidectomy. Surgery. 2001;129(3):318-23.
51. Olson JA, Jr., DeBenedetti MK, Baumann DS, Wells SA, Jr. Parathyroid autotransplantation during thyroidectomy. Results of long-term follow-up. Ann Surg. 1996;223(5):472-8; discussion 8-80.
52. Sitges-Serra A, Lorente-Poch L, Sancho J. Parathyroid autotransplantation in thyroid surgery. Langenbecks Arch Surg. 2018;403(3):309-15.
53. Wang B, Zhu CR, Liu H, Yao XM, Wu J. The Accuracy of Near Infrared Autofluorescence in Identifying Parathyroid Gland During Thyroid and Parathyroid Surgery: A Meta-Analysis. Front Endocrinol (Lausanne). 2021;12:701253.
54. Benmiloud F, Godiris-Petit G, Gras R, Gillot JC, Turrin N, Penaranda G, et al. Association of Autofluorescence-Based Detection of the Parathyroid Glands During Total Thyroidectomy With Postoperative Hypocalcemia Risk: Results of the PARAFLUO Multicenter Randomized Clinical Trial. JAMA Surg. 2020;155(2):106-12.
55. Kim DH, Kim SW, Kang P, Choi J, Lee HS, Park SY, et al. Near-Infrared Autofluorescence Imaging May Reduce Temporary Hypoparathyroidism in Patients Undergoing Total Thyroidectomy and Central Neck Dissection. Thyroid. 2021;31(9):1400-8.
56. Vidal Fortuny J, Sadowski SM, Belfontali V, Guigard S, Poncet A, Ris F, et al. Randomized clinical trial of intraoperative parathyroid gland angiography with indocyanine green fluorescence predicting parathyroid function after thyroid surgery. Br J Surg. 2018;105(4):350-7.

57. Clarke BL, Vokes TJ, Bilezikian JP, Shoback DM, Lagast H, Mannstadt M. Effects of parathyroid hormone rhPTH(1-84) on phosphate homeostasis and vitamin D metabolism in hypoparathyroidism: REPLACE phase 3 study. Endocrine. 2017;55(1):273-82.
58. Bilezikian JP, Clarke BL, Mannstadt M, Rothman J, Vokes T, Lee HM, et al. Safety and Efficacy of Recombinant Human Parathyroid Hormone in Adults With Hypoparathyroidism Randomly Assigned to Receive Fixed 25-µg or 50-µg Daily Doses. Clin Ther. 2017;39(10):2096-102.
59. Tabacco G, Tay YD, Cusano NE, Williams J, Omeragic B, Majeed R, et al. Quality of Life in Hypoparathyroidism Improves With rhPTH(1-84) Throughout 8 Years of Therapy. J Clin Endocrinol Metab. 2019;104(7):2748-56.

11

Chapter 11

Dutch summary

Schildklierchirurgie kent vele indicaties, van goedaardige schildkliernodi en de ziekte van Graves tot aan (vermoedelijke) schildklierkanker. Hoewel de overleving van patiënten met een schildklieraandoening, waaronder schildklierkanker, uitstekend is, kan een chirurgische behandeling complicaties en een ernstige belasting voor deze patiënten met zich meebrengen. De voordelen van een chirurgische behandeling zullen dus altijd moeten opwegen tegen de risico's daarvan. Het eerste deel van dit proefschrift geeft dan ook inzicht in de verfijningsmogelijkheden van chirurgische en niet-chirurgische strategieën bij patiënten met verschillende schildklieraandoeningen. In het tweede deel zullen we ons richten op hypoparathyreoïdie, de belangrijkste complicatie na schildklierchirurgie.

Benigne schildkliernodi

Historisch gezien heeft Nederland een conservatieve benadering bij de diagnostiek van schildkliernodi. Over het algemeen beperkt de diagnostiek zich tot de patiënten met een palpabele en/of symptomatische schildkliernodus en niet in incidenteel gevonden schildkliernodi (1), in tegenstelling tot richtlijnen uit andere landen (2-5). Gelukkig blijken de meeste schildkliernodi na diagnostiek goedaardig en vereisen geen medische of chirurgische interventie, tenzij ze klachten veroorzaken door mechanische compressie. Vooral bij deze patiënten moeten de behandelstrategieën minimaal invasief zijn, gezien het goedaardige karakter van de ziekte. In **hoofdstuk 3** rapporteerden we daarom de resultaten van radiofrequente ablatie (RFA) bij patiënten met een symptomatische goedaardige schildkliernodus (SBTN) en evalueerden we hun gezondheid gerelateerde en schildklier gerelateerde kwaliteit van leven (QoL). We lieten zien dat RFA een effectieve behandeloptie is met een volumereductie van de schildkliernodi tot 70% na één jaar en 80% na twee jaar. Dit is in overeenstemming met de huidige bekende literatuur (6-9). Bovendien werd na RFA behandeling een significante verbetering gezien in lichamelijk welzijn en algehele schildklier gerelateerde QoL en werd een absolute verbetering gezien in struma gerelateerde klachten en cosmetische klachten. Het totale complicatiepercentage was 9,0%, waarvan 3 (4,5%) mineure complicaties, waaronder één hematoom en voorbijgaande stemveranderingen bij twee patiënten. De overige 3 (4,5%) werden als majeur beschouwd, waarvan één n. laryngeus superior letsel waarvoor logopedie nodig was en twee nodus rupturen. Het complicatiepercentage van 9,0% in ons cohort is hoger dan het eerder beschreven percentage van 3,3% in een cohort van 1459 patiënten (10). Verschillen kunnen verklaard worden door de kleinere groepsgrootte en verschillen in procedurele ervaring, aangezien deze studie werd gestart in de initiatiefase van RFA in onze centra. Hoewel het aantal complicaties hoger ligt in ons cohort, had slechts één patiënt permanente stemveranderingen. Dit benadrukt echter dat, net als bij chirurgische interventies, de klachten van de patiënt moeten worden afgewogen tegen de nadelen van de ingreep en dat patiënten goed geïnformeerd moeten worden over de risico's. Een recent gerandomiseerd gecontroleerd onderzoek liet zien dat thermale ablatie voor SBTN superieur was aan chirurgie wat betreft de patiënttevredenheid en schildklier gerelateerde QoL (11). Thermale ablatie werd echter gedefinieerd als RFA en microgolfablatie en het effect van RFA alleen werd niet geëvalueerd. Een ander belangrijk punt is de kosteneffectiviteit van RFA. Tot op heden heeft slechts één Chinese retrospectieve studie hierover gerapporteerd. Zij lieten zien dat RFA hogere directe kosten met zich meebrengt in vergelijking met een thyreoïdectomie (12). Een toegenomen beschikbaarheid en gebruik van RFA kunnen echter mogelijk de kosten verlagen. Bovendien wordt verwacht dat resultaten van langetermijnstudies zullen laten zien dat regelmatige echogeleide vervolgonderzoeken wellicht niet nodig zullen zijn in de toekomst. Desalniettemin kunnen we, rekening houdend met bovenstaande factoren, concluderen dat RFA een geschikt alternatief is voor chirurgische behandeling van de SBTN en kan worden aangeboden aan patiënten die in aanmerking komen voor behandeling vanwege de ernst van de klachten. Deze conclusie wordt ook onderschreven in de 2020 European Thyroid Association praktijkrichtlijn voor het gebruik van beeldgeleide ablatie van goedaardige schildkliernodi, waarin RFA wordt aanbevolen als een alternatief voor chirurgische behandeling of observatie (13).

Indeterminante schildkliernodi

Ongeveer 15 tot 30% van de schildkliernodi wordt geclassificeerd als indeterminant na echografiegeleide fijne naaldaspiratie (FNA) en bij deze patiënten wordt dan ook vaak een diagnostische hemithyreoïdectomie aanbevolen (14). Postoperatief blijkt tweederde goedaardig te zijn, wat er op wijst dat verfijning van de risicostratificatie noodzakelijk is om het aantal diagnostische operaties te verminderen. In **hoofdstuk 4** hebben we de klinische bruikbaarheid van de Afirma Gene Expression Classifier (GEC) in Nederland onderzocht door de impact op chirurgische behandeling en de concordantie tussen de GEC resultaten en definitieve histopathologie te beschrijven. Daarnaast hebben we post-hoc de mogelijke impact van het gebruik van de nieuwere GSC/XA in dit cohort geëvalueerd. Deze studie onderzocht voor het eerst de klinische bruikbaarheid van de GEC in een Europees land met restrictief diagnostisch beleid. Onze resultaten laten zien dat toevoeging van de GEC aan het diagnostisch proces geen invloed had op het percentage operaties bij patiënten met een indeterminante schildkliernodus, aangezien 72% werd geclassificeerd als GEC verdacht wat een diagnostische operatie rechtvaardigde. De eerste GEC validatiestudie behaalde een specificiteit van 52% (15). Deze resultaten werden bevestigd in een multicenter clinical utility studie. Deze studie rapporteerde een GEC benigne percentage van 51%, wat betekent dat de helft van alle indeterminante schildkliernodi werden gereclassificeerd als benigne en daardoor mogelijk het aantal diagnostische operaties verminderde (16). Later rapporteerde een grote meta-analyse van 19 studies een gepoold GEC benigne percentage van 45% (bereik 26 – 61%) in 2568 inderminante nodi (17). In de huidige Nederlandse onderzoekspopulatie behoorde het GEC benigne percentage met 26% tot de laagste. Als gevolg hiervan verschilde het operatiepercentage van 72,1% niet van ons historische cohort en is het percentage vergelijkbaar met de literatuur (18). We zijn niet de eersten die laten zien dat de institutionele operatiepercentages niet veranderden na implementatie van de GEC (19). Het lage GEC benigne percentage in de Nederlandse populatie kan door verschillende factoren verklaard worden. Ten eerste zou het restrictieve diagnostische beleid in Nederland door selectie kunnen hebben geleid tot verschillen in patiënten populaties, waardoor de verhouding van verschillende histologische subtypen van schildkliernodi beïnvloed kan worden (1, 20, 21). Dit onderstreept de behoefte aan data van verschillende populaties. Ten tweede, zo het relatief lage GEC benigne percentage verklaard kunnen worden door het studie design. Er zou enige vorm van bias kunnen zijn ontstaan doordat de GEC test op een tweede FNA is uitgevoerd. Dit is in tegenstelling tot de eerste validatie studie, die de GEC test direct op de eerste FNA heeft uitgevoerd (15). Dit had kunnen zorgen voor exclusie van meer niet-Hürthle cel en Bethesda III laesies en daarmee kunnen leiden tot de concentratie van Hürthle cel dominatne cytologie en histologische folliculaire carcinomen en Hürthle cel adenomen in het prospectieve cohort. Tevens hebben meerdere studies laten zien dat de schildkliernodi met Hürthle cel dominante morfologie vaker als GEC verdacht worden geclassificeerd, wat leidt tot een hoger aantal operaties (22-26). Om deze reden werd de Gene Sequencing Classifier (GSC) ontwikkeld, welke een hogere specificiteit zou hebben met behoud van een hoge negatief voorspellende waarde resulterend in vermindering van het aantal operaties (27, 28). De post-hoc analyse van de GSC-test in **hoofdstuk 4** bevestigt de stijging in het benigne percentage en dus een mogelijke daling in het aantal diagnostische operaties. De GSC heeft echter zes gevallen van kanker als goedaardig geclassificeerd. Deze studie ondersteunt momenteel geen wijdverbreide implementatie van de Afirma GEC en/of GSC test in de diagnostiek van schildkliernodi in een Europees land met een restrictief diagnostische beleid. Deze resultaten tonen beperkingen van zowel de GEC- als de GSC-test in schildkliernodi met Hürthlecel morfologie. Deze data zouden andere (Europese) landen moeten aanmoedigen om de klinische bruikbaarheid van genetische testen te beoordelen in hun specifieke populaties, voorafgaand aan wijdverbreide implementatie. Aangezien het veld van de moleculaire biologie snel evolueert, wordt gezocht naar nieuwe markers die mogelijk de risicostratificatie van indeterminante schildkliernodi kunnen verbeteren. Andere testen, zoals de ThyroSeq v3, laten veelbelovende resultaten zien met een benigne percentage van 61%, wat aangeeft dat tot 61% van de operaties kan worden vermeden bij patiënten met een indeterminante nodus (29). Ondertussen richt het onderzoek zich ook op andere diagnostische modaliteiten om de risicostratificatie van indeterminante nodi te verfijnen. De EfFECTS-studie bestudeerde de implementatie van de FDG-PET/CT als een uitsluitingstest in de diagnostiek van indeterminante schildkliernodi. De resultaten tonen dat FDG-PET/CT gedreven diagnostiek van indeterminante schildkliernodi het aantal diagnostische operaties met 40% vermindert (30). Helaas heeft de FDG-PET/CT niet bijgedragen aan een vermindering van onnodige operaties bij patiënten met Hürthle cel nodi, wat eens te meer de uitdaging van moleculaire tests in Hürthle cel laesies onderstreept. Een ander veelbelovend onderzoeksgebied is het gebruik van deep learning gebaseerde artificiële intelligentie modellen om te differentiëren tussen benigne en maligne nodi. Deze modellen kunnen worden ontworpen om afwijkingen in schildkliernodi te detecteren die verder gaan dan het menselijke zicht en kunnen worden gebruikt op zowel fijne naald aspiraties als echografiebeelden. Eerdere studies hebben aangetoond dat deze modellen de potentie hebben om de evaluatie van fijne naald aspiraten en de diagnostische nauwkeurigheid van radiologen verder te verbeteren (31, 32). Er zijn echter meer studies nodig om de rol van artificiële intelligentie voor patiënten met een indeterminante schildkliernodus in de klinische praktijk te evalueren.

Gedifferentieerde schildklierkanker

In **hoofdstuk 5** en **6** laten we zien dat het diagnostische proces ook een belangrijke rol speelt bij gedifferentieerde schildklierkanker (DTC). Om overdiagnostiek en overbehandeling te voorkomen, heeft de 2015 American Thyroid Association (ATA) een aantal aanbevelingen geformuleerd (2). Hierbij wordt een restrictiever diagnostisch beleid van (incidenteel gevonden) schildkliernodi gecombineerd met de de-escalatie van behandeling. Voordat de-escalatie van behandeling geïmplementeerd kan worden in de Nederland, moet beoordeeld worden of de Nederlandse populatie vergelijkbaar is met de VS populatie. In **hoofdstuk 5** hebben we met behulp van gegevens van de Nederlandse Kankerregistratie beoordeeld of een patiënt met een laag risico DTC in de VS gelijk is aan een laag risico DTC patiënt uit Nederland en of de de-escalatie van behandeling kan worden geëxtrapoleerd naar de Nederlandse populatie. In **hoofdstuk 5** uiten we onze twijfel over de gelijkenis van de VS en Nederlandse populatie. De ATA-richtlijn uit 2015 beveelt aan om een diagnostische echografie uit te voeren bij alle patiënten met een vermoedelijke schildkliernodus die bij ander beeldvormend onderzoek per toeval is ontdekt. Zoals eerder vermeld, pleit de Nederlandse schildklierkanker richtlijn ervoor om alleen verdere diagnostiek te verrichten bij patiënten met een palpabele schildkliernodus en af te zien van verdere diagnostiek bij incidenteel gevonden schildkliernodi, met uitzondering van de FDG-PET/CT-positieve schildkliernodi (1). Deze verschillen in richtlijnen resulteren in verschillende populaties door selectie. Dit hebben we bevestigd door de landelijke gegevens van de Nederlandse Kankerregistratie te vergelijken met gegevens uit de Nationale Kanker Database uit de VS, waarop de ATA-richtlijn uit 2015 zijn aanbevelingen heeft gebaseerd. Bij de analyse van het 1-4 cm cohort (T1b en T2), vonden we dat de Nederlandse populatie een hoger aandeel van 2-4 cm PTC's heeft dan de VS populatie, wat een bekende prognostische factor is. In de Nederlandse populatie is niet alleen een lager aandeel van 1-2 cm PTC's waargenomen, maar ook een lager percentage lymfkliermetastasen en afstandsmetastasen. Om deze reden stellen we dat de Nederlandse populatie minder incidenteel gevonden indolente tumoren heeft een daarom twijfelen we dan ook aan de veiligheid van de implementatie van de-escalatie van behandeling volgens de 2015 ATA-richtlijn in Nederland. Alvorens we de-escalatie van behandeling kunnen implementeren, is er behoefte aan gegevens van Nederlandse bodem waarin totale thyreoïdectomie gevolgd door ablatie met radioactief jodium wordt vergeleken met hemithyreoïdectomie gevolgd door actieve surveillance.

Bovenstaande principes gelden ook voor de extrapolatie van actieve surveillance in de plaats van directe chirurgie voor patiënten met een unifocaal papillair schildkliermicrocarcinoom (mPTC) zonder lymfekliermetastasen. In **hoofdstuk 6** hebben we de rol van actieve surveillance geëvalueerd in de Nederlandse populatie. We vonden dat 15,7% van het totale aantal schildklierkanker diagnoses mPTC's waren. In een tijdsbestek van 11 jaar zou slechts 3,1% van alle patiënten met schildklierkanker en 19,5% van alle mPTC's mogelijk in aanmerking komen voor actieve surveillance. Dit staat in contrast met een recente studie uit de VS, die stelt dat 25% van alle patiënten met schildklierkanker potentiële kandidaten voor actieve surveillance zouden zijn (33). Dit bevestigt eens te meer het lagere percentage laag-risico schildklierkanker in vergelijking met andere landen (~50% van alle schildklierkankers in de VS is een mPTC). Dit is het resultaat van een reeds tien jaar durende restrictieve diagnostische strategie die gericht is op het verminderen van de detectie van kleine, indolente tumoren (34). Dit heeft wel als gevolg dat Nederlandse patiënten die in aanmerking zouden kunnen komen voor actieve surveillance een hogere incidentie van lymfkliermetastasen (13,6%) hebben in vergelijking met een actieve surveillance studie van Ito *et al* (3,8%) (35). Deze studie werd echter uitgevoerd in een setting waar geen restrictieve diagnostische strategie werd toegepast en laat zien dat verschillen in diagnostische protocollen resulteren in verschillende populaties door selectie en daardoor waarschijnlijk het biologische gedrag van mPTC's in een populatie zullen beïnvloeden. Anders gezegd, als een restrictiever diagnostisch protocol wordt gebruikt, dan worden minder indolente mPTC-incidentalomen gevonden. Dit zal leiden tot minder patiënten die in aanmerking komen voor actieve surveillance. Wanneer ze echter in aanmerkingen komen, kunnen ze relatief meer lymfekliermetastasen hebben met mogelijk een agressievere biologie. Er zijn echter meer gegevens nodig om deze hypothese te bevestigen. Ondanks de hogere incidentie van lymfekliermetastasen in de Nederlandse mPTC populatie, zijn de overlevingscijfers van schildklierkanker in Nederland uitstekend en vergelijkbaar of zelfs hoger dan de internationale overlevingscijfers, ongeacht de restrictievere diagnostiek (36). De gelijke overlevingscijfers tonen aan dat het Nederlandse protocol een uitstekende strategie is om overdiagnostiek en overbehandeling van PTC te voorkomen. Vanwege het beperkte aantal patiënten dat in aanmerking zou komen voor actieve surveillance en door de hogere incidentie van lymfekliermetastasen als gevolg van patiëntselectie, zijn wij van mening dat een nationaal gestandaardiseerd actieve surveillance protocol een beperkte toegevoegde waarde heeft bij het voorkomen van overbehandeling van PTC. Als er echter incidenteel een mPTC wordt gevonden, ondanks het restrictieve protocol (bijv. door een 18FDG-PET(/CT) scan), dan kan actieve surveillance op individuele basis worden aangeboden nadat de risico's en voordelen van chirurgie versus actieve surveillance worden besproken met de patiënt. Als een dergelijke strategie zou worden geïmplementeerd, dan zou het advies zijn om follow-upgegevens van patiënten die actieve surveillance ondergaan te verzamelen in een prospectieve nationale database. Het blijft echter nog steeds onduidelijk met welke frequentie en hoe lang patiënten moeten worden vervolgd in een actieve surveillance protocol. Aanvullende studies zijn nodig om dit te onderzoeken, maar ook de impact op de kwaliteit van leven moet worden onderzocht. Desalniettemin zijn wij van mening dat het belangrijkste doel moet zijn om overdiagnostiek te voorkomen door diagnostische protocollen aan te passen in plaats van te focussen op het verbeteren van actieve surveillance protocollen. Tot slot heeft een recente meta-analyse gesuggereerd dat RFA een veilige en efficiënte methode is om geselecteerde laag-risico mPTC's te behandelen. Deze studie liet zien dat 79% van de tumoren volledig was verdwenen na RFA en slechts 1,5% van alle gevallen had tumorprogressie (37). De meeste data zijn echter afkomstig van kleine case series uit voornamelijk Aziatische landen en langetermijn gegevens ontbreken. Voorafgaand aan de implementatie moet de rol en de indicatie van RFA bij de behandeling van mPTC onderzocht worden door middel van gerandomiseerd gecontroleerde studies of prospectieve registraties, vooral in landen met een restrictief diagnostisch protocol zoals Nederland.

Multidisciplinaire zorg

Richtlijnen bevelen het gebruik van een multidisciplinaire behandeling en gestructureerde zorgpaden aan als de standaardbehandeling bij patiënten met schildklierkanker (2, 38). Om gestandaardiseerde regionale zorg voor patiënten met schildkliernodi en schildklierkanker te verwezenlijken, werd het Schildklier Netwerk (een samenwerking tussen tien ziekenhuizen in regio Zuidwest Nederland) in januari 2016 opgericht. In **hoofdstuk 2** hebben we een kwalitatieve evaluatie van het Schildklier Netwerk uitgevoerd, met een kwantitatieve analyse van second opinions voor patiënten met schildkliernodi in regio Zuidwest Nederland. We vonden dat de oprichting van het Schildklier Netwerk, met daarbij de oprichting van het regionale multidisciplinaire tumoroverleg (MTD), heeft geleid tot een significante daling van 23% in second opinions van de Schildklier Netwerk ziekenhuizen naar het academisch centrum met behoud van verwijzingen voor tertiaire zorg. Daarnaast was het academisch centrum betrokken bij 20% meer patiënten dan voor de start van de samenwerking. Kwalitatieve evaluatie liet zien dat zowel het uniforme zorgtraject als het regionale MTD hoog gewaardeerd werden. De volgende stap zal zijn om de eerstelijnszorg te integreren in het Schildklier Netwerk en om het effect van de oprichting van het Schildklier Netwerk op de kwaliteit van zorg en de patiënttevredenheid te beoordelen.

Hypoparathyreoïdie

Ondanks dat persisterende hypoparathyreoïdie een veel voorkomende complicatie met een hoge ziektelast is, ontbreekt uniformiteit in definitie, diagnose en behandelprotocollen. Voor het diagnosticeren, behandelen en voorkomen van persisterende hypoparathyreoïdie is een internationaal gestandaardiseerde definitie nodig. In **hoofdstuk 7** hebben we een nieuwe pragmatische definitie van persisterende hypoparathyreoïdie geëvalueerd in een retrospectief multicenter cohortstudie. Gebruikmakend van deze definitie, rapporteerden we een incidentie van 7,9% van persisterende hypoparathyreoïdie. Deze nieuwe definitie omvat zowel het gebruik van actief vitamine D met of zonder calciumsuppletie als een poging om de suppletie af te bouwen. Actief afbouwen van vitamine D- en calciumsuppletie wordt bij patiënten met persisterende hypoparathyreoïdie vaak over het hoofd gezien en leidt vaak tot levenslange overbehandeling (39). We stellen daarom voor om deze nieuwe definitie te gebruiken, welke een goed beeld geeft van de werkelijke incidentie van persisterende hypoparathyreoïdie. De 2021 Europese consensusverklaring over bijschildklieraandoeningen benadrukt de noodzaak om te controleren op chroniciteit door de suppletie af te bouwen, wat is opgenomen in de eerste definitie die we in **hoofdstuk 7** hebben voorgesteld (40). Bovendien wordt verondersteld dat het gebruik van verschillende definities de incidentie van persisterende hypoparathyreoïdie zou kunnen beïnvloeden (41). In **hoofdstuk 7** hebben we laten zien dat, afhankelijk van de gebruikte definitie, de incidentie van persisterende hypoparathyreoïdie varieerde tussen 11,8% en 23,9%. Deze variatie wordt weerspiegeld door de incidentie van persisterende hypoparathyreoïdie in de literatuur, aangezien deze sterk varieert van 1,5% tot 16,7% en daarom blijft de werkelijke incidentie onbekend (42-47). De studie in **hoofdstuk 8** werd uitgevoerd om de werkelijke incidentie van postoperatieve persisterende hypoparathyreoïdie na totale- of completerende thyreoïdectomie te evalueren in een populatie van de Nederlandse universitaire ziekenhuizen. We vonden dat persisterende hypoparathyreoïdie, gedefinieerd als het gebruik van actief vitamine D met of zonder calciumsuppletie ten minste 1 jaar na operatie, optrad bij 15,0% van de patiënten na totale- of completerende thyreoïdectomie. Dit percentage is ongunstig in vergelijking met gegevens van single center studies uit hoog volume centra die incidenties van minder 5% rapporteren, maar vergelijkbaar met gegevens uit andere multicenter studies die hogere incidenties rapporteren. Onze hogere incidentie kan worden verklaard door de uitdagende case-mix van universitaire ziekenhuizen. Deze hypothese wordt ondersteund door studies waarin hogere incidenties persisterende hypoparathyreoïdie worden gezien na uitgebreidere operaties en halsklierdissecties (44, 48). Daarnaast is de rol van het actief afbouwen van suppletie niet onderzocht in deze studie, wat de incidentie zou kunnen beïnvloeden. Deze studie geeft een beter inzicht in de omvang van deze complicatie en benadrukt meer realistische risico's voor patiënten die een uitgebreide en complexe schildklieroperatie ondergaan. In **hoofdstuk 9** hebben we laten zien dat PTH waarden kunnen worden gebruikt om patiënten met een hoog risico op persisterende hypoparathyreoïdie te identificeren. We hebben aangetoond dat een >70% verlaging van het PTH op de eerste postoperatieve dag een betrouwbare voorspeller is voor persisterende hypoparathyreoïdie. De kracht van ons onderzoek is dat de we de reference change value (RCV), ook wel kritisch verschil genoemd, hebben gebruikt om deze significante PTH verandering van meer dan 70% te berekenen. De RCV is gebaseerd op intra-individuele biologische variatie voor PTH en de analytische variatie van het laboratorium. Voor de klinische toepassing raden we aan om preoperatief en op de eerste postoperatieve dag een serum PTH te meten en de verandering in PTH te berekenen. Indien de procentuele verandering van het PTH lager is dan de ziekenhuisspecifieke RCV voor PTH, dan is er een zeer laag risico op persisterende hypoparathyreoïdie en vice versa. Dit wordt ondersteund door de eerder genoemde Europese consensusverklaring over bijschildklieraandoeningen, waarin PTH metingen voor de operatie en één dag na de operatie worden aanbevolen om het risico op persisterende hypoparathyreoïdie te voorspellen (40). Daarnaast hebben we aangetoond dat het serum PTH kan worden gebruikt om te anticiperen op langere ziekenhuisopnames en dat het mogelijk kan worden gebruikt als hulpmiddel voor patiënt specifieke afbouw- en follow-up schema’s om de ziektelast voor patiënten te verminderen. In de toekomst moeten we ons niet alleen focussen op de de-escalatie van behandeling om complicaties en morbiditeit te voorkomen, maar moeten we ons ook richten op technieken die de bijschildklieren en hun functie kunnen behouden. Onderzoek laat zien dat het aantal bijschildklieren in situ (PGRIS) van cruciaal belang is bij het voorkomen van persisterende hypoparathyreoïdie (49). Autotransplantatie van accidenteel verwijderde bijschildklieren wordt al tientallen jaren aanbevolen om postoperatieve hypoparathyreoïdie te voorkomen (50). Sommigen bevelen zelfs de routinematige autotransplantatie van één bijschildklier aan (51). Anderzijds hebben studies aangetoond dat autotransplantatie het risico op persisterende hypoparathyreoïdie niet vermindert en mogelijk zelfs zou kunnen veroorzaken (43, 49). Hoewel het al tientallen jaren wordt aanbevolen, blijft de autotransplantatie van bijschildkleiren controversieel en er wordt gesuggereerd dat het in situ laten van goed gevasculariseerde bijschildklierweefsel meer voordelen heeft (52). Om onbedoelde verwijdering of devascularisatie van de bijschildklieren te voorkomen, moeten technieken die de identificatie en het in situ bewaren vergemakkelijken worden onderzocht. Recente en veelbelovende ontwikkelingen zijn het gebruik van nabij-infrarood autofluorescentie en bijschildklierangiografie met indocyaninegroen (ICG) tijdens schildklierchirurgie. Nabij-infrarood autofluorescentie kan worden gebruikt om de bijschildklieren te identificeren tijdens schildklier- en bijschildklierchirurgie (53). Studies laten zien dat het gebruik van nabij-infrarood autofluorescentie het percentage directe postoperatieve hypocalciëmie verlaagt (54, 55). Het effect op persisterende hypoparathyreoïdie is echter nog discutabel en zal uit toekomstig onderzoek nog moeten blijken. Hetzelfde geldt voor ICG, dat de vascularisatie van de bijschildklier betrouwbaar kan voorspellen, maar de klinische toepassing bij het voorkomen van persisterende hypoparathyreoïdie blijft onbekend (56). Bovendien moet de behandeling van persisterende hypoparathyreoïdie onder de loep worden genomen, aangezien dit de enige endocriene deficiëntie is die niet wordt gesubstitueerd met het ontbrekende hormoon. In 2015 keurden de FDA en in 2017 de EMA het gebruik van recombinant humaan parathyroïdhormoon (1-84) (rhPTH(1-84)) goed voor persisterende hypoparathyreoïdie. Studies hebben aangetoond dat patiënten die rhPTH (1-84) kregen, in staat waren om meer dan 50% van hun calcium- en actieve vitamine D suppletie te verminderen, met een stabiele nierfunctie en subjectieve verbetering van de kwaliteit van leven gemeten middels de SF-36 vragenlijst (57-59). Het is echter nog niet duidelijk wat de ideale doserings- en toedieningsschema’s zijn en wat de langetermijneffecten op de calciumhomeostase en veiligheid zijn.

Conclusie

Het doel van dit proefschrift was om de chirurgische strategieën van benigne, indeterminante en maligne schildkliernodi te verfijnen en nieuwe inzichten te verschaffen in de behandeling van postoperatieve hypoparathyreoïdie. We toonden aan dat benigne schildkliernodi effectief behandeld kunnen worden met RFA. Tevens wordt routinematige implementatie van de Afirma GEC en GSC voor de risicostratificatie van indeterminante schildkliernodi in een land met restrictieve diagnostiek momenteel niet ondersteund. Vervolgens dient de-escalatie van behandeling met een hemithyreoidectomie voor 1-4 cm DTC en AS voor mPTC niet te worden geëxtrapoleerd naar de Nederlandse populatie voordat we data van Nederlandse bodem in handen hebben. Bovendien kunnen PTH waarden gebruikt worden om patiënten met een hoog risico op persisterende hypoparathyreoïdie te identificeren. De incidentie van persisterende hypoparathyreoïdie is afhankelijk van de gehanteerde definitie en actief vitamine D gebruik en het afbouwen van suppletie dienen te worden opgenomen in de definitie van persisterende hypoparathyreoïdie. Tot slot dient de zorg voor patiënten met schildkliernodi en schildklierkanker multidisciplinair en, indien mogelijk, regionaal plaats te vinden door middel van een samenwerking tussen verschillende ziekenhuizen. Samenvattend zijn er vele indicaties voor schildklierchirurgie en de overlevingscijfers voor de meeste schildklieraandoeningen zijn uitstekend. Daarom moet de verfijning van behandeling plaatsvinden in elke stap van het traject van de patiënt, op een zodanige manier dat deze de beste prognose heeft met de minst ingrijpende behandelingsoptie, resulterend in minimale complicaties en morbiditeit.

Referenties

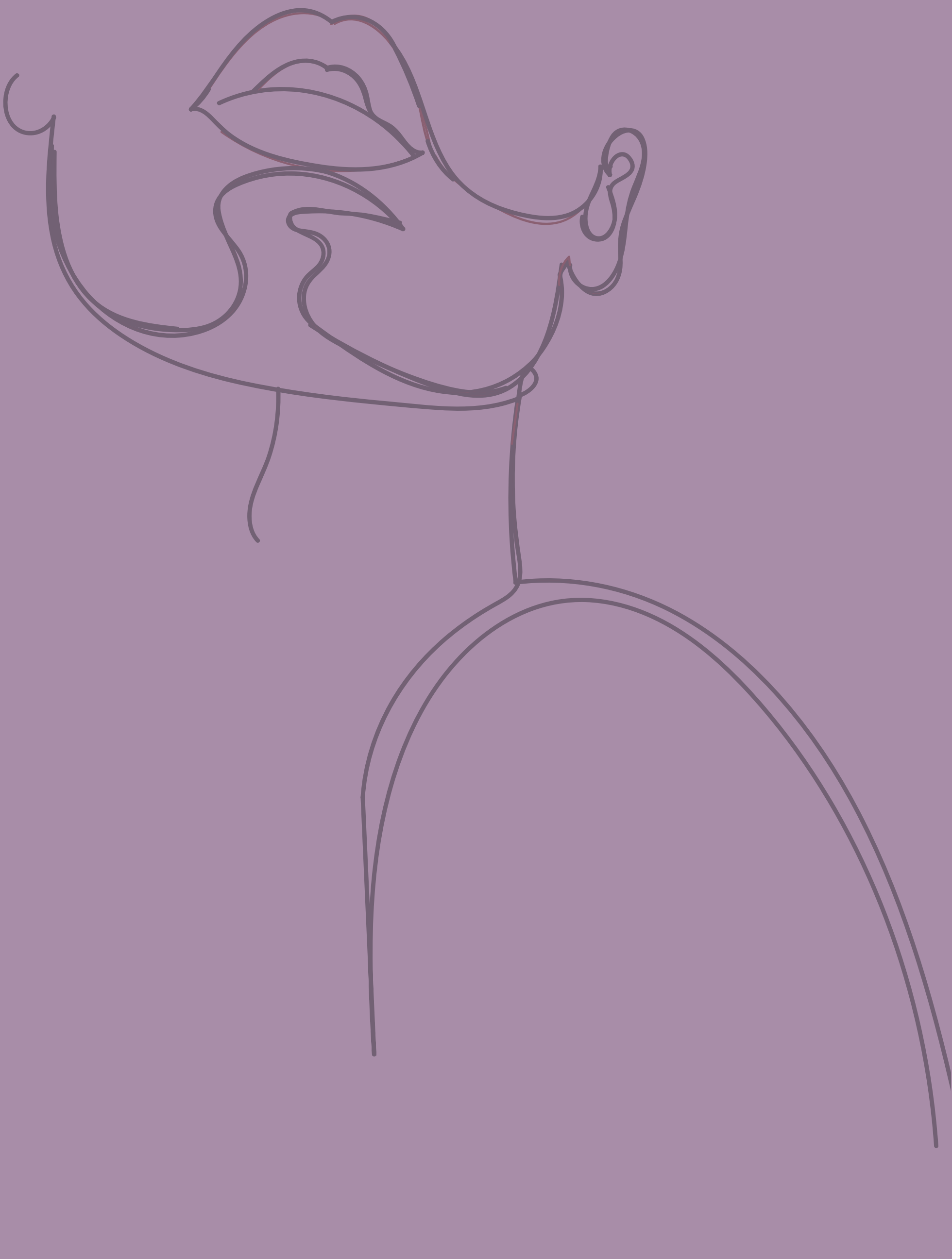
1. Links T. Richtlijn voor de diagnostiek, behandeling en follow-up van patiënten met gedifferentieerd (niet-medullair) schildkliercarcinoom 2015 [updated 16-02-2015. Available from: https://richtlijnendatabase.nl/richtlijn/schildkliercarcinoom/algemeen.html.
2. Haugen BR, Alexander EK, Bible KC, Doherty GM, Mandel SJ, Nikiforov YE, et al. 2015 American Thyroid Association Management Guidelines for Adult Patients with Thyroid Nodules and Differentiated Thyroid Cancer: The American Thyroid Association Guidelines Task Force on Thyroid Nodules and Differentiated Thyroid Cancer. Thyroid. 2016;26(1):1-133.
3. Wémeau JL, Sadoul JL, d'Herbomez M, Monpeyssen H, Tramalloni J, Leteurtre E, et al. Guidelines of the French society of endocrinology for the management of thyroid nodules. Ann Endocrinol (Paris). 2011;72(4):251-81.
4. Pacini F, Basolo F, Bellantone R, Boni G, Cannizzaro MA, De Palma M, et al. Italian consensus on diagnosis and treatment of differentiated thyroid cancer: joint statements of six Italian societies. J Endocrinol Invest. 2018;41(7):849-76.
5. Yi KH. The Revised 2016 Korean Thyroid Association Guidelines for Thyroid Nodules and Cancers: Differences from the 2015 American Thyroid Association Guidelines. Endocrinol Metab (Seoul). 2016;31(3):373-8.
6. Cesareo R, Palermo A, Pasqualini V, Simeoni C, Casini A, Pelle G, et al. Efficacy and safety of a single radiofrequency ablation of solid benign non-functioning thyroid nodules. Arch Endocrinol Metab. 2017;61(2):173-9.
7. Spiezia S, Garberoglio R, Milone F, Ramundo V, Caiazzo C, Assanti AP, et al. Thyroid nodules and related symptoms are stably controlled two years after radiofrequency thermal ablation. Thyroid. 2009;19(3):219-25.
8. Deandrea M, Trimboli P, Garino F, Mormile A, Magliona G, Ramunni MJ, et al. Long-Term Efficacy of a Single Session of RFA for Benign Thyroid Nodules: A Longitudinal 5-Year Observational Study. J Clin Endocrinol Metab. 2019;104(9):3751-6.
9. Trimboli P, Castellana M, Sconfienza LM, Virili C, Pescatori LC, Cesareo R, et al. Efficacy of thermal ablation in benign non-functioning solid thyroid nodule: A systematic review and meta-analysis. Endocrine. 2020;67(1):35-43.
10. Baek JH, Lee JH, Sung JY, Bae JI, Kim KT, Sim J, et al. Complications encountered in the treatment of benign thyroid nodules with US-guided radiofrequency ablation: a multicenter study. Radiology. 2012;262(1):335-42.
11. Jin H, Lin W, Lu L, Cui M. Conventional thyroidectomy vs thyroid thermal ablation on postoperative quality of life and satisfaction for patients with benign thyroid nodules. Eur J Endocrinol. 2021;184(1):131-41.
12. Yue WW, Wang SR, Li XL, Xu HX, Lu F, Sun LP, et al. Quality of Life and Cost-Effectiveness of Radiofrequency Ablation versus Open Surgery for Benign Thyroid Nodules: a retrospective cohort study. Sci Rep. 2016;6:37838.

13. Papini E, Monpeyssen H, Frasoldati A, Hegedüs L. 2020 European Thyroid Association Clinical Practice Guideline for the Use of Image-Guided Ablation in Benign Thyroid Nodules. Eur Thyroid J. 2020;9(4):172-85.
14. Hegedus L. Clinical practice. The thyroid nodule. N Engl J Med. 2004;351(17):1764-71.
15. Alexander EK, Kennedy GC, Baloch ZW, Cibas ES, Chudova D, Diggans J, et al. Preoperative diagnosis of benign thyroid nodules with indeterminate cytology. N Engl J Med. 2012;367(8):705-15.
16. Alexander EK, Schorr M, Klopper J, Kim C, Sipos J, Nabhan F, et al. Multicenter clinical experience with the Afirma gene expression classifier. J Clin Endocrinol Metab. 2014;99(1):119-25.
17. Valderrabano P, Hallanger-Johnson JE, Thapa R, Wang X, McIver B. Comparison of Postmarketing Findings vs the Initial Clinical Validation Findings of a Thyroid Nodule Gene Expression Classifier: A Systematic Review and Meta-analysis. JAMA Otolaryngol Head Neck Surg. 2019;145(9):783-92.
18. Wang CC, Friedman L, Kennedy GC, Wang H, Kebebew E, Steward DL, et al. A large multicenter correlation study of thyroid nodule cytopathology and histopathology. Thyroid. 2011;21(3):243-51.
19. Sacks WL, Bose S, Zumsteg ZS, Wong R, Shiao SL, Braunstein GD, et al. Impact of Afirma gene expression classifier on cytopathology diagnosis and rate of thyroidectomy. Cancer Cytopathol. 2016;124(10):722-8.
20. Lončar I, van Dijk SPJ, Metman MJH, Lin JF, Kruijff S, Peeters RP, et al. Active Surveillance for Papillary Thyroid Microcarcinoma in a Population with Restrictive Diagnostic Workup Strategies. Thyroid. 2021;31(8):1219-25.
21. Metman MJH, Lončar I, Kruijff S, Engelsman AF, van Ginhoven TM. Is less always more in a national well-differentiated thyroid cancer population? Eur J Surg Oncol. 2020;46(4 Pt A):709-11.
22. Brauner E, Holmes BJ, Krane JF, Nishino M, Zurakowski D, Hennessey JV, et al. Performance of the Afirma Gene Expression Classifier in Hurthle Cell Thyroid Nodules Differs from Other Indeterminate Thyroid Nodules. Thyroid. 2015;25(7):789-96.
23. Parajuli S, Jug R, Ahmadi S, Jiang XS. Hurthle cell predominance impacts results of Afirma gene expression classifier and ThyroSeq molecular panel performance in indeterminate thyroid nodules. Diagn Cytopathol. 2019;47(11):1177-83.
24. Harrell RM, Bimston DN. Surgical utility of Afirma: effects of high cancer prevalence and oncocytic cell types in patients with indeterminate thyroid cytology. Endocr Pract. 2014;20(4):364-9.
25. Lastra RR, Pramick MR, Crammer CJ, LiVolsi VA, Baloch ZW. Implications of a suspicious afirma test result in thyroid fine-needle aspiration cytology: an institutional experience. Cancer Cytopathol. 2014;122(10):737-44.
26. McIver B, Castro MR, Morris JC, Bernet V, Smallridge R, Henry M, et al. An independent study of a gene expression classifier (Afirma) in the evaluation of cytologically indeterminate thyroid nodules. J Clin Endocrinol Metab. 2014;99(11):4069-77.
27. Patel KN, Angell TE, Babiarz J, Barth NM, Blevins T, Duh QY, et al. Performance of a Genomic Sequencing Classifier for the Preoperative Diagnosis of Cytologically Indeterminate Thyroid Nodules. JAMA Surg. 2018;153(9):817-24.

28. San Martin VT, Lawrence L, Bena J, Madhun NZ, Berber E, Elsheikh TM, et al. Real-world Comparison of Afirma GEC and GSC for the Assessment of Cytologically Indeterminate Thyroid Nodules. J Clin Endocrinol Metab. 2020;105(3).
29. Steward DL, Carty SE, Sippel RS, Yang SP, Sosa JA, Sipos JA, et al. Performance of a Multigene Genomic Classifier in Thyroid Nodules With Indeterminate Cytology: A Prospective Blinded Multicenter Study. JAMA Oncol. 2019;5(2):204-12.
30. de Koster EJ, de Geus-Oei LF, Brouwers AH, van Dam E, Dijkhorst-Oei LT, van Engen-van Grunsven ACH, et al. [(18)F]FDG-PET/CT to prevent futile surgery in indeterminate thyroid nodules: a blinded, randomised controlled multicentre trial. Eur J Nucl Med Mol Imaging. 2022.
31. Peng S, Liu Y, Lv W, Liu L, Zhou Q, Yang H, et al. Deep learning-based artificial intelligence model to assist thyroid nodule diagnosis and management: a multicentre diagnostic study. Lancet Digit Health. 2021;3(4):e250-e9.
32. Kezlarian B, Lin O. Artificial Intelligence in Thyroid Fine Needle Aspiration Biopsies. Acta Cytol. 2021;65(4):324-9.
33. Roman BR, Gupta P, Tuttle RM, Morris LGT, Lohia S. Assessing the Number of Candidates There Are for Active Surveillance of Low-risk Papillary Thyroid Cancers in the US. JAMA Otolaryngol Head Neck Surg. 2020;146(6):585-6.
34. Davies L, Welch HG. Current thyroid cancer trends in the United States. JAMA Otolaryngol Head Neck Surg. 2014;140(4):317-22.
35. Ito Y, Miyauchi A, Kihara M, Higashiyama T, Kobayashi K, Miya A. Patient age is significantly related to the progression of papillary microcarcinoma of the thyroid under observation. Thyroid. 2014;24(1):27-34.
36. Husson O, Haak HR, van Steenbergen LN, Nieuwlaat WA, van Dijk BA, Nieuwenhuijzen GA, et al. Rising incidence, no change in survival and decreasing mortality from thyroid cancer in The Netherlands since 1989. Endocr Relat Cancer. 2013;20(2):263-71.
37. van Dijk SPJ, Coerts HI, Gunput STG, van Velsen EFS, Medici M, Moelker A, et al. Assessment of Radiofrequency Ablation for Papillary Microcarcinoma of the Thyroid: A Systematic Review and Meta-analysis. JAMA Otolaryngol Head Neck Surg. 2022.
38. Perros P CS, Boelaert K, Evans C, Evans RM, Gerrard GE, Gilbert JA, Harrison B, Johnson SJ, Giles TE, Moss L, Lewington V, Newbold KL, Taylor J, Thakker RV, Watkinson J, Williams GR. British Thyroid Association Guidelines for the Management of Thyroid Cancer 2014 [Available from: https://onlinelibrary.wiley.com/doi/pdf/10.1111/cen.12515.
39. Perros P, Boelaert K, Colley S, Evans C, Evans RM, Gerrard Ba G, et al. Guidelines for the management of thyroid cancer. Clin Endocrinol (Oxf). 2014;81 Suppl 1:1-122.
40. Bollerslev J, Rejnmark L, Zahn A, Heck A, Appelman-Dijkstra NM, Cardoso L, et al. European Expert Consensus on Practical Management of Specific Aspects of Parathyroid Disorders in Adults and in Pregnancy: Recommendations of the ESE Educational Program of Parathyroid Disorders. Eur J Endocrinol. 2021;186(2):R33-63.
41. Mehanna HM, Jain A, Randeva H, Watkinson J, Shaha A. Postoperative hypocalcemia--the difference a definition makes. Head Neck. 2010;32(3):279-83.

42. Kim SM, Kim HK, Kim KJ, Chang HJ, Kim BW, Lee YS, et al. Recovery from Permanent Hypoparathyroidism After Total Thyroidectomy. Thyroid. 2015;25(7):830-3.
43. Asari R, Passler C, Kaczirek K, Scheuba C, Niederle B. Hypoparathyroidism after total thyroidectomy: a prospective study. Arch Surg. 2008;143(2):132-7; discussion 8.
44. Díez JJ, Anda E, Sastre J, Pérez Corral B, Álvarez-Escolá C, Manjón L, et al. Prevalence and risk factors for hypoparathyroidism following total thyroidectomy in Spain: a multicentric and nation-wide retrospective analysis. Endocrine. 2019;66(2):405-15.
45. Chadwick DR. Hypocalcaemia and permanent hypoparathyroidism after total/bilateral thyroidectomy in the BAETS Registry. Gland Surg. 2017;6(Suppl 1):S69-S74.
46. Annebäck M, Hedberg J, Almquist M, Stålberg P, Norlén O. Risk of Permanent Hypoparathyroidism After Total Thyroidectomy for Benign Disease: A Nationwide Population-based Cohort Study From Sweden. Ann Surg. 2020.
47. Jørgensen CU, Homøe P, Dahl M, Hitz MF. High incidence of chronic hypoparathyroidism secondary to total thyroidectomy. Dan Med J. 2020;67(5).
48. Giordano D, Valcavi R, Thompson GB, Pedroni C, Renna L, Gradoni P, et al. Complications of central neck dissection in patients with papillary thyroid carcinoma: results of a study on 1087 patients and review of the literature. Thyroid. 2012;22(9):911-7.
49. Lorente-Poch L, Sancho JJ, Ruiz S, Sitges-Serra A. Importance of in situ preservation of parathyroid glands during total thyroidectomy. Br J Surg. 2015;102(4):359-67.
50. Lo CY, Lam KY. Routine parathyroid autotransplantation during thyroidectomy. Surgery. 2001;129(3):318-23.
51. Olson JA, Jr., DeBenedetti MK, Baumann DS, Wells SA, Jr. Parathyroid autotransplantation during thyroidectomy. Results of long-term follow-up. Ann Surg. 1996;223(5):472-8; discussion 8-80.
52. Sitges-Serra A, Lorente-Poch L, Sancho J. Parathyroid autotransplantation in thyroid surgery. Langenbecks Arch Surg. 2018;403(3):309-15.
53. Wang B, Zhu CR, Liu H, Yao XM, Wu J. The Accuracy of Near Infrared Autofluorescence in Identifying Parathyroid Gland During Thyroid and Parathyroid Surgery: A Meta-Analysis. Front Endocrinol (Lausanne). 2021;12:701253.
54. Benmiloud F, Godiris-Petit G, Gras R, Gillot JC, Turrin N, Penaranda G, et al. Association of Autofluorescence-Based Detection of the Parathyroid Glands During Total Thyroidectomy With Postoperative Hypocalcemia Risk: Results of the PARAFLUO Multicenter Randomized Clinical Trial. JAMA Surg. 2020;155(2):106-12.
55. Kim DH, Kim SW, Kang P, Choi J, Lee HS, Park SY, et al. Near-Infrared Autofluorescence Imaging May Reduce Temporary Hypoparathyroidism in Patients Undergoing Total Thyroidectomy and Central Neck Dissection. Thyroid. 2021;31(9):1400-8.
56. Vidal Fortuny J, Sadowski SM, Belfontali V, Guigard S, Poncet A, Ris F, et al. Randomized clinical trial of intraoperative parathyroid gland angiography with indocyanine green fluorescence predicting parathyroid function after thyroid surgery. Br J Surg. 2018;105(4):350-7.

57. Clarke BL, Vokes TJ, Bilezikian JP, Shoback DM, Lagast H, Mannstadt M. Effects of parathyroid hormone rhPTH(1-84) on phosphate homeostasis and vitamin D metabolism in hypoparathyroidism: REPLACE phase 3 study. Endocrine. 2017;55(1):273-82.
58. Bilezikian JP, Clarke BL, Mannstadt M, Rothman J, Vokes T, Lee HM, et al. Safety and Efficacy of Recombinant Human Parathyroid Hormone in Adults With Hypoparathyroidism Randomly Assigned to Receive Fixed 25-μg or 50-μg Daily Doses. Clin Ther. 2017;39(10):2096-102.
59. Tabacco G, Tay YD, Cusano NE, Williams J, Omeragic B, Majeed R, et al. Quality of Life in Hypoparathyroidism Improves With rhPTH(1-84) Throughout 8 Years of Therapy. J Clin Endocrinol Metab. 2019;104(7):2748-56.



Appendices

LIST OF PUBLICATIONS

Lončar I, Dulfer RR, Massolt ET, Timman R, de Rijke YB, Franssen GJH, et al. Postoperative parathyroid hormone levels as a predictor for persistent hypoparathyroidism. Eur J Endocrinol. 2020;183(2):149-59.

Metman MJH, **Lončar I,** Kruijff S, Engelsman AF, van Ginhoven TM. Is less always more in a national well-differentiated thyroid cancer population? Eur J Surg Oncol. 2020;46(4 Pt A):709-11.

Lončar I, van Dijk SPJ, Metman MJH, Lin JF, Kruijff S, Peeters RP, et al. Active Surveillance for Papillary Thyroid Microcarcinoma in a Population with Restrictive Diagnostic Workup Strategies. Thyroid. 2021;31(8):1219-25.

Lončar I, Noltes ME, Dickhoff C, Engelsman AF, Schepers A, Vriens MR, et al. Persistent Postthyroidectomy Hypoparathyroidism in the Netherlands. JAMA Otolaryngol Head Neck Surg. 2021;147(11):959-65.

Lončar I, van Dijk SPJ, van Velsen EFS, Buijk SE, Niemeijer ND, Veeken CJ, et al. Radiofrequency Ablation for Benign Symptomatic Thyroid Nodules in the Netherlands: Successful Introduction of a Minimally Invasive Treatment Option Improving Quality of Life. J Vasc Interv Radiol. 2022.

van Dijk SPJ, **Lončar I,** van Veen-Berkx E, Edward Visser W, Peeters RP, van Noord C, et al. Establishing a Multicenter Network for Patients With Thyroid Nodules and Cancer: Effects on Referral Patterns. Otolaryngol Head Neck Surg. 2022:1945998221086203.

Lončar I, van Kinschot CMJ, van Dijk SPJ, Franssen GJH, Visser EE, Peeters RP, et al. Persistent post-thyroidectomy hypoparathyroidism: A multicenter retrospective cohort study. Scand J Surg. 2022;111(2):14574969221107282.

Publications not in this thesis

van Dijk SPJ, Coerts HI, **Lončar I,** Verhoef C, Kruijff S, Engelsman AF, et al. Deescalating Follow-up After Hemithyroidectomy for Patients With Low-risk Papillary Thyroid Microcarcinoma. JAMA Otolaryngol Head Neck Surg. 2022.

Liu J, **Lončar I,** Collée JM, Bolla MK, Dennis J, Michailidou K, et al. rs2735383, located at a microRNA binding site in the 3'UTR of NBS1, is not associated with breast cancer risk. Sci Rep. 2016;6:36874.

LIST OF CONTRIBUTING AUTHORS

N.D. Bouvy
Department of Surgery, Maastricht University Medical Center, Maastricht, the Netherlands

S.E. Buijk
Department of Surgery, IJsseland Hospital, Capelle aan den Ijssel, the Netherlands

J.W.A. Burger
Department of Surgery, Catharina Hospital, Eindhoven, the Netherlands

M. Castro Cabezas
Department of Internal Medicine, Franciscus Gasthuis and Vlietland Rotterdam, Rotterdam, the Netherlands

C. Dickhoff
Department of Surgery, Amsterdam UMC, Amsterdam, the Netherlands

S.P.J. van Dijk
Department of Surgical Oncology, Erasmus MC Cancer Institute, Rotterdam, the Netherlands

W. Dinkelaar
Department of Radiology, Albert Schweitzer Hospital, Dordrecht, the Netherlands

R.R. Dulfer
Department of Surgery, ZGT Hospital, Almelo/Hengelo, the Netherlands

C.H.J. van Eijck
Department of Surgical Oncology, Erasmus MC Cancer Institute, Rotterdam, the Netherlands

A.F. Engelsman
Department of Surgery, Amsterdam UMC, Amsterdam, the Netherlands

A.C.H. van Engen - van Grunsven
Department of Pathology, Radboud University Medical Center, Nijmegen, the Netherlands

G.J.H. Franssen
Department of Surgical Oncology, Erasmus MC Cancer Institute, Rotterdam, the Netherlands

T.M. van Ginhoven
Department of Surgical Oncology, Erasmus MC Cancer Institute, Rotterdam, the Netherlands

B.M. van Hemel
Department of Pathology, University Medical Center Groningen, University of Groningen, Groningen, the Netherlands

F.A.L. van der Horst
Department of Clinical Chemistry, Reinier de Graaf Gasthuis, Delft, the Netherlands

F.J. van Kemenade
Department of Pathology, Erasmus MC, Rotterdam, the Netherlands

C.M.J. van Kinschot
Department of Internal Medicine, Academic Center for Thyroid Diseases, Erasmus MC, Rotterdam, the Netherlands

S. Kruijff
Department of Surgical Oncology, University Medical Center Groningen, Groningen, the Netherlands

J.F. Lin
Department of Surgical Oncology, University Medical Center Groningen, Groningen, the Netherlands

T.P. Links
Department of Internal Medicine, University Medical Center Groningen, Groningen, the Netherlands

E.T. Massolt
Department of Internal medicine, Albert Schweitzer Hospital, Dordrecht, the Netherlands

M.J.H. Metman
Department of Surgical Oncology, University Medical Center Groningen, Groningen, the Netherlands

E.M. von Meyenfeldt
Department of Surgical Oncology, Albert Schweitzer Hospital, Dordrecht, the Netherlands

A. Moelker
Department of Radiology and Nuclear Medicine, Erasmus MC, University Medical Center, Rotterdam, the Netherlands

F.H. van Nederveen
Laboratory for Pathology, PAL Dordrecht, Dordrecht, the Netherlands

R. Netea - Maier
Department of Internal Medicine, Radboud University Medical Center, Nijmegen, the Netherlands

N.D. Niemeijer
Department of Internal Medicine, IJsseland Hospital, Capelle aan den Ijssel, the Netherlands

M.E. Noltes
Department of Surgical Oncology, University Medical Center Groningen, Groningen, the Netherlands

C. van Noord
Department of Internal Medicine, Maasstad Ziekenhuis, Dordrecht, the Netherlands

R.P. Peeters
Department of Internal Medicine, Academic Center for Thyroid Diseases, Erasmus MC, Rotterdam, the Netherlands

Y.B. de Rijke
Department of Clinical Chemistry, Erasmus MC, Rotterdam, the Netherlands

A. Schepers
Department of Surgery, Leiden University Medical Center, Leiden, the Netherlands

M. Schouten
Erasmus Centre for Healthcare Governance, Erasmus School of Health Policy and Management, Erasmus University Rotterdam, Rotterdam, the Netherlands.

P.C. Smit
Department of Surgery, Reinier de Graaf Gasthuis, Delft, the Netherlands

R. Timman
Department of Psychiatry Section of Medical Psychology and Psychotherapy, Erasmus MC, University Medical Center Rotterdam, Rotterdam, the Netherlands

C.J. Veeken
Department of Radiology, IJsseland Hospital, Capelle aan den Ijssel, the Netherlands

E. van Veen-Berkx
Erasmus Centre for Healthcare Governance, Erasmus School of Health Policy and Management, Erasmus University Rotterdam, Rotterdam, the Netherlands.

E.F.S van Velsen
Department of Internal Medicine, Academic Center for Thyroid Diseases, Erasmus MC, Rotterdam, the Netherlands

W.E. Visser
Department of Internal Medicine, Academic Center for Thyroid Diseases, Erasmus MC, Rotterdam, the Netherlands

M.R. Vriens
Department of Surgery, University Medical Center Utrecht, Utrecht, the Netherlands

PHD PORTFOLIO

	Courses	ECTS
2017	Systematic literature search in PubMed	0.5
2018	Open Clinica course	0.3
	Biostatistical Methods I: Basic Principles	5.7
2019	BROK 'Basiscursus regelgeving Klinisch Onderzoek'	1.5
	Research Integrity	0.3
2020	Biomedical English Writing	2.0
	Presentation	
2017	Novel Strategies in the workup and treatment of thyroid nodules *Schildkliersymposium De Kuip, Rotterdam*	0.5
2018	A rare case of Cushing's syndrome *8th ESES Congress, Amsterdam*	1.0
2019	Radiofrequency ablation of symptomatic benign thyroid nodules *Science Day Department of Surgery Erasmus MC, Rotterdam*	1.0
	Eerste ervaringen met radiofrequente ablatie van symptomatische benigne schildkliernodi *Najaarsdag NVvH, Ede*	1.0
	Radiofrequency ablation of symptomatic benign thyroid nodules: 3-Year experience *Schildkliersymposium De Kuip, Rotterdam*	0.5
2020	Postoperative parathyroid hormone levels as a predictor for persistent hypoparathyroidism after total thyroidectomy *Science Day Department of Surgery Erasmus MC, Rotterdam*	1.0
	Active surveillance for papillary thyroid microcarcinoma in the Netherlands *ESSO Virtual*	1.0
2022	Post-thyreoïdectomie Hypoparathyreoïdie: Stand van zaken in Nederland *2e DHSG bijschildklier Symposium, Kamerik*	1.0
	Conferences	
2017	Schildkliersymposium De Kuip, Rotterdam	0.3
2018	Science Day Department of Surgery Erasmus MC, Rotterdam	0.3
	Chirurgendagen NVvH, Veldhoven (1 day)	0.3
	8th ESES congress, Amsterdam	1.0
	Oprichtingssymposium DTCG, Rotterdam	0.3
	1e DHSG bijschildklier Symposium, Amersfoort	0.3
2019	Science Day Department of Surgery Erasmus MC, Rotterdam	0.3
	Najaarsdag NVvH, Ede	0.3
	Chirurgendagen NVvH, Veldhoven (2 days)	0.6
	SEOHS 2019	0.3
	Schildkliersymposium De Kuip, Rotterdam	0.3
2020	Science Day Department of Surgery Erasmus MC, Rotterdam	0.3
	ESSO Virtual	0.6
2022	2e DHSG bijschildklier Symposium, Kamerik	0.3

	Teaching activities	ECTS
2016-2018	Erasmus Anatomy Research Project Tutor	3.0
2018	Neck ultrasound workshop surgery residents	0.3
	Anatomy teaching assistant	1.0
	Zorgacademie teaching assistant	1.0
2019	Supervising master thesis medical student S.P.J. van Dijk	1.0
2020	Supervising bachelor medical students Y.M. Mulder and H.C. Coerts	2.0
	Thyroid surgery lecture medical interns	0.3
	Other activities	
2018	Organization neck ultrasound course 8th ESES congress, Amsterdam	1.0
2018-2022	Member of the Young DHSG	3.0
2018-2022	Peer reviewer: Thyroid, International Journal of Surgery	2.0

ABOUT THE AUTHOR

Ivona Lončar was born on September 20th, 1992 in Ossendrecht, the Netherlands as the oldest daughter of Franjo Lončar and Ružica Mihaljević and sister of Marko. After graduating from secondary school in 2009 she started her Bachelor degree in Biology and Medical Laboratory Research at the Avans Hogeschool in Breda. During this study she developed her interest in medicine and after obtaining her degree in 2013 she was accepted for medical school at Erasmus University Rotterdam in 2014. During medical school she worked in the medical student-team at the department of thoracic surgery and as a teaching assistant in practical clinical skills (PKV-team). Her interest in anatomy got her involved in the Erasmus Anatomy Research Project (EARP) as a student and as a tutor. In her third year she started as a research assistant under the supervision of dr. T.M. van Ginhoven. After finishing her preclinical years of medical school she started a fulltime PhD candidacy from June 2018 until January 2021 at the department of Surgical Oncology and Gastrointestinal Surgery (dr. T.M. van Ginhoven, prof. dr. C.H.J. van Eijck) and the department of Internal Medicine (prof. dr. R.P. Peeters). The results of her research are presented in this thesis. Ivona is currently finishing her clinical internships and is expected to obtain her medical degree in June of 2023.