

SHARED DECISION MAKING IN DIFFERENTIATED THYROID CANCER



ROSALIE KOOT

**RADBOD
UNIVERSITY
PRESS**

Radboud
Dissertation
Series

Shared decision making in differentiated thyroid cancer

Rosalie Koot



This publication has been made possible by KWF

Shared decision making in differentiated thyroid cancer

Rosalie Koot

Radboud Dissertation Series

ISSN: 2950-2772 (Online); 2950-2780 (Print)

Published by RADBOUD UNIVERSITY PRESS

Postbus 9100, 6500 HA Nijmegen, The Netherlands

www.radbouduniversitypress.nl

Design: Proefschrift AIO | Annelies Lips

Cover: Ellen Pankras-van Bentum

Printing: DPN Rikken/Pumbo

ISBN: 9789465152691

DOI: 10.54195/ 9789465152691

Free download at: <https://doi.org/10.54195/ 9789465152691>

© 2026 Rosalie Koot

**RADBOUD
UNIVERSITY
PRESS**

This is an Open Access book published under the terms of Creative Commons Attribution-Noncommercial-NoDerivatives International license (CC BY-NC-ND 4.0). This license allows reusers to copy and distribute the material in any medium or format in unadapted form only, for noncommercial purposes only, and only so long as attribution is given to the creator, see <http://creativecommons.org/licenses/by-nc-nd/4.0/>.

Shared decision making in differentiated thyroid cancer

Proefschrift ter verkrijging van de graad van doctor
aan de Radboud Universiteit Nijmegen
op gezag van de rector magnificus prof. dr. J.M. Sanders,
volgens besluit van het college voor promoties
in het openbaar te verdedigen op

woensdag 8 juli 2026
om 10.30 uur precies

door

Anna Wilhelmina Adriana Koot
geboren op 16 oktober 1986
te Houten

Promotoren:

Prof. dr. R.T. Netea-Maier

Prof. dr. R.P.M.G. Hermens

Copromotoren:

Dr. P.F.M. Stalmeier

Dr. P.B. Ottevanger

Manuscriptcommissie:

Prof. dr. R.P. Takes

Prof. dr. T.P. Links (Rijksuniversiteit Groningen)

Dr. J.J. van Tol-Geerdink

TABLE OF CONTENTS

Chapter 1	General introduction and outline of the thesis	7
Chapter 2	The Impact of the Extent of Surgery on the Long-Term Outcomes of Patients with Low-Risk Differentiated Non-Medullary Thyroid Cancer: A Systematic Meta-Analysis. <i>J Clin Med.</i> 2020 Jul 21;9(7):2316.	21
Chapter 3	Needs, Preferences, and Values during Different Treatment Decisions of Patients with Differentiated Thyroid Cancer. <i>J Pers Med.</i> 2021 Jul 20;11 (7):682.	43
Chapter 4	Patient decision aids for patients with differentiated thyroid carcinoma: development process and alpha & beta testing. <i>Front Endocrinol (Lausanne).</i> 2023 May 31;14:1162537.	65
Chapter 5	Effect of a Patient Decision Aid on Shared Decision Making in Patients with Differentiated Thyroid Cancer: A Randomized Controlled Trial. <i>The Oncologist, Volume 31, Issue 5, May 2026, oyag126.</i>	89
Chapter 6	Position paper from the Endocrine Task Force of the European Organization for Research and Treatment of Cancer (EORTC) on the management and shared decision making in patients with low-risk micro papillary thyroid carcinoma. <i>Eur J Cancer.</i> 2023 Jan;179:98-112.	111
Chapter 7	General discussion	139
Chapter 8	Summary and Dutch Summary (Nederlandse samenvatting)	160
Appendices	Research Data Management	168
	List of publications	170
	PhD portfolio	172
	About the author	174
	Acknowledgments (Dankwoord)	175



Chapter 1

General introduction and outline of the thesis

General introduction

This thesis is part of the COMBO study. The focus is on research regarding shared decision making (SDM) in patients with differentiated thyroid cancer (DTC).

This introduction provides a brief overview of DTC. It highlights the current knowledge on the pathogenesis, diagnostics and treatment strategies. Subsequently, the process of SDM and decision support tools were described. At the end, an overview of the aim and outline of this thesis is given.

Differentiated thyroid cancer

DTC, arising from thyroid follicular epithelial cells, accounts for the vast majority of thyroid cancers (1) (Figure 1). Papillary thyroid carcinoma (PTC), follicular thyroid carcinoma (FTC) and oncocytic carcinoma of the thyroid (OCA) are the most common variants of DTC and represent together more than 90% of all thyroid cancers (WHO). Over the past decades there was a worldwide increase in the incidence of DTC. In 2023 there was a incidence of thyroid cancer in the Netherlands of 2.4/100.000/year in males and 6.1/100.000/year in females (2, 3) (Figure 2). The rising incidence rates were almost entirely due to more PTC cases, and have not been associated with an increase in DTC mortality (4, 5). The more widespread use of sensitive imaging techniques, biopsy procedures (e.g. fine-needle aspiration cytology (FNAC)) and medical surveillance, along with improved access to healthcare, have facilitated the detection of numerous clinically indolent cases (4). However, due to more awareness of over-diagnosis, thyroid cancer incidence has reached a plateau or even decreased during the most recent years (6, 7).

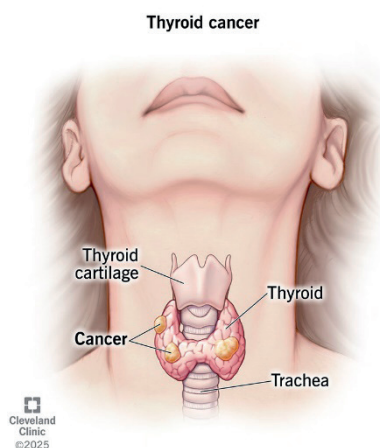
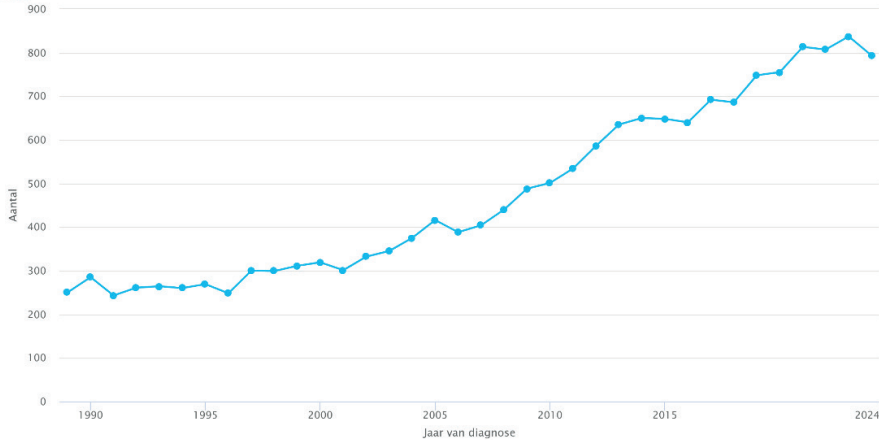


Figure 1. Thyroid cancer (Cleveland clinic 2025)

Incidentie per jaar, Aantal

Papillair en folliculair schildklier carcinoom

Geslacht: Man en vrouw | Leeftijdsgroep: Totaal | Regio: Nederland | Stadium: Totaal



2024, 2023: Deze cijfers betreffen voorlopige gegevens.

Bron: NKR
Gewijzigd op: 27 januari 2025

Figure 2. Incidence rates 1990-2023 differentiated thyroid cancer (NKR)

Diagnosis

In all patients with suspicion of a clinically relevant thyroid nodule a diagnostic neck ultrasound should be performed. An ultrasound is required to describe the characteristics of the thyroid nodule(s) and to assess the cervical lymph nodes. To categorize thyroid nodules on malignancy risk and to adequately select patients who require FNAC, Kwak et al. developed the Thyroid Imaging Reporting and Data System (TIRADS) criteria in 2011 based on the sonographic features of thyroid nodules (8). When thyroid cancer is suspected ultrasound guided FNA is performed. The aspirated material is then described by the pathologist using the Bethesda-system, which is a valid method for reporting thyroid cytopathology (9, 10). Based on the Bethesda classification a decision is made whether or not to perform surgery as an additional diagnostic modality (Bethesda 3 or 4) or as a treatment (Bethesda 5 or 6).

Initial and ongoing staging

When thyroid cancer is diagnosed, different staging systems can be used. The American Joint Committee on Cancer/Union for International Cancer Control (AJCC/UICC) updated in 2017 the tumor node metastasis (TNM) staging system and is optimized to predict mortality from DTC (11). Moreover, the risk stratification proposed by the most recent American Thyroid Association (ATA) and European Society of Medical Oncology (ESMO) guidelines predicts recurrence, which is a

relevant outcome measure in DTC (1, 4). The overall estimated risk of recurrence is classified as low (intrathyroidal DTC, ≤ 5 lymph node micro-metastases $< 0.2\text{cm}$), intermediate (aggressive histology, minor extrathyroidal extension, vascular invasion, or > 5 involved lymph nodes $0.2\text{-}3\text{cm}$) or high (gross extra thyroidal extension, incomplete tumor resection, distant metastases, or lymph node $> 3\text{cm}$). These staging systems can be used as guidance for initial treatment strategies. The initial risk stratification is revised during follow-up to reflect the evolution of disease and responses to treatments (dynamic risk stratification). It is based on response to therapy, on which patients should be stratified during their follow-up as: excellent response, biochemical incomplete response, structural incomplete response or indeterminate response. This stratification system can predict both recurrence and mortality and can guide the intensity of follow-up.

Treatment

Traditionally, a total thyroidectomy (TT) is the recommended surgical approach for DTCs, followed by postoperative radioactive iodine (RAI) therapy to ablate the remaining (microscopic) thyroid remnants and life-long thyroid hormone suppressive therapy. Until recently, low-risk patients underwent similar primary treatment as those with high-risk disease and therefore, faced the risk of complications and burden of treatment. For these patients, clinical guidelines such as, the ATA (1), the European Thyroid Association (ETA) (12), and the ESMO (4), currently recommend a more limited and individualized approach towards diagnosis and treatment of patients with low-risk DTC. In low-risk DTCs $< 1\text{cm}$, removal of only the affected lobe (lobectomy) is currently standard of care and for selected patients with larger DTCs $1\text{-}4\text{cm}$, a unilateral lobectomy also can be a safe alternative. Several large retrospective studies showed no difference between the extent of surgery on the oncological outcomes in terms of overall survival and recurrence rates in these carefully selected patients (13-21). Recently, Lin et al. showed that thyroid lobectomy is not associated with increased recurrence rates in the Dutch population (21). Moreover, accumulating evidence indicates that active surveillance (22-24) or minimally invasive treatments (MIT), particularly thermal ablation (e.g. laser ablation (LA), radiofrequency ablation (RFA) and microwave ablation (MWA)); with comparable results with respect to local disease control and low complication rates could be safe alternatives for patients with low-risk DTCs $< 1\text{cm}$ (25-31). After treatment, follow-up is performed using neck ultrasound and thyroglobulin measurements. This is a sensitive marker of the presence of (malignant) thyroid cells in the body.

The prognosis of most DTC patients is favorable with a 15-year overall survival rate as high as 95%. Nonetheless, after primary treatment up to 30% of the DTC patients

develop recurrent disease and/or distant metastases. Of these, approximately 40% become resistant to conventional treatment. These patients have a less favorable prognosis with an average life expectancy of 3-5 years. In case of recurrent disease, surgical removal of metastases and/or RAI treatment are the preferred treatment modalities. For patients with RAI refractory DTC that are not amenable to surgery, other local treatment options are available, such as external beam radiotherapy and more recently introduced image-guided MIT. In unresectable DTC, MIT may be used for symptomatic tumor volume reduction and to reduce symptoms caused by distant metastases (25). Tyrosine kinase inhibitors (TKIs), lenvatinib and sorafenib should be considered the standard first-line systemic therapy for RAI refractory DTC (32). Treatment with a TKI can lead to partial response or disease stabilization (33-36). Unfortunately, despite frequently occurring responses, survival effects of these drugs are unknown. For these patients, an important unanswered question regards the optimal timing of starting TKIs. For those who are asymptomatic or only mild symptomatic, starting the treatment too early may expose them to side effects and impair quality of life, without evidence of a known survival benefit.

Each of the above mentioned treatment decisions have their own harms and benefits with similar long-term oncologic outcomes. In order to better individualize the treatment, avoiding overtreatment and preserving quality of life, involving patients in decision making to SDM is important.

Shared decision making

SDM between patients and healthcare professionals is becoming the norm across Western societies as the preferred model to engage patients in the process of deciding about diagnosis, treatment or follow-up when more than one medically reasonable option is available (37). In the early 1980s SDM appeared for the first time in a presidential commission on ethics (38). However, an article in 1997 by sociologist Cathy Charles brought the term SDM back in research literature (39). In 2006 Makoul and Clayman showed that there was no shared definition of SDM, hereafter essential elements of SDM were identified (40). Since then, models of SDM were simplified and becoming a key component of patient-centered care. In 2010, SDM was defined as “an approach where clinicians and patients share the best available evidence when faced with the task of making decisions, and where patients are supported to consider options, to achieve informed preferences”. Elwyn and colleagues proposed a three-talk model, including (1) choice talk, (2) option talk, and (3) decision talk that is practical for healthcare professionals (41). In the Netherlands, a four steps model is preferred. Particularly the third step, decision talk is subdivided into two separate steps. This model describes SDM as a deliberation

process that respects what matters most to patients (37). The following steps were distinguished (Figure 3):

- 1) The professional informs the patient that a decision is to be made and that the patient's opinion is important.
- 2) The professional explains the options and the pros and cons of each relevant option.
- 3) The professional and patient discuss the patient's preferences; the professional supports the patient in deliberation.
- 4) The professional and patient discuss patient's decisional role preference, make or defer the decision, and discuss possible follow-up.

SDM is appropriate in many situations and particularly indicated in clinical situations where the "best" option may differ between people, depending on what matters to them (42). Particularly in the field of oncology, there is great value in SDM. An increasing variety of cancer treatments is being developed and multiple treatment options are available with side-effects that may significantly affect the patients' quality of life (43, 44). The evidence supporting many decisions in cancer care is limited or incomplete, and individuals differ in how they weigh the trade-offs of different choices. Although, the large majority of patients and healthcare professionals prefer SDM, it is still a challenge to implement SDM on a large scale. Healthcare professionals feel that it is difficult to apply SDM. Addressing patients' needs and values is probably the most difficult part of SDM. Values are discussed in a minority of decision-making consultations (45). Different patients have different views on decisions, and so do healthcare professionals. What is important to one person might be different from what is important to others. A communication program for healthcare professionals as part of implementation of SDM may be an effective way of improving SDM. However, in general, many training programs for improving communication skills exist, varying widely in format and content. Thus far, little high-quality research to draw robust conclusions about their effectiveness is available (46-49). On the other hand, it's difficult for patients to explore their values and preferences. Therefore, decision-support tools are suitable instruments to support decision-making.

Decision-support tools

Decision-support tools, such as option grids, pamphlets, flyers or patient decision aids (PtDAs) support SDM between patients and healthcare professionals. The latter is of special interest in this thesis. In 2005 the International Patient Decision Aid Standards (IPDAS) Collaboration established a set of criteria for enhancing the quality of PtDA

content, development and evaluation (50). According to these IPDAS criteria, PtDAs are evidence-based tools designed to help patients make specific and deliberated choices among healthcare options. PtDAs generally improve patients' knowledge, result in more realistic treatment expectations, participation in decision making and reduce indecisiveness (51). One goal of PtDAs is to ensure that each decision is consistent with the patients' values. The process of clarifying and expressing values is an important aspect of SDM and thus of PtDAs. Within PtDAs, this process is supported by explicit values clarification methods. Explicit values clarification methods in PtDAs require patients to interact with something such as a worksheet or an interactive website to consider what matters to them and which option they prefer. Such methods have been shown to improve decision outcomes such as better alignment with patients' values and decreasing decisional conflict (51-53). There are several explicit values clarification methods used. Which method fits best may depend on the context (54, 55). A recent systematic review of Witteman *et al.* showed that to support health decisions that align with values, a multicriteria decision analysis, which led to more values-congruent decisions can be used (55).

Aim and outline of the thesis

The aim of this study was to describe the development process of different PtDAs in patients with DTC, in combination with a communication training in SDM for healthcare professionals and to evaluate the effect on SDM, observed in recorded conversations.

To compare the clinical outcomes in patients with low-risk DTC based on two surgical modes, a systematic meta-analysis of the available literature about the extent of surgery (thyroid lobectomy versus total thyroidectomy) was provided in **chapter 2**. The arguments for and against thyroid lobectomy and total thyroidectomy according to the definition and recommendation of the ATA were discussed.

The next chapter (**chapter 3**) describes the results of focus group interviews. We acquire insights from the perspectives of patients and healthcare professionals according to the needs, preferences and values of patients with DTC during different treatment decisions. In addition, more attention was given to values communication, given the difficulty of exploring values.

In order to provide decision support, in **chapter 4** we describe the development process and alpha & beta testing of different PtDAs. These PtDAs were used in our randomized controlled trial (RCT).

In **chapter 5** we present the results from our prospective multicenter RCT which was performed in the Netherlands.

Chapter 6 is a position paper from the European Organisation for Research and Treatment of Cancer (EORTC) and describes the current management and SDM in patients with low-risk micro papillary thyroid carcinoma.

Chapter 7 provides a general discussion of the previously presented findings, and offers future perspectives of shared decision making in patients with DTC.

Finally a summary is given in the last chapter, **Chapter 8**.

References

1. Ringel MD, Sosa JA, Baloch Z, Bischoff L, Bloom G, Brent GA, et al. 2025 American Thyroid Association Management Guidelines for Adult Patients with Differentiated Thyroid Cancer. *Thyroid*. 2025;35(8):841-985.
2. Pizzato M, Li M, Vignat J, Laversanne M, Singh D, La Vecchia C, et al. The epidemiological landscape of thyroid cancer worldwide: GLOBOCAN estimates for incidence and mortality rates in 2020. *Lancet Diabetes Endocrinol*. 2022;10(4):264-72.
3. Dutch guideline differentiated thyroid cancer 2024 [Available from: https://richtlijnendatabase.nl/richtlijn/schildklier carcinoom_2024/startpagina_-_schildklier carcinoom_2024.html].
4. Filetti S, Durante C, Hartl D, Leboulleux S, Locati LD, Newbold K, et al. Thyroid cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up†. *Ann Oncol*. 2019;30(12):1856-83.
5. Houten PV, Netea-Maier RT, Smit JW. Differentiated thyroid carcinoma: An update. *Best Pract Res Clin Endocrinol Metab*. 2023;37(1):101687.
6. Lamartina L, Leboulleux S, Borget I, Schlumberger M. Global thyroid estimates in 2020. *Lancet Diabetes Endocrinol*. 2022;10(4):235-6.
7. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2020. *CA Cancer J Clin*. 2020;70(1):7-30.
8. Kwak JY, Han KH, Yoon JH, Moon HJ, Son EJ, Park SH, et al. Thyroid imaging reporting and data system for US features of nodules: a step in establishing better stratification of cancer risk. *Radiology*. 2011;260(3):892-9.
9. Cibas ES, Ali SZ. The 2017 Bethesda System for Reporting Thyroid Cytopathology. *Thyroid*. 2017;27(11):1341-6.
10. Auger M, Nayar R, Khalbuss WE, Barkan GA, Benedict CC, Tambouret R, et al. Implementation of the Bethesda System for Reporting Thyroid Cytopathology: observations from the 2011 thyroid supplemental questionnaire of the College of American Pathologists. *Arch Pathol Lab Med*. 2013;137(11):1555-9.
11. Tuttle RM, Haugen B, Perrier ND. Updated American Joint Committee on Cancer/Tumor-Node-Metastasis Staging System for Differentiated and Anaplastic Thyroid Cancer (Eighth Edition): What Changed and Why? *Thyroid*. 2017;27(6):751-6.
12. Durante C, Hegedüs L, Czarniecka A, Paschke R, Russ G, Schmitt F, et al. 2023 European Thyroid Association Clinical Practice Guidelines for thyroid nodule management. *Eur Thyroid J*. 2023;12(5).
13. 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.
14. Bilimoria KY, Bentrem DJ, Ko CY, Stewart AK, Winchester DP, Talamonti MS, et al. Extent of surgery affects survival for papillary thyroid cancer. *Ann Surg*. 2007;246(3):375-81; discussion 81-4.
15. Barney BM, Hitchcock YJ, Sharma P, Shrieve DC, Tward JD. Overall and cause-specific survival for patients undergoing lobectomy, near-total, or total thyroidectomy for differentiated thyroid cancer. *Head Neck*. 2011;33(5):645-9.
16. Matsuzu K, Sugino K, Masudo K, Nagahama M, Kitagawa W, Shibuya H, et al. Thyroid lobectomy for papillary thyroid cancer: long-term follow-up study of 1,088 cases. *World J Surg*. 2014;38(1):68-79.
17. Mendelsohn AH, Elashoff DA, Abemayor E, St John MA. Surgery for papillary thyroid carcinoma: is lobectomy enough? *Arch Otolaryngol Head Neck Surg*. 2010;136(11):1055-61.
18. Rovira A, Nixon IJ, Simo R. Papillary microcarcinoma of the thyroid gland: current controversies and management. *Curr Opin Otolaryngol Head Neck Surg*. 2019.

19. Nixon IJ, Ganly I, Patel SG, Palmer FL, Whitcher MM, Tuttle RM, et al. Thyroid lobectomy for treatment of well differentiated intrathyroid malignancy. *Surgery*. 2012;151(4):571-9.
20. Rodriguez Schaap PM, Botti M, Otten RHJ, Dreijerink KMA, Nieveen van Dijkum EJM, Bonjer HJ, et al. Hemithyroidectomy versus total thyroidectomy for well differentiated T1-2 N0 thyroid cancer: systematic review and meta-analysis. *BJS Open*. 2020;4(6):987-94.
21. Lin JF, Rodriguez Schaap PM, Metman MJH, Nieveen van Dijkum EJM, Dickhoff C, Links TP, et al. Thyroid Lobectomy for Low-Risk 1-4 CM Papillary Thyroid Cancer is not Associated with Increased Recurrence Rates in the Dutch Population with a Restricted Diagnostic Work-Up. *World J Surg*. 2023;47(5):1211-8.
22. Jeon MJ, Kim WG, Kim TY, Shong YK, Kim WB. Active Surveillance as an Effective Management Option for Low-Risk Papillary Thyroid Microcarcinoma. *Endocrinol Metab (Seoul)*. 2021;36(4):717-24.
23. Sugitani I. Active surveillance of low-risk papillary thyroid microcarcinoma. *Best Pract Res Clin Endocrinol Metab*. 2022;101630.
24. Sugitani I, Ito Y, Takeuchi D, Nakayama H, Masaki C, Shindo H, et al. Indications and Strategy for Active Surveillance of Adult Low-Risk Papillary Thyroid Microcarcinoma: Consensus Statements from the Japan Association of Endocrine Surgery Task Force on Management for Papillary Thyroid Microcarcinoma. *Thyroid*. 2021;31(2):183-92.
25. Mauri G, Hegedüs L, Bandula S, Cazzato RL, Czarniecka A, Dudeck O, et al. European Thyroid Association and Cardiovascular and Interventional Radiological Society of Europe 2021 Clinical Practice Guideline for the Use of Minimally Invasive Treatments in Malignant Thyroid Lesions. *Eur Thyroid J*. 2021;10(3):185-97.
26. Cho SJ, Baek SM, Na DG, Lee KD, Shong YK, Baek JH. Five-year follow-up results of thermal ablation for low-risk papillary thyroid microcarcinomas: systematic review and meta-analysis. *Eur Radiol*. 2021;31(9):6446-56.
27. Choi Y, Jung SL. Efficacy and Safety of Thermal Ablation Techniques for the Treatment of Primary Papillary Thyroid Microcarcinoma: A Systematic Review and Meta-Analysis. *Thyroid*. 2020;30(5):720-31.
28. Cui T, Jin C, Jiao D, Teng D, Sui G. Safety and efficacy of microwave ablation for benign thyroid nodules and papillary thyroid microcarcinomas: A systematic review and meta-analysis. *Eur J Radiol*. 2019;118:58-64.
29. Kim HJ, Cho SJ, Baek JH. Comparison of Thermal Ablation and Surgery for Low-Risk Papillary Thyroid Microcarcinoma: A Systematic Review and Meta-Analysis. *Korean J Radiol*. 2021;22(10):1730-41.
30. Shen K, Xue S, Xie Y, Wang H, Li J, Sun Y, et al. Comparison of thermal ablation and routine surgery for the treatment of papillary thyroid microcarcinoma: a systematic review and Meta-analysis. *Int J Hyperthermia*. 2020;37(1):913-24.
31. Tong M, Li S, Li Y, Li Y, Feng Y, Che Y. Efficacy and safety of radiofrequency, microwave and laser ablation for treating papillary thyroid microcarcinoma: a systematic review and meta-analysis. *Int J Hyperthermia*. 2019;36(1):1278-86.
32. Fugazzola L, Elisei R, Fuhrer D, Jarzab B, Leboulleux S, Newbold K, et al. 2019 European Thyroid Association Guidelines for the Treatment and Follow-Up of Advanced Radioiodine-Refractory Thyroid Cancer. *Eur Thyroid J*. 2019;8(5):227-45.
33. Brose MS, Nutting CM, Jarzab B, Elisei R, Siena S, Bastholt L, et al. Sorafenib in radioactive iodine-refractory, locally advanced or metastatic differentiated thyroid cancer: a randomised, double-blind, phase 3 trial. *Lancet*. 2014;384(9940):319-28.
34. Schlumberger M, Tahara M, Wirth LJ, Robinson B, Brose MS, Elisei R, et al. Lenvatinib versus placebo in radioiodine-refractory thyroid cancer. *N Engl J Med*. 2015;372(7):621-30.

35. Fleeman N, Houten R, Chaplin M, Beale S, Boland A, Dundar Y, et al. A systematic review of lenvatinib and sorafenib for treating progressive, locally advanced or metastatic, differentiated thyroid cancer after treatment with radioactive iodine. *BMC Cancer*. 2019;19(1):1209.
36. Rendl G, Sipos B, Becherer A, Sorko S, Trummer C, Raderer M, et al. Real-World Data for Lenvatinib in Radioiodine-Refractory Differentiated Thyroid Cancer (RELEVANT): A Retrospective Multicentric Analysis of Clinical Practice in Austria. *Int J Endocrinol*. 2020;2020:8834148.
37. Stiggelbout AM, Pieterse AH, De Haes JC. Shared decision making: Concepts, evidence, and practice. *Patient Educ Couns*. 2015;98(10):1172-9.
38. Medicine PsCftSoEPI, Biomedical, . BR. Making health care decisions v. 1: President's Commission for the Study of Ethical Problems in Medicine and ...; 1982.
39. Charles C, Gafni A, Whelan T. Shared decision-making in the medical encounter: what does it mean? (or it takes at least two to tango). *Soc Sci Med*. 1997;44(5):681-92.
40. Makoul G, Clayman ML. An integrative model of shared decision making in medical encounters. *Patient Educ Couns*. 2006;60(3):301-12.
41. Elwyn G, Frosch D, Thomson R, Joseph-Williams N, Lloyd A, Kinnersley P, et al. Shared decision making: a model for clinical practice. *J Gen Intern Med*. 2012;27(10):1361-7.
42. Kane HL, Halpern MT, Squiers LB, Treiman KA, McCormack LA. Implementing and evaluating shared decision making in oncology practice. *CA Cancer J Clin*. 2014;64(6):377-88.
43. Llewellyn-Thomas HA, Crump RT. Decision support for patients: values clarification and preference elicitation. *Med Care Res Rev*. 2013;70(1 Suppl):50s-79s.
44. Politi MC, Studts JL, Hayslip JW. Shared decision making in oncology practice: what do oncologists need to know? *Oncologist*. 2012;17(1):91-100.
45. Kunneman M, Marijnen CA, Baas-Thijssen MC, van der Linden YM, Rozema T, Muller K, et al. Considering patient values and treatment preferences enhances patient involvement in rectal cancer treatment decision making. *Radiother Oncol*. 2015;117(2):338-42.
46. Légaré F, Adekpedjou R, Stacey D, Turcotte S, Kryworuchko J, Graham ID, et al. Interventions for increasing the use of shared decision making by healthcare professionals. *Cochrane Database Syst Rev*. 2018;7(7):Cd006732.
47. Légaré F, Politi MC, Drolet R, Desroches S, Stacey D, Bekker H. Training health professionals in shared decision-making: an international environmental scan. *Patient Educ Couns*. 2012;88(2):159-69.
48. Légaré F, Stacey D, Turcotte S, Cossi MJ, Kryworuchko J, Graham ID, et al. Interventions for improving the adoption of shared decision making by healthcare professionals. *Cochrane Database Syst Rev*. 2014(9):Cd006732.
49. Diouf NT, Menear M, Robitaille H, Painchaud Guérard G, Légaré F. Training health professionals in shared decision making: Update of an international environmental scan. *Patient Educ Couns*. 2016;99(11):1753-8.
50. Elwyn G, O'Connor A, Stacey D, Volk R, Edwards A, Coulter A, et al. Developing a quality criteria framework for patient decision aids: online international Delphi consensus process. *Bmj*. 2006;333(7565):417.
51. Stacey D, Légaré F, Lewis K, Barry MJ, Bennett CL, Eden KB, et al. Decision aids for people facing health treatment or screening decisions. *Cochrane Database Syst Rev*. 2017;4(4):Cd001431.
52. Peinado S, Paquin RS, Rini C, Roche M, Butterfield RM, Berg JS, et al. Values clarification and parental decision making about newborn genomic sequencing. *Health Psychol*. 2020;39(4):335-44.

53. Munro S, Stacey D, Lewis KB, Bansback N. Choosing treatment and screening options congruent with values: Do decision aids help? Sub-analysis of a systematic review. *Patient Educ Couns.* 2016;99(4):491-500.
54. Llewellyn-Thomas HA, Crump RT. Decision support for patients: values clarification and preference elicitation. *Med Care Res Rev.* 2013;70(1 Suppl):50s-79s.
55. Witteman HO, Ndjaboue R, Vaisson G, Dansokho SC, Arnold B, Bridges JFP, et al. Clarifying Values: An Updated and Expanded Systematic Review and Meta-Analysis. *Med Decis Making.* 2021;41(7):801-20.



Chapter 2

The impact of the extent of surgery on the long-term outcomes of patients with low-risk differentiated non-medullary thyroid cancer: a systematic meta-analysis

Andreea Bojoga^{1,†}, Anna Koot^{2,3,†}, Johannes Bonenkamp⁴, Johannes de Wilt⁴, Joanna Int'Hout², Peep Stalmeier², Rosella Hermens⁵, Johannes Smit³, Petronella Ottevanger⁶ and Romana Netea-Maier³

¹ National Institute of Endocrinology "C.I. Parhon", 011863 Bucharest, Romania

² Radboud Institute for Health Sciences, Department for Health Evidence, Radboud University Medical Center, 6500 HB Nijmegen, The Netherlands

³ Department of Internal Medicine, Division of Endocrinology, Radboud University Medical Center, 6525 GA Nijmegen, The Netherlands

⁴ Department of Surgical Oncology, Radboud University Medical Center, 6525 GA, Nijmegen, The Netherlands;

⁵ Scientific Institute for Quality of Healthcare (IQ Healthcare), Radboud University Medical Center, 6500 HB Nijmegen, The Netherlands

⁶ Department of Internal Medicine, Division of Oncology, Radboud University Medical Center, 6525 GA Nijmegen, The Netherlands

[†] These authors contributed equally to the manuscript

Abstract

Background: Recently, the management of patients with low-risk differentiated non-medullary thyroid cancer (DTC), including papillary and follicular thyroid carcinoma subtypes, has been critically appraised, questioning whether these patients might be overtreated without a clear clinical benefit. The American Thyroid Association (ATA) guideline suggests that thyroid lobectomy (TL) could be a safe alternative for total thyroidectomy (TT) in patients with DTC up to 4 cm limited to the thyroid, without metastases.

Methods: We conducted a meta-analysis to assess the clinical outcomes in patients with low-risk DTC based on the extent of surgery. The risk ratio (RR) of recurrence rate, overall survival (OS), disease-free survival (DFS) and disease specific survival (DSS) were estimated. In total 16 studies with 175,430 patients met the inclusion criteria.

Results: Overall, low recurrence rates were observed for both TL and TT groups (7 vs. 7%, RR 1.10, 95% CI 0.61–1.96, $I^2 = 72\%$), and no statistically significant differences for OS (TL 94.1 vs. TT 94.4%, RR 0.99, CI 0.99–1.00, $I^2 = 53\%$), DFS (TL 87 vs. TT 91%, RR 0.96, CI 0.89–1.03, $I^2 = 85\%$), and DSS (TL 97.2 vs. TT 95.4%, RR 1.01, CI 1.00–1.01, $I^2 = 74\%$).

Conclusion: The high degree of heterogeneity of the studies is a notable limitation. Conservative management and appropriate follow-up instead of bilateral surgery would be justifiable in selected patients. These findings highlight the importance of shared-decision making in the management of patients with small, low-risk DTC.

Introduction

Differentiated non-medullary thyroid cancer (DTC) is the most common endocrine malignancy and accounts for 85% of thyroid cancer [1]. Epidemiological studies have shown that its incidence has increased continuously worldwide over the past three decades, which has been largely attributed to the diagnosis of small, often incidentally detected tumors, due to improvement and wider use of diagnostic techniques [2–5]. DTC includes papillary thyroid carcinoma (PTC) and follicular thyroid carcinoma (FTC) subtypes, with PTC representing more than two thirds of the DTC [6,7]. The majority of patients with DTC have a favorable prognosis with an excellent long-term overall survival rate, with less than 10% of patients being expected to die of the disease in 10 years or more [7–11].

There is controversy on the optimal treatment of patients with DTC, raising the question whether some of the patients with low-risk DTC might be overtreated and therefore at risk for complications of these treatments without having a clear benefit in terms of oncological outcome. Until recently, total thyroidectomy (TT) followed by postoperative radioactive iodine (RAI) treatment to ablate the thyroid remnant tissue or as an adjuvant therapy was recommended for the majority of patients by many international guidelines. Over the past decade, clinical practice has shifted towards a more individualized approach. In particular, better understanding of the biology and excellent outcomes of these tumors has led to recommending a more conservative approach for low-risk patients [12]. TT is no longer recommended for patients with radically removed microcarcinoma as it is recognized that these tumors have an excellent outcome and prospective and retrospective evidence suggests that many of the patients with indolent papillary microcarcinomas might even be followed-up conservatively [13,14]. However, for the patients with low-risk DTC, i.e., with tumors between 1 and 4 cm, there is more controversy regarding the extent of surgery. While the majority of publications have not found the extent of surgery to impact on the survival of these patients, some report a higher risk for recurrent disease in thyroid lobectomy (TL) [15–18].

The role of conservative limited surgery versus more extensive surgery for patients with low-risk DTC has not been studied in prospective randomized controlled trials, as large sample size and a long-term follow-up would be required [19,20]. Therefore, recommendations and practice are based on retrospective data, which bare inherent sources of collection and analytical bias [21,22]. Moreover, the low-risk category has been differently defined in various studies. The most recent guideline of the American Thyroid Association (ATA) recommends that TL could be

a safe alternative for TT in the treatment of patients with unifocal DTC up to 4 cm in diameter limited to the thyroid, without preoperatively known risk factors such as suspicious lymph nodes on the preoperative ultrasound and without distant metastases at presentation [23].

The purpose of this meta-analysis is to compare the clinical outcomes in adult patients with low-risk DTC based on two surgical modes, TL versus TT, and discuss in that light the arguments for and against TL and TT in low-risk DTC according to the definition and recommendation of the ATA.

Materials and Methods

The meta-analysis was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) guidelines [24]. We searched for relevant studies up to May 2019 using MEDLINE (Pubmed) database. Additional studies were identified by hand searching references in original articles and review articles. All studies selected for the meta-analysis met the following criteria: (1) articles reporting comparison outcomes for TL and TT in patients with “low-risk” DTC (PTC and FTC subtypes) regardless of the definition used and (2) the outcomes of interest were recurrence rates, overall survival (OS), disease free survival (DFS) and/or disease specific survival (DSS). In the analysis, recurrences were considered as indicated in the individual studies and defined exclusively as new structural recurrences (either in the thyroid bed or in the nonremoved thyroid tissue, the (cervical) lymph nodes, or distant metastases) confirmed by imaging and/or pathological examination. The major exclusion criteria were: (1) abstracts, reviews, age ≤ 18 , non-English language, (2) duplicate data, (3) no reported outcomes mentioned, (4) studies focusing exclusively on microcarcinoma, (5) with less than 50 patients per arm. Patients were classified using various scoring systems (AJCC/TNM, AMES, ATA). A comparison between different scoring systems and editions of AJCC/TNM applied in included studies to define “low-risk” can be seen in Table S1 and S2 Comparison of the AJCC UICC 3rd, 6th, 7th and 8th edition [23,25–28]. Low-risk AMES score is equivalent to stages I and II according to the TNM / AJCC staging system, [29] and patients included in the low-risk group will be TNM / AJCC stage I or II depending on their age, tumor size and lymph node status, having a proven high survival rate [12,26]. For the meta-analysis, we selected patients described as having tumors between 1–4 cm limited to the thyroid, without evidence of locoregional or distant metastases. The search terms were as follows: MeSH terms: “thyroid neoplasms”, “thyroidectomy” and keywords: “non-medullary thyroid

neoplasm", "thyroid surgery", "lobectomy", "low risk thyroid carcinoma" (the detailed presentation of the search procedure is available in Table S3).

Data Extraction

Two authors (A.B. and A.K.) extracted all relevant data independently. The following data were extracted: year of publication, first author's name, country of study origin, % female, mean age, study design, surgical approach, follow-up duration, use of radioactive iodine (RAI), inclusion of high-risk patients and outcomes assessed. The data were reviewed by a third author (R.N.-M.). Disagreements were resolved through consensus.

Risk of Bias Assessment

We used a component approach to assess risk of bias for all included studies. The components were subdivided into five separate domains based on the Cochrane Risk-of-Bias In Non-Randomized Studies-of Interventions (ROBINS-I tool) [30]. The following domains and components, which could potentially bias a reported association between extent of surgery and outcome in thyroid cancer patients, were included [31].

Pre-Intervention

Domain 1: Bias due to confounding (see below)

Domain 2: Bias in selection of participants into the study Inclusion of patients (consecutive inclusion of all patients eligible or a random sample is considered low risk of bias).

Definition of low risk thyroid cancer?

At Intervention

Domain 3: Bias in classification of intervention. Were intervention groups clearly defined?

Post Intervention

Domain 4: Bias due to missing data TNM-stage available (see below) Reporting of high-risk patients (see below) Reporting of RAI treatment (see below) Reporting number of patients included per treatment arm (see below)

Domain 5: Bias in measurement of outcomes

Loss to follow-up (<5% is considered low risk of bias)

Criteria for extent of surgery (see below)

Reporting of outcome definition

Matched cohorts reported no bias of confounding. As the type of surgery procedure was not always clearly described, adequately reporting the criteria used for the extent of surgery was considered a low risk of bias. Availability of TNM-stage was considered adequate if the article mentioned T1–T4. Reporting of high-risk patients was considered adequate if the article mentioned T3–T4, N1 and/or M1 stage or mentioned numbers of high-risk patients with well-defined criteria for high risk. Reporting of RAI treatment was considered adequate if the numbers of patients receiving RAI treatment were mentioned. Reporting the number of patients included per treatment arm was considered adequate if the article mentioned the number of patients for each type of surgery.

Statistical Analysis

Pooled RR's, 95% confidence intervals (95% CI) and 95% prediction intervals were calculated using random effects models (the inverse variance method, empirical Bayes estimator for τ^2 and continuity correction of 0.5 in studies with zero cell frequencies). Heterogeneity among studies was evaluated using the I² statistic [32]. We present the median proportion in the studies as the proportion per group. Subgroup analyses were conducted according to design, sample size, year of publication and duration of follow-up after TL and TT, to assess their potential contributions to outcomes. R version 3.5.3, with package meta version 4.9-5 was used for the analysis of the data [33,34]. Sensitivity analyses were performed to estimate the influence of each individual study on the overall risk ratio (RR). Studies were considered to have a low risk of bias if they met at least ten (out of eleven) of the above-mentioned criteria for low risk of bias. Articles were considered intermediate risk of bias if they met up to nine of the above-mentioned criteria for risk of bias. The potential publication bias was evaluated with a funnel plot [35].

Results

Characteristics of the Selected Studies

In total, 106 abstracts and titles were obtained through electronic search, and 17 articles identified through manual search. The detailed search yielded no randomized controlled trials. Fortyfour articles were found eligible, of which the results of 23 articles were examined in detail; 16 studies met the inclusion/exclusion criteria, which resulted in 175,430 patients. Figure 1 shows the details of the study selection process and the exclusion criteria. Characteristics of the 16 included studies are listed in Table 1.

Table 1. Characteristics of the selected studies included in the meta-analysis.

Authors/Year of Publication	Country	Female (%)	Mean Age (Y)	Time of Surgery Stated	Study Design	Surgical Approach		Follow-Up	Outcomes Assessed	RAI Given (%)	Histological Subtypes Included	High Risk Patients Included (%)
						TL	TT					
Samaan 1983 [36]	USA	73	NA	1951–1975	Retrospective cohort study	105	491	6–30 Y	Recurrence, OS	yes (34%)	PTC, FTC, HCC	yes
Shah 1993 [37]	USA	62	57	1930–1980	Retrospective matched cohort study	73	73	20 Y	Recurrence, DFS	yes *	PTC, FTC	yes
Shaha 1997 [38]	USA	74	31	1930–1985	Retrospective cohort study	280	90	20 Y	Recurrence, DSS	NA	PTC, FTC	no
Hay 1998 [15]	USA	NA	43	1940–1991	Retrospective cohort study	185	1082	16 Y	Recurrence, DFS, DSS	yes	PTC	no
Sanders 1998 [39]	USA	72	44	1940–1990	Retrospective cohort study	224	795	0–47 Y	Recurrence, OS, DSS	NA	PTC, FTC, HCC	yes
Haigh 2004 [40]	USA	77	NA	1988–1995	Retrospective population-based cohort	739	3663	1 mo–12 Y	OS	yes	PTC	Yes **
Bilimoria 2007 [16]	USA	76	43	1985–1998	Retrospective population-based cohort	8946	43,227	5.8 Y	Recurrence, OS	yes	PTC	yes
Mendelsohn 2010 [41]	USA	78	44	1988–2001	Retrospective population-based cohort	5964	16,760	9.1 Y	OS, DSS	yes	PTC	yes
Hassanain 2010 [29]	Canada	73	NA	1982–2002	Retrospective cohort study	126	54	4–25 Y	Recurrence, DFS	yes (28.3%)	PTC, FTC	yes
Ito 2010 [17]	Japan	94	51.1 ± 12.4	1987–2005	Retrospective cohort study	1601	1037	0.5–34 Y	Recurrence, DSS	yes (0.1%)	PTC	no
Barney 2010 [11]	USA	NA	NA	1983–2002	Retrospective population-based cohort	3266	12,598	2 mo–19.9 Y	OS, DSS	yes	PTC, FTC	yes
Vaisman 2011 [42]	USA	84	45 ± 13	1986–2005	Retrospective cohort study	72	217	0.5–34 Y	Recurrence, DSS	no	PTC, HCC	no
Nixon 2012 [43]	USA	79	46	1986–2005	Retrospective cohort study	361	528	13 mo–24.3 Y	Recurrence, OS, DSS	yes	PTC, FTC, HCC	yes
Ebina 2014 [18]	Japan	76	54 ± 14	1993–2010	Retrospective cohort study	791	176	3–20 Y	Recurrence, DFS, DSS	yes	PTC	yes ***

Table 1. Continued

Authors/Year of Publication	Country	Female (%)	Mean Age (Y)	Time of Surgery Stated	Study Design	Surgical Approach		Follow-Up	Outcomes Assessed	RAI Given (%)	Histological Subtypes Included	High Risk Patients Included (%)
						TL	TT					
Adam 2014 [44]	USA	80	NA	1998–2011	Retrospective population-based cohort	6849	54,926	5–14.9 Y	OS	yes	PTC	yes
Kuba 2017 [45]	Japan	86	53	1994–2008	Retrospective matched cohort study	120	53	11 mo–20.8 Y	OS, DFS	yes	PTC	yes

Percentage was rounded up to a closest integer. Y: years, mo: months, TT: total thyroidectomy, TL: thyroid lobectomy, OS: overall survival, DFS: disease free survival, DSS: disease specific survival, RAI: radioactive iodine, PTC: papillary thyroid carcinoma, FTC: follicular thyroid carcinoma, HCC: Hürthle cell carcinoma, NA: not available; * "only a few received RAI" (not otherwise specified). ** The total cohort included 18% high-risk patients, however separate analysis available for the low-risk cohort, therefore only those patients were included in the meta-analysis. *** The total cohort included 19% high-risk patients, however separate analysis available for the low-risk cohort, therefore only those patients were included in the meta-analysis.

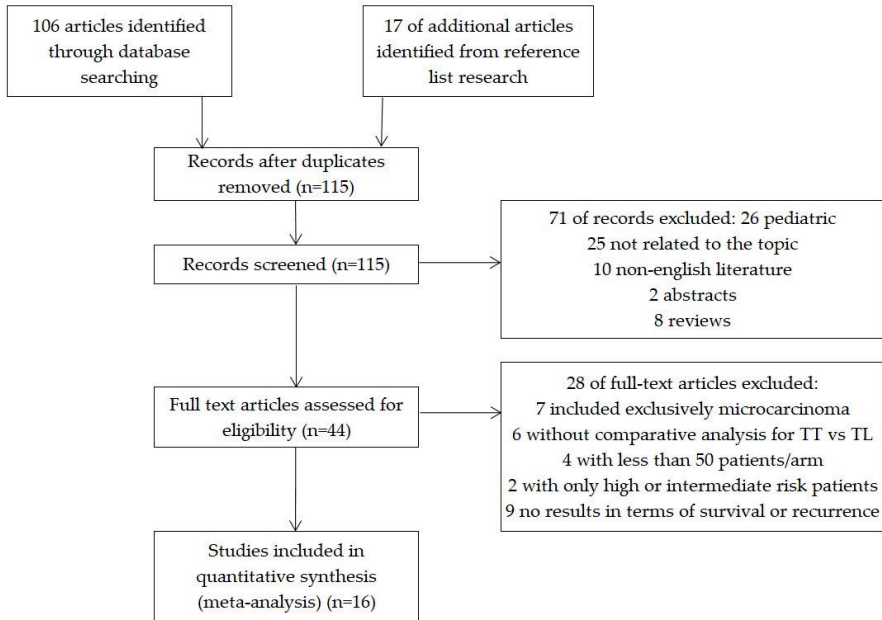


Figure 1. Flow chart for study selection.

Any Thyroid Cancer-Related Recurrence

The meta-analysis of any DTC-related recurrence was based on 60,534 patients in 11 studies with a median follow-up of 10 years. Median recurrence rates were 7% in the TL group and 7% in the TT group. Most of the studies only described overall recurrence rates, compared by extent of surgery [16,17,29,36,42]. Two studies also included recurrence rates for distant metastases [37,39]. Four of the included studies reported the local, regional and distant metastases recurrence rates [15,18,38,43]. Overall, similar tumor recurrence rates were observed for the TL group and the TT group (RR = 1.10, CI 0.61 to 1.96, I² = 72%) (Figure 2). No significant difference was observed between the two surgical methods. There was a marked statistical heterogeneity. The subgroup analyses showed no significant impact of design, sample size, year of publication or time of duration on the results (data not shown).

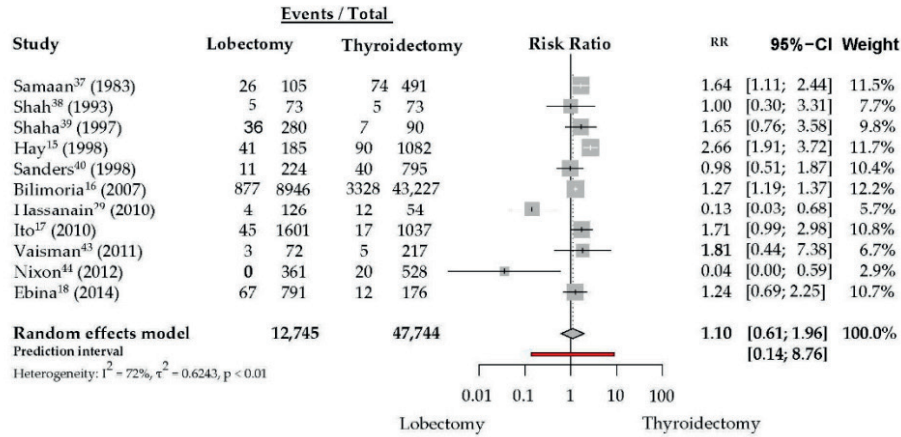


Figure 2. Recurrence rates of differentiated thyroid carcinoma after total thyroidectomy versus lobectomy.

Survival Outcomes

The meta-analysis of DFS included 5967 patients in seven studies with a median follow-up of 10 years. Median DFS rates were 87% in the TL group and 91% in the TT group. No significant difference was observed between the two surgical methods for DFS (RR 0.96, CI 0.89 to 1.03, $I^2 = 85\%$). There was a marked statistical heterogeneity (Figure 3A).

The meta-analysis of OS was based on 160,084 patients in 11 studies with a median follow-up of 7 years. Median OS rates were 93% in the TL group and 93% in the TT group. There was a marked statistical heterogeneity. No significant difference was observed between the two surgical methods for OS (RR 0.99, CI 0.99 to 1.00, $I^2 = 53\%$). There was a marked statistical heterogeneity (Figure 3B). The meta-analysis of DSS included 43,715 patients in 10 studies with a median follow-up of 11 years. Median DSS rates were 98% in the TL group and 99% in the TT group. No significant difference was observed between the two surgical methods for DSS (RR 1.01, CI 1.00 to 1.01, $I^2 = 74\%$). There was a marked statistical heterogeneity (Figure 3C).

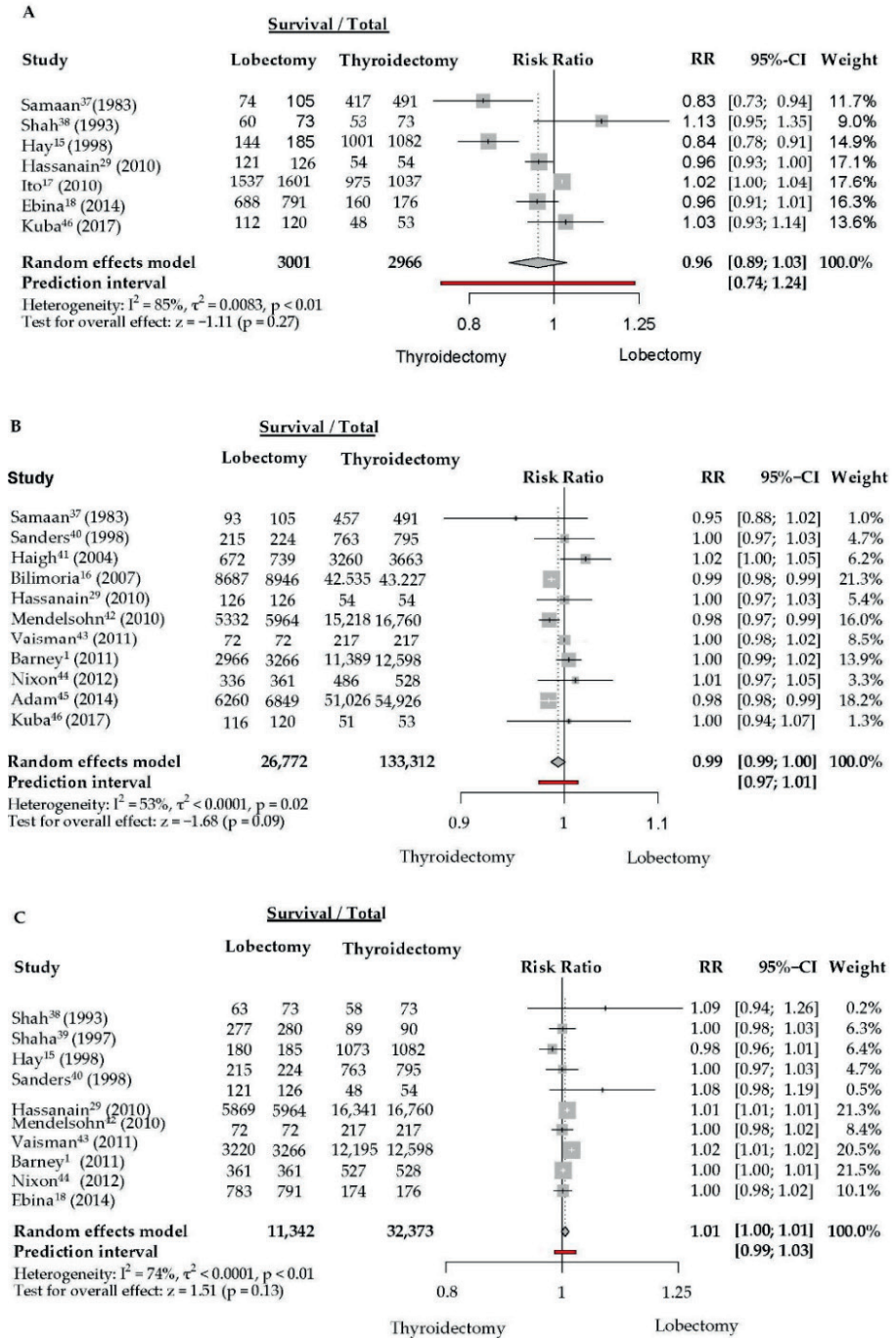


Figure 3. Survival rates of thyroid carcinoma after total thyroidectomy versus lobectomy. (A) DFS; (B) OS; (C) DSS.

Sensitivity Analysis

The results demonstrate that there is one individual study with an extreme effect on the overall RR for recurrence rates[29](Figure 4).

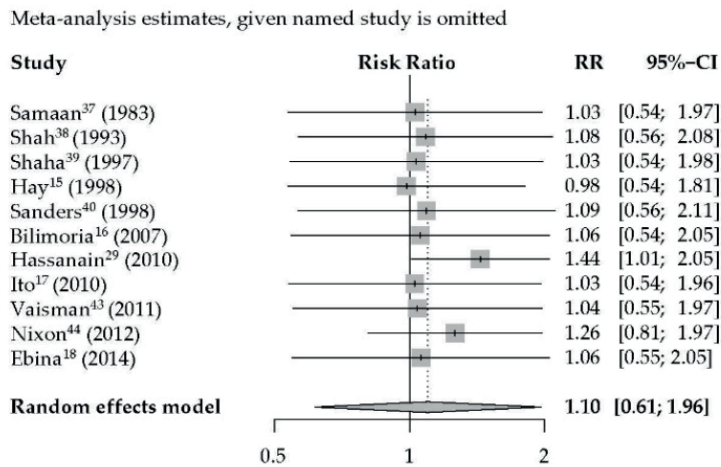


Figure 4. Sensitivity analysis for recurrence rates of well-differentiated thyroid carcinoma after thyroid lobectomy versus total thyroidectomy. DFS, OS and DSS showed no extreme effect and were not shown.

Risk of Bias Assessment

Only two studies (13%) had a matched cohort and no bias of confounding. Definition of low-risk patients was adequately reported in 13 articles (81%). Inclusion of consecutive patients or use of a random sample was explicitly stated in 15 articles (94%). Loss to follow up was reported in six articles (37.5%), one of these six articles reported a loss to follow up of <5%. Four of these six articles also included patients who underwent less than a lobectomy or a subtotal thyroidectomy, procedures that are regarded as inferior in terms of oncologic outcome [29,38,39,46]. Some of the studies that clearly defined which of the patients had these insufficient surgeries also included a separate analysis for these [1,31,36,37,44]. Criteria for extent of surgery were met in 14 articles (87.5%). Reporting of outcome definition was adequate in 16 articles (100%). Availability of T-stage was adequate in 15 articles (94%). Reporting high risk patients was adequate in 12 articles (75%) (see also Table S4). Reporting of RAI treatment was adequate in 13 articles (81%) (see also Table S4). Reporting number of patients per treatment arm was adequate in 16 articles (100%).

One article showed low risk of bias (met ten out of eleven criteria), and five articles showed intermediate risk of bias (met nine out of eleven criteria). There was no study that met all eleven criteria. The risk of bias for each study is reported in Table S5.

Publication Bias

Publication bias was examined by funnel plots. No clear indication of publication bias was observed for recurrence rates (Figure 5).

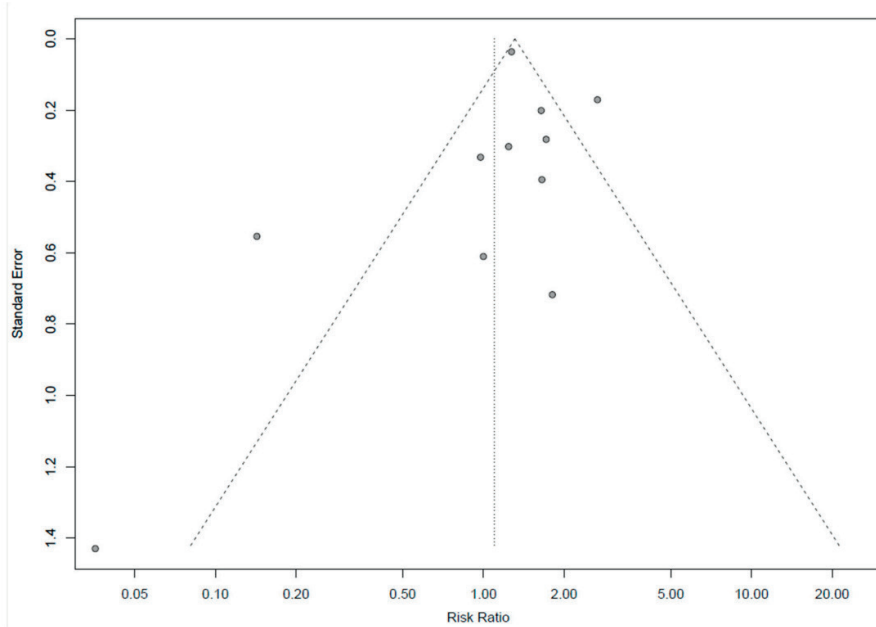


Figure 5. Funnel plot of recurrence rate for publication bias. Each point represents a separate study for the indicated association. OS, DFS and DFS had similar outcomes and are not shown.

Discussion

To our knowledge, this study is the first meta-analysis focusing on the outcome of surgical extension in terms of recurrence and survival in patients with low-risk DTC 1–4 cm without clinical evidence of locoregional or distant metastases. Our meta-analysis shows no statistically significant differences between TL versus TT regarding DTC-related recurrence, DSS, OS and DFS rates.

The effect of the extent of surgery for patients with low risk DTC on patients' outcome has long been a matter of discussion partly because of a lack of evidence-based randomized data from prospective studies. The early study of Mazzaferri et al. showed a statistically significant advantage of TT in comparison to TL regarding both recurrence and survival [47]. These results were later supported by Bilimoria et al., who showed, in a large retrospective analysis of 52,173 patients in the National Cancer Database (NCDB), that lobectomy resulted in higher risk of recurrence and

death for tumors larger than 1 cm [16]. Nonetheless, the study of Mazzaferri was done before the era of contemporary risk stratification and since then preoperative evaluation and follow-up has improved [47]. Moreover, Bilimoria et al. presented only data on OS and lacked significant data about potential high-risk features [16]. Therefore, a critical reappraisal was done by Adam et al., who applied an analysis of a more contemporary (1998–2006) NCDB cohort of patients. This study showed that OS was similar in patients undergoing TL versus TT for tumors 1–4 cm after multivariable adjustment for clinical and pathological factors [44]. Even in patients with high risk features like extracapsular invasion and clinical evidence of lymph node metastasis, Haigh et al. reported that extent of thyroidectomy had no notable effect on estimated survival [40]. Mendelsohn et al. showed that after controlling for tumor size, multivariate analysis revealed no survival difference between TT versus TL [41]. Other studies, not meeting the selection criteria for this meta-analysis, also report excellent long-term clinical outcomes in selected low-risk patients [46,48–52]. Our meta-analysis supports the lack of a significant effect of the extent of surgery on the survival outcome in the low-risk patient category amenable for TL according to the ATA guidelines.

Lower complication rate, avoiding iatrogenic hypothyroidism and shorter duration of surgery are important arguments for preferring TL. Nonetheless, there could be several reasons for preferring a TT. One reason is the concern regarding an increased risk for recurrent or residual disease (e.g., persistence of microscopic lymph node metastases or multifocal tumor localizations in the opposite thyroid lobe). In addition, distant metastases could be missed and might only become apparent on whole body scans performed after ablative treatment with RAI, as limited surgery is usually not followed by treatment with RAI. In this meta-analysis, both local and distant metastases recurrence rates were low. There was no statistically significant difference of local recurrences in TL compared to TT, and distant metastases recurrence rates were higher in TT. Of note, only five studies [17,18,29,36,45] mentioned ultrasound as a routine preoperative assessment but only in patients evaluated since 2005 [43], while all studies also included patients who were treated before 2005. Thus, malignancies in the contralateral remnant lobe and small cervical lymph node metastases might have been missed, resulting in suboptimal treatment in these patients.

A second reason for preferring TT is that bilateral tumor localizations are found in 20% to 85% of patients with PTC after total or completion thyroidectomy, but the majority are considered occult carcinoma [7,53,54]. Proponents of TT argue that this feature is associated with a higher risk of recurrence and thus, reoperation [36,54]. Mazzaferri and Huang have shown that in patients with three or more foci of PTC or

FTC (any size), there was a higher cancer-related mortality rate, but this association was not present after adjustment for multivariate analysis [21]. Other studies do not report an association between tumor multicentricity and prognosis, thus the clinical significance of occult carcinoma is questionable [39,53,55,56]. Of the studies included in this meta-analysis that mentioned multicentricity, none showed an association between multicentricity and prognosis [17,18,29,37,44,45].

A third reason is that microscopical lymph node metastases are also likely to be found in histopathological samples (up to 90% in the central compartment and up to 40% in the lateral compartment) [7], but these remain quiescent in the vast majority of patients, with only 10% developing clinically significant disease [7,12]. The risk of persistent micro-nodal disease also persists in patients who had TT if prophylactic lymph node dissection has not been performed, a procedure that is not routinely done in patients without clinical or radiological evidence of lymph node metastases. Because of the lack of prospective studies, a conservative surgical approach should be complemented with radiological follow-up by neck ultrasound, preferably performed by expert radiologists in order to detect the small volume nodal disease that might develop into gross recurrent disease requiring additional treatment. Our analysis indicates that even if the risk of recurrent disease in low-risk patients is present, this risk remains low regardless of the extent of surgery, and with proper management it does not impact the long-term survival of the patients. Moreover, it has been argued that these recurrent tumors are amenable for salvage surgery and therefore a “stepwise” approach to therapy of these patients could be an acceptable alternative for the minority of patients in which the disease recurs, while the limited surgery might suffice for the oncologic control of the remaining low-risk patients [23].

A fourth and important reason to prefer TT over TL is routine use of RAI ablation in the majority of patients with tumors 1 cm or greater. In terms of outcome, RAI ablation has not been shown to clearly benefit the low-risk group patients in the absence of any high-risk features, while being associated with some side effects [23,57,58]. However, RAI ablation facilitates follow-up by enabling the use of thyroglobulin (Tg) as a reliable marker of a favorable prognosis. Though the Tg levels are less reliable in patients who have undergone TL [59,60], Tg level trends combined with neck ultrasound can be effective follow-up methods for these patients as well [12,57,61].

Our study has some limitations which should be considered by the interpretation of the data. Due to the lack of randomized prospective studies, our estimates were based on non-randomized retrospective studies which are prone to selection bias,

are limited by the availability of patient data and are characterized by a high degree of heterogeneity. The sensitivity analysis demonstrates that there is one individual study with an extreme effect on the overall RR for recurrence rates. Hassanain et al. showed a much higher recurrence rate in the more extensive surgery patients, which indicates selection bias [29]. Only two articles had no bias of confounding on the effect of intervention because of a matched cohort. Therefore only one article included had a low risk of bias and five articles had an intermediate risk of bias according to the Cochrane Risk-of-Bias In Non-Randomized Studies-of Interventions (ROBINS-I) tool [30]. Inclusion of high-risk patients, using various staging systems, inclusion of tumors larger than 4 cm (six studies, incomplete data in another three studies), use of other surgical interventions such as nodulectomy, local excision, and subtotal thyroidectomy, which are considered to be inappropriate for thyroid cancer treatment [62,63](in 12 of the included studies) likely biased the outcome in favor of one surgical approach over the other. Furthermore, the comparison of these studies is influenced by adjuvant therapies such as RAI or external beam radiation therapy, routine thyroid stimulating hormone suppression, and lymph node dissection. RAI in particular was administered more often in the patients that had undergone TT, most likely reflecting the selection bias towards more unfavorable clinical features or the local protocols. However, this might rather have conferred a clinical benefit to those who had TT instead of TL. Notably, the two cohort studies [38,46] in which propensity score matching for clinical features of the cohorts of patients having TT and TL was done resulted in a similar outcome. Verburg et al. showed, in a recent systematic review on the potential benefits of RAI treatment in low-risk patients, that the results of different studies are mixed, largely because of multiple potential sources of bias and heterogeneity with respect to RAI treatment protocols and activities applied. This precludes, for the moment, a definitive answer to this question and strengthens the need for well-designed randomized clinical trials [64]. As time to disease recurrence in low risk DTC can be very long, mean follow-up period in some studies might not have been sufficient, thus affecting the survival and recurrence outcome as an end point. Nonetheless, the majority of studies included 10 to 20 years of follow-up, which is largely reassuring.

When selecting the optimal surgical extent in patients with low-risk DTC, the goal is to minimize the risk of death from disease and recurrence, while avoiding potential iatrogenic injury from overtreatment. Disease-related characteristics are critical, and risk stratification is paramount. Individual patient values and preferences, as well as surgeons' experience and quality of follow-up and patients' adherence to follow-up should also be considered when making this decision [65].

Conclusion

TL is a safe procedure for treatment of low-risk DTC patients, with excellent oncological outcomes and potentially lower treatment side effects. Initial risk assessment and ongoing dynamic risk stratification can reduce the uncertainty about disease persistence and individualize follow-up and treatment in order to reduce recurrence rate, the risk of completion thyroidectomy, and patient anxiety. However, it is important to inform the patients about the expected outcomes for both TL and TT with respect to morbidity, need for hormone replacement and the risk of reoperation. Thus, shared decision-making should be considered when the choice for the most appropriate surgical approach is being made.

References

1. Barney, B.M.; Hitchcock, Y.; Sharma, P.; Shrieve, D.C.; Tward, J.D. Overall and cause-specific survival for patients undergoing lobectomy, near-total, or total thyroidectomy for differentiated thyroid cancer. *Head Neck* 2010, 33, 645–649, doi:10.1002/hed.21504.
2. Davies, L.; Welch, H.G. Current thyroid cancer trends in the United States. *JAMA Otolaryngol. Head Neck Surg.* 2014, 140, 317–322, doi:10.1001/jamaoto.2014.1.
3. Morris, L.G.; Myssiorek, D. Improved detection does not fully explain the rising incidence of well-differentiated thyroid cancer: A population-based analysis. *Am. J. Surg.* 2010, 200, 454–461, doi:10.1016/j.amjsurg.2009.11.008.
4. Welch, H.G.; Black, W.C. Overdiagnosis in cancer. *J. Natl. Cancer Inst.* 2010, 102, 605–613.
5. Harach, H.R.; Franssila, K.O.; Wassenius, V.-M. Occult papillary carcinoma of the thyroid. A “normal” finding in Finland. A systematic autopsy study. *Cancer* 1985, 56, 531–538, doi:10.1002/1097-0142(19850801)56:33.0.co;2-3.
6. Byrd, J.K.; Yawn, R.J.; Wilhoit, C.S.T.; Sora, N.D.; Meyers, L.; Fernandes, J.; Day, T. Well Differentiated Thyroid Carcinoma: Current Treatment. *Curr. Treat. Options Oncol.* 2012, 13, 47–57, doi:10.1007/s11864-011-0173-1.
7. Sosa, J.A.; Udelsman, R. Total thyroidectomy for differentiated thyroid cancer. *J. Surg. Oncol.* 2006, 94, 701–707.
8. Murthy, S.P.; Balasubramanian, D.; Anand, A.; Limbachiya, S.V.; Subramaniam, N.; Nair, V.; Thankappan, K.; Iyer, S. Extent of Thyroidectomy in Differentiated Thyroid Cancers—Review of Evidence. *Indian J. Surg. Oncol.* 2017, 9, 90–96, doi:10.1007/s13193-017-0661-2.
9. Kim, S.H.; Roh, J.-L.; Gong, G.; Cho, K.-J.; Choi, S.-H.; Nam, S.Y.; Kim, S.Y. Differences in the recurrence and survival of patients with symptomatic and asymptomatic papillary thyroid carcinoma: An observational study of 11,265 person-years of follow-up. *Thyroid* 2016, 26, 1472–1479.
10. Davies, L.; Welch, H.G. Thyroid Cancer Survival in the United States. *Arch. Otolaryngol. Head Neck Surg.* 2010, 136, 440–444, doi:10.1001/archoto.2010.55.
11. Nixon, I.; Shah, J.P. Well differentiated thyroid cancer: Are we over treating our patients? *Eur. J. Surg. Oncol.* 2014, 40, 129–132, doi:10.1016/j.ejso.2013.12.003.
12. Tarasova, V.; Tuttle, R.M. Current Management of Low Risk Differentiated Thyroid Cancer and Papillary Microcarcinoma. *Clin. Oncol.* 2017, 29, 290–297, doi:10.1016/j.clon.2016.12.009.
13. 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* 2013, 24, 27–34, doi:10.1089/thy.2013.0367.
14. Sugitani, I.; Fujimoto, Y. Management of low-risk papillary thyroid carcinoma: Unique conventional policy in Japan and our efforts to improve the level of evidence. *Surg. Today* 2010, 40, 199–215, doi:10.1007/s00595-009-4034-5.
15. Hay, I.D.; Grant, C.S.; Bergstrahl, E.J.; Thompson, G.B.; van Heerden, J.A.; Goellner, J.R. Unilateral total lobectomy: Is it sufficient surgical treatment for patients with AMES low-risk papillary thyroid carcinoma? *Surgery* 1998, 124, 958–966.
16. Bilimoria, K.Y.; Bentrem, D.J.; Ko, C.Y.; Stewart, A.K.; Winchester, D.P.; Talamonti, M.S.; Sturgeon, C. Extent of surgery affects survival for papillary thyroid cancer. *Ann. Surg.* 2007, 246, 375–384, doi:10.1097/sla.0b013e31814697d9.

17. Ito, Y.; Miyauchi, A. Excellent Prognosis for Patients with Solitary T1N0M0 Papillary Thyroid Carcinoma Who Underwent Thyroidectomy and Elective Lymph Node Dissection without Radioiodine Therapy: Reply to Letter. *World J. Surg.* 2010, 35, 233–234, doi:10.1007/s00268-010-0734-7.
18. Ebina, A.; Sugitani, I.; Fujimoto, Y.; Yamada, K. Risk-adapted management of papillary thyroid carcinoma according to our own risk group classification system: Is thyroid lobectomy the treatment of choice for lowrisk patients? *Surgery* 2014, 156, 1579–1589, doi:10.1016/j.surg.2014.08.060.
19. Udelsman, R.; Lakatos, E.; Ladenson, P. Optimal Surgery for Papillary Thyroid Carcinoma. *World J. Surg.* 1996, 20, 88–93, doi:10.1007/s002689900016.
20. Mazzaferri, E.L.; Jhiang, S.M. Long-term impact of initial surgical and medical therapy on papillary and follicular thyroid cancer. *Am. J. Med.* 1994, 97, 418–428.
21. Nixon, I. The Surgical Approach to Differentiated Thyroid Cancer. *F1000Research* 2015, 4, 1366, doi:10.12688/f1000research.7002.1.
22. Gibelli, B.; Dionisio, R.; Ansarin, M.; Mohssen, A. Role of hemithyroidectomy in differentiated thyroid cancer. *Curr. Opin. Otolaryngol. Head Neck Surg.* 2015, 23, 99–106, doi:10.1097/moo.0000000000000142.
23. Haugen, B.R.; Alexander, E.K.; Bible, K.C.; Doherty, G.M.; Mandel, S.J.; Nikiforov, Y.E.; Pacini, F.; Randolph, G.W.; Sawka, A.M.; Schlumberger, M.; 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– 133.
24. Moher, D.; Liberati, A.; Tetzlaff, J.; Altman, D.G. Preferred reporting items for systematic reviews and metaanalyses: The PRISMA statement. *J. Clin. Epidemiol.* 2009, 62, 1006–1012.
25. Cady, B.; Rossi, R. An expanded view of risk-group definition in differentiated thyroid carcinoma. *Surgery* 1988, 104, 947–953.
26. Tuttle, R.M.; Haugen, B.; Perrier, N.D. Updated American Joint Committee on Cancer/Tumor-Node Metastasis Staging System for Differentiated and Anaplastic Thyroid Cancer (Eighth Edition): What Changed and Why? *Thyroid* 2017, 27, 751–756, doi:10.1089/thy.2017.0102.
27. Bearhs, O.H.; Henson, D.E. *AJCC Manual for Staging Cancer*, 3rd ed.; J.B. Lippincott Company: Philadelphia, PA, USA, 1988; pp. 61–62.
28. Greene, F.I.; Page, D.L. *AJCC Manual for Staging Cancer*, 6th ed.; Springer: New York, NY, USA, 2002; pp. 77–79.
29. Hassanain, M.; Wexler, M.J. Conservative management of well-differentiated thyroid cancer. *Can. J. Surg.* 2010, 53, 109–118.
30. Sterne, J.A.C.; Hernan, M.A.; Reeves, B.C.; Savović, J.; Berkman, N.D.; Viswanathan, M.; Henry, D.; Altman, D.G.; Ansari, M.T.; Boutron, I.; et al. ROBINS-I: A tool for assessing risk of bias in non-randomized studies of interventions. *BMJ* 2016, 355, i4919, doi:10.1136/bmj.i4919.
31. Broersen, L.H.A.; Jha, M.; Biermasz, N.R.; Pereira, A.M.; Dekkers, O.M. Effectiveness of medical treatment for Cushing's syndrome: A systematic review and meta-analysis. *Pituitary* 2018, 21, 631–641, doi:10.1007/s11102-018-0897-z.
32. Higgins, J.P.T.; Thompson, S.G.; Deeks, J.; Altman, D.G. Measuring inconsistency in meta-analyses. *BMJ* 2003, 327, 557–560, doi:10.1136/bmj.327.7414.557.
33. R Development Core Team. *R: A Language and Environment for Statistical Computing*; R Foundation for Statistical Computing: Vienna, Austria, 2019. Available online: <http://www.R-project.org> (accessed on 28 may 2019).

34. Schwarzer, G. meta: An R package for meta-analysis. *R News* 2007, 7, 40–45, version 4.9-5, 2007.
35. Egger, M.; Smith, G.D.; Schneider, M.; Minder, C. Bias in meta-analysis detected by a simple, graphical test. *BMJ* 1997, 315, 629–634, doi:10.1136/bmj.315.7109.629.
36. Samaan, N.A.; Maheshwari, Y.K.; Nader, S.; Hill, C.S.; Schultz, P.N.; Haynie, T.P.; Hickey, R.C.; Clark, R.L.; Goepfert, H.; Ibanez, M.L.; et al. Impact of therapy for differentiated carcinoma of the thyroid: An analysis of 706 cases. *J. Clin. Endocrinol. Metab.* 1983, 56, 1131–1138, doi:10.1210/jcem-56-6-1131.
37. Shah, J.P.; Loree, T.R.; Dharker, D.; Strong, E.W. Lobectomy versus total thyroidectomy for differentiated carcinoma of the thyroid: A matched-pair analysis. *Am. J. Surg.* 1993, 166, 331–335, doi:10.1016/s0002-9610(05)80326-5.
38. Shaha, A.R.; Shah, J.P.; Loree, T.R. Low-risk differentiated thyroid cancer: The need for selective treatment. *Ann. Surg. Oncol.* 1997, 4, 328–333.
39. Sanders, L.E.; Cady, B. Differentiated thyroid cancer: Reexamination of risk groups and outcome of treatment. *Arch. Surg.* 1998, 133, 419–425.
40. Haigh, P.I.; Urbach, D.R.; Rotstein, L.E. Extent of Thyroidectomy Is Not a Major Determinant of Survival in Low- or High-Risk Papillary Thyroid Cancer. *Ann. Surg. Oncol.* 2004, 12, 81–89, doi:10.1007/s10434-004-1165-1.
41. Mendelsohn, A.H.; Elashoff, D.A.; Abemayor, E.; St John M.A. Surgery for papillary thyroid cancer: Is lobectomy enough? *Arch. Otolaryngol. Head Neck Surg.* 2010, 136, 1055–1061, doi:10.1001/archoto.2010.181.
42. Vaisman, F.; Shaha, A.; Fish, S.; Tuttle, R.M. Initial therapy with either thyroid lobectomy or total thyroidectomy without radioactive iodine remnant ablation is associated with very low rates of structural disease recurrence in properly selected patients with differentiated thyroid cancer. *Clin. Endocrinol.* 2011, 75, 112–119, doi:10.1111/j.1365-2265.2011.04002.x.
43. Nixon, I.J.; Ganly, I.; Patel, S.G.; Palmer, F.L.; Whitcher, M.M.; Tuttle, R.M.; Shaha, A.; Shah, J.P. Thyroid lobectomy for treatment of well differentiated intrathyroid malignancy. *Surgery* 2012, 151, 571–579, doi:10.1016/j.surg.2011.08.016.
44. Adam, M.A.; Pura, J.; Gu, L.; Dinan, M.A.; Tyler, D.S.; Reed, S.D.; Scheri, R.; Roman, S.A.; Sosa, J.A. Extent of Surgery for Papillary Thyroid Cancer Is Not Associated With Survival. *Ann. Surg.* 2014, 260, 601–607, doi:10.1097/sla.0000000000000925.
45. Kuba, S.; Yamanouchi, K.; Hayashida, N.; Maeda, S.; Adachi, T.; Sakimura, C.; Kawakami, F.; Yano, H.; Matsumoto, M.; Otsubo, R.; et al. Total thyroidectomy versus thyroid lobectomy for papillary thyroid cancer: Comparative analysis after propensity score matching: A multicenter study. *Int. J. Surg.* 2017, 38, 143–148, doi:10.1016/j.ijsu.2016.09.083.
46. Craig, W.; Smart, L.; Fielding, S.; Ramsay, C.; Krukowski, Z.H. Long term outcomes of simple clinical risk stratification in management of differentiated thyroid cancer. *Surgeon* 2018, 16, 283–291, doi:10.1016/j.surge.2018.01.007.
47. Mazzaferri, E.L.; Young, R.L.; Oertel, J.E.; Kemmerer, W.T.; Page, C.P. Papillary thyroid carcinoma: The impact of therapy in 576 patients. *Medicine (Baltimore)* 1977, 56, 171–196.
48. Choi, J.B.; Lee, S.G.; Kim, M.J.; Kim, T.H.; Ban, E.J.; Lee, C.R.; Lee, J.; Kang, S.-W.; Jeong, J.J.; Nam, K.-H.; et al. Oncologic outcomes in patients with 1-cm to 4-cm differentiated thyroid carcinoma according to extent of thyroidectomy. *Head Neck* 2018, 41, 56–63, doi:10.1002/hed.25356.
49. Momesso, D.P.; Vaisman, F.; Caminha, L.S.C.; Pessoa, C.H.C.N.; Corbo, R.; Vaisman, M. Surgical approach and radioactive iodine therapy for small well-differentiated thyroid cancer. *J. Endocrinol. Investig.* 2014, 37, 57–64, doi:10.1007/s40618-013-0015-z.

50. Matsuzu, K.; Sugino, K.; Masudo, K.; Nagahama, M.; Kitagawa, W.; Shibuya, H.; Ohkuwa, K.; Uruno, T.; Suzuki, A.; Magoshi, S.; et al. Thyroid Lobectomy for Papillary Thyroid Cancer: Long-term Follow-up Study of 1,088 Cases. *World J. Surg.* 2013, 38, 68–79, doi:10.1007/s00268-013-2224-1.
51. Chow, T.L.; Choi, C.Y.; Lam, S.H. Disease control of differentiated thyroid carcinomas by hemithyroidectomy. *Singap. Med. J.* 2010, 51, 311–314.
52. Cady, B.; Sedgwick, C.E.; Meissner, W.A.; Bookwalter, J.R.; Romagosa, V.; Werber, J. Changing Clinical, Pathologic, Therapeutic, and Survival Patterns in Differentiated Thyroid Carcinoma. *Ann. Surg.* 1976, 184, 541–553, doi:10.1097/0000658-197611000-00003.
53. Pitt, S.C.; Sippel, R.S.; Chen, H. Contralateral papillary thyroid cancer: Does size matter? *Am J. Surg.* 2009, 197, 342–347.
54. Huang, H.; Liu, S.; Xu, Z.; Ni, S.; Zhang, Z.; Wang, X. Long-term outcome of thyroid lobectomy for unilateral multifocal papillary carcinoma. *Medicine (Baltimore)* 2017, 96, e7461, doi:10.1097/md.00000000000007461.
55. DeGroot, L.J.; Kaplan, E.L.; McCormick, M.; Straus, F.H. Natural History, Treatment, and Course of Papillary Thyroid Carcinoma. *J. Clin. Endocrinol. Metab.* 1990, 71, 414–424, doi:10.1210/jcem-71-2-414.
56. Grigsby, P.W.; Reddy, R.M.; Moley, J.F.; Hall, B.L. Contralateral papillary thyroid cancer at completion thyroidectomy has no impact on recurrence or survival after radioiodine treatment. *Surgery* 2006, 140, 1043–1049, doi:10.1016/j.surg.2006.08.007.
57. Schwartz, C.; Bonnetain, F.; Dabakuyo, S.; Gauthier, M.; Cueff, A.; Fieffe, S.; Cochet, I.; Crevisy, E.; Dalac, A.; Papathanassiou, D.; et al. Impact on Overall Survival of Radioactive Iodine in Low-Risk Differentiated Thyroid Cancer Patients. *J. Clin. Endocrinol. Metab.* 2012, 97, 1526–1535, doi:10.1210/jc.2011-2512.
58. Sawka, A.M.; Thephamongkhon, K.; Brouwers, M.; Thabane, L.; Browman, G.; Gerstein, H.C. Clinical review 170: A systematic review and meta-analysis of the effectiveness of radioactive iodine remnant ablation for well-differentiated thyroid cancer. *J. Clin. Endocrinol. Metab.* 2004, 89, 3668–3676.
59. Peiris, A.N.; Medlock, D.; Gavin, M. Thyroglobulin for Monitoring for Thyroid Cancer Recurrence. *JAMA* 2019, 321, 1228, doi:10.1001/jama.2019.0803.
60. Park, S.; Jeon, M.J.; Oh, H.-S.; Lee, Y.-M.; Sung, T.-Y.; Han, M.; Han, J.M.; Kim, T.Y.; Chung, K.-W.; Kim, W.B.; et al. Changes in Serum Thyroglobulin Levels After Lobectomy in Patients with Low-Risk Papillary Thyroid Cancer. *Thyroid* 2018, 28, 997–1003, doi:10.1089/thy.2018.0046.
61. Harvey, R.D.; Matheson, N.A.; Grabowski, P.S.; Rodger, A.B. Measurement of serum thyroglobulin is of value in detecting tumour recurrence following treatment of differentiated thyroid carcinoma by lobectomy. *Br. J. Surg.* 1990, 77, 324–326, doi:10.1002/bjs.1800770329.
62. Duren, M.; Yavuz, N.; Bukey, Y.; Ozyegin, M.A.; Gundogdu, S.; Açbay, O.; Hatemi, H.; Uslu, I.; Onsel, C.; Aksoy, F.; et al. Impact of initial surgical treatment on survival of patients with differentiated thyroid cancer: Experience of an endocrine surgery center in an iodine-deficient region. *World J. Surg.* 2000, 24, 1290–1294, doi:10.1007/s002680010214.
63. Friedman, M.; Pacella, B.L. Total versus subtotal thyroidectomy. Arguments, approaches, and recommendations. *Otolaryngol. Clin. N. Am.* 1990, 23, 413–427.
64. Verburg, F.; Flux, G. Differentiated Thyroid Cancer Patients Potentially Benefitting From Postoperative I-131 Therapy: A Review of the Literature of the Past Decade. *Eur. J. Nucl. Med. Mol. Imaging* 2020, 47, 78–83.
65. Asimakopoulos, P.; Nixon, I. Surgical management of primary thyroid tumours. *Eur. J. Surg. Oncol. (EJSO)* 2018, 44, 321–326, doi:10.1016/j.ejso.2016.12.015



Chapter 3

Needs, preferences, and values during different treatment decisions of patients with differentiated thyroid cancer

Anna Koot^{1,2}, Romana Netea-Maier², Petronella Ottevanger³, Rosella Hermens⁴,
Peep Stalmeier¹

¹ Radboud Institute for Health Sciences, Department for Health Evidence, Radboud University Medical Center, 6500 HB Nijmegen, the Netherlands.

² Department of Internal Medicine, Division of Endocrinology, Radboud University Medical Center, 6525 GA Nijmegen, the Netherlands.

³ Department of Internal Medicine, Division of Oncology, Radboud University Medical Center, 6525 GA Nijmegen, the Netherlands.

⁴ Radboud Institute for Health Sciences, Scientific Institute for Quality of Healthcare (IQ Healthcare), Radboud University Medical Center, 6500 HB Nijmegen, the Netherlands.

Abstract

Background: The purpose of this study was to identify the needs, preferences, and values of patients with differentiated thyroid cancer (DTC) and the physicians treating patients with DTC regarding two different treatment decisions, namely: the extent of primary surgery (low-risk patients) and the tyrosine kinase inhibitor (TKI) treatment (high-risk patients).

Methods: A qualitative study was conducted. There were two physician focus groups discussing the extent of primary surgery. One included endocrinologists (n = 4) and surgeons (n = 5), and the other included nuclear medicine physicians (n = 3) treating patients with low-risk DTC. The physicians focus group discussing waiting or starting TKIs included endocrinologists (n = 2) and oncologists (n = 5) treating patients with advanced radioactive iodide (RAI) refractory DTC. Moreover, one patient focus group per treatment decision took place. In total 13 patients and 19 physicians participated. Interviews were audio-taped, fully transcribed verbatim, and analyzed.

Results: Several themes were identified. Patients, but not physicians, mentioned the importance of a strong doctor–patient relationship. Patients in both treatment decision groups wanted to receive more detailed information, whereas physicians preferred providing more general information. Patients in the TKI decision group focused on palliative care, whereas physicians focused more on the effect and benefit of TKIs.

Conclusions: Considering the identified themes in DTC, based on the patients' needs, preferences, and values, enables us to improve doctor–patient communication and to develop decision support tools.

Keywords: differentiated thyroid cancer; information needs and preferences; focus group interview

Introduction

Most patients with low-risk differentiated thyroid cancer (DTC) have an excellent long-term prognosis [1–4]. Up to 30% of DTC patients develop recurrent disease and/or distant metastases. Patients with distant metastases have a five-years survival rate of approximately 50%, which is worse in those with advanced radioactive iodide (RAI) refractory DTC [5,6]. Therefore, considering the relatively high survival rates for both low-risk and high-risk DTC survivors, maintaining long-term quality of life (QOL) is important.

Recently, clinical practice shifted towards more individualized approaches, and patients are involved in trade-offs between the harms and benefits of different approaches [7]. For patients with low-risk DTC and patients with RAI refractory DTC, the optimal treatment is debated, as insufficient evidence is available regarding the harms and benefits of treatments in relation to the oncological outcome. As such, some low-risk DTC patients might undergo overtreatment, thus negatively affecting QOL. The American Thyroid Association (ATA) guidelines suggest considering patient preferences, as for some low-risk patients, thyroid lobectomy (TL) alone may be a sufficient initial treatment [8,9]. Similarly, for asymptomatic or mildly symptomatic RAI refractory DTC patients, premature starting of tyrosine kinase inhibitors (TKIs) may expose patients to side-effects and worsening QOL. The recent European Thyroid Association (ETA) guidelines stated that the decision to start TKIs should include patient-related medical factors and patient preferences with respect to treatment goals and values, as well as the acceptance of adverse effects [10]. However, a recommendation on how to shape the communication process is lacking.

Doctor–patient communication could be improved to consider the patients' perspective by using shared decision making (SDM). Accordingly, physicians provide patients with information on existing options and consider patients' needs in order to enable a personalized treatment choice [11]. In this process, important life goals are involved, and these should be explored together with the patient [12–15]. In practice, however, talking about values is difficult, and values are discussed in a minority of decision-making consultations [11]. Moreover, exploring values is complicated by different perspectives of physicians and patients [16].

To facilitate SDM in doctor–patient communication, it is important to determine the patients' needs. Decision-support tools, such as decision aids and values clarification exercises, exist to inform patients and help them explore their values [17,18]. These

tools can be applied in clinical practice. These instruments are not yet available for all patients with DTC. For developing such tools, knowledge about patients' and physicians' needs is required. Previous studies have explored the patients' needs in patients with papillary microcarcinoma (PMC) [19–23] and in patients with larger low-risk DTC (>1 cm) requiring treatment [24–30]. However, particularly the differences between patients' and physicians' needs have not previously been investigated.

To reduce miscommunication between patients and their physicians, we aimed to identify the needs of DTC patients in two different treatment decision groups in preference-sensitive decision making, as stated in the ATA and ETA guidelines [9,10]: (1) the extent of primary surgery, including the need for subsequent ablation of thyroid remnants with RAI in patients with low-risk DTC (>1 cm), and (2) starting TKIs in patients with advanced RAI refractory DTC. Our aim was to, on the one hand, address the differences and similarities between the two treatment decision-making groups (regarding low-risk and high-risk patients), and on the other hand, between perspectives of physicians and patients for both decisions. In addition to previous studies, more attention was given to values communication, given the difficulty in exploring values and to help physicians to discriminate between their own and patients' values.

Materials and Methods

Study Design

We performed a qualitative study using semi-structured focus group interviews. The aim of the interviews was to identify in-depth needs, preferences, and values of DTC patients in two different treatment decision groups and in physicians treating DTC patients. This study is part of the COMBO study (COMmunication Booster, NCT03905369), aiming to develop, evaluate, and implement decision-support tools for DTC patients. Twelve hospitals (six academic and six non-academic) in the Netherlands participated. The Dutch patient association "Schilddukler Organisatie Nederland (SON)" was also involved. The Medical Ethical Committee (CMO) of the region Arnhem–Nijmegen approved the study protocol (MEC-2018-4521). The study is in agreement with the COREQ checklist [31].

Setting

In the Netherlands, DTC patients undergo treatment in both academic (high- and low-risk patients) and non-academic hospitals (mainly low-risk patients) involving multidisciplinary teams of specialists. Long-term follow-up is generally carried out

by endocrinologists. Patients with advanced RAI refractory disease requiring TKI treatment are followed-up by oncologists.

Participants

Patients

Two treatment decision-making groups were involved, namely: (1) patients with low-risk DTC according to the ATA criteria [9] who had surgery, and (2) patients with advanced RAI refractory DTC who started or considered TKIs. The inclusion criteria for the low-risk group were being diagnosed with DTC, having been treated with surgery within one year, and being capable of understanding their treatment trajectory as judged by their physician. Inclusion criteria for the advanced disease group were patients who started or considered TKIs within one year and were capable of understanding their treatment trajectory as judged by their physician. Six academic hospitals with expertise in DTC treatment throughout the Netherlands, as well as the Dutch patient association SON, selected patients for participation in the interviews. After physicians asked their patients to participate in the interviews, participants were approached by the researcher (A.K.) by telephone. Participation was voluntary. All participants provided written informed consent alongside answers to some demographic questions.

In total, two patient focus groups were organized. One focus group included low-risk DTC patients ($n = 6$) discussing thyroid lobectomy or total thyroidectomy, including the need for the subsequent ablation of thyroid remnants with RAI. The other focus group included patients with advanced disease ($n = 7$), discussing the watchful waiting approach or starting with TKIs decision. The patient focus group interviews took place in the main investigating center (Radboud University Medical Center). The interviewee had no treatment relationship with the participants.

Physicians

Physicians (endocrinologists, surgeons, nuclear medicine physicians, and oncologists) from the above-mentioned expertise centers with extensive expertise on the treatment of patients with DTC were approached by the researcher (A.K.) by email. All physicians provided verbal informed consent and answered several questions regarding their clinical experience. In total, three physician focus groups were organized. To discuss the thyroid lobectomy or total thyroidectomy decision, two focus groups were organized, as follows: one included endocrinologists ($n = 4$) and surgeons ($n = 5$), and one included nuclear medicine physicians ($n = 3$) treating patients with low-risk DTC. To discuss the decision between watchful waiting or

starting with TKIs, another focus group was held, including endocrinologists (n = 2) and oncologists (n = 5) treating patients with advanced RAI refractory DTC.

Data Collection

An expert panel developed an interview guide (Table A1). For both patients and physicians, the interview guide contained three sections, open-ended questions, and optional questions to elaborate each topic. The three sections referred to the diagnostic, treatment, and evaluation phases of DTC care. The interviewer (A.K., first author, female, MD endocrinology, PhD student, trained in interviewing techniques by a qualitative research expert) started by explaining the process of the interview. Next, open-ended questions, not provided in advance, were asked concerning the information given by the physician during the consultation in the specific treatment phase. The open-ended questions, focused on needs, preferences, and values; communication with the health care provider; strong and weak points of the received health care; and points to improve the current health care. Finally, patients were invited to give their opinion about the content to be included in a decision-support tool. The focus group interviews were conducted between May and December 2019. All of the focus group interviews lasted between 26 and 94 min and were audio-taped. One additional observer attended each focus group and field notes were made during the focus group interviews (R.N.-M. or P.O.). A pilot for the interview was performed with the first and fourth author (female, senior researcher, experience with qualitative research). Patients did not receive questions in advance and were not informed about the use of the framework to analyse the data using the Picker domains [32,33].

Analysis

First, all five focus group interviews were transcribed verbatim and qualitatively analyzed using ATLAS.ti, 8.4.15 [34]. Two researchers (A.K. and a second coder; female, experienced coder) independently analyzed all of the transcripts. The perspectives of patients and physicians and the two different treatment decisions were analyzed separately. The eight-dimension Picker domains were used as a basis for our analyses (Table A2) [32]. Expressed needs, preferences, and values were categorized into one of the eight Picker domains, particularly involvement in decisions and respect for preferences, coordination and integration of care, clear information, and communication and emotional support. All interviews were open coded independently by both researchers. Open coding allows for an exploration of the ideas and meaning that were contained in the raw data. Once codes were created using open coding, they were analyzed using the axial coding process. This analysis enabled researchers to identify connections between the codes [35]. For axial coding, two concept coding trees were made, one for the surgery decision and

one for the TKI decision. Both researchers could add, remove, or move the codes of the coding tree. The codes were compared and discussed until a consensus was reached. Thereafter, the codes were categorized into similar themes and subthemes within one of the domains. We aimed to fit all themes into the Picker domains, and a new domain was proposed if the codes would not fit.

Results

All of the invited patients and physicians agreed to participate. The patient and physician characteristics are displayed in Table 1. Sixteen themes and sixty-three subthemes were categorized for low-risk DTC patients and their respective physicians. Fifteen themes and thirty-eight subthemes were categorized for patients with advanced DTC and their respective physicians. The themes and subthemes fitted within four of the eight Picker domains (Table A2) [32]; one additional domain occurred, namely values (Tables 2–5 and Figure 1). Table 2 shows the qualitative results for the surgery decision regarding “thyroid lobectomy or total thyroidectomy” and Table 3 shows several quotes fitted to the corresponding themes for the decision regarding “thyroid lobectomy or total thyroidectomy”. Table 4 shows the qualitative results for the decision “to wait or start with TKIs”, and Table 5 shows several quotes fitted to the corresponding themes for the decision “to wait or start with TKIs”. The identified domains were as follows.

Table 1. Characteristics of participating patients and physicians

Characteristics of Patients (n = 13)	Number n(%)
TKIs	7 (54)
Not started	4 (57)
Started	3 (43)
Average time from progressive advanced disease (mean), m	6.9
Site of distant metastases	
* Lung	6 (60)
* Bone	3 (30)
* Other	1 (10)
Characteristics of physicians (n = 19)	Number n(%)
Sex:	
Male	7 (37)
Female	12 (63)
Working in university hospital	15 (100)
Medical specialty:	
Endocrinologist	6 (32)
Oncologist	5 (26)
Surgeon	5 (26)
Nuclear medicine physician	3 (16)
Experience in years	
0–10	1 (5)
11–20	11 (58)
>20	7 (37)

y: years, m: months; * site of distant metastases

Table 1. Continued

Characteristics of Patients (n = 13)	Number n(%)
Sex:	
Male	7 (54)
Female	6 (46)
Age, mean (range), y	57 (31–84)
Caucasian	13 (100)
Married/living together	13 (100)
Educational level:	
High school or less	2 (16)
Vocational education	11 (84)
University	0 (0)
Treatment:	
Surgery	6 (46)
Thyroid lobectomy	3 (50)
Total thyroidectomy	3 (50)
Average time from surgery (mean), m	10.5
Complication rate	1 (17)

Table 2. Qualitative results for the surgery decision regarding “thyroid lobectomy or total thyroidectomy”. Expressed needs, preferences, and values of patients and of physicians with DTC.

Information Needs for Surgery Decision Making			
Domain	Theme		Description of Corresponding Items
	Patients	Physicians	
1. Involvement in decisions and respect for preferences	Personalized care regarding patient values • Deliberation • Phone number of the oncology nurse for support Doctor–patient relationship Time to accept the diagnosis	Personalized care regarding patient values • Deliberation Doctor–patient relationship Time to accept the diagnosis	Patients and physicians: Physicians listen to the patient, take the patient seriously, and incorporate the patient’s wishes into the treatment plan. In addition, patients should be enabled through enough time and attention given to the patient. Patients: Patients need a doctor who takes care and is available most of the time. Integrity and mutual respect are necessary for a good doctor–patient relation. Physicians: Physicians should be available to answer questions. Integrity and mutual respect are necessary for a good doctor–patient relationship. Patients and physicians: After hearing the diagnosis, most patients need time to accept the diagnosis and deal with the consequences.
2. Coordination and integration of care	Clarity about healthcare process • Follow-up • Way of informing ¹ Multidisciplinary team Patient support groups Fellow patients	Clarity about healthcare process • Follow-up • Way of informing ¹ Multidisciplinary team	Patients and physicians: The healthcare path should make clear what to expect. This means all steps in follow-up should be made clear. Patients want to receive information about the healthcare process on paper or digitally. Patients and physicians: Patients need to know a person from the multidisciplinary team who can answer questions and address health-related issues. The contact-person should be regularly available. A tumor board, where physicians can discuss difficult cases with other healthcare providers, is important. Patients: When confronted with illness, patients seek professional help and advice from their doctors, and also rely on support from family members, peers, and fellow patients.

Table 2. Continued

Information Needs for Surgery Decision Making			
Domain	Theme		Description of Corresponding Items
	Patients	Physicians	
3. Clear information and communication	Information about diagnosis • Thyroid • Thyroid cancer • (Lymph node) metastases • Tumor location • Tumor size • Tumor growth • Thyroid cancer type • Clear, neutral, and stepwise way • Diagnosis being told by physician Information about prognosis • Nothing about prognosis • Survival • Treatment opportunity • No difference in treatment outcome Information about treatment options • Thyroid lobectomy • Total thyroidectomy • Radioactive iodine • Active surveillance • SDM with physician • Format of explanation² Information about risks and complications • Surgery - General - Anesthesia - Second surgery • Complications • Parathyroid gland • Vocal cord • Infection • Risk of wait and see • Psychological pressure after decision • Consequence of surgery • Recurrence Information about medication • Thyroid hormone substitution • Additional supplements • Pregnancy • Need for thyroid hormone substitution treatment • Medication adjustment • Side effects • Quality of life Information about recovery after treatment • Possible (negative) effects associated with each treatment - Changes in daily life - Weight loss/gain - Recurrence - Psychological aspects - Low calcium level - Fluctuations in thyroid function • Duration of recovery	Information about diagnosis • Thyroid cancer • Thyroid cancer type • Clear, neutral and stepwise way • Diagnosis being told by physician Information about prognosis • Survival • Treatment opportunity • No difference in treatment outcome Information about treatment options • Radioactive iodine • Active surveillance • SDM with physician Information about risks and complications • Surgery • Second surgery • Complications • Parathyroid gland • Vocal cord • Tracheostoma • Psychological pressure after decision • Radioactive iodine Information about medication • Medication adjustment • Quality of life Information about recovery after treatment • Duration of recovery	Patients: Patients need clear, honest, and complete information about the diagnosis. Physicians need to tell every aspect of the diagnosis. Information on the internet should be of good quality. Physicians: Patients need short and general information about the diagnosis. If not, there are concerns about the amount of information that will be forgotten. Patients and physicians: Information about the prognosis needs to be honest. To talk about treatment opportunities and outcomes is important. Especially when there is no difference in treatment outcomes. Patients: Clear and detailed information about different treatment options is important in SDM. With clear information, patients can deliberate which option fits them best. Physicians: To talk about all treatment options is important in SDM. With clear but short information, patients are able to deliberate which option fits them best. Patients and physicians: Information about the risks and complications during and after treatment is important in order to make a considered decision. The amount and consequences of complications in daily life are essential in SDM. Patients: Before patients can make a decision, it is important to have clear and extensive information about the medication. What are risks and benefits of this medication. In addition, the impact on quality of life is an important part of information about medication. Physicians: Before patients can make a decision, it is important to have complete information about the medication. Especially about the difficulties of medication adjustment. In addition, the impact of quality of life is an important part of information about medication. Patients: The possible effects after treatment are important. Patients specifically want to know what changes will take place in daily life. Physicians: Physicians mention that information about recovery is most important to patients.
4. Emotional support	Personalized psychological support for emotional problems • Reassurance • Multidisciplinary consultation		Patients: To offer psychological care to every patient is important. There should be the option to involve family and friends, for example the option to bring relatives to hospital appointments. Reassure patients through clear communication and the possibility of discussing with other healthcare providers.

Table 2. Continued

Information Needs for Surgery Decision Making			
Domain	Theme		Description of Corresponding Items
	Patients	Physicians	
5. Values	- Regarding functioning in daily life • Work • Sport • Holiday • Future • Family • Quality of life • Pregnancy - Regarding behavior • Self-determination • Medical decision by physician • Fear - Side-effects - Medical values • Had cancer before - Medical values • Information • Decision • enetics • Medication • Quick treatment • Recovery • Conservative surgery • Extensive surgery	- Regarding functioning in daily life • Quality of life - Regarding behavior • Fear - Recurrence - Voice • Had cancer before - Medical values • Information • Medication • Quick treatment • Conservative surgery	Patients and physicians: Values are about “what matters to me”. Values are an important part of health care decisions. Strengthening and clarifying patients’ values and preferences in the consultation is important. Values deliberation is a core step in the consultation, where the values of physicians and patients come together to reach a treatment decision

SDM—shared decision making; ¹ To inform patients by paper or digitally/e-mail; ² Treatment options have to be told in a detailed way.

Table 3. Quotes of patients and physicians corresponding to some of the themes for the surgery decision regarding “thyroid lobectomy or total thyroidectomy”.

Domain	Theme	Quotes Patients	Quotes Physicians
1. Involvement in decisions and respect for preferences	Time for processing the diagnosis	“It is important that you have time for processing the diagnosis and that you can think about the treatment options.”	“The diagnosis of thyroid cancer can cause anxiety and uncertainty about the future. Therefore, it is important to give patients time to process the diagnosis and make the right decision.”
2. Coordination and integration of care	Multidisciplinary team	“An important part of the decision making was the involvement of a tumor board.”“An oncology nurse is important for practical issues.”	“When we talk about a patient in our tumor board, it is possible to discuss the different treatment options and to decide if a patient is suitable for shared decision making.”“We have an oncology nurse who takes excellent care of our patients. Patients feel reassured by having a contact person.”
3. Clear information and communication	Information about prognosisInformation about medication	“I only remembered that it was treatable.”“It took a year to adjust on thyroid medication, it is necessary to receive information about this process in advance.”	“I think it is important to tell patients about their type of cancer and that there are excellent treatment options with a very good prognosis.”“It is important to say something about the adjustment of thyroid medication and the possibility of reducing quality of life.”
4. Emotional support	Personalized psychological support for emotional problems	“I wavered for a very long time, I was afraid to make the wrong treatment decision. When I discussed this with my physician, she reassured me and helped me with my decision.”	-

Table 4. Qualitative results for the advanced disease decision regarding “wait or start with TKI’s”. Expressed information on the needs, preferences, and values of patients with and of physicians treating patients with DTC.

Information Needs for TKI Decision Making			
Domain	Theme		Description of Corresponding Items
	Patients	Physicians	
1. Involvement in decisions and respect for preferences	Personalized care regarding patient values • Deliberation • Phone number of the oncology nurse for support Doctor–patient relationship Time to accept the diagnosis	Personalized care regarding patient values • Deliberation • Phone number of the oncology nurse for support Doctor–patient relationship	Patients and physicians: Healthcare providers listen to the patient, take the patient seriously, and incorporate the patient’s wishes into the treatment plan. In addition, patients should be enabled so that there is enough time and attention for the patient. Patients: Patients need a doctor who takes care and is available most of the time. Integrity and mutual respect are necessary for a good doctor–patient relationship. Physicians: Physicians should be available to answer questions from patients. Integrity and mutual respect are necessary for a good doctor–patient relationship. Patients: After hearing the diagnosis, most patients need time to accept the diagnosis and deal with the consequences.
2. Coordination and integration of care	Clarity about healthcare process • Follow-up • Way of informing¹ Multidisciplinary team Patient support groups Fellow patients	Clarity about healthcare process • Follow-up • Way of informing¹ Multidisciplinary team	Patients and physicians: The healthcare path should make clear what to expect. This means all steps in follow-up should be made clear. Patients want to receive information about the healthcare process on paper or digitally. Patients and physicians: Patients need to know a person from the multidisciplinary team to answer questions and address health-related issues. The contact-person should be regularly available. In addition, involving oncology nurses might result in saving time during the consult with the doctor, and their involvement is described as a more personal contact. A tumor board, where physicians can discuss difficult cases with other healthcare providers. Patients: When confronted with illness, patients seek professional help and advice from their doctors, and also rely on support from family members, peers and fellow patients.

Table 4. Continued

Information Needs for TKI Decision Making			
Domain	Theme		Description of Corresponding Items
	Patients	Physicians	
3. Clear information and communication	Information about diagnosis • Thyroid cancer • (Lymph node) metastases • Tumor growth Information about prognosis • Palliation Information about treatment options • Active surveillance • SDM with physician • TKIs • Information by physician Information about medication • Side effects • Quality of life • Dosage • Information by physician • When to provide information • When to start with medication • TKIs • Sources of information ³ Information about recovery after treatment • Possible (negative) effects associated with each treatment - Changes in daily life	Information about diagnosis • Tumor growth Information about prognosis • Benefit of treatment • Palliation • Communication of risk information ² Information about treatment options • Active surveillance • SDM with physician • Possibility to stop with TKIs • There is no wrong decision Information about medication • Side effects • Quality of life • Dosage • Information by physician • When to provide information • When to start with medication • TKIs • Sources of information ³	Patients: Patients need clear, honest, and complete information about the diagnosis. Physicians need to discuss every aspect of the diagnosis. Information on the internet should be of a good quality. Physicians: Patients need short and general information about the diagnosis. If such information is not given, physicians raise concerns about the amount of information that will be forgotten. Patients: Information about the prognosis needs to be honest. After all, it is a palliative treatment. Talking about treatment opportunities and outcomes is important. Physicians: Information about the prognosis needs to be honest. Physicians want to focus on the benefits of treatment, but after all, it is a palliative treatment. To talk about treatment opportunities and outcomes is important. Patients: Clear and detailed information about different treatment options is important in SDM. With clear information patients can deliberate which option fits best. Physicians: To talk about all treatment options is important in SDM. With clear, but short information, patients are able to deliberate which option fits best. Patients: Before patients are able to decide, it is important to have clear and extensive information about the medication. What are the risks and benefits of this medication. In addition, the impact on quality of life is an important part of the information about medication. Physicians: Before patients are able to decide, it is important to have complete information about the medication. Especially about the side effects. In addition, the impact on quality of life is an important part of information about medication. Patients: The possible effects after treatment are important. Patients especially want to know what changes will occur in daily life.
	Personalized psychological support for emotional problems • Reassurance • Multidisciplinary consultation • Family	Personalized psychological support for emotional problems • Reassurance	Patients: To offer psychological care to every patient is important. There should be the option to involve family and friends, for example the option to bring relatives to hospital appointments. Reassure patients by clear communication and the possibility of discussing with other healthcare providers. Physicians: Reassure patients by clear communication and the possibility of discussing with other healthcare providers.

Table 4. Continued

Information Needs for TKI Decision Making			
Domain	Theme		Description of Corresponding Items
	Patients	Physicians	
5. Values	Regarding functioning in daily life • Work • Sport • Holiday • Future • Family • Quality of life • Autonomy Regarding behavior • Self-determination • Deferral of medical decision to physician • Fear - Side-effects - Symptoms - Dying • Done everything Medical values • Information • Decision	Regarding functioning in daily life • Work • Holiday • Family Regarding behavior • Fear - Dying • Done everything	Patients and physicians: Values are about “what matters to me”. Values are an important part of health care decisions. Strengthening and clarifying patients’ values and preferences in the consultation is important. Values deliberation is a core step in the consultation, where values of physicians and patients come together to reach a treatment decision.

SDM—shared decision making; ¹ To inform patients by paper or digitally / e-mail; ² Visually inform patients about survival and recurrence;³ Different sources of information were the pharmacy, package leaflet of the medicine, and the internet.**Table 5.** Quotes of patients and physicians corresponding to some of the themes for the advanced disease decision regarding “wait or start with TKI’s”.

Domain	Theme	Quotes Patients	Quotes Physicians
1. Involvement in decisions and respect for preferences	Time for processing the diagnosis	“The fact that you switch from an endocrinologist to an oncologist with a waiting room full of patients with cancer was a real change for me.”	
2. Coordination and integration of care	Multidisciplinary team	“A case manager can help, advise, and reassure when there are problems.”	“We discuss all patients in our tumor board and decide if whether they are a candidate for treatment with TKIs.”
3. Clear information and communication	Information about prognosis Information about medication	“You know that it is not a curative treatment and that there will be a moment when the medication is not longer working or that you have to stop because of the side effects.” “Information about the side effects was clear and detailed.” “What are the side effects and what can you expect?”	“It is important to inform patients about the possible benefit, but also that it is not a curative treatment.” “I especially talk about the side effects and quality of life.”
4. Emotional support, empathy and respect	Personalized psychological support for emotional problems	“Family means everything, my granddaughter is always aware that I cannot do everything. They give so much love.”	“Patients fear death, so your role as a physician who supports and reassures is important.”
5. Values	Regarding functioning in daily life	“Quality of life is the most important value in many different aspects of life. Maintaining quality of life is important for being able to participate in sport and work, but especially for experiencing family events.”	“What I think is important, some patients are still working and that is also quality of life. Patients just want to keep doing social things, work, to go on a holiday.”

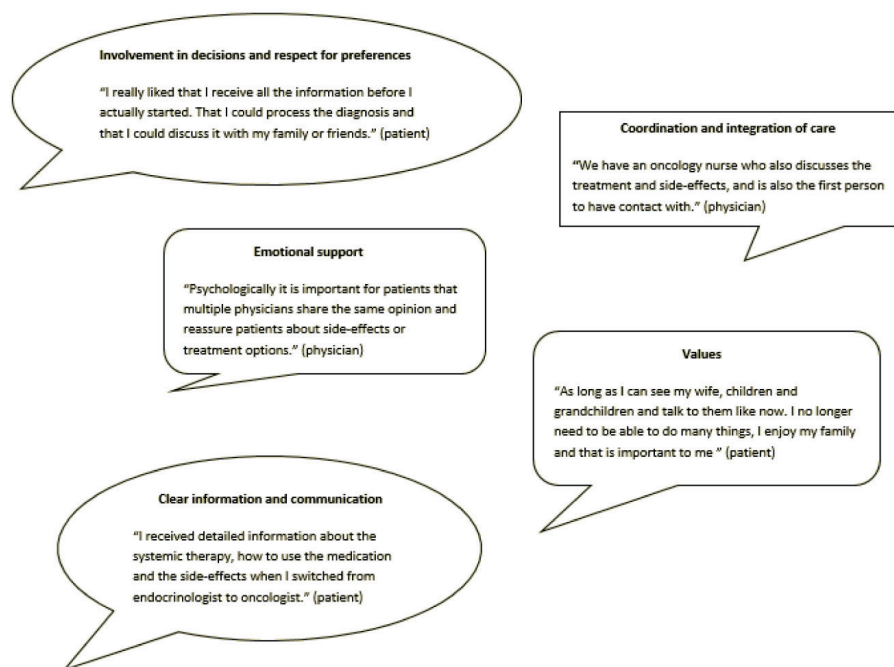


Figure 1. Quotes expressed by patients with DTC and by physicians treating patients with DTC for each Picker domain.

Involvement in Decisions and Respect for Preferences

The importance of a good doctor–patient relationship was most often mentioned by patients with advanced RAI refractory DTC. Patients indicated the importance of discussing the treatment steps with family and friends, and listening to patients' needs and preferences. They indicated needing a doctor who takes care and is available most of the time. Integrity and mutual respect were necessary for a good doctor–patient relationship. For patients treated with surgery, it was important to be involved in their treatment process and to discuss the options with their physician. The patients in both treatment decision groups needed time to cope with the diagnosis and its consequences. Physicians in both treatment decision groups mentioned that patient involvement in the treatment process was important. The difference between patients and physicians in this domain was the importance of a good doctor–patient relationship. This theme was rarely mentioned by physicians.

Coordination and Integration of Care

Themes mentioned by patients and physicians for both treatment decisions were the involvement of a multidisciplinary team and information process. It was

important to have a contact person for questions and problems. Patients and physicians for both decisions mentioned that they considered an oncology nurse as the most suitable multidisciplinary team member. A tumor board should be available to discuss difficult cases with other healthcare providers. For both patients and physicians, paper and digital ways of informing were considered equally important, and adequate ways to inform patients. In this domain there were no differences between patients and physicians.

Clear Information and Communication

Patients in both decision groups needed clear, honest, and complete information. They also wanted to receive detailed information. The two important themes for patients in the surgery decision group were general information about DTC and treatment options. For patients in the TKI decision group, general information about advanced RAI refractory DTC and medication was important. In both groups, patients were not at all or only slightly satisfied with the amount of information received. They wanted to receive more information. Patients in both groups felt they were not involved in decision making, “there was nothing to choose”. Important themes for physicians discussing the surgery decision also involved general information about DTC and treatment options. Physicians mentioned most often “giving information about the prognosis”, especially if patients were considered to benefit from treatment with TKIs. The main difference in this domain was the detailed information patients wanted to receive, whereas physicians wanted to give more general and short information. In the TKI treatment decision group, physicians wanted to give information about the benefit of therapy, whereas patients were more focused on palliative care.

Emotional Support, Empathy and Respect

Patients mentioned the importance of offering psychological care. In both decision groups, emotional support and the involvement of family was important, as well as reassurance by health care providers. In both groups, patients felt reassured by their physician, they also felt that there was sufficient psychological support. Only physicians in the TKI decision group mentioned reassurance by health care providers. The vast majority of involved physicians did not mention emotional support or psychological care, which was the main difference between patients and physicians in this domain. Although few physicians did not mention it often, they apparently succeeded in reassuring the patients.

Values

Values were an important part of health care decisions, “what matters to me”. For patients who started or considered TKIs, the values mentioned most often involved

functioning in daily life, for example, maintaining QOL and family milestones. In the surgery decision group, values regarding medical outcomes involved recovery and physical changes after treatment. In addition, the value “I need surgery, there is something in my body that does not belong there” was often mentioned. Physicians in the TKI decision group believed that values about daily life were important. Physicians in the surgery decision group mentioned medical values most often. The main difference was that patients wanted to discuss values more.

Discussion

This qualitative study investigated the perspectives of patients with low-risk (>1 cm) DTC and advanced tumors, regarding the extent of surgery or starting TKIs. We studied the differences between physician and patient perspectives, as well as the differences and similarities between the aspects involved in these two decisions. The main themes emerging from both patient and physician interviews were the involvement of a multidisciplinary team and a way of being informed, general information on DTC and treatment options, reassurance by health care providers, medical values, and values regarding functioning in daily life. The main differences in perspective between patients and physicians were that only patients mentioned the importance of a good doctor–patient relationship, patients desired detailed information about their diagnosis, patients focused on palliative treatment whereas physicians focused on the benefit of therapy, and only patients mentioned the need for psychological care and emotional support. These differences provide valuable information on the perspective of patients with DTC and physicians that can be used when designing decision aid instruments. These differences are elaborated below.

Regarding the doctor–patient relationship, patients in both treatment decision groups appreciated a good doctor–patient relationship, whereas physicians did not mention this often. Pitt et al. also showed that patients with low-risk DTC (>1 cm) wished for a strong patient–surgeon relationship, in line with the findings in patients with other malignancies [24]. This was particularly important for patients with DTC, who remained in follow-up and required medical guidance and support for many years, even after remission.

Regarding the desire to receive detailed information, patients from both decision groups wanted to receive more detailed information about DTC, treatment options, and aftercare, whereas physicians from both decisions groups preferred providing more general and short information. We hypothesize that this difference arises from

the fact that physicians are limited with respect to the available consultation time and have concerns about how much of the information is remembered. However, ensuring that the information is individualized and patients are involved in the treatment process was a strong preference of our participants. This preference is corroborated by studies focusing on needs in DTC survivors after primary treatment. Such studies show that survivors usually receive information related to their diagnosis, prognosis, and primary treatment; however, information on long-term effects, recurrence, and aftercare is scarce [25–28,30]. Likewise, a systematic review of Hyun et al. showed that cancer survivors in general perceive many unmet needs, and these needs extend to aftercare [29]. Previous studies among other cancer types also showed the importance of providing patients with disease specific information about cure, spread of disease, and side effects. There are some possible explanations for this need for information: (1) it can increase trust in the caring physician and reduce possible feelings of uncertainty and doubt, and (2) it might be used as a coping strategy to gain control and to understand what is happening to body and mind [36–39].

Regarding the difference in the TKI decision group, physicians focused more on the effect and benefit of TKIs, whereas patients were focused more on palliative care. Physicians may focus more on the effects and benefits of TKIs because they prescribe TKIs when they believe there is a positive effect and benefit of therapy. We hypothesize that the physicians' knowledge of the progression free survival (PFS) benefit shown in patients treated with TKIs in the randomized controlled trials plays an important role in this result. This could particularly be the case when patients may not be sufficiently aware of these results [40,41]. Another explanation for the differences in focus is that patients' awareness of having an incurable disease might generate more thoughts regarding their quality of life and the availability of palliative care. No other studies focused specifically on the needs and preferences in patients with advanced metastatic DTC. Because DTC is generally a slowly progressive cancer type, patients with metastatic disease often have long-time survival while maintaining a good QOL. Therefore, a comparison with other patients with disseminated malignant tumors could not be used to corroborate our findings, which highlights the relevance of the present DTC-specific findings.

Our results indicate the importance of talking with patients about their values: values regarding treatment and decision, and values about daily life were mentioned by both patients and physicians. Identifying such values is relevant because, in practice, values are voiced or discussed in a minority of consultations [11], and to talk about values is the most difficult part of doctor–patient communication. Other studies have showed the importance of talking about values, e.g., the systematic

review of Hyun et al. found that psychosocial information and supportive care needs may be insufficiently met in DTC survivors [29]. The emotional reaction “I need surgery, there is something in my body that does not belong there” was also found by Pitt et al. [39]. In other cancers, the importance of the involvement of family and friends was also found [36–38].

Strengths and Limitations

A strength of our study is that, on the one hand, it contrasts differences and similarities between two treatment decision-making groups (regarding low-risk and high-risk patients), and on the other hand, it contrasts differences between the perspectives of physicians and patients for both decisions. Our study has some limitations. Because of logistic difficulties, only one focus group interview per treatment decision could be organized. Therefore, our results may not give an understanding of all of the issues involved [42]. Furthermore, physicians and patients with DTC in other cultural or geographical settings may have needs that we did not identify, which could impact generalizability. In general, the results of a qualitative study cannot be generalized, although the results can be of major importance for the specialists in the field. This underscores the need for similar cross-cultural validation studies in other countries.

Conclusions

In conclusion, this study illustrates the needs, preferences, and values in patients with DTC in two different treatment decision groups in both low-risk and high-risk patients. While many of these are recognized and are overlapping with those of the physicians treating patients with DTC, some are clearly different and potentially not sufficiently addressed in daily practice. Communication may be improved by (1) meeting patients’ needs with respect to stage-specific information provision about the disease and its consequences, (2) raising awareness among the physicians to inquire about and address patients’ needs with respect to emotional and psychological support, and (3) addressing patients’ concerns about palliative care. This may help physicians to improve their communication and better meet patient needs. The results of this study can also be used to develop decision support tools to make current doctor–patient communication more SDM-based.

Acknowledgments: We thank all of the interviewees and the Dutch patient association SON for their input and cooperation with the development of the information needs, preferences, and values of patients with DTC, as well as the participating hospitals in the COMBO study for their input. We also thank Anita Oude Bos for help with identifying codes.

References

1. Cabanillas, M.E.; McFadden, D.G.; Durante, C. Thyroid cancer. *Lancet* 2016, 388, 2783–2795.
2. Durante, C.; Montesano, T.; Torlontano, M.; Attard, M.; Monzani, F.; Tumino, D.; Costante, G.; Meringolo, D.; Bruno, R.; Trulli, F.; et al. Papillary Thyroid Cancer: Time Course of Recurrences during Postsurgery Surveillance. *J. Clin. Endocrinol. Metab.* 2013, 98, 636–642.
3. Murthy, S.P.; Balasubramanian, D.; Anand, A.; Limbachiya, S.V.; Subramaniam, N.; Nair, V.; Thankappan, K.; Iyer, S. Extent of Thyroidectomy in Differentiated Thyroid Cancers—Review of Evidence. *Indian J. Surg. Oncol.* 2018, 9, 90–96.
4. Kim, S.H.; Roh, J.-L.; Gong, G.; Cho, K.-J.; Choi, S.-H.; Nam, S.Y.; Kim, S.Y. Differences in the Recurrence and Survival of Patients with Symptomatic and Asymptomatic Papillary Thyroid Carcinoma: An Observational Study of 11,265 Person-Years of Follow-Up. *Thyroid* 2016, 26, 1472–1479.
5. Ibrahim, E.Y.; Busaidy, N.L. Treatment and surveillance of advanced, metastatic iodine-resistant differentiated thyroid cancer. *Curr. Opin. Oncol.* 2017, 29, 151–158.
6. Jayarangaiah, A.; Sidhu, G.; Brown, J.; Barret-Campbell, O.; Bahtiyar, G.; Youssef, I.; Arora, S.; Skwiersky, S.; McFarlane, S.I. Therapeutic options for advanced thyroid cancer. *Int. J. Clin. Endocrinol. Metab.* 2019, 5, 26–34.
7. Oostendorp, L.J.; Ottevanger, P.B.; van der Graaf, W.T.; Peters, M.E.; Hermens, R.P.; Stalmeier, P.F. Exploring the Routine Administration of Decision Aids for Palliative Chemotherapy to Patients by Nurses: A Qualitative Study Among Nurses and Oncologists. *Cancer Nurs.* 2015, 38, 270–278.
8. Tuttle, R.M. Controversial Issues in Thyroid Cancer Management. *J. Nucl. Med.* 2018, 59, 1187–1194.
9. Haugen, B.R.; Alexander, E.K.; Bible, K.C.; Doherty, G.M.; Mandel, S.J.; Nikiforov, Y.E.; Pacini, F.; Randolph, G.W.; Sawka, A.M.; Schlumberger, M.; 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, 1–133.
10. Fugazzola, L.; Elisei, R.; Fuhrer, D.; Jarzab, B.; Leboulleux, S.; Newbold, K.; Smit, J. 2019 European Thyroid Association Guidelines for the Treatment and Follow-Up of Advanced Radioiodine-Refractory Thyroid Cancer. *Eur. Thyroid J.* 2019, 8, 227–245.
11. Kunneman, M.; Marijnen, C.A.; Baas-Thijssen, M.C.; van der Linden, Y.M.; Rozema, T.; Muller, K.; Geijssen, E.D.; Stiggelbout, A.M.; Pieterse, A.H. Considering patient values and treatment preferences enhances patient involvement in rectal cancer treatment decision making. *Radiother. Oncol.* 2015, 117, 338–342.
12. Abhyankar, P.; Bekker, H.L.; Summers, B.A.; Velikova, G. Why values elicitation techniques enable people to make informed decisions about cancer trial participation. *Health Expect.* 2010, 14, 20–32.
13. Llewellyn-Thomas, H.A.; Crump, R.T. Decision support for patients: Values clarification and preference elicitation. *Med. Care Res. Rev.* 2013, 70, 50–79.
14. Pieterse, A.H.; de Vries, M.; Kunneman, M.; Stiggelbout, A.M.; Feldman-Stewart, D. Theory-Informed design of values clarification methods: A cognitive psychological perspective on patient health-related decision making. *Soc. Sci. Med.* 2013, 77, 156–163.
15. Stiggelbout, A.M.; Pieterse, A.H.; de Haes, J.C. Shared decision making: Concepts, evidence, and practice. *Patient Educ. Couns.* 2015, 98, 1172–1179.
16. Stalmeier, P.F.; van Tol-Geerdink, J.J.; van Lin, E.N.T.; Schimmel, E.; Huizenga, H.; van Daal, W.A.; Leer, J.W. Doctors' and patients' preferences for participation and treatment in curative prostate cancer radiotherapy. *J. Clin. Oncol.* 2007, 25, 3096–3100.

17. Stacey, D.; Légaré, F.; Col, N.F.; Bennett, C.L.; Barry, M.J.; Eden, K.B.; Holmes-Rovner, M.; Llewellyn-Thomas, H.; Lyddiatt, A.; Thomson, R.; et al. Decision aids for people facing health treatment or screening decisions. *Cochrane Database Syst. Rev.* 2017, 4.
18. Fagerlin, A.; Pignone, M.; Abhyankar, P.; Col, N.; Feldman-Stewart, D.; Gavaruzzi, T.; Kryworuchko, J.; Levin, C.A.; Pieterse, A.H.; Reyna, V.; et al. Clarifying values: An updated review. *BMC Med. Inform. Decis. Mak.* 2013, 13, S8.
19. D'Agostino, T.A.; Shuk, E.; Maloney, E.K.; Zeuren, R.; Tuttle, R.M.; Bylund, C.L. Treatment decision making in early-stage papillary thyroid cancer. *Psycho-Oncology* 2018, 27, 61–68.
20. Jensen, C.B.; Saucke, M.C.; Francis, D.O.; Voils, C.I.; Pitt, S.C. From Overdiagnosis to Overtreatment of Low-Risk Thyroid Cancer: A Thematic Analysis of Attitudes and Beliefs of Endocrinologists, Surgeons, and Patients. *Thyroid* 2020, 30, 696–703.
21. Doubleday, A.R.; Saucke, M.C.; Bates, M.F.; Pitt, S.C. Patient-surgeon decision-making about treatment for very low-risk thyroid cancer. *Trends Cancer Res.* 2019, 14, 79–89.
22. Nickel, B.; Brito, J.P.; Barratt, A.; Jordan, S.; Moynihan, R.; McCaffery, K. Clinicians' Views on Management and Terminology for Papillary Thyroid Microcarcinoma: A Qualitative Study. *Thyroid* 2017, 27, 661–671.
23. Nickel, B.; Brito, J.P.; Moynihan, R.; Barratt, A.; Jordan, S.; McCaffery, K. Patients' experiences of diagnosis and management of papillary thyroid microcarcinoma: A qualitative study. *BMC Cancer* 2018, 18, 242.
24. Pitt, S.C.; Wendt, E.; Saucke, M.C.; Voils, C.I.; Orne, J.; Macdonald, C.L.; Connor, N.P.; Sippel, R.S. A Qualitative Analysis of the Preoperative Needs of Patients with Papillary Thyroid Cancer. *J. Surg. Res.* 2019, 244, 324–331.
25. Morley, S.; Goldfarb, M. Support Needs and Survivorship Concerns of Thyroid Cancer Patients. *Thyroid* 2015, 25, 649–656.
26. Goldfarb, M.; Casillas, J. Unmet information and support needs in newly diagnosed thyroid cancer: Comparison of adolescents/young adults (AYA) and older patients. *J. Cancer Surviv.* 2014, 8, 394–401.
27. Husson, O.; Mols, F.; Oranje, W.A.; Haak, H.R.; Nieuwlaat, W.A.; Netea-Maier, R.T.; Smit, J.W.A.; Van De Poll-Franse, L.V.; Poll-Franse, L.V. Unmet information needs and impact of cancer in (long-term) thyroid cancer survivors: Results of the PROFILES registry. *Psycho-Oncology* 2014, 23, 946–952.
28. Sawka, A.M.; Brierley, J.D.; Tsang, R.W.; Rotstein, L.; Ezzat, S.; Goldstein, D.P. Unmet Information Needs of Low-Risk Thyroid Cancer Survivors. *Thyroid* 2016, 26, 474–475.
29. Hyun, Y.G.; Alhashemi, A.; Fazelzad, R.; Goldberg, A.S.; Goldstein, D.P.; Sawka, A.M. A Systematic Review of Unmet Information and Psychosocial Support Needs of Adults Diagnosed with Thyroid Cancer. *Thyroid* 2016, 26, 1239–1250.
30. Roberts, K.J.; Lepore, S.J.; Urken, M.L. Quality of Life After Thyroid Cancer: An Assessment of Patient Needs and Preferences for Information and Support. *J. Cancer Educ.* 2008, 23, 186–191.
31. Tong, A.; Sainsbury, P.; Craig, J. Consolidated criteria for reporting qualitative research (COREQ): A 32-item checklist for interviews and focus groups. *Int. J. Qual. Health Care* 2007, 19, 349–357.
32. Atlas.ti. ATLAS.ti.com. Scientific Software Development GmbH. Qualitative Data Analysis. Version 8.4.15 ed.; Atlas.ti: Berlin, Germany, 2018.
33. Picker Institute. Principles of Patient-Centered Care. Available online: https://www.picker.org/about-us/picker-principles-of-person-centred-care/Oxford,_2019 (accessed on 22 February 2021).
34. Decuir-Gunby, J.T.; Marshall, P.L.; McCulloch, A.W. Developing and Using a Codebook for the Analysis of Interview Data: An Example from a Professional Development Research Project. *Field Methods* 2010, 23, 136–155.

35. Van Overveld, L.F.; Takes, R.P.; Turan, A.S.; Braspenning, J.C.; Smeele, L.E.; Merkkx, M.A.; Hermens, R.P.; Dutch Head and Neck Audit Group. Needs and preferences of patients with head and neck cancer in integrated care. *Clin. Otolaryngol.* 2018, 43, 553–561.
36. Wallberg, B.; Michelson, H.; Nystedt, M.; Bolund, C.; Degner, L.F.; Wilking, N. Information needs and preferences for participation in treatment decisions among Swedish breast cancer patients. *Acta. Oncol.* 2000, 39, 467–476.
37. Beaver, K.; Booth, K. Information needs and decision-making preferences: Comparing findings for gynaecological, breast and colorectal cancer. *Eur. J. Oncol. Nurs.* 2007, 11, 409–416.
38. Feldman-Stewart, D.; Tong, C.; Brundage, M.; Bender, J.; Robinson, J. Prostate cancer patients' experience and preferences for acquiring information early in their care. *Can. Urol. Assoc. J.* 2018, 12, 219–225.
39. Pitt, S.C.; Saucke, M.M.C.; Wendt, M.E.M.; Schneider, D.F.; Orne, J.; Macdonald, C.L.; Connor, N.P.; Sippel, R.S. Patients' Reaction to Diagnosis with Thyroid Cancer or an Indeterminate Thyroid Nodule. *Thyroid* 2021, 31, 580–588.
40. Schlumberger, M.; Tahara, M.; Wirth, L.J.; Robinson, B.; Brose, M.S.; Elisei, R.; Habra, M.A.; Newbold, K.; Shah, M.H.; Hoff, A.O.; et al. Lenvatinib versus placebo in radioiodine-refractory thyroid cancer. *N. Eng. J. Med.* 2015, 372, 621–630.
41. Brose, M.S.; Nutting, C.M.; Jarzab, B.; Elisei, R.; Siena, S.; Bastholt, L.; de la Fouchardiere, C.; Pacini, F.; Paschke, R.; Shong, Y.K.; et al. Sorafenib in radioactive iodine-refractory, locally advanced or metastatic differentiated thyroid cancer: A randomized, double-blind, phase 3 trial. *Lancet* 2014, 384, 319–328.
42. Hennink, M.M.; Kaiser, B.N.; Weber, M.B. What Influences Saturation? Estimating Sample Sizes in Focus Group Research. *Qual. Health Res.* 2019, 29, 1483–1496.



Chapter 4

Patient decision aids for patients with differentiated thyroid carcinoma: development process and alpha and beta testing

Anna Koot^{1,2}, Rosella Hermens³, Petronella Ottevanger⁴, Romana Netea-Maier², Peep Stalmeier¹, COMBO study group

¹Radboud Institute for Health Sciences, Department for Health Evidence, Radboud University Medical Center, Nijmegen, the Netherlands.

²Department of Internal Medicine, Division of Endocrinology, Radboud University Medical Center, Nijmegen, the Netherlands.

³Radboud Institute for Health Sciences, Scientific Institute for Quality of Healthcare (IQ Healthcare), Radboud University Medical Center, Nijmegen, the Netherlands.

⁴Department of Internal Medicine, Division of Oncology, Radboud University Medical Center, Nijmegen, the Netherlands.

Collaborators COMBO study group:

Marieke Snel, Noortje van der Kleij-Corssmit, Johannes Bonenkamp, Koen Dreijerink, Evelien van Dam, Gard Nieuwenhuijzen, Mariel Keemers, Lieke Welling, Iris van der Ploeg, Sanne Engelen, Danielle Dercks, Frans Geenen.

Abstract

Background: Patient decision aids (PtDAs) are structured clinical tools that facilitate shared decision-making. Two important treatment decisions for patients with differentiated thyroid cancer (DTC), which could benefit from PtDAs, are as follows (1): the extent of surgery decision in patients with low-risk DTC and (2) the decision to start or delay starting the treatment with tyrosine kinase inhibitors (TKIs) in patients with advanced tumors.

Material and methods: PtDAs for these two decisions were developed using the International Patient Decision Aids Standards (IPDAS) quality criteria in an iterative process of prototype development via alpha and beta testing by patients and physicians. The information content of the PtDAs was based on the available literature, current guidelines, and patient's needs, preferences, and values.

Results: The web-based PtDAs underwent two rounds of alpha testing, revisions, and beta testing. The PtDAs have the same structure, consisting of six steps: a general introduction, information about the treatment options, comparing the treatment options, knowledge questions, a values clarification exercise, and saving the information. The alpha testing (n = 8 patients, n = 10 physicians) showed that the PtDAs were highly acceptable and usable for decision-making. Results of the beta testing in 20 patients showed that two patients did not use the PtDA; the other 18 patients found that the PtDAs were readable (n = 17) and helpful (n = 14) for decision-making. All patients recommend using the PtDAs.

Conclusions: Evidence-based PtDAs were created for patients with DTC for two different treatment decisions. Our final version was judged to be clear, balanced, and helpful in decision-making.

Keywords: thyroid cancer, shared decision making, surgery, tyrosine kinase inhibitor, decision aid.

Introduction

Differentiated thyroid cancer (DTC) is rapidly increasing in incidence throughout the world, mostly as a result of the increased use of diagnostic imaging and surveillance (1–3). Primary treatment for most patients with DTC consists of surgical removal of the thyroid (total thyroidectomy), followed by treatment with radioactive iodide (I131, RAI) to ablate the remaining thyroid remnants or destroy (microscopic) DTC remnants. This is followed by life-long thyroid hormone therapy (4, 5). In patients with low-risk tumors smaller than 1 cm, the removal of only the affected lobe (lobectomy) is currently the standard of care. These patients do not require RAI treatment, and most of them maintain normal thyroid function. Several studies, including a recent meta-analysis (6), suggest that this more conservative approach results in similar long-term outcomes and therefore could be applied also in selected patients with low-risk tumors larger than 1 cm. However, because there are no prospective randomized controlled clinical trials (RCTs), comparing different surgical approaches for patients with low-risk DTC larger than 1 cm, management recommendations are currently based on retrospective data (7). After primary treatment, the majority of patients with DTC have an excellent long-term prognosis (1, 8–11).

Nonetheless, after primary treatment, up to 30% of the DTC patients develop recurrent disease and/or distant metastases. These patients have a less favorable prognosis amounting to an average life expectancy of 3–5 years for those with tumors that are nonresponsive to RAI (12, 13). For patients with metastatic disease, both local and systemic treatments are available, but overall complete remission is only seen in one-third of cases (14) and, while these treatments can improve DTC-related symptoms and disease-free survival, there is no evidence that these treatments result in a clear improvement of the overall survival (OS).

Therefore, for both patients with low-risk DTC and with RAI-refractory advanced DTC, there is a discussion about the optimal treatment strategy that better balances the risks and benefits for the individual patients and their personal preferences. As such, some patients with low-risk DTC might currently undergo overtreatment, which could negatively affect their quality of life (QOL) (6).

The current guidelines of the American Thyroid Association (ATA) state that less aggressive therapy, for example, a thyroid lobectomy and a tailored follow-up, can be equally acceptable and explicitly mention room for patients' preferences (15). Similarly, for asymptomatic or mildly symptomatic RAI-refractory DTC patients,

an important unanswered question regards the optimal timing of starting tyrosine kinase inhibitors (TKIs). For those who are asymptomatic or only mildly symptomatic, starting the treatment too early may expose them to side effects and worsen their QOL without evidence of a survival benefit (16). The recent European Thyroid Association (ETA) guidelines state that the decision to start TKIs should include patient-related medical factors and patients' preferences with respect to treatment goals and patient values, and acceptance of adverse effects (17).

Given the different benefits and harms of surgery and TKI treatment, the care for patients with DTC should be better personalized. Patients could be informed using plain-language, evidence-based information about these decisions. Patient decision aids (PtDAs) are suitable instruments to support decision-making. Studies have shown that PtDAs generally improve patient knowledge, result in more realistic patient treatment expectations, increase active patient participation in decision-making, and reduce indecisiveness (4, 18). Currently, no PtDAs for DTC patients for the above-mentioned treatment decisions are available. This study presents the development process and alpha and beta testing of different PtDAs in order to provide decision support for two treatment decisions in patients with DTC (1): the extent of surgery in patients with low-risk DTC larger than 1 cm, and (2) the decision to wait or start with TKIs in patients with asymptomatic or mildly symptomatic advanced, RAI-refractory DTC.

Materials and methods

Development process

The development of the PtDAs was part of the Communication Booster (COMBO) study (NCT03905369), which aimed to develop, evaluate, and implement decision-support tools for DTC patients. Thirteen hospitals (six academic and seven non-academic) in the Netherlands participated, as well as the Dutch patient association "Schilddukler Organisatie Nederland (SON)." In the study, we randomized patients into an intervention or control group. Patients in both groups received general information about DTC from their physicians. In addition, the intervention group received also the PtDA. The Medical Ethical Committee (CMO) of the region Arnhem–Nijmegen approved the study protocol (MEC-2018-4521).

The International Patient Decision Aids Standards (IPDAS) were used to guide the development of the PtDAs and were based on behavioral and decision-making theories underlying the Ottawa Decision Support Framework (19–21). To guide

the development process, recommendations by Coulter et al. (21) and the Dutch Guideline were consulted (22). The development process is shown in Figure 1 and was performed by a project group consisting of a PhD student who is also a medical doctor (AK), a decision-making scientist (PS), an endocrinologist (RN-M), an implementation scientist (RH), and an oncologist (PO), assisted by a patient and physician expert panel. None of these patients or physicians had any conflicts of interest.

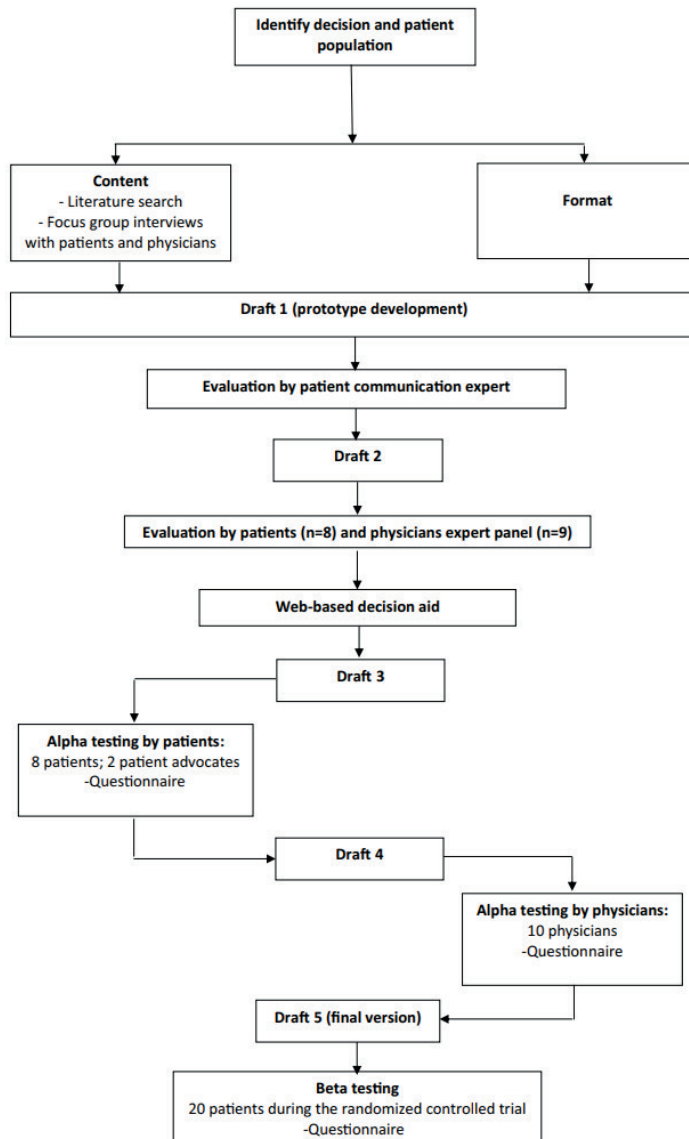
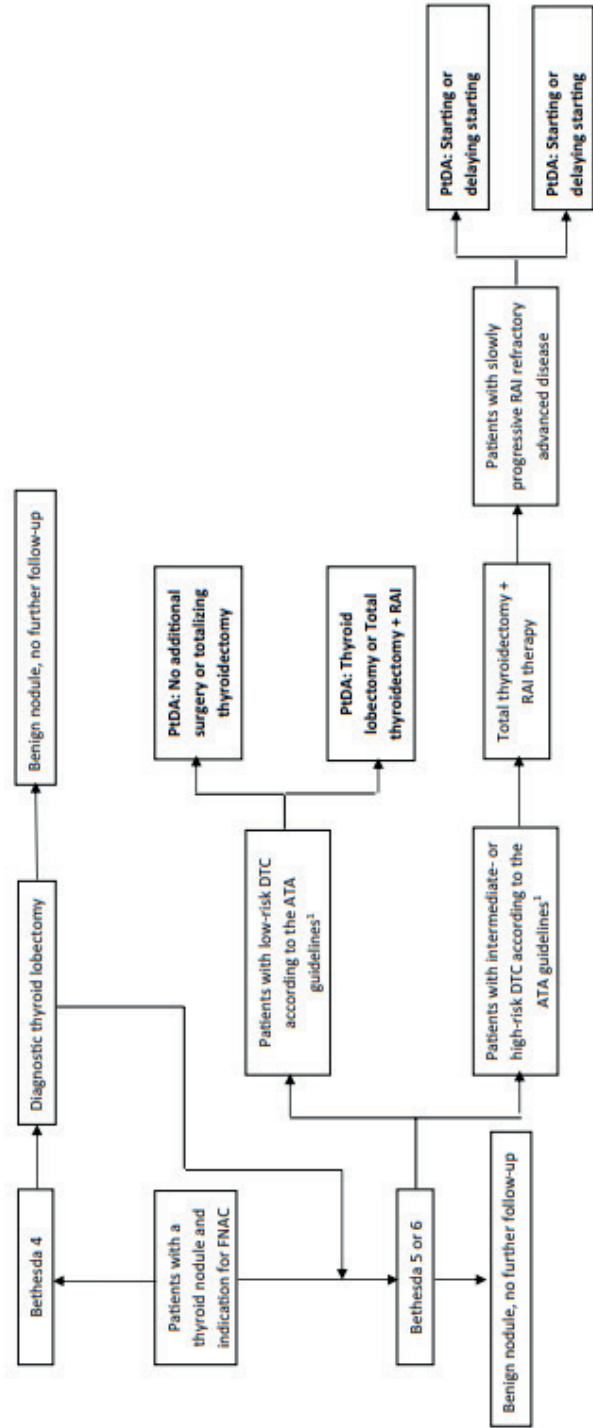


Figure 1. Development process of the patient's decision aids.

Figure 2. Overview of the different decision aids in the Netherlands.



FNAC: Fine Needle Aspiration Cytology, DTC: Differentiated Thyroid Cancer, RAI: radioactive iodine
ATA: American Thyroid Association, Low-risk: intrathyroidal DTC, no evidence of extrathyroidal extension, vascular invasion or metastases, Intermediate-risk: microscopic extrathyroidal extension, cervical lymph node metastases, RAI-avid disease in the neck outside the thyroid bed, vascular invasion, or aggressive tumor histology. High-risk: gross extrathyroidal extension, incomplete tumor resection, distant metastases, or inappropriate post-operative serum Thyroglobulin values, PTDA: Patient Decision Aid.

Scope and purpose of PtDAs

The scope and purpose of the PtDAs were defined by the project group. Meetings were held with the project group to reach a consensus on the scope, purpose, and target audience. The main scope was to improve informed choice regarding two different treatment decisions in patients with DTC. Therefore, the project group agreed to develop a PtDA for each treatment decision (Figure 2). The target audience for the first PtDA was defined as patients with low-risk DTC (> 1 cm) according to the ATA criteria (15), considering the extent of thyroid surgery. For the second PtDA, the target group consisted of patients with advanced RAI-refractory asymptomatic or mildly symptomatic DTC considering whether to wait or start with TKI treatment.

Content and format

The first part of the COMBO study consisted of a literature review for clinical parameters, resulting in a meta-analysis of the extent of surgery decision (6), followed by focus groups with patients with DTC and physicians (endocrinologists, surgeons, oncologists, nuclear medicine physicians) treating patients with DTC to explore patients' needs, preferences, and values regarding the two treatment decisions, which resulted in a focus group paper (23). Based on the identified needs, guidelines, literature review, and the expertise in the project group, domains were determined that were important for decision-making in this setting: (1) risks and (2) benefits of both treatment decisions; (3) oncological outcomes in both treatment decisions; and (4) patients' personal values in decision-making. For the first three domains, we collected available literature (6, 24–26); for the fourth domain, values mentioned by patients and physicians were extracted from the focus group interviews (23). The development was an iterative process (Figure 1), with the content and format informed by the IPDAS guidelines. An online, web-based format was chosen by the project group to provide a PtDA that is tailored to a treatment decision. This resulted in the prototype draft.

Methods of alpha & beta testing and revision

The first drafts of the two PtDAs ("thyroid lobectomy or total thyroidectomy" and "to wait or start with TKIs") were finished after an iterative process of revising and reviewing the prototype content with the project group. In order to ensure the PtDAs were accessible to a broad audience, these drafts were evaluated on readability by communication experts experienced in increasing readability ("Stichting Makkelijk Lezen") (27). The reading level aimed to enable 95% of the Dutch population to understand the text, level A2-B1, according to the Common European Framework of for Languages (28). This resulted in the second draft (29) (Figure 1).

The second draft was sent by email to two different panels, consisting of eight patients and nine physicians (Figure 1). The eight patients made a decision regarding DTC in the past (four with low-risk DTC and four with advanced disease). The nine physicians consisted of two endocrinologists, two surgeons, and five oncologists treating patients with DTC. Patients and physicians were asked to evaluate this draft of the PtDA on clear language, content, layout, and comprehensibility. They were recruited from participating Dutch academic hospitals. Feedback on the PtDAs was also given by two patient advocates recruited from the patient association SON (Figure 1). This resulted in a third draft with a web-based format.

This third web-based draft was developed and alpha-tested by patients who made a decision regarding DTC in the past (Figure 1). The patients were recruited by endocrinologists from the participating Dutch academic hospitals, who asked one or two of their patients to participate in a face-to-face interview about the PtDA. After verbal consent, patients were approached by the investigator (AK) by telephone. Eight patients (four with low-risk DTC and four with advanced disease) were willing to participate (Table 1). All interviews were conducted by AK, and further interviews were determined by data saturation. The first part of the interview was unstructured using a think-aloud method (30). The second part was semi-structured, and participants were asked to fill out a questionnaire on content, structure, length, readability, balance, comprehensibility, relevance, reliability, completeness, and usability (Figure 1; Table 2). This resulted in the fourth draft.

As suggested by Coulter (21), physicians were invited to participate in alpha testing as well. Therefore, the fourth draft was sent to an expert panel of 10 physicians (two endocrinologists, six surgeons, and two oncologists) from academic and nonacademic Dutch hospitals, all specializing in treating patients with DTC. None of them were involved in the initial development of the PtDA. They were asked to assess the PtDA for usability, acceptability of the content and format, practicality of use in the clinical pathways, and their perceived efficacy. They were further asked whether they would be willing to hand out this PtDA to their patients and at what moment in time. Their suggestions were incorporated to create the final fifth version (Figure 1), which was deemed acceptable for clinical use. The number of interviews was, again, determined by data saturation (Figure 1; Table 1). In addition to the quantitative evaluation, the quality of the fourth draft was tested against the IPDAS criteria.

Table 1. Demographic characteristics of patients and physicians who participated in the alpha testing.

	Patients (<i>n</i> = 8)	Physicians (<i>n</i> = 10)
Mean age in years (range)	42 (35–72)	45 (36–62)
Sex (<i>N</i> , %female)	6	8
Caucasian (<i>N</i> , %)	8	10
Level of education		
High school or less	2	
Vocational education	4	
University	2	
Type of treatment		
Surgery		
Thyroid lobectomy	2	
Total thyroidectomy	2	
Systemic therapy		
Lenvatinib	1	
Sorafenib	3	
Type of professional (<i>N</i> , %)		
Endocrinologist		2
Surgeon		6
Oncologist		2
Type of hospital (<i>N</i> , %)		
Academic		4
Non-academic		6
Years of experience as professional (<i>N</i> , %)		
0–5 years		3
5–10 years		2
10–15 years		0
15–20 years		3
>20 years		2

Table 2. Alpha testing among DTC patients and physicians treating

	Draft 3: Low-risk DTC patients (n = 4)	Draft 3: Advanced disease patients (n = 4)	Draft 4: Physician's low-risk DTC (n = 8)	Draft 4: Physician's advanced disease (n = 2)
Length				
Too long	0	0	0	0
Too short	0	0	0	0
Just right	4	4	8	2
Amount of information				
Too much	0	0	0	0
Too little	2	0	0	0
Just right	2	4	8	2
Information balanced?				
Yes	3	4	8	2
Biased towards thyroid lobectomy	1		0	
Biased towards total thyroidectomy	0		0	
Biased towards systemic therapy		0		0
Biased towards watchful waiting		0		0
DA is comprehensible in general?				
Good	4	4	5	2
Moderate	0	0	3	0
Bad	0	0	0	0
Risks comprehensible?				
Good	4	4	5	1
Moderate	0	0	3	1
Bad	0	0	0	0
Readability				
Good	4	3	8	2
Moderate	0	1	0	0
Bad	0	0	0	0
DA reliable?				
Yes	3	4	8	2
No	0	0	0	0
Missing	1	0	0	0
Confusing items?				
Yes	0	0	2	0
No	4	4	6	2
Missing items?				
Yes	0	0	0	0
No	4	4	8	2

Table 2. Continued

	Draft 3: Low-risk DTC patients (n = 4)	Draft 3: Advanced disease patients (n = 4)	Draft 4: Physician's low-risk DTC (n = 8)	Draft 4: Physician's advanced disease (n = 2)
Navigation through DA?				
Good	4	2	8	2
Moderate	0	2	0	0
Bad	0	0	0	0
Values clarification exercise helpful?				
Yes	4	4	8	2
No	0	0	0	0
DA helpful in decision making?				
Yes	4	4	8	2
No	0	0	0	0
Recommend use of DA?				
Yes	4	4	8	2
No				

Beta testing

The beta testing, or “real-world testing,” was organized during the ongoing randomized controlled COMBO trial (RCT, NCT03905369). The first 20 participants (Figure 1; Table 3) in the intervention group who received the PtDA and who were not involved in the design phase were asked to evaluate the feasibility of the PtDA with a questionnaire containing questions on usefulness, length, amount of information, comprehensibility, and reliability (Table 4). The quality of the PtDAs was tested using the IPDAS criteria.

Table 3. Demographic characteristics of patients who participated in the beta testing

	Patients (n = 20)
Mean age in years (range)	52.5 (25–73)
Sex (N, %female)	14
Level of education	
High school or less	4
Vocational education	12
University	3
Unknown	1
Type of treatment	
Surgery	15
Systemic therapy	5

Table 4. Beta testing during the RCT among DTC patients.

	Patients (n=20)
DA used before the conversation with your physician	
Yes	18
No	2
Partly	0
Why not or partly used?	
Too difficult	0
Too much information	0
No time to read the DA	1
No need for a DA	1
	Patients (n=18)
How much time (minutes) did you spend on the DA?	45
Values clarification exercise helpful?	
Yes	15
No	3
Better knowledge after reading the DA?	
Yes	15
No	3
Timing	
Too early	0
Too late	6
Just right	12
Length	
Too long	1
Too short	1
Just right	16
Amount of information	
Too much	0
Too little	2
Just right	16
Information balanced?	
Yes	16
No	2
DA is comprehensible in general?	
Good	16
Moderate	2
Bad	0
Readability	
Too easy	1

Table 4. Continued

	Patients (n=20)
Too difficult	0
Just right	17
DA reliable	
Yes	18
No	0
Information in a logical order?	
Yes	17
No	1
Grade (0-10)	
0	0
1	0
2	0
3	0
4	0
5	0
6	2
7	6
8	5
9	4
10	1
Recommend use of DA?	
Yes	18
No	0

Results

Development process

Content and format Both PtDAs were divided into a general introduction and six steps: general information about DTC; treatment options; comparison of the treatment options; important items; values clarification exercise; and saving the information. The general introduction indicated for whom the PtDA was applicable and contained an explanation of how to use the PtDA. The first step gave general information about DTC. In step 2, the treatment options with the main risks, benefits, and oncological outcomes are presented. In step 3, patients could compare the treatment options. In step 4, patients were asked to answer factual knowledge questions to check for comprehension. Step 5 contained a values clarification exercise with five statements. These were based on patients' values extracted from

the focus group interviews (Figure 3) (23). Patients could indicate the importance of each statement on a four-point Likert importance scale ranging from not important to very important. The next page contained two empty boxes. Box 1 asked patients to tell what matters in their lives in general, and box 2 asked for their concerns regarding treatment. They were also asked to indicate which option they preferred and the strength of this preference. In the last step, patients were stimulated to save their answers using email or printing options and to bring these answers along and discuss them with their physicians in the next consultation.

Patients and physicians' expert panel

The second draft of the extent of surgery PtDA was revised by four patients and three physicians. One patient and all three physicians suggested developing two separate PtDAs for "thyroid lobectomy or total thyroidectomy" and "no additional surgery or totalizing thyroidectomy" because of the different treatment options (Figure 2). Percentages of complications and a note on life-long adjustment difficulties of substitution with thyroid hormones were added.

The second draft of the TKI PtDA was revised by four patients and five physicians. One patient and all five physicians suggested developing two separate PtDAs, one for sorafenib and one for lenvatinib, the two TKIs that are currently approved for use and reimbursed in the Netherlands, because of different outcome percentages and adverse events (Figure 2). More detailed information about the effect of TKIs, adverse events, and information on the palliative character of TKIs were added, as were progression-free survival rates. Both patients and physicians indicated that the general information about DTC was not appropriate for patients with metastatic disease because these patients were already familiar with thyroid cancer, so this information was deleted. In the end, four separate PtDAs for the extent of the surgery decision and the TKI decision were developed (Figure 2). Based on this information, the third draft was developed in the form of web-based PtDAs.

Results of alpha & beta testing and revision

Alpha testing 1: patients

The third draft was alpha-tested by four patients treated with surgery and four with advanced disease. Their baseline characteristics are presented in Table 1. All patients were satisfied with the content, format, and layout. Length and the amount of information were assessed "just right" by all participants. The information was predominantly judged as balanced and comprehensible, and participants preferred 100-person diagrams for risk communication (31). All participants found the PtDAs

useful for decision-making if they had to choose between the treatment options. Participants also suggested some minor changes. To improve the relevance of the extent of surgery, they suggested including more general information about low-risk DTC. To increase the usability of the TKI PtDAs, it was suggested to clarify the navigation through the PtDAs. Lastly, to increase readability, one participant suggested changing the colors of the 100-person diagrams. Other results from the questionnaire are shown in Table 2.

Alpha testing 2: physicians

The fourth draft was evaluated by 10 physicians (two endocrinologists, six surgeons, and two oncologists) from academic and nonacademic hospitals, all of whom specialized in treating patients with DTC. Their baseline characteristics are presented in Table 1. Overall, they were satisfied with the content, format, and layout of the PtDAs. Length and the amount of information were assessed “just right” by all physicians.

For the extent of surgery PtDAs, physicians suggested adjusting the surgery time for thyroid lobectomy as compared to total thyroidectomy because the duration of surgery is not the same for both procedures. There was a discussion about the presented recurrence rates (RR). For the extent of surgery PtDA, physicians suggested reducing the RR for total thyroidectomy from 7% to 4%, based on the following literature regarding the addition of RAI: The mean percentage of RR after the addition of RAI is 4% (32–35). A recent review by Verburg et al. (26) showed that literature published in the last decade offers data that support adjuvant postoperative RAI in DTC patients. Recently, Leboulleux et al. (36) showed in an RCT that the RAI ablation did not result in a significant oncological benefit in patients with low-risk tumors smaller than 2 cm and therefore could possibly be omitted in these cases. The latter represents only a part of the patients targeted by this PtDA, and omitting the RAI ablation for low-risk patients who underwent total thyroidectomy is currently not routinely applied in the Netherlands. All the abovementioned suggestions were admitted in the PtDAs. For the TKI PtDAs, there were no specific suggestions.

Other results from the questionnaire are shown in Table 2. All physicians mentioned that they would recommend the use of the PtDAs. Figure 3 shows the values clarification exercise of the final version of the “thyroid lobectomy or total thyroidectomy” PtDA.

Step 5 ‘what is important to you?’:

You have the choice to remove either half or the entire thyroid gland. Together with your doctor, you may choose the option which suits you best. This depends on what is important to you. Below, you may indicate how important certain statements are to you.

Your doctor invites you to take your answers to the next consultation.

Statement	Not important		Very important	
1. If I have my entire thyroid removed, I have to take thyroid hormone tablets for life.	0	0	0	0
2. Medication adjustment of thyroid hormone can decrease my quality of life.	0	0	0	0
3. If I have half my thyroid removed, I may be able to go home on the same day.	0	0	0	0
4. If I have my entire thyroid removed, I am twice as likely to have (temporary) complications.	0	0	0	0
5. If I have my entire thyroid removed, I can get additional radioactive iodide therapy.	0	0	0	0
6. The chance that my tumor will come back is slightly smaller if the entire thyroid gland is removed followed by additional radioactive iodide therapy.	0	0	0	0

Your doctor or nurse can be more involved if they know what is important in your daily life, for instance your family, work or hobbies. You may enter this below.

Your doctor or nurse can be more involved if they know what concerns you most. You may enter this below.

My choice

You have thought about what is important to you. Which treatment do you prefer at the moment?

- ☐ Thyroid lobectomy
- ☐ Total thyroidectomy
- ☐ Don't know

How strong is the above preference?

- ☐ Not strong
- ☐ Rather strong
- ☐ Strong
- ☐ Very strong

Figure 3. Example of the values clarification exercise of the extent of surgery PtDA (translated from Dutch into English).

Beta testing

The final version was beta- tested during the RCT of the COMBO study. All participants in the intervention group were asked to fill out a questionnaire about the feasibility of the PtDA. A total of 20 participants were already included in this intervention group. Their baseline characteristics are presented in Table 3. Two participants did not use the PtDA. The other 18 participants were satisfied with the content, format, and layout of the PtDAs (Table 4). Length and the amount of information were assessed “just right” by 89% of participants; the median grade was 8 out of 10, and all participants recommended using the PtDA. Almost all suggested handing over the PtDA as early as possible after the diagnosis, ahead of the decision appointment at home, and also to include more details about their current daily life. They also suggested including the option of active surveillance.

IPDAS criteria

The IPDAS collaboration checklist was used to estimate the quality of the PtDAs (20). Of the 64 items on the checklist, 55 quality criteria were applicable to our PtDAs given the scope of the PtDAs. The final version of the PtDAs met 52 out of the 55 applicable IPDAS criteria (95%). Among the 23 criteria for “content,” 21 criteria were met. The two unmet criteria were on listing the option of doing nothing and viewing personalized probabilities based on their own situation. Among the 26 criteria in the “development process,” 25 were met. The one unmet criterion was the provision of alternative methods to understand the information, such as audio or video options. Lastly, after the beta test, the six criteria for “effectiveness” were all met.

Discussion

This article describes the systematic development and pilot testing of web-based PtDAs for patients with low-risk (> 1 cm) DTC regarding the extent of primary surgery and for patients with advanced disease regarding starting or delaying the start of TKI treatment. We performed alpha testing with patients and physicians and beta testing with patients. To make the PtDA accessible to every eligible patient, it was written in the A2-B1 language level according to the Common European Framework of for Languages (28). The PtDAs were considered clear, balanced, and helpful for decision-making. The amount of information, length, presentation, and clarity of information received positive feedback. None of the participants indicated that the content was confusing. The criteria for evidence-based PtDA development that have been established by the IPDAS were followed (20). Our PtDAs met 52 of 55 quality criteria for content, development process, and effectiveness as formulated

in the IPDAS checklist. Patients acting as reviewers who made a treatment decision in the past indicated they would have preferred to use the present PtDAs, if they had been available at the time of decision-making.

Most, but not all, of the IPDAS criteria were met. For example, listing the option of active surveillance was recommended in the IPDAS criteria. However, we did not include active surveillance in the PtDA for the extent of the surgery decision. At this moment, in national and international guidelines, active surveillance for low-risk DTC patients is not mentioned as a primary treatment option. In recent years, there has been emerging evidence on the safety of active surveillance as an option for the management of micro papillary thyroid carcinomas (mPTCs < 1 cm). More research is necessary before including this option in the PtDA for patients with low-risk tumors larger than 1 cm. When available, these data can be incorporated into a future version of the PtDA. Regarding the criteria to provide information on “viewing probabilities based on their own situation,” we assessed that based on the current knowledge, we could not provide additional information that might better individualize the prediction of the outcomes. For example, although we hypothesize that in general elderly patients have a higher risk of complications or adverse events, length of hospital stay, and mortality (37), we could not find whether and to what extent the risks are higher specifically in elderly DTC patients. A third criterion we did not meet was “the provision of alternative methods to understand the information, such as audio or video options.” Patient participants in our focus group interviews did not prefer audio and/or video options to understand information.

To the best of our knowledge, these are the first documented PtDAs aiming to support DTC patients in these two treatment decisions. Regarding PtDAs in low-risk DTC patients (1–4 cm), there is only one published PtDA focusing on RAI therapy in patients with low-risk papillary thyroid cancer (PTC) (4). This PtDA is limited to the decision to follow or omit RAI treatment after a total thyroidectomy. On the other hand, Brito et al. (38) and Pitt et al. (39, 40) recently developed a treatment choice tool (paper cards) for patients with DTC. These tools included the option of active surveillance, implying that these tools are also useful for informed patients with mPTC. Both tools need further testing before being implemented on a broad scale.

Our PtDAs were designed to facilitate conversations about treatment options for DTC patients in two different treatment decisions. In general, PtDAs have been shown to improve patient knowledge of the health care decision, decrease decisional conflict, and facilitate shared decision-making (18). Patients who use a PtDA are more often satisfied with the choice than those who receive standard

counseling (18). However, PtDAs promote conversations between physicians and patients and do not replace the need for a patient–physician consultation. Treatment options still need to be explained to patients to help individualize the trade between harms and benefits according to the patient’s specific situation and clinical situation. PtDAs facilitate a preference-based decision in which patient values and preferences are incorporated (41). By clarifying patients’ values, PtDAs encourage the treatment option that best fits the patient. Therefore, a values clarification exercise was added asking patients to select arguments for and against a treatment option. Feldman-Stewart et al. showed in an RCT in patients with early-stage prostate cancer that values clarification exercises led to better preparation for decision-making and to less regret at the > 1-year follow-up (42).

Strengths and limitations

A strength of our study is the structured development process of the PtDAs, which systematically uses the input of patients, physicians, and patient advocates. Involving patients in all stages of development yielded important insights. Furthermore, our statements in the values clarification exercise were based on patients’ values extracted from the focus group interviews (23). Another strength is that we developed four very specific PtDAs for each of the decision steps to support decision-making for the full decision trajectory of DTC patients.

A limitation in the development process of the PtDAs is the reliability of evidence regarding the information presented about the clinical outcomes of the different options. This limitation is inherent to the lack of prospective trials on head-to-head comparisons of the treatment options, which can provide the highest level of evidence. Nonetheless, shared-decision making is appropriate for situations where there is insufficient evidence that one option is superior to another, which is also the case for the decisions for which the PtDA has been developed in the present study. Moreover, the information provided in the PtDAs is based on the best available evidence. First, regarding the extent of surgery, only retrospective trials are available, showing no differences in oncological outcomes in terms of RR and OS (6). Second, for the use of TKIs, only two RCTs are available (24, 25). The outcome in terms of OS has not been published yet. Additionally, in daily practice, the effect of TKIs can be different, as the treatment regimens used in practice may differ from regimens used in the RCTs, particularly because of ad hoc individualized dose adjustments in patients who are deemed more prone to toxicity or who develop AEs. Furthermore, information desired in rural locations or other countries may differ, potentially making the PtDAs less applicable in settings where less accurate diagnostic tools or less experienced physicians are available.

As DTC research continues, new studies may require updating of outcome rates and treatment modalities. Moreover, a prospective randomized controlled trial is ongoing (NCT03905369) investigating the effect and implementation of the PtDAs.

Conclusion

Novel evidence-based PtDAs were created for patients with DTC. These PtDAs were positively evaluated to support patients and physicians in shared decision-making by patients having undergone the treatments, patient advocates, and physicians. The PtDAs address an important need for DTC patients and aim to increase patient knowledge and guide patients toward an informed decision (23). The PtDAs will be made publicly available after the large prospective trial has been completed.

Acknowledgments

We thank all patients, patient advocates, and physicians from collaborating hospitals who reviewed several drafts of the DAs.

References

1. Cabanillas ME, McFadden DG, Durante C. Thyroid cancer. *Lancet* (2016) 388 (10061):2783–95. doi: 10.1016/S0140-6736(16)30172-6
2. McLeod DS, Sawka AM, Cooper DS. Controversies in primary treatment of low-risk papillary thyroid cancer. *Lancet* (2013) 381(9871):1046–57. doi: 10.1016/S0140-6736(12)62205-3
3. 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. doi: 10.1056/NEJMp1604412
4. Sawka AM, Straus S, Brierley JD, Tsang RW, Rotstein L, Rodin G, et al. Decision aid on radioactive iodine treatment for early stage papillary thyroid cancer—a randomized controlled trial. *Trials* (2010) 11:81. doi: 10.1186/1745-6215-11-81
5. Oncoline. Schildklier carcinoom. (2015). Available at: <https://richtlijnendatabase.nl/richtlijn/schildklier carcinoom/algemeen.html>.
6. Bojoga A, Koot A, Bonenkamp J, de Wilt J, Inthout J, Stalmeier P, et al. The impact of the extent of surgery on the long-term outcomes of patients with low-risk differentiated non-medullary thyroid cancer: a systematic meta-analysis. *J Clin Med* (2020) 9(7):2316. doi: 10.3390/jcm9072316
7. Tuttle RM. Controversial issues in thyroid cancer management. *J Nucl Med* (2018) 59(8):1187–94. doi: 10.2967/jnumed.117.192559
8. Durante C, Montesano T, Torlontano M, Attard M, Monzani F, Tumino S, et al. Papillary thyroid cancer: time course of recurrences during postsurgery surveillance. *J Clin Endocrinol Metab* (2013) 98(2):636–42. doi: 10.1210/jc.2012-3401
9. Murthy SP, Balasubramanian D, Anand A, Limbachiya SV, Subramaniam N, Nair V, et al. Extent of thyroidectomy in differentiated thyroid cancers—review of evidence. *Indian J Surg Oncol* (2018) 9(1):90–6. doi: 10.1007/s13193-017-0661-2
10. Kim SH, Roh JL, Gong G, Cho KJ, Choi SH, Nam SY, et al. Differences in the recurrence and survival of patients with symptomatic and asymptomatic papillary thyroid carcinoma: an observational study of 11,265 person-years of follow-up. *Thyroid* (2016) 26(10):1472–9. doi: 10.1089/thy.2016.0238
11. Lamartina L, Grani G, Durante C, Borget I, Filetti S, Schlumberger M. Follow-up of differentiated thyroid cancer - what should (and what should not) be done. *Nat Rev Endocrinol* (2018) 14(9):538–51. doi: 10.1038/s41574-018-0068-3
12. Ibrahim EY, Busaidy NL. Treatment and surveillance of advanced, metastatic iodine-resistant differentiated thyroid cancer. *Curr Opin Oncol* (2017) 29(2):151–8. doi: 10.1097/CCO.0000000000000349
13. Babu G, Kainickal CT. Update on the systemic management of radioactive iodine refractory differentiated thyroid cancer (Review). *Mol Clin Oncol* (2021) 14 (2):35. doi: 10.3892/mco.2020.2197
14. Durante C, Haddy N, Baudin E, Leboulleux S, Hartl D, Travaglini JP, et al. Long-term outcome of 444 patients with distant metastases from papillary and follicular thyroid carcinoma: benefits and limits of radioiodine therapy. *J Clin Endocrinol Metab* (2006) 91(8):2892–9. doi: 10.1210/jc.2005-2838
15. 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. doi: 10.1089/thy.2015.0020

16. Fleeman N, Houten R, Bagust A, Richardson M, Beale S, Boland A, et al. Lenvatinib and sorafenib for differentiated thyroid cancer after radioactive iodine: a systematic review and economic evaluation. *Health Technol Assess.* (2020) 24(2):1–180. doi: 10.3310/hta24020
17. Fugazzola L, Elisei R, Fuhrer D, Jarzab B, Leboulleux S, Newbold K, et al. 2019 European Thyroid association guidelines for the treatment and follow-up of advanced radioiodine-refractory thyroid cancer. *Eur Thyroid J* (2019) 8(5):227–45. doi: 10.1159/000502229
18. Stacey D, Légaré F, Col NF, Bennett CL, Barry MJ, Eden KB, et al. Decision aids for people facing health treatment or screening decisions. *Cochrane Database Syst Rev* (2014) 1:CD001431. doi: 10.1002/14651858.CD001431.pub4
19. Volk RJ, Llewellyn-Thomas H, Stacey D, Elwyn G. Ten years of the international patient decision aid standards collaboration: evolution of the core dimensions for assessing the quality of patient decision aids. *BMC Med Inform Decis Mak.* (2013) 13 Suppl 2(Suppl 2):S1. doi: 10.1186/1472-6947-13-S2-S1
20. Elwyn G, O'Connor A, Stacey D, Volk R, Edwards A, Coulter A, et al. Developing a quality criteria framework for patient decision aids: online international Delphi consensus process. *Bmj* (2006) 333(7565):417. doi: 10.1136/bmj.38926.629329.AE
21. Coulter A, Stilwell D, Kryworuchko J, Dolan Mullen P, Ng CJ, van der Weijden T. A systematic development process for patient decision aids. *BMC Med Inform Decis Mak.* (2013) 13 Suppl 2(Suppl 2):S2. doi: 10.1186/1472-6947-13-S2-S2
22. Kvdg CBO. Handleiding keuzehulpontwikkeling. (2009). Available at: <https://docplayer.nl/7361403-Handleiding-keuzehulpontwikkeling.html>.
23. Koot A, Netea-Maier R, Ottevanger P, Hermens R, Stalmeier P. Needs, preferences, and values during different treatment decisions of patients with differentiated thyroid cancer. *J Personalized Med* (2021) 11(7):682. doi: 10.3390/jpm11070682
24. Schlumberger M, Tahara M, Wirth LJ, Robinson B, Brose MS, Elisei R, et al. Lenvatinib versus placebo in radioiodine-refractory thyroid cancer. *N Engl J Med* (2015) 372(7):621–30. doi: 10.1056/NEJMoa1406470
25. Brose MS, Nutting CM, Jarzab B, Elisei R, Siena S, Bastholt L, et al. Sorafenib in radioactive iodine-refractory, locally advanced or metastatic differentiated thyroid cancer: a randomised, double-blind, phase 3 trial. *Lancet* (2014) 384(9940):319–28. doi: 10.1016/S0140-6736(14)60421-9
26. Verburg FA, Flux G, Giovannella L, van Nostrand D, Muylle K, Luster M. Differentiated thyroid cancer patients potentially benefitting from postoperative I-131 therapy: a review of the literature of the past decade. *Eur J Nucl Med Mol Imaging.* (2020) 47(1):78–83. doi: 10.1007/s00259-019-04479-1
27. Lezen SM, Hoefnagel M, Bakker H. Keurmerk gewone taal. (2003). Available at: www.stichtingmakkelijklezen.nl.
28. Cambridge University Press & Assessment. (2023). Available at: <https://www.cambridgeenglish.org/exams-and-tests/cefr>.
29. Heij K VW. Schrijven in eenvoudig nederlands. Den Haag: Sdu uitgevers (2006).
30. Lundgrén-Laine H, Salanterä S. Think-aloud technique and protocol analysis in clinical decision-making research. *Qual Health Res* (2010) 20(4):565–75. doi: 10.1177/1049732309354278
31. Hawley ST, Zikmund-Fisher B, Ubel P, Jankovic A, Lucas T, Fagerlin A. The impact of the format of graphical presentation on health-related knowledge and treatment choices. *Patient Educ Couns.* (2008) 73(3):448–55. doi: 10.1016/j.pec.2008.07.023
32. Tuttle RM, Tala H, Shah J, Leboef R, Ghossein R, Gonen M, et al. Estimating risk of recurrence in differentiated thyroid cancer after total thyroidectomy and radioactive iodine remnant ablation: using response to therapy variables to modify the initial risk estimates predicted by the new American thyroid association staging system. *Thyroid* (2010) 20(12):1341–9. doi: 10.1089/thy.2010.0178

33. Castagna MG, Maino F, Cipri C, Belardinni V, Theodoropoulou A, Cevnini G, et al. Delayed risk stratification, to include the response to initial treatment (surgery and radioiodine ablation), has better outcome predictivity in differentiated thyroid cancer patients. *Eur J Endocrinol* (2011) 165(3):441–6. doi: 10.1530/EJE-11-0466
34. Molinaro E, Giani C, Agate L, Biagini A, Bianchi F, Brozzi F, et al. Patients with differentiated thyroid cancer who underwent radioiodine thyroid remnant ablation with low-activity ¹³¹I after either recombinant human TSH or thyroid hormone therapy withdrawal showed the same outcome after a 10-year follow-up. *J Clin Endocrinol Metab* (2013) 98(7):2693–700. doi: 10.1210/jc.2012-4137
35. Brassard M, Borget I, Edet-Sanson A, Giraudet A-L, Mundler O, Toubreau M, et al. Long-term follow-up of patients with papillary and follicular thyroid cancer: a prospective study on 715 patients. *J Clin Endocrinol Metab* (2011) 96(5):1352–9. doi: 10.1210/jc.2010-2708
36. Leboulleux S, Bournaud C, Chougnet CN, Zerdoud S, Al Ghuzlan A, Catargi B, et al. Thyroidectomy without radioiodine in patients with low-risk thyroid cancer. *N Engl J Med* (2022) 386(10):923–32. doi: 10.1056/NEJMoa2111953
37. Turrentine FE, Wang H, Simpson VB, Jones RS. Surgical risk factors, morbidity, and mortality in elderly patients. *J Am Coll Surg* (2006) 203(6):865–77. doi: 10.1016/j.jamcollsurg.2006.08.026
38. Brito JP, Moon JH, Zeuren R, Kong SH, Kim YG, Iniguez-Ariza NM, et al. Thyroid cancer treatment choice: a pilot study of a tool to facilitate conversations with patients with papillary microcarcinomas considering treatment options. *Thyroid* (2018) 28(10):1325–31. doi: 10.1089/thy.2018.0105
39. Pitt SC, Saucke MC. Thyroid cancer treatment choice toolkit. University of Wisconsin - Madison School of Medicine and Public Health - Department of Surgery. (2017). Available at: <https://www.hipxchange.org/ThyroidCancerTreatmentChoice>.
40. Pitt SC, Saucke MC. Novel decision support interventions for low-risk thyroid cancer. *JAMA Otolaryngol Head Neck Surg* (2020) 146(11):1079–81. doi: 10.1001/jamaoto.2020.2279
41. Fagerlin A, Pignone M, Abhyankar P, Col N, Feldman-Stewart D, Gavaruzzi T, et al. Clarifying values: an updated review. *BMC Med Inform Decis Mak.* (2013) 13 Suppl 2(Suppl 2):S8. doi: 10.1186/1472-6947-13-S2-S8
42. Feldman-Stewart D, Tong C, Siemens R, Alibhai S, Pickles T, Robinson J, et al. The impact of explicit values clarification exercises in a patient decision aid emerges after the decision is actually made: evidence from a randomized controlled trial. *Med Decis Making.* (2012) 32(4):616–26. doi: 10.1177/0272989X11434601



Chapter 5

Effect of a patient decision aid on shared decision making in patients with differentiated thyroid cancer: a randomized controlled trial

Anna Koot^{1,2}, Nelleke Ottevanger³, Rosella Hermens¹, Annemijn Aarts⁴, Janneke Walraven³, Han Bonenkamp⁵, Johannes de Wilt⁵, Grard Nieuwenhuijzen⁶, Alexander van der Veen⁶, Mariel Keemers⁷, Wouter Zandee⁸, Charlotte Blanken⁹, Maarten van Aken¹⁰, Rogier Donders¹, Peep Stalmeier^{1,*}, Romana Netea-Maier^{2,*}; on behalf of the COMBO study group

¹ Science Department IQ Health, Radboud University Medical Center, Nijmegen, 6525 GA, The Netherlands

² Department of Internal Medicine, Division of Endocrinology, Radboud University Medical Center, Nijmegen, 6525 GA, The Netherlands

³ Department of Internal Medicine, Division of Oncology, Radboud University Medical Center, Nijmegen, 6525 GA, The Netherlands

⁴ Department of Obstetrics & Gynecology, Amsterdam University Medical Center, Location Amsterdam Medical Center, Amsterdam, 1105 AZ, The Netherlands

⁵ Department of Surgical Oncology, Radboud University Medical Center, Nijmegen, 6525 GA, The Netherlands

⁶ Department of Surgery, Catharina Hospital, Eindhoven, 5623 EJ, The Netherlands

⁷ Department of General Surgery, Canisius-Wilhelmina Hospital, Nijmegen, 6532 SZ, The Netherlands

⁸ Department of Endocrinology, University Medical Center Groningen, Groningen, 9713 GZ, The Netherlands

⁹ Department of Surgery, Rijnstate Hospital, Arnhem, 6815 AD, The Netherlands

¹⁰ Department of Internal Medicine, Haga Hospital, The Hague, 2545 AA, The Netherlands

*Shared last authorship

Abstract

Background: Over the last decades optimal treatment for patients with differentiated thyroid cancer (DTC) is debated. Two treatment decisions for patients who could benefit from more individualized approaches and shared decision making (SDM), are the extent of surgery decision in patients with low-risk DTC, and the decision to start or delay the treatment with Tyrosine Kinase Inhibitors (TKIs) in patients with advanced DTC. Our aim is to examine the effect of a Patient Decision Aid (PtDA) on observed SDM, in physicians trained in SDM. **Methods:** In this multicenter RCT (2020-2024), all physicians (n=26) received a 5-hour SDM training. Patients (n=86) with DTC were randomized to receive a PtDA or care as usual. The primary outcome was the observed SDM as rated by blinding observers with the observing patient involvement in decision making (OPTION5) scale from audio-recorded consultations. Secondary outcomes included well-being measures, information-related measures, and decision-related measures. **Results:** Mean OPTION5 scores were 52 (range 0-100) for the PtDA and 54 (range 0-100) for the usual care group. The PtDA did not improve observed SDM, nor the secondary outcomes. Results of the Beta testing (n=33) showed that the PtDA was readable (n=30) and helpful for decision making (n=28). All patients recommended using the PtDA. **Conclusion:** In this RCT, with high baseline SDM quality provided by trained physicians, PtDAs did not further improve SDM quality. Nevertheless, since all patients recommended the PtDA, future studies should establish the potential benefit of PtDAs, particularly as SDM training is usually not provided.

Trial registration. ClinicalTrials.gov NCT03905369

Introduction

Most patients with differentiated thyroid cancer (DTC) have a favorable prognosis with an excellent long-term overall survival except for those with advanced radioactive iodine (RAI) refractory disease (1). For this reason, clinical practice has shifted towards a more individualized approach, and patients are involved in trade-offs between the harms and benefits of different approaches (2). Particularly for patients with low-risk DTC eligible for primary surgery, and patients with advanced RAI refractory DTC, the optimal treatment is debated. As insufficient evidence is available regarding the harms and benefits of treatment in relation to the oncological outcomes and potential overtreatment could unnecessarily affect quality of life (QOL). The American Thyroid Association (ATA) and European Society of Medical Oncology (ESMO) guidelines suggest considering patient preferences, as for some low-risk patients, thyroid lobectomy (TL) alone may be sufficient initial treatment (3, 4). Similarly, for patients with advanced RAI refractory disease, the recent European Thyroid Association (ETA) and ESMO guidelines state that the decision about when to start TKIs should include patient preferences with respect to treatment goals, and what patients find important (patient values), regarding benefits and adverse effects of the treatments (5). Therefore, shared decision making (SDM) is required (3, 5).

SDM has been promoted to improve conversations between physicians and their patients and to support patients in making informed decisions that best fit their personal preferences, circumstances, and concerns (6). Physicians provide patients with information on existing options and consider patients' needs, preferences, and values to enable a personalized treatment choice (7). In this process, important life goals such as work, sport or family may be involved, and these should be explored together with the patient (8, 9). In practice, however, applying SDM in the consultation room and talking about values is difficult. Values are discussed in a minority of decision-making consultations (7). Of the SDM skills, exploring patient values is the most difficult one and complicated by different perspectives of physicians and patients (8). Moreover, a specific communication training to develop SDM skills was not routinely used and programs vary widely (10). In a recent survey conducted within the EORTC Thyroid Carcinoma Group, only 32% of expert physicians reported having received dedicated SDM training (11).

Our aim is to test three recently developed PtDAs to support abovementioned treatment decisions (12). A prospective multicenter randomized controlled trial (RCT), the COMBO (COMmunication BOoster) trial was done, to investigate the

added value of these PtDAs on observed SDM in recorded conversations. In general, various SDM training programs for physicians exist, though there is uncertainty whether they are effective (13). Only one study investigated the added value of a PtDA to specific communication training on the quality of SDM in patients facing palliative treatment for advanced cancers (14). In our trial, all physicians received a dedicated training in SDM to improve the congruence or agreement in values communication between patients and physicians, and to prevent baseline inequalities between the groups. Patients were randomized into two arms, with or without a PtDA. We hypothesized that the PtDAs improve observed SDM. Secondary patient outcomes included well-being measures, information-related measures, and decision-related measures.

Methods

This paper complies with the SUNDAE checklist for evaluation of PtDA studies (15) and the Consolidated Standards of Reporting Trials (CONSORT) statement (16).

Ethical approval and informed consent

The COMBO study (COMMunication BOoster) is registered at ClinicalTrials.gov (NCT03905369). The Medical Ethical Committee (METC) of the region Arnhem-Nijmegen approved the study protocol (METC-2018-4521). Patients provided written consent for participation. Due to lagging patient inclusion, the power calculation was reappraised. The initial power calculation was too conservative. The adjusted power calculation was submitted to and approved by our sponsor, Dutch Cancer Society.

Design

Between March 2020 and April 2024, 86 DTC patients, eligible for inclusion, were randomized (1:1) to receive the PtDA (intervention group) or information as usual (control group) (Figure 1). All participating physicians were trained in SDM.

Setting

Thirteen (of the 25 contacted) hospitals (six academic and seven non-academic) specialized in DTC care in the Netherlands, and the Dutch Thyroid patient association (SchildklierNL) participated. DTC patients are treated in both academic (high- and low-risk patients) and non-academic hospitals (mainly low-risk patients) involving multidisciplinary teams of specialists. The follow-up is carried out by endocrinologists. Patients with advanced RAI refractory disease requiring TKI treatment, are followed-up by oncologists.

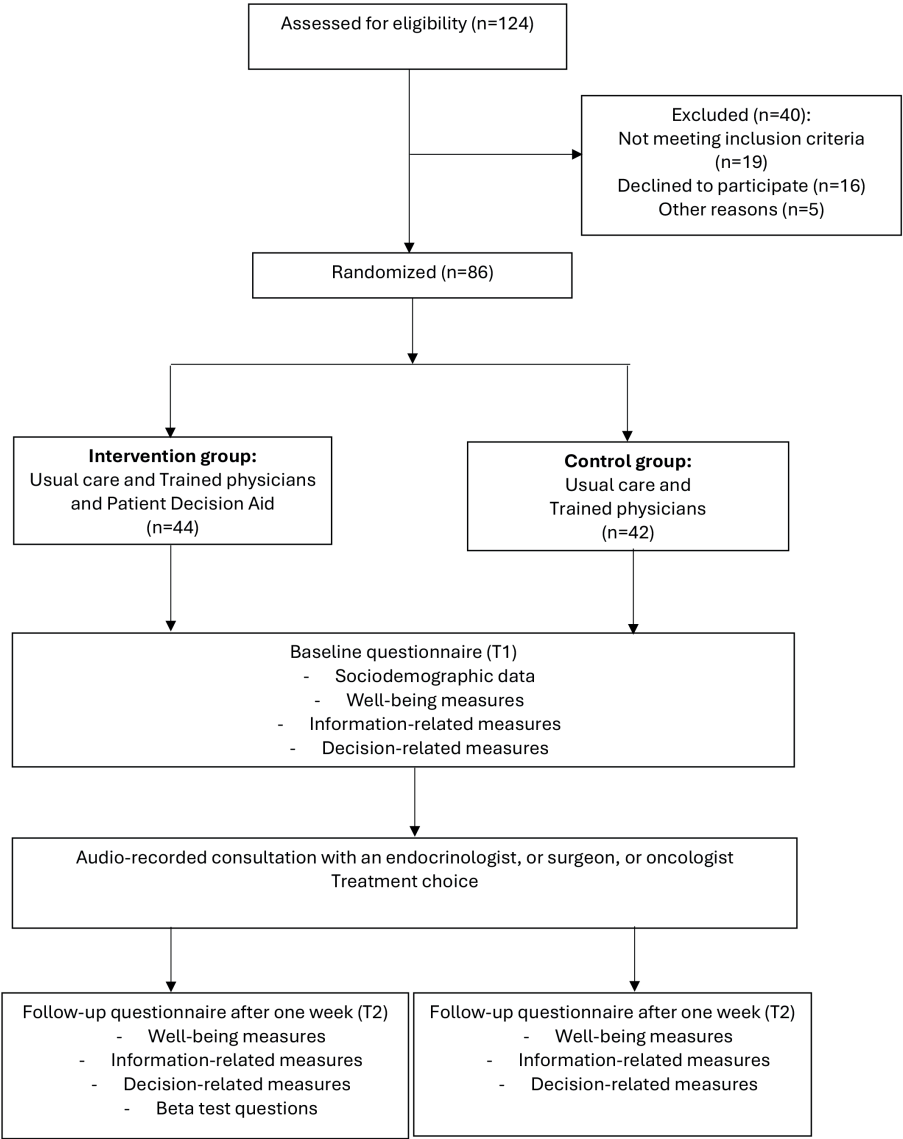


Figure 1. Study design

Procedure

Eligible patients were identified by endocrinologists, surgeons, or oncologists and discussed in the local tumor board. Next, the treating physician or nurse informed the patient about the diagnosis, the two available treatment options and trial. After written consent, patients were randomized into two arms, either to receive a PtDA or not before their appointment about the treatment choice. Tumor

characteristics were collected from the patients' medical files. Patients filled out a baseline questionnaire (T1). About one to two weeks later, the SDM consultation took place, which was audio-recorded. Recordings were rated by blinded assessors. Two assessors started double coding a set of ten audio-recordings, and resulting scores were discussed. Inter rater agreement was calculated after each set of ten and considered sufficient if the Intraclass Correlation was higher than .60 reflecting substantial agreement (17). When the Inter Rater agreement was insufficient, this process was repeated. After the first set of ten consultations, the Inter Rater agreement was calculated. The intraclass correlation turned out to be sufficient and strong (0.81). The remaining recordings were scored independently by two raters without further discussions. Patient outcomes were again assessed with a questionnaire one week after the conversation (T2) (Figure 1).

Participants

Patients

Three groups of patients were eligible: 1) patients with low-risk DTC according to the ATA criteria (3), to decide between a TL or TT, 2) patients with low-risk DTC according to the ATA criteria to decide between active surveillance or totalizing thyroidectomy after diagnostic lobectomy, and 3) patients with advanced RAI refractory DTC, to decide between starting or delay starting TKI treatment (either Sorafenib or Lenvatinib, both approved for first line systemic treatment for patients in the Netherlands). Exclusion criteria were contra-indications for surgery or TKI treatment, mental or cognitive problems as assessed by the physician and/or inadequate knowledge of the Dutch language.

Physicians

Eight endocrinologists, six oncologists, and twelve surgeons specialized in DTC care and trained in SDM, participated.

Randomization and blinding

Central randomization took place using a computer-generated randomization list. The same randomization process took place for the whole cohort, regardless the PtDA offered. Participating physicians were blinded to the intervention assignment though the PtDA may have come up in the consultation.

Interventions

Development of the PtDAs

All PtDAs were developed according to the International Patients Decision Aids Standards (IPDAS) (18). We previously described the development process of the PtDAs used in the present study (12). The PtDAs were online, containing general information about DTC, presenting the treatment options, comparing the treatment options, knowledge questions about thyroid cancer and a values clarification exercise, to help patients to choose. The VCE included statements and open-ended questions to explore patients' needs, preferences and values. Patients were encouraged to share their answers with their physician. The PtDAs developed in this study relate to the situation in the Netherlands and cannot be directly implemented in other countries, because of differences in healthcare practices, clinical guidelines, and specific cultural aspects that influence the needs perceived by patients from different backgrounds. Nonetheless, upon translation and adaptation they can be validated cross-culturally and disseminated in other countries as well (18). The hyperlink and translated PtDAs can be found in Supplementary Dataset 1.

SDM communication training

The training (5 hours) was based on a model with four essential SDM steps (19): 1) choice, process and division of roles, 2) inform about the options and pros and cons, 3) explore patients' needs, preferences and values, 4) make or defer a decision together with the patient. The training started with an e-learning about SDM lasting 30 minutes. Next, physicians received a group training by an experienced trainer lasting three and a half hours. This group training had a special focus on values clarification. The final part of the training, consisted of a 60 minutes individual session with feedback on an audio-recorded consultation, received about 4 weeks after the group training. Additionally, participants received a pocket-size card presenting the four SDM steps with example phrases. The physicians participating in the present study evaluated the training as positive. The training was accredited by the Dutch Association of Internal Medicine (3 CME credits).

Patient measures

Baseline characteristics

Outcome measures are presented in Supplementary Table 1. Characteristics are presented in Table 1.

Table 1. Patient and physician characteristics

Patients			
Sociodemographics	Decision Aid	Usual care	Total
Female gender (n, %)	30 (75)	24 (68.6)	54 (72)
Age, mean (SD)	55.85 (14.9)	55.51 (16.3)	55.69 (15.5)
Living with partner (n, %)	31 (77.5)	27 (77.1)	58 (77.3)
Employed (n, %)	24 (60)	22 (62.9)	46 (61.3)
Children (n, %)	30 (75)	27 (77.1)	57 (76)
College education or more (n, %)	16 (40)	11 (31.4)	27 (36)
Religiously affiliated (n, %)	10 (25)	9 (25.7)	19 (25.3)
Tumour characteristics			
Low-risk DTC (n, %)	36 (81.8)	32 (76.2)	68 (79)
Diameter nodule on ultrasound (n, %)			67 (77.9)
10-20mm (n, %)			24 (27.9)
20-30mm (n, %)			28 (32.6)
30-40mm (n, %)			15 (17.4)
Bethesda classification			67 (77.9)
Category X (n, %)			4 (4.7)
Category 0 (n, %)			0 (0)
Category I (n, %)			2 (2.3)
Category II (n, %)			1 (1.2)
Category III (n, %)			3 (3.5)
Category IV (n, %)			6 (7.0)
Category V (n, %)			22 (25.6)
Category VI (n, %)			29 (33.7)
Histopathology tumor type			68 (79.1)
PTC (n, %)			63 (73.3)
FTC (n, %)			3 (3.5)
Other (n, %)			2 (2.3)
TNM stage			68 (79.1)
T1 (n, %)			6 (7.0)
T2 (n, %)			20 (23.3)
T3 (n, %)			41 (47.7)
NX (n, %)			3 (3.5)
N0 (n, %)			65 (75.6)
MX (n, %)			58 (67.4)
M0 (n, %)			10 (11.6)

Table 1. Continued

Patients			
Advanced RAI refractory DTC	8 (18.2)	10 (23.8)	18 (21)
TNM stage (n, %)			18 (21)
Tx (n, %)			1 (1.2)
T2 (n, %)			3 (3.5)
T3 (n, %)			9 (10.5)
T4 (n, %)			5 (5.8)
Nx (n, %)			2 (2.3)
N0 (n, %)			6 (7.0)
N1 (n, %)			10 (11.6)
Mx (n, %)			1 (1.2)
M0 (n, %)			9 (10.5)
M1 (n, %)			8 (9.3)
Physicians			
Sociodemographics			
Female gender (n, %)			14 (63.3)
Age in years, mean (SD)			52
Years of experience, median (range)			13 (5-25)
Communication skills training during:			
Medical school, yes (n, %)			0 (0)
Residency, yes (n, %)			2 (7.7)
Post-education, yes (n, %)			4 (23.1)
Type of hospital			
Academic (n, %)			6 (46.2)
Non-academic (n, %)			7 (53.8)

Primary outcome

The primary outcome was observed SDM as assessed from the audio-recorded consultations using the Observing Patient Involvement in Decision-Making (OPTION5) instrument (19), with 5 items: (1) Are multiple options presented?, (2) Is a partnership with the patient established?, (3) Are the options described?, (4) Is the patient asked for their preferences?, (5) Are patients' preferences included in the decision about next steps? Items are scored from 1 (no effort to involve the patient) to 4 (exemplary effort to involve the patient). The sum of these items was rescaled from 0-100 (20). Two independent and experienced assessors, blinded to the research questions and randomization assignment, independently rated the recordings, applying the OPTION5 coding scheme (19). These assessors started double coding a set of ten audio recordings, and resulting scores were discussed. Inter rater agreement was calculated after each set of ten and considered sufficient if the Intraclass Correlation was higher

than .60, reflecting substantial agreement (17). When the Inter Rater agreement was insufficient, this process was repeated. After the first set of ten consultations, the Inter Rater agreement was calculated. The Intraclass correlation turned out to be sufficient and strong (0.81). The remaining recordings were scored independently by two raters without further discussions. Because the study focused on the general effect of PtDAs rather than a single decision-specific tool, we deliberately used a composite outcome, and the study was powered accordingly.

Secondary outcomes

Patient-reported SDM

Patients gave their evaluation of the SDM process using CollaboRATE, 3-items, ranging from 0 (no effort) to 9 (all possible effort) addressing explanations, preference elicitation, and preference integration (21).

Well-being and worries

Patients rated their *general health* during the last week on an 11-point scale ranging from 0 (very bad) to 10 (excellent).

Cancer worries were scored with three questions (22, 23), on a 4-point scale ranging from 1 (not at all) to 4 (always). *Trust in physician* was measured with the Wake-Forest Trust in Physician questionnaire, ten items scored on a 5-point scale, ranging from 1 (totally disagree) to 5 (totally agree) (24).

Information-related outcomes

Subjective knowledge patients rated their own knowledge about DTC using three questions, on a 10-point scale ranging from 1 (very bad) to 10 (excellent), which were subsequently averaged.

Objective knowledge on DTC was measured with five statements (right/wrong), generated by independent experts.

Two additional questions were asked: 'having received any *undesired information* (yes/no)' and whether 'treatment options were presented in a *balanced way* (yes/no)'.

Decision-related outcomes

Strength of treatment preference was asked on a 5-point scale ranging from 0 (no preference) to 4 (very strong preference).

The Decision Evaluation Scales measures patient experiences with the decision using three scales, namely satisfaction-uncertainty, informed choice, and decision control (25), and measured on a 5-point scale, ranging from 1 (totally disagree) to 5 (totally agree). Having weighed the pros and cons was assessed by asking about three items, measured on a 5-point scale, ranging from 1 (totally disagree) to 5 (totally agree) (26).

Preference for decision-making Perceived participation in decision making was measured with two decision-making items from the Problem-Solving Decision-Making Scale (PSDM) (27). These were measured on a 5-point scale ranging from 1 (doctor alone) to 5 (I alone). *Perceived involvement* was assessed after the decision using the same questions in the past tense. Patients were also asked whether they felt they had a choice (yes/no), and whether their opinion regarding the treatment mattered (yes/no) (28).

Values agreement

Patients values were asked with two questions weighing QOL against survival (29). Measured on a 5-item scale ranging from 1 (not agree) to 5 (totally agree). The items were: 'If a treatment can prolong my life, I will always accept it, whatever the side effects may be', and 'If a treatment that prolongs my life results in such complications that I am prevented from leading a normal life, I would not have it'. Physicians answered two identical questions but now preceded by: 'Which preference does the patient have?'.

Statistical analysis

Descriptive statistics as percentages or means (with standard deviation; SD) were used. Differences between OPTION5 scores between the PtDA and usual care (UC) group were tested using t-tests. All remaining tests were descriptive and done with t-tests for independent samples; if a baseline measure was available, analysis of covariance (ANCOVA) were conducted. The level of values agreement between physician and patient was analyzed using Cohen's kappa. Patient and physician scales were dichotomized. Tests were considered statistically significant if $p < 0.05$. We used SPSS Statistics v. 27.0 (IBM, Armonk, NU USA).

Sample size

The effect size for improvement of the OPTION5 score was estimated to be 1. This effect size was reduced to 0.64 to account for 1) contamination as each physician sees both intervention and control patients, and 2) the effect of the communication training which may elevate OPTION5 scores in both arms, thus reducing possible differences. To detect an effect size of 0.64, with a two-sided test and $\alpha = 0.05$, and a power of 0.80, a total of 78 patients are needed.

Results

Participants

In total 86 consecutive patients were included: 44 (51.2%) were randomized in the PtDA group and 42 (48.8%) in the UC group (Figure 1). Fourteen physicians included patients in the trial. Patient and physician characteristics are shown in Table 1.

Audio-recordings of consultations were collected for 78 (90.7%) patients, 73 (84.9%) patients returned the T2 questionnaire. Physicians' questionnaires were received for 65 (75.6%) consultations.

Primary outcome: observed SDM

The intervention had no effect on observed SDM as measured with the OPTION5 (Table 2). Of the five OPTION items, item 2 (establish a partnership) scored lowest in the UC group and item 5 (preferences included in the decision) scored lowest in the PtDA group. Item 1 (present multiple options) the highest in both groups. Differences between the PtDA and UC groups for the five OPTION items separately were also not statistically significant. Mean OPTION5 scores were respectively 52 (range 25-90, PtDA group) and 54 (range 15-90, UC group).

Table 2. Mean observer OPTION5 scores between the PtDA and usual care group, scaled to a score out of 100.

Short description of items	PtDA group (n = 38)	Usual care group (n = 40)
Item 1: Does the clinician present multiple options?*	14.2 (2.8)	14.2 (2.8)
Item 2: Does the clinician establish a partnership with the patient?*	7.9 (3.6)	7 (5.2)
Item 3: Are the options described?*	11.6 (3.2)	11.7 (3.6)
Item 4: Does the clinician ask the patient for their preferences?*	10.9 (3.6)	12.4 (4.0)
Item 5: Are the patients' preferences included in the decision about next steps?*	7.7 (3.2)	8.8 (4.0)
OPTION5**, mean (SD)	52 (14.5)	54 (13.6)

* Range 0-20. ** Range 0-100.

Secondary outcomes

No differences were found between the PtDA and UC group for the CollaboRATE scores, general health, cancer worries, and trust in the physician (Table 3).

No differences were found for objective and subjective knowledge, receiving undesired information and balanced presentation of the information (Table 3).

No differences were found in strength of treatment preference, decision satisfaction-uncertainty, informed choice and decision control between the two groups (Table 3). At follow-up (T2), no differences were found regarding treatment preferences. Most patients reported having a treatment preference (91.8%); out of these, most (61.2%) favored the more conservative option. There was no values

agreement between patients and physicians about relative importance of the values QOL and survival (Table 4).

The PtDA was evaluated with Beta testing during the trial (Table 5) by thirty-three (75%) out of 44 patients in the PtDA group. Twenty-seven (81.8%) said they used the PtDA and 21 of these (77.8%) filled out the values clarification exercise and thought it was helpful in the decision making (Table 5). Twenty-two (81.5%) patients mentioned the PtDA improved their knowledge about DTC, length and amount of information was considered right by 23 (85.2%) and 25 (92.6%) patients, respectively. Comprehensibility (25, 92.6%) and credibility (27, 100%) were good. The overall grade was 7.7. All patients indicated that they would recommend the PtDA.

Table 3. Unadjusted mean scores (SD) and results from the ANCOVA comparing the PtDA and usual care group.

	Group	T1	T2	F	P
Well-being ^a					
General health	PtDA (n = 36)	6.83 (1.63)	6.92 (1.30)	0.030	0.86
	Usual care (n = 33)	6.67 (1.34)	6.88 (0.96)		
Cancer worries	PtDA (n = 36)	2.25 (0.65)	2.04 (0.61)	2.9	0.09
	Usual care (n = 32)	2.10 (0.60)	2.16 (0.57)		
Trust in physician	PtDA (n = 36)		4.44 (0.59)	0.64	0.92
	Usual care (n = 32)		4.43 (0.51)		
Information related ^a					
Information unpleasant	PtDA (n = 36)	1.92 (0.28)	1.86 (0.35)	0.07	0.80
	Usual care (n = 32)	1.94 (0.25)	1.84 (0.37)		
Information balanced	PtDA (n = 38)		3.11 (0.76)	0.69	0.25
	Usual care (n = 35)		2.91 (0.61)		
Subjective knowledge	PtDA (n = 33)	6.10 (1.37)	6.81 (0.95)	0.004	0.95
	Usual care (n = 27)	6.30 (1.15)	6.87 (1.01)		
Objective knowledge	PtDA (n = 38)		4.0 (0.64)	1.5	0.99
	Usual care (n = 35)		4.0 (0.79)		
Decision related ^a					
Decision satisfaction-uncertainty	PtDA (n = 38)		4.1 (0.57)	0.20	0.20
	Usual care (n = 35)		3.9 (0.59)		
Informed choice	PtDA (n = 38)		4.1 (0.61)	0.008	0.17
	Usual care (n = 35)		3.9 (0.60)		
Decision control	PtDA (n = 38)		4.2 (0.64)	0.063	0.45
	Usual care (n = 35)		4.1 (0.68)		
Weighing pros and cons	PtDA (n = 38)		3.78 (0.59)	1.43	0.55
	Usual care (n = 35)		3.86 (0.47)		
Treatment preference	PtDA (n = 36)	1.50 (0.81)	1.25 (0.55)	1.38	0.24
	Usual care (n = 32)	1.66 (0.83)	1.44 (0.67)		
Strength of treatment preference	PtDA (n = 36)	2.33 (1.43)	3.03 (1.16)	0.61	0.44
	Usual care (n = 32)	2.13 (1.34)	2.78 (1.21)		
Values	PtDA (n = 36)	3.33 (0.51)	3.60 (0.83)	1.82	0.18
	Usual care (n = 32)	3.60 (0.69)	3.61 (0.67)		
Preference for decision making	PtDA (n = 36)	3.43 (0.74)	3.60 (0.83)	0.01	0.91
	Usual care (n = 32)	3.42 (0.76)	3.61 (0.67)		
Perceived involvement	PtDA (n = 36)		1.07 (0.21)	1.12	0.62
	Usual care (n = 32)		1.05 (0.15)		
CollaboRATE	PtDA (n = 20)		7.60 (0.48)	0.005	0.85
	Usual care (n = 20)		7.57 (0.60)		

Abbreviations: SD, standard deviation; ANCOVA, analysis of covariance; PtDA, Patient Decision Aid.

^aP < .05.

^aMore information on the scales can be found in Table 1.

Table 4 Agreement between patients and physicians about the importance of values.

	Physicians	Not agree <i>n</i> (%)	Agree <i>n</i> (%)	Total <i>n</i> (%)	Cohen's kappa
Patients	Question 1 'If a treatment can prolong my life, I will always accept it, whatever the side effects may be'				
	Not agree	27(47)	9(16)	36(63)	
	Agree	9(16)	12(21)	21(37)	
	Total	36(63)	21(37)	57(100)	0.321*
	Question 2 'If a treatment that prolongs my life results in such complications that I am prevented from leading a normal life, I would not have it'				
	Not agree	7(12)	14(25)	21(37)	
	Agree	11(19)	25(44)	36(63)	
	Total	18(32)	39(68)	57(100)	0.029

**P* < .05.

Table 5. Results of Bèta testing questionnaire.

Bèta testing <i>n</i> %	44 (100)
Filled out questionnaire	33 (75)
Used PtDA	27 (81.8)
Filled out values clarification exercise	21 (77.8)
Values clarification exercise helpful in decision making	21 (77.8)
Improved knowledge	22 (81.5)
Length just right	23 (85.2)
Amount of information just right	25 (92.6)
Comprehensibility good	25 (92.6)
Credibility good	27 (100)
Recommend PtDA	27 (100)
Time burden (range in minutes, mean)	10-90 (39)
Average grade (range 0-10)	7.7

Discussion

To our knowledge, this is the first RCT to evaluate the impact of a PtDA on observed SDM in patients with low-risk and advanced RAI refractory DTC. The PtDAs were evaluated for effectiveness on SDM while all physicians received a SDM training. In contrast to our hypothesis, the PtDAs did not elevate observed SDM in this setting. Secondary patient reported outcomes were also not affected. Nevertheless, patients mentioned that the PtDA was readable and helpful for decision making and they recommended using the PtDA.

Regarding other PtDAs in low-risk DTC patients (1-4cm), there is only one published PtDA focused on RAI therapy (30). This PtDA is limited to the decision to follow or omit RAI treatment after TT. On the other hand Brito et al (31) and Pitt et al (32, 33) developed a treatment choice tool (paper cards) for patients with DTC. These tools included the option of active surveillance, implying that these tools are also useful for informed patients with mPTC. More recently, O'Neill et al (34) developed a decision aid for patients with Bethesda 3-6 thyroid nodules for de-escalation of surgery. All these tools need further testing a RCT.

The mean OPTION5 scores of 52-54 (full-scale of 0-100), in both groups are relatively high. In contrast, lower OPTION5 scores of 23 were found in patient groups with cancer, diabetes and depression (35); scores ranging from 16.8-28.3 were reported among untrained specialists in the Netherlands from 18 different disciplines (36-38). Thus, the training yielded a high level of OPTION5 scores of the trained physicians in our study (39). In line with this, a training, together with a PtDA, resulted in higher mean OPTION5 scores of 37.8 in patients undergoing vascular surgery (40). Likewise, higher scores of about 50-54 were reported in physicians using an option grid for osteoarthritis of the knee (41), or when a multilevel implementation program was used in breast cancer patients including a communication training without a PtDA (42). High OPTION5 scores may further be explained by participation and motivation bias as only half of the approached hospitals consented to participate.

Importantly, there is no consensus about the level of an acceptable OPTION5 score. The manual of the Observer OPTION5 suggest that a sum score of ≥ 75 (0-100) represents a skilled effort, involving substantive phrases or sentences (20). Overall, despite the relatively high OPTION5 scores in our study, there was no values agreement between patients and physicians, indicating that physicians could not estimate to what extent treatment values were important to patients. In our study, only eight conversations achieved a sum score of ≥ 75 , with a tendency to improve values agreement. However, physicians reaching these scores were more focused on item 3 (describing the options) and 4 (preference elicitation) with still only minimal values agreement. It remains thus unclear whether and how values agreement can be improved. Thereby, based on the data from this study, we cannot establish whether the outcome would have been different if the study would have focused only on one patient population, having for example advanced DTC or low-risk DTC. A subsequent study focusing on the additive value of PtDAs in the different patient populations, potentially having different informational needs and decision preferences depending on the decision they face and, the phase of the disease is warranted.

The high OPTION5 scores in our study, may have resulted in a ceiling effect precluding additional improvement in the intervention group. This is in line with Henselmans et al (14) reporting OPTION5 scores of 50 in trained physicians without further improvements after adding a communication aid in a palliative setting. This ceiling effect could also explain why in contrast to previous studies (13, 43), no positive effects on the secondary outcomes were found. DTC specific factors could have affected the results as well. Patients with advanced DTC are more familiar with the disease given its lengthy course, explaining the lack of improvement of knowledge with the PtDA. Furthermore, the low level of cancer worries in both groups suggests that there is little room for improvement regardless the use of a PtDA. A recent study also showed that regardless of chosen treatment decision (TL or TT), patients with low-risk DTC reported low levels of DTC related fear and worries (44).

Despite the lack of improvements on primary and secondary outcomes, most patients appreciated the PtDA, highlighting the importance of its future routine implementation. However, the current evidence indicates that the implementation of PtDAs remains challenging (45). Often SDM consultations take place directly after sharing the cancer diagnosis, which may find the patient unprepared for participation in the decision making, thus optimal timing of the PtDA is a main logistic barrier (46). In our study, some patients felt they did not have the time to use the PtDA sufficiently while others may have received additional sufficient information already before the SDM consultation from their referring physician, limiting the utility of the PtDA. Having access to the PtDA, before the SDM consultation, ensuring sufficient time to examine it and ensuring comprehensibility for patients with limited health literacy remain essential (47). In addition, training physicians in shared decision-making skills should be prioritized. Although various training options exist, including online programs, their optimal effectiveness remains to be studied.

Strengths and limitations

Apart from its prospective randomized trial design, the study is strengthened by the contribution of physicians from different backgrounds, patients, and patient advocates in designing and assessing the PtDAs. The focus on patients' values in the communication training for physicians and in the values clarification exercise present in the PtDA for patients, makes this study unique in its potential to improve values agreement between physicians and patients. Furthermore, the execution of the study in the context of direct clinical environment despite differences in logistics between hospitals, makes the results more relevant for current practice.

Some limitations must be acknowledged. First, we trained all physicians participating in the study, resulting in the lack of a control group and heterogeneity of the intervention group, second two types of patient groups and different physician specialties were included possibly increasing variability. However, this is also a positive characteristic as it reflects clinical practice. Third, despite our efforts to blind the physicians, the recordings indicate that use of the PtDA was noticed by them, potentially affecting the physicians' behavior and quality of SDM. Fourth, as no OPTION5 scores were obtained before the training of physicians, the effect of the training cannot be assessed. Lastly, generalizability is limited as the study likely underestimates the effect of a PtDA in this trained population, because in current clinical practice most physicians are untrained.

Conclusion

Mean OPTION5 scores were high compared to other trials but the PtDA did not lead to higher SDM and patient outcomes. Nevertheless, all patients recommended the PtDA. Therefore, given positive results of PtDAs in the literature in untrained physicians, we consider, our PtDAs are useful to support physicians and patients in decision making (13), because usually training is not available. Future research should focus on ways to improve SDM.

Acknowledgements: We thank M. Schuurman and E. Visserman for their collaboration in scoring the audio-recorded conversations. We thank all patients and physicians of collaborating hospitals who participated in the COMBO study.

References

1. Lim H, Devesa SS, Sosa JA, Check D, Kitahara CM. Trends in Thyroid Cancer Incidence and Mortality in the United States, 1974-2013. *Jama*. 2017;317(13):1338-48.
2. Tuttle RM. Controversial Issues in Thyroid Cancer Management. *J Nucl Med*. 2018;59(8):1187-94.
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. Filetti S, Durante C, Hartl D, Leboulleux S, Locati LD, Newbold K, et al. Thyroid cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up†. *Ann Oncol*. 2019;30(12):1856-83.
5. Fugazzola L, Elisei R, Fuhrer D, Jarzab B, Leboulleux S, Newbold K, et al. 2019 European Thyroid Association Guidelines for the Treatment and Follow-Up of Advanced Radioiodine-Refractory Thyroid Cancer. *Eur Thyroid J*. 2019;8(5):227-45.
6. Stiggelbout AM, Van der Weijden T, De Wit MP, Frosch D, Légaré F, Montori VM, et al. Shared decision making: really putting patients at the centre of healthcare. *Bmj*. 2012;344:e256.
7. Kunneman M, Marijnen CA, Baas-Thijssen MC, van der Linden YM, Rozema T, Muller K, et al. Considering patient values and treatment preferences enhances patient involvement in rectal cancer treatment decision making. *Radiother Oncol*. 2015;117(2):338-42.
8. Abhyankar P, Bekker HL, Summers BA, Velikova G. Why values elicitation techniques enable people to make informed decisions about cancer trial participation. *Health Expect*. 2011;14 Suppl 1(Suppl 1):20-32.
9. Llewellyn-Thomas HA, Crump RT. Decision support for patients: values clarification and preference elicitation. *Med Care Res Rev*. 2013;70(1 Suppl):50s-79s.
10. Légaré F, Adekpedjou R, Stacey D, Turcotte S, Kryworuchko J, Graham ID, et al. Interventions for increasing the use of shared decision making by healthcare professionals. *Cochrane Database Syst Rev*. 2018;7(7):Cd006732.
11. Koot A, Soares P, Robenshtok E, Locati LD, de la Fouchardiere C, Luster M, et al. Position paper from the Endocrine Task Force of the European Organisation for Research and Treatment of Cancer (EORTC) on the management and shared decision making in patients with low-risk micro papillary thyroid carcinoma. *Eur J Cancer*. 2023;179:98-112.
12. Koot A, Hermens R, Ottevanger P, Netea-Maier R, Stalmeier P. Patient decision aids for patients with differentiated thyroid carcinoma: development process and alpha and beta testing. *Front Endocrinol (Lausanne)*. 2023;14:1162537.
13. Stacey D, Lewis KB, Smith M, Carley M, Volk R, Douglas EE, et al. Decision aids for people facing health treatment or screening decisions. *Cochrane Database Syst Rev*. 2024;1(1):Cd001431.
14. Henselmans I, van Laarhoven HWM, van Maarschalkerweerd P, de Haes H, Dijkgraaf MGW, Sommeijer DW, et al. Effect of a Skills Training for Oncologists and a Patient Communication Aid on Shared Decision Making About Palliative Systemic Treatment: A Randomized Clinical Trial. *Oncologist*. 2019.
15. Sepucha KR, Abhyankar P, Hoffman AS, Bekker HL, LeBlanc A, Levin CA, et al. Standards for UNiversal reporting of patient Decision Aid Evaluation studies: the development of SUNDAE Checklist. *BMJ Qual Saf*. 2018;27(5):380-8.
16. Cuschieri S. The CONSORT statement. *Saudi J Anaesth*. 2019;13(Suppl 1):S27-s30.

17. Landis JR, Koch GG. The measurement of observer agreement for categorical data. *Biometrics*. 1977;33(1):159-74.
18. Beaton DE, Bombardier C, Guillemin F, Ferraz MB. Guidelines for the process of cross-cultural adaptation of self-report measures. *Spine (Phila Pa 1976)*. 2000;25(24):3186-91.
19. Stubenrouch FE, Pieterse AH, Falkenberg R, Santema TK, Stiggelbout AM, van der Weijden T, et al. OPTION(5) versus OPTION(12) instruments to appreciate the extent to which healthcare providers involve patients in decision-making. *Patient Educ Couns*. 2016;99(6):1062-8.
20. Elwyn G GS, Barr P. Observer OPTION-5 Manual. Measuring shared decision making by assessing recordings or transcripts of encounters from clinical settings. Manual The Dartmouth Institute for Health Policy and Clinical Practice; 2018
21. Barr PJ, Thompson R, Walsh T, Grande SW, Ozanne EM, Elwyn G. The psychometric properties of CollaboRATE: a fast and frugal patient-reported measure of the shared decision-making process. *J Med Internet Res*. 2014;16(1):e2.
22. Lerman C, Trock B, Rimer BK, Jepson C, Brody D, Boyce A. Psychological side effects of breast cancer screening. *Health Psychol*. 1991;10(4):259-67.
23. Stefanek ME, Helzlsouer KJ, Wilcox PM, Houn F. Predictors of and satisfaction with bilateral prophylactic mastectomy. *Prev Med*. 1995;24(4):412-9.
24. Bachinger SM, Kolk AM, Smets EM. Patients' trust in their physician--psychometric properties of the Dutch version of the "Wake Forest Physician Trust Scale". *Patient Educ Couns*. 2009;76(1):126-31.
25. Stalmeier PF, Roosmalen MS, Verhoef LC, Hoekstra-Weebers JE, Oosterwijk JC, Moog U, et al. The decision evaluation scales. *Patient Educ Couns*. 2005;57(3):286-93.
26. Stalmeier PF, Roosmalen MS. Concise evaluation of decision aids. *Patient Educ Couns*. 2009;74(1):104-9.
27. Deber RB, Kraetschmer N, Irvine J. What role do patients wish to play in treatment decision making? *Arch Intern Med*. 1996;156(13):1414-20.
28. Whelan TJ, Levine MN, Gafni A, Lukka H, Mohide EA, Patel M, et al. Breast irradiation postlumpectomy: development and evaluation of a decision instrument. *J Clin Oncol*. 1995;13(4):847-53.
29. Stiggelbout AM, de Haes JC, Kiebert GM, Kievit J, Leer JW. Tradeoffs between quality and quantity of life: development of the QQ Questionnaire for Cancer Patient Attitudes. *Med Decis Making*. 1996;16(2):184-92.
30. Sawka AM, Straus S, Rodin G, Thorpe KE, Ezzat S, Gafni A, et al. Decision aid on radioactive iodine treatment for early stage papillary thyroid cancer: update to study protocol with follow-up extension. *Trials*. 2015;16:302.
31. Brito JP, Moon JH, Zeuren R, Kong SH, Kim YG, Iñiguez-Ariza NM, et al. Thyroid Cancer Treatment Choice: A Pilot Study of a Tool to Facilitate Conversations with Patients with Papillary Microcarcinomas Considering Treatment Options. *Thyroid*. 2018;28(10):1325-31.
32. Pitt SC, Saucke MC. Novel Decision Support Interventions for Low-risk Thyroid Cancer. *JAMA Otolaryngol Head Neck Surg*. 2020;146(11):1079-81.
33. Pitt SC, Saucke MC. Thyroid Cancer Treatment Choice Toolkit: University of Wisconsin - Madison School of Medicine and Public Health - Department of Surgery; [Available from: <https://www.hipxchange.org/ThyroidCancerTreatmentChoice>].

34. O'Neill CJ, Alam A, Chapman M, Carlson M, Clark-Pitrolo S, Fradgley EA, et al. Development of a Decision Aid for Patients With Low-Risk Thyroid Cancer: A Mixed-Methods Analysis of Feedback From Both Patient and Clinicians. *World J Surg.* 2025;49(10):2782-93.
35. Couët N, Desroches S, Robitaille H, Vaillancourt H, Leblanc A, Turcotte S, et al. Assessments of the extent to which health-care providers involve patients in decision making: a systematic review of studies using the OPTION instrument. *Health Expect.* 2015;18(4):542-61.
36. Driever EM, Stiggelbout AM, Brand PLP. Shared Decision-making in Different Types of Decisions in Medical Specialist Consultations. *J Gen Intern Med.* 2022;37(12):2966-72.
37. Mathijssen EGE, Vriezekolk JE, Popa CD, van den Bemt BJF. Shared decision making in routine clinical care of patients with rheumatoid arthritis: an assessment of audio-recorded consultations. *Ann Rheum Dis.* 2020;79(2):170-5.
38. Baghus A, Giroldi E, van Geel J, Leferink A, van de Pol MHJ, Sanders A, et al. Shared decision-making performance of general practice residents: an observational study combining observer, resident, and patient perspectives. *Fam Pract.* 2024;41(1):50-9.
39. Coulter A, Stilwell D, Kryworuchko J, Mullen PD, Ng CJ, van der Weijden T. A systematic development process for patient decision aids. *BMC Med Inform Decis Mak.* 2013;13 Suppl 2(Suppl 2):S2.
40. Stubenrouch FE, Peters LJ, de Mik SML, Klemm PL, Peppelenbosch AG, Schreurs S, et al. Improving Shared Decision Making in Vascular Surgery: A Stepped Wedge Cluster Randomised Trial. *Eur J Vasc Endovasc Surg.* 2022;64(1):73-81.
41. Elwyn G, Pickles T, Edwards A, Kinsey K, Brain K, Newcombe RG, et al. Supporting shared decision making using an Option Grid for osteoarthritis of the knee in an interface musculoskeletal clinic: A stepped wedge trial. *Patient Educ Couns.* 2016;99(4):571-7.
42. van Veenendaal H, Peters LJ, van Weele E, Hendriks MP, Schuurman M, Visserman E, et al. Effects and Working Mechanisms of a Multilevel Implementation Program for Applying Shared Decision-Making while Discussing Systemic Treatment in Breast Cancer. *Curr Oncol.* 2022;30(1):236-49.
43. Oostendorp LJM, Ottevanger PB, Donders ART, van de Wouw AJ, Schoenaker IJH, Smilde TJ, et al. Decision aids for second-line palliative chemotherapy: a randomised phase II multicentre trial. *BMC Med Inform Decis Mak.* 2017;17(1):130.
44. Lee S, Antunez AG, Sinco B, Saucke MC, Bushaw KJ, Dream S, et al. Cancer-related Fear and Worry in Patients with Low-Risk Thyroid Cancer: A Longitudinal Cohort Study. *J Clin Endocrinol Metab.* 2024.
45. Montori VM, Kunneman M, Brito JP. Shared Decision Making and Improving Health Care: The Answer Is Not In. *Jama.* 2017;318(7):617-8.
46. Hsu C, Liss DT, Frosch DL, Westbrook EO, Arterburn D. Exploring Provider Reactions to Decision Aid Distribution and Shared Decision Making: Lessons from Two Specialties. *Med Decis Making.* 2017;37(1):113-26.
47. Richter R, Jansen J, Bongaerts I, Damman O, Rademakers J, van der Weijden T. Communication of benefits and harms in shared decision making with patients with limited health literacy: A systematic review of risk communication strategies. *Patient Educ Couns.* 2023;116:107944.



Chapter 6

Position paper from the Endocrine Task Force of the European Organization for research and treatment of cancer (EORTC) on the management and shared decision making in patients with low-risk micro papillary thyroid carcinoma

Anna Koot¹, Paula Soares², Eyal Robenshtok³, Laura D Locati⁴,
Christelle de la Fouchardiere⁵, Markus Luster⁶, Massimo Bongiovanni⁷, Rosella Hermens⁸,
Petroneilla Ottevanger⁹, Frans Geenen¹⁰, Beate Bartes¹¹, Harald Rimmele¹²,
Cosimo Durante¹³, Els Nieveen-van Dijkum¹⁴, Peep Stalmeier¹⁵, Marek Dedecjus¹⁶,
Romana Netea-Maier¹⁷

¹Department of Internal Medicine, Division of Endocrinology, Radboud University Medical Center, 6525 GA Nijmegen, the Netherlands; Radboud Institute for Health Sciences, Department for Health Evidence, Radboud University Medical Center, 6500 HB Nijmegen, the Netherlands.

²Institute for Research and Innovation in Health - i3S/Institute of Molecular Pathology and Immunology of the University of Porto-IPATIMUP, 4200-135 Porto, Portugal; Faculty of Medicine of the University of Porto, Alameda Prof. Hernani Monteiro, 4200-319 Porto, Portugal.

³Endocrinology and Metabolism Institute, Rabin Medical Center, Sackler Faculty of Medicine, Tel-Aviv University, Israel.

⁴Department of Internal Medicine and Therapeutics, University of Pavia, Pavia, Italy; Translational Oncology Unit, IRCCS Istituto Clinico Scientifici Maugeri, Pavia, Italy.

⁵Medical Oncology Department, Centre Léon Bérard, Lyon, France.

⁶Department of Nuclear Medicine, University Hospital Marburg, Marburg, Germany.

- ⁷ Internal Medicine Unit, Department of Medicine, Ospedale di Circolo di Rho, ASST Rhodense, Milan, Italy.
- ⁸ Scientific Institute for Quality of Healthcare (IQ Healthcare), Radboud University Medical Center, 6500 HB Nijmegen, the Netherlands.
- ⁹ Department of Internal Medicine, Division of Oncology, Radboud University Medical Center, 6525 GA Nijmegen, the Netherlands.
- ¹⁰ Schildklierorganisatie Nederland (SON), the Netherlands.
- ¹¹ Vivre sans Thyroïde (VST), France.
- ¹² Bundesverband Schilddrüsenkrebs - Ohne Schilddrüse Leben e.V., Germany.
- ¹³ Department of Translational and Precision Medicine, Sapienza University of Rome, 00161 Rome, Italy.
- ¹⁴ Department of Surgery, Amsterdam UMC Location University of Amsterdam, Cancer Center Amsterdam, the Netherlands.
- ¹⁵ Radboud Institute for Health Sciences, Department for Health Evidence, Radboud University Medical Center, 6500 HB Nijmegen, the Netherlands.
- ¹⁶ Department of Endocrine Oncology and Nuclear Medicine, Maria Skłodowska-Curie National Research Institute of Oncology, Warsaw, Poland.
- ¹⁷ Department of Internal Medicine, Division of Endocrinology, Radboud University Medical Center, 6525 GA Nijmegen, the Netherlands.

Abstract

The incidence of differentiated thyroid cancer (DTC) has been increasing worldwide, mostly, as an increase in the incidental detection of micro papillary thyroid carcinomas (microPTCs), many of which are potentially overtreated, as suggested by the unchanged mortality. Several international guidelines have suggested a less aggressive approach. More recently, it has been shown that active surveillance or minimally invasive treatments (MIT) are good alternatives for the management of these patients. In this context, patient participation in the decision-making process is paramount. The Endocrine Task Force of the European Organisation for Research and Treatment of Cancer (EORTC) has undertaken the task to establish consensus and define its position based on the scientific evidence concerning, 1) the current state of diagnostic and management options in microPTCs, including the current opinion of physicians about shared decision making (SDM), 2) the available evidence concerning patients' needs and the available decision instruments, and 3) to provide practical suggestions for implementation of SDM in this context. To improve SDM and patients' participation, knowledge gaps and research directions were highlighted.

Keywords: Papillar, Thyroid, Microcarcinoma, Treatment options, Shared decision making

Introduction

Differentiated non-medullary thyroid carcinoma (DTC) is the most common endocrine malignancy. The incidence of DTC has increased worldwide during the last decades, largely as a result of increased diagnostic scrutiny and the wider accessibility of imaging and surveillance [1-3]. Of these, often incidental findings, papillary thyroid carcinoma (PTC) accounts for the majority of the malignant lesions, a histologic type characterised as a slow-growing indolent tumour, with an excellent prognosis and low mortality rate. Approximately half of these are intrathyroidal tumours <1 cm in size, also known as low-risk micro papillary thyroid carcinomas (microPTCs) [4]. The updated 2022 WHO classification [5] recommends detailed subtyping of papillary microcarcinomas similar to their counterparts that exceed 1 cm and recommends not designating them as a subtype of PTC. Therefore, in this paper low-risk microPTCs are defined as PTCs <1 cm in size, with or without known *BRAF*, *TERT* or *RET* mutation, and no other worrisome features such as extrathyroidal extension, aggressive histology, vascular invasion or lymph node or distant metastases [6]. Because other histological types of microcarcinoma such as follicular and oncocytic thyroid microcarcinomas are extremely rare and there are insufficient studies comparing the outcome of different management strategies for these tumours; they will remain outside the scope of this paper.

In patients with microPTCs, the most recent American Thyroid Association (ATA) and European Society of Medical Oncology (ESMO) guidelines [6,7] recommend a more limited approach towards diagnosis and treatment. As such, they recommend abstaining from screening for thyroid tumours in asymptomatic subjects and additional diagnosis by fine needle aspiration (FNA) in nodules detected on thyroid ultrasound which are smaller than 1 cm. If a microPTC is diagnosed, thyroid lobectomy (TL) would be the initial surgical procedure [6,7]. In contrast, for larger DTCs (>1 cm) confined to the thyroid, in most countries the recommended therapy consists of a total thyroidectomy (TT) followed by postoperative radioactive iodide (RAI) treatment to ablate the thyroid remnant tissue or as an adjuvant therapy [6]. However, a recent randomised controlled prospective study by Leboulleux *et al.* showed no benefit of post-operative RAI therapy in low-risk tumours 1–2 cm in size, after a follow-up of three years [8], and Lin *et al.* already showed in 2009 that RAI was not associated with a reduction in risk of recurrent overall or disease specific survival in patients with non-metastatic microPTC [9]. Over the past decade increasing evidence indicates an even more conservative approach for low-risk DTCs (>1 cm) or even watchful waiting for microPTCs (<1 cm) is a safe alternative. Based on findings of investigators at two Japanese institutions,

the Japanese Clinical Practice Guidelines for Thyroid Tumours introduced active surveillance without surgery as one of the management options for microPTC [10-12]. The safety of closely watching or delaying surgery in microPTC patients was later tested and confirmed in different countries around the world [13-16], with this option entering the latest international guidelines' recommendations [6,7]. Recently, minimally invasive treatments (MIT) could also be offered to these patients when expertise with these techniques is available [17], but the exact place of MIT in the management of microPTC as an alternative for surgery or active surveillance remains to be defined.

At this moment, active surveillance or MIT therapy as treatment options have not been widely implemented in clinical practice, and the majority of patients with microPTCs undergo thyroid surgery and many are potentially overtreated [18-20]. Prerequisites for a less aggressive treatment are data considering survival, optimal pre-operative diagnostics including pre-operative molecular profiling of the tumour, adequate surgery and post-operative follow-up. As the ATA guidelines acknowledge the importance of patient preferences in the decision-making process [6], the individual needs, preferences and values of the patients need to be explored and communicated between patients and physicians to ensure shared decision making (SDM). When patients face preference-sensitive decisions, physicians have an important role in realising SDM [21]. Encouraging patients' participation in the decision process requires on one hand appropriate communication skills from the physicians and on the other hand a detailed knowledge and understanding on the patients' needs. To facilitate SDM in the doctor-patient communication, decision-support tools such as decision aids (DAs) and values clarification exercises are valuable tools to inform patients and help them explore their values [22,23].

In this paper, we aim to present the following: 1) the current state of diagnostic and treatment approaches towards microPTCs including the current opinion of physicians about SDM, 2) the available evidence concerning patients' needs and the available decision instruments, 3) and to provide practical suggestions based on the available evidence, which can help the clinicians managing patients with microPTC. In addition, knowledge gaps and research directions will be highlighted to improve SDM and improve patients' participation and empowerment; this will be done for DTC patients in general and for microPTC patients in particular. The members of the Endocrine Task Force (ETF) of the European Organisation for Research and Treatment of Cancer (EORTC) recognise the importance of addressing these issues. They also provide an ideal platform to design and perform prospective trials assessing different management strategies for low-risk patients, and to

conduct studies to increase awareness of the importance of the SDM process in the management of patients with microPTC. The EORTC ETF is also helpful to tailor the decision-making process in a country/culture-specific manner to improve the care for patients with microPTC with respect to doctor-patient communication, information provision, patients' participation in the decision process about their treatment, and patient empowerment.

Methods

The committee (LDL, RN-M, MD, CF, MB) was assigned to prepare this position paper in collaboration with representatives of patient organisations from the Netherlands (Schilddklierorganisatie Nederland (SON)), France (Vivre sans Thyroïde) and Germany (Bundesverband Schilddrüsenkrebs – Ohne Schilddrüse Leben e.V.). They have identified the implementation of SDM in the management of patients with microPTC as an item of interest requiring a position statement. To determine the current knowledge and opinion on SDM of the members of the EORTC ETF, we developed a questionnaire used to undertake a survey among the members of the EORTC ETF. The questionnaire contained three domains (views and knowledge, applying SDM, and barriers and facilitators) and a total of 25 questions (Supplementary Tables 1 and 2).

The committee invited all members of the EORTC ETF specialised in thyroid cancer to contribute to the position paper in November 2021. The participants included four endocrinologists (AK, ER, RN-M, CD), one researcher (PS), one molecular pathologist (MB), two surgeons (MD, EN-D), one nuclear medicine physician (ML), three oncologists (PO, CF, LDL), one expert in development of DA instruments and SDM (PSt) and one expert in implementation and evaluation of innovative tools in healthcare (RH) from seven different European countries (France, Germany, Israel, Italy, Poland, Portugal, The Netherlands) and representatives of the aforementioned patient organisations (FG, BB, HR).

The committee selected specific areas to be addressed: 1) epidemiology of microPTC; 2) current recommendations in national and international guidelines with respect to management of microPTC; 3) management options for microPTC 4) SDM in diagnosis and treatment of patients with microPTC including: needs and preferences of patients with microPTC with respect to SDM, available decision instruments, potential barriers and facilitators for SDM, 5) knowledge gaps and research directions.

Literature search

A literature search was conducted by the authors, focused on management of microPTC and SDM. The databases searched were PubMed, and the Cochrane Library. The search languages were English, German, French, Italian, Polish, Israeli, and Dutch.

Consensus meeting

The committee organised a consensus meeting in which the members shared their clinical knowledge and experience and discussed the above-mentioned specific areas in an on-line meeting, found general agreement and formulated concluding statements.

Preparation of manuscript

The committee members drafted the position paper based on the available literature and the results of the consensus meeting.

Results

Epidemiology of microPTC

MicroPTC is a malignant tumour with follicular cell differentiation, usually forming papillary structures and presenting the distinctive features of PTC like-nuclei (large, clear, irregular, with grooves and pseudo-inclusions). The classification is made based on the tumour morphology and size (<1 cm). This size criteria as a classifier starts to be questioned, arguing that there is no solid biological basis indicating 10 mm in size as the boundary between extremely low and low-risk microPTCs [24]. MicroPTMCs could be characterised by mutations or rearrangements in genes belonging to the MAPK pathway (*BRAF*, *RAS*, and *RET/PTC*). MicroPTCs constitutes now nearly half of the diagnosed PTCs, and most of them are incidental findings in patients subjected to routine imaging examination for a medical condition. The paradigmatic example is that of South Korea in the beginning of the century [25], with 15 times rising of PTC incidence after the implementation of thyroid-cancer screening using ultrasonography. Notably, no increase in the mortality rate was detected, indicating that these subclinical latent cancers do not tend to progress to aggressive disease. MicroPTCs are also a frequent finding in autopsy studies (1.5%–35.6%), and in patients who undergo partial or TT for benign thyroid diseases [26]. The screening experience in the Fukushima Thyroid Examination (FTE) campaign, that started in 2012, also raises concerns about over-diagnosis with disputable opinions whether the lesions identified are radiation-induced or a screening effect as the radiation exposure of the thyroid gland was low [27].

Therefore, screening in children and young adults, even after potential radiation exposure, should only be performed when there is a clear rationale and not routinely.

Given the absence of clinical significance of most of these tumours, in 2003 it has been suggested to change their terminology from 'incidental papillary thyroid microcarcinoma' to 'papillary thyroid microtumour', in order to take out the heavy 'carcinoma', and to avoid anxiety and overtreatment of these tumours [28].

It must however be stressed that rare cases of microPTC might present with significant disease, occasionally with local and (rarely) with distant metastatic disease. These tumours behave similar as PTC.

Statement 1: *Most microPTCs are incidental findings that often remain subclinical latent and rarely progress to clinically aggressive disease. The occasional microPTCs presenting with local and distant metastatic disease are kept out here and represent a different clinical entity.*

Views and knowledge about SDM and its current use among the EORTC ETF physicians

In total 38 physicians (response rate 5%) completed the questionnaire. Most of the physicians were endocrinologists (32%) or oncologists (35%). Fifty-nine per cent work in a university hospital and 35% in a comprehensive cancer center. Most (84%) of the respondents had >12 h a week direct patient contact (Supplementary Table 1).

First, we asked physicians about their views and knowledge on SDM. Almost all (97%) respondents indicated that they knew what SDM means and they had sufficient knowledge (84%) to properly apply SDM. They considered SDM to be very important and to lead to better patient care. Nevertheless, only 32% of respondents received a specific training in SDM (Supplementary Table 2).

Second, we asked how physicians apply SDM in consultations in which treatment decisions are made. If more options were available, 91% of physicians indicate that they discuss this almost always with their patients and 97% inform their patients orally. For example, they describe benefits and/or side-effects (89%), they give information about the treatment options (84%), they discuss what matters most to their patient (74%), and they provide information on long-term medical outcomes (82%). Most of the physicians did not use a decision tool or instrument (74%) (Supplementary Table 2).

Third, we asked about barriers and facilitators of SDM. Possible barriers involve lack of time, organisational factors, and patient characteristics. Most often mentioned facilitators were the access to specific decision tools, availability of specific training (e.g. individual/group communication training, e-learning), and also organisational factors.

Statement 2: *Participating physicians agree on the importance of applying SDM in patients with microPTC.*

Current recommendations in national and international guidelines

The accumulating evidence and awareness regarding the indolent course of microPTC have led to significant changes in international guidelines in the last decade. In the past, nodules <1 cm were routinely biopsied based on previous [29-31] guidelines. The 2015 ATA guidelines caused a major shift with the recommendation not to biopsy nodules <1 cm (without extra-thyroidal extension or suspicious lymph nodes), together with the option for active surveillance if such nodules were biopsied and found cancerous [6]. This recommendation has been reiterated in the 2017 ETA ultrasound guidelines [32], and in the 2019 ESMO guidelines (which also included 1 cm nodules) [7]. This recommendation has been lately confirmed in 2022 with the most recent ESMO guidelines [7].

Table 1. Management recommendations for nodules ≤1cm in the European guidelines published after 2015.

Country	Type	Year	FNA ^a of suspicious nodules ≤1 cm	Active surveillance for FNA ^a proven PTMC	Recommended surgery for PTMC ^b
UK [37]	National Multidisciplinary Guidelines	2016	Yes	No mention	Lobectomy, discuss at MDT ^c
EU [39]	ETA Ultrasound Guidelines	2017	Selective	Yes	No mention
Poland [36]	Guidelines of National Societies	2018	Yes/follow-up is acceptable	Yes	Lobectomy is acceptable
Italy [33]	Consensus of six Italian societies	2018	5–9 mm: FNA/follow-up	Yes	Lobectomy may be considered
EU [7]	ESMO Clinical Practice Guidelines	2019	No	Yes	Lobectomy
Spain [38]	Spanish Society of Medical Oncology guidelines	2019	Selective (based on clinical suspicion)	No mention	lobectomy may be sufficient
Switzerland [35]	Multidisciplinary approach	2019	No mention	No mention	Lobectomy
Belgium [34]	National Practice Guidelines	2020	Selective (beneath capsule, growth)	Yes	Lobectomy may be sufficient

^a Fine needle aspiration.

^b Patients with a single focus of PTMC <1 cm without extra-thyroidal extension, lymph node involvement, or high risk histology.

^c Multidisciplinary team.

While these guidelines are based on size alone, recent studies demonstrated that not all microscopic suspicious nodules are suitable for follow-up. In 2021, microPTC guidelines were published by the Japan Association of Endocrine Surgery, which introduced a new concept of 'low-risk' and 'high-risk' PTMC based on patients' age (below or above 20 years) and nodule location (adherence to the trachea or to the course of the recurrent laryngeal nerve (RLN)). These characteristics were valuable as prognostic parameters and for the decision process [11]. The recommendation of

the currently available guidelines across Europe for the diagnosis and management of microPTC, are summarised in Table 1 [7,33-39].

Statement 3: *Current guidelines agree in the implementation of a more conservative management approach towards subcentimetric thyroid nodules and microPTC.*

Management options for patients with microPTC

Several approaches are available for asymptomatic patients with microPTC without clinical or imaging evidence of disseminated disease: 1) TL, 2) TT (with or without I-131 ablation), 3) MIT therapy to ablate the tumour or 4) active surveillance. Currently, there are no trials comparing these options head-to-head. The evidence with respect to the outcomes of patients with microPTC treated by different approaches or those undergoing active surveillance is provided from either retrospective or prospective, non-randomised observational trials. In a recent systematic review, Chou *et al.* showed that active surveillance and immediate surgery have similar oncological outcomes, but the quality of evidence remains low in almost all included studies. Therefore, methodological limitations preclude strong conclusions [40]. Traditionally TT was a standard of care in this group of patients; however recent guidelines suggest lobectomy for the patients with microPTC. Depending on factors such as the extent of thyroidectomy and underlying thyroid function, lifelong thyroid hormone replacement treatment may be required. It should be mentioned however that TT appears to be an over-treatment reserved to only very select cases such as patients with a history of radiation therapy to the neck in paediatric age. Of notice, also for low-risk thyroid carcinoma patients with tumours >1 cm, a current prospective study is ongoing (HoT trial (ISRCTN17004671)) in the United Kingdom, investigating the non-inferiority of TL compared to TT. The majority of the guidelines do not recommend additional treatment with I-131 for microPTC, but indicate that this could be carefully considered in the presence of clinical factors rendering the tumour a higher risk of recurrent disease such as multifocality, histological features indicating invasiveness of the tumour or a more aggressive phenotype, presence of metastatic disease, the context of familial thyroid carcinoma, a history of radiation exposure at a young age, or presence of molecular features such as coexistent *TERT* promotor and *BRAF V600E* mutation [30,41-43]. However, Leboulleux *et al.* showed in a recent prospective study that although 43% of patients in their series had multifocal disease, there was no benefit of I-131 on oncological outcome in terms of recurrence rate after a follow-up period of three years. Moreover, no I-131 uptake has been observed in 70% of *BRAF* mutated PTC and in >90% of *BRAF-TERT* mutated PTC [8].

Given concern about potential overtreatment of small, low-risk PTCs, active surveillance has been proposed for such tumours [7,32-34,36]. There is increasing evidence, that for selected patients with microPTC, active surveillance may be an alternative to surgery. Moreover, progress in techniques of MIT therapy has taken place and these techniques are also becoming an option for treatment of microPTC [17]. To date, none of the national guidelines for the management of patients with thyroid carcinoma have incorporated the MIT therapy in their recommendations. Recently, the ETA has published guidelines for the use of MIT therapy for treatment of patients with thyroid carcinoma, among which an important part is dedicated to microPTC [17]. Nevertheless, limiting factors represent the lack of broadly available expertise with these techniques and the lack of head-to-head comparative studies with either surgery and/or active surveillance. A recent propensity matched cohort study, has shown that in terms of risk of complications, duration of hospitalisation, blood loss and the costs were lower in MIT treated patients compared to TL [44]. Both procedures require long-term ultrasound follow-up, similar to the patients receiving active surveillance. The latter have no risks associated with an invasive procedure and no risk of iatrogenic hypothyroidism but do require lifelong follow-up and some patients will require surgery at some point because of tumour progression. A robust cost-effectiveness analysis to compare surgery, MIT and active surveillance is currently not available and is therefore paramount.

Table 2 summarises the outcome of the different therapeutic options for patients with microPTC and presents the clinical and demographic characteristics that can guide the patients and physicians in the decision process, and Fig. 1 represents the ultrasound characteristics for selection of candidates for active surveillance or MIT therapy and for immediate surgery. Regardless the management option, there is no risk of cancer related mortality or distant metastatic spread. The recurrence rate is similar after all treatment options and on average it varies between 0.6 and 2.5% in the cervical lymph nodes [13,45-47] and from 0.8 to 3.2% in the contralateral thyroid lobe [47,48]. After a 5-year follow-up, tumour enlargement has been observed in 5.3% of the patients undergoing active surveillance [13]. On the long-term, tumour enlargement was reported in 12–23% of the patients [48-50]. On average 1.6% and 2.6% of the patients undergoing TL and MIT, respectively, undergo delayed thyroid surgery [47,51] and up to 32% of patients undergoing active surveillance [13], not limited to those showing disease progression. Because, active surveillance [13,48-50] and MIT therapy [47,52] are not yet widespread, the available literature with respect to these treatment modalities is more limited in terms of number of available studies, total number of patients included in the respective studies and duration of follow-up. Therefore, gathering more data on the

outcome of patients opting for active surveillance, preferably randomised trials of European citizens is paramount. Nonetheless, the available literature indicates that they could be offered as alternatives with similar oncological outcome of carefully selected patients who do not prefer (or refuse) surgery or for which surgery is not feasible or less attractive because of severe comorbidities. For these patients, when they do not feel comfortable with or cannot adhere to active surveillance, and do wish to undergo surgical treatment, MIT can be offered if the expertise is available, but one should remain aware of the potential risks and costs of the procedure and the need for long term follow-up, though the precise frequency of follow-up procedures has not yet been defined. The patients on active surveillance that present microPTC growth are amenable for surgery. An increase in size of ≥ 3 mm or reaching a maximal diameter of >10 mm have been mentioned as indicators of progression [11], though immediate surgery may not always be required as further growth after initial enlargement continues only in a minority of patients and many cases show tumour shrinkage [53]. Nonetheless, surgery can be performed in growing nodules depending on the patient preferences or other clinical factors.

In selecting patients that are candidates for different treatments, several clinical criteria have been described. Both active surveillance and MIT therapy can be considered in low-risk microPTC according to the Japan Association of Endocrine Surgery and the ETA [11,17]. The Japan Association of Endocrine surgeons does not support active surveillance in patients with microPTC showing a potentially more aggressive clinical phenotype on cytology (such as tall cell variant PTC), for tumours located along or invading the RLN or tumours that are adherent to or invading the trachea, and in patients younger than 20 years. The latter because of lack of outcome data for this age group. Moreover, when surgery is required for coexistent thyroid or parathyroid disease, patients are not amenable for active surveillance. According to the ETA guidelines, MIT therapy should not be considered in patients with cytological or molecular worrisome features (such as presence of a *TERT* promotor and *TP53* mutations) or multifocality. Also, presence of subcapsular, posterior or paratracheal localisation, extrathyroidal extension and young age do not favour MIT therapy [17]. Therefore, weighing the different treatment options requires multidisciplinary expertise and risks of potential overtreatment in terms of a disbalance between benefits, risks, patients distress and anxiety, and medical costs should be critically assessed.

Statement 4: *Presently, several treatment modalities with similar oncologic outcomes are available for patients with microPTC, 1) TL, 2), TT, 3) MIT therapy, and 4) active surveillance. Specific patient and tumour characteristics and potential risks of overtreatment have to be considered with the multidisciplinary team before making a treatment choice.*

Table 2. Management options for patients with PTMC

	Total thyroidectomy (with or without I-131 ^a)	Thyroid lobectomy	Active surveillance	Minimally invasive thermal (MIT) therapy
Definition:	Surgical removal of the thyroid gland	Surgical removal of half of the thyroid gland	Closely monitoring the thyroid cancer over time	US-guided treatments with TA, EA, laser, RFA, LA, or MWA ^a
Factors deemed amenable for the treatment option [15,16]:				
Patients characteristics	- Young age - No relevant comorbidities - Family history of thyroid cancer - Radiation therapy to the neck at paediatric age	- Young age - No relevant comorbidities - No family history of thyroid cancer	- Older age (e.g. >60 years) - Relevant comorbidities - No family history of thyroid cancer - Informed about possible surgical intervention in the future if necessary - Willing to participate in follow-up plans - Actively choosing active surveillance	- Older age (e.g. >60 years) - Relevant comorbidities - No family history of thyroid cancer - Actively choosing MIT therapy
Pathology features	- Worrisome morphological features - High-risk molecular pattern	- Absence of worrisome morphological features - No high-risk molecular pattern (if assessed)	- Absence of worrisome morphological features - No high-risk molecular pattern (if assessed)	- Absence of worrisome morphological features - No high-risk molecular pattern (if assessed)
Ultrasonographic features	- Subcapsular, posterior, paratracheal location - Extrathyroidal spread - Lymph node metastases	- Subcapsular, posterior, paratracheal location - No extrathyroidal spread - Absence of lymph node metastases	- Solitary thyroid lesion - Well defined margins - No capsular contact - No evidence of extrathyroidal spread - Absence of lymph node metastases	- Solitary thyroid lesion - Central location - Well defined margins - No capsular contact - No evidence of extrathyroidal spread - Absence of lymph node metastases
Characteristics of medical team	- High-volume thyroid surgery	- High-volume thyroid surgery	- High-quality neck ultrasonography	- High-quality neck ultrasonography
Treatment duration	90–120 min	60–90 min	Not applicable	10–30 min
Complication rate (mean% (95% CI))	18% ^d [43]	7.8% (4.6–13.1) ^b [45] 1% ^d [43]	Not applicable	3.3% (1.7–6.2) ^b [43] Major 0.7% (0–1.5) ^d [50] 2.6% (0.6–11.1) [45]
Delayed thyroid surgery (mean% (95% CI))	Not applicable	1.6% (0.5–4.9) [45]	8.7% to 32.0% [12]	
Recurrence rate:				
Tumour enlargement (≥3 mm) (mean% (95% CI))	Not applicable	Not applicable	12–23% [46–48] 5.3% (4.4–6.4) ^d [12]	Not available
Locoregional recurrence (mean%)	1.5–1.6% (cervical lymph nodes) ^b [43,44]	0.6% (cervical lymph nodes) ^b [43,44] 0.88–3.2% (contralateral lobe) ^b [43,44] 0% [45]	1.6% (1.1–2.4) ^d [12]	2.6% (1.2–5.5) [45]
Distant metastases	Not available	0% [45]	0% ^d [12]	0% [45]
Costs of the procedure	Costs of surgery and hospitalisation	Costs of surgery and hospitalisation	Leave of absence of the procedure	Costs of the MIT therapy
Costs of follow-up	Costs of the follow-up visits (duration: temporary)	Costs of the follow-up visits (duration: temporary)	Costs of the follow-up visits (duration: indefinite)	Costs of the follow-up visits (duration: indefinite)

^a US-guided: ultrasound guided, TA: thermal ablation, EA: ethanol ablation, RFA: radiofrequency ablation, LA: laser ablation, MWA: microwave ablation.

^b Complications included for the surgery group: voice changes 4.3% (1.5% permanent), hypoparathyroidism 3.2% and wound infections 1%. Complications in the ablation group included voice changes 3.3% (0.8% permanent).

^c Highest complication rates reported for MWA 5.1% (2.8–7.3), for RFA 2.6% (0–5.1), and for LA 0.6% (0–2.5). In this systematic review and meta-analysis the pooled proportion estimates for overall complication rate was 3.2% (1.1–5.1) and for major complications rate 0.7% (0–1.5). All 11 major complications were voice changes, including one permanent and 10 transient voice change lasting for at least one month.

^d After 5 years of follow-up.

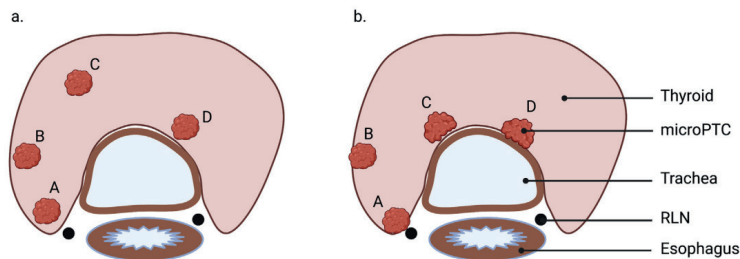


Fig. 1. Schematic representation of eN0, eM0, microPTC characteristics for selection of candidates for active surveillance or MIT (a) and for immediate surgery (b). a) Solitary thyroid nodule with well defined margins, surrounded by a normal thyroid tissue rim, not adjacent to recurrent laryngeal nerve (RLN) (A, B, C). Tumours touching the trachea with acute angle between the tumour and trachea (D). b) Solitary thyroid nodule adjacent to (or invading) RLN (A), with subcapsular localisation not surrounded by normal thyroid tissue rim or with suspicion of extrathyroidal extension (B). Tumours invading or touching the trachea with an obtuse angle between the tumour and trachea (C, D).

SDM in the management of microPTC

The decision on which approach is to be implemented should be preference-based and should reflect patients' goals and values. On the other hand, the knowledge about the treatment decision-making process for patients with microPTC is limited. Moreover, personal history or perceptions about cancer or thyroidectomy, contextual factors, family considerations, and trust in health care providers strongly influence treatment choices. Undergoing unnecessary treatment that does not reflect patients' goals and values may result in patients' dissatisfaction and loss of trust to the medical healthcare provider. SDM may provide a more appropriate solution for the proper selection of the optimal microPTCs treatment for the individual patient.

When patients are diagnosed with cancer, they are challenged with managing complex information about their diagnosis, treatment options, side-effects and the impact on quality and length of life, and social and professional functioning [54,55]. Engaging individuals with cancer in their treatment decision making has received increased attention as a key element of patient-centred cancer care and communication [55,56]. SDM is a collaborative process by which patients and their healthcare clinicians make medical decisions together, using the scientific expertise of the health care team while considering the preferences of the patient [57]. At each step of the decision process, patients rely on their clinicians to support them by providing information in a clear manner, describing treatment options, and helping them manage uncertainty, especially when situations of clinical equipoise are present [54,58].

Specifically, in the field of oncology, several institutions (the National Comprehensive Cancer Network (NCCN), the Center for Medicare and Medicaid Innovation (CMMI) and the American Society of Clinical Oncology (ASCO)) highlight the need for more widespread implementation of SDM. SDM has been gaining prominence in oncology practice with the increasing use of evidence-based guidelines related to diagnosis, complex treatment options, the inherent challenges of the risk communication process, and the emergence of value assessment frameworks.

Early detection of certain cancers has been a major goal of cancer care. This mindset has been disseminated to the public, such that the preference of early-stage diagnosis and early treatment is difficult to overcome. In Europe, given the difficulty in avoiding overtreatment of low-risk thyroid cancer, it is necessary to decrease the number of diagnoses of low-risk tumours. This is a substantial barrier to overcome when advocating for a strategy such as active surveillance.

According to the existing clinical trials, appropriately selected microPTC patients, active surveillance is a safe and effective treatment option [11,48,59, 60, 61]. Nevertheless, Hedman *et al.* reported that 48% of the thyroid cancer survivors continued to have concerns about having a recurrence, even after 14–17 years after the diagnosis, although the investigators also observed, in 89% of the survivors, that the disease did not influence their view on life [62]. Smulever and Pitoia [63], and Oh *et al.* [64] reported a state of anxiety in most of the patients. Discomfort with the idea of active surveillance extends to clinicians, who report dissatisfaction with active surveillance as a strategy, citing lack of confidence in the quality of the literature, a belief that patients will be more satisfied with surgical therapy, and fear of eventual development of metastatic disease [65,66]. Despite these studies, Sawka *et al.* recently showed that approximately three-quarters of the participants in their study chose active surveillance over surgery [67]. In a report of the perspectives of patients who underwent active surveillance, Davies *et al.* showed that 60% of the respondents said their worries decreased over time, and 83% agreed that undergoing active surveillance was the best decision [68]. Abovementioned results were also confirmed in a recent review from Wei *et al.* [69]. Participants who were given the option of active surveillance or surgery overwhelmingly chose the more conservative option throughout the studies, with a range of 70–84% [67,69-73]. Several studies compared the quality of life (QOL) in patients who underwent immediate surgery and those who received active surveillance. For example, Jeon *et al.* [74] reported that psychological problems in daily life were less frequent in the active surveillance group than in the group that underwent TL. Patients with microPTC who underwent TL experienced more health-related problems and the incidence of unfavourable events was highest in the immediate surgery group according to Oda *et al.* [75]. In a multicentre, longitudinal study, Kong *et al.* [76] reported a better psychological health at baseline and physical and psychological health at follow-up in the active surveillance group. Similar results were also found by Nakamura *et al.* [77] and Moon *et al.* [78]; patients in the surgery group had more complaints and were more anxious and depressed than the active surveillance group.

Another treatment modality is MIT therapy, with the same satisfactory therapeutic effects but minimal post-operative trauma, and that can significantly improve the patients' QOL [79]. Studies comparing patients who underwent MIT therapy and who underwent immediate surgery showed that patients who underwent MIT therapy experienced a better QOL [80]. For example Lan *et al.* showed less physical and emotional problems in patients who underwent MIT therapy. Patients were not more concerned about the progression of the disease [81]. Although in general

most patients and physicians prefer SDM, there is a lack of literature in SDM with respect to both diagnosis and treatment of patients with microPTC.

Statement 5: *Applying SDM is paramount for patients with microPTC for whom more treatment options with similar oncologic outcomes are available. Choosing a non-surgical approach by patients with microPTC who were given this option, was associated with less anxiety and a better quality of life.*

Exploring the needs and preferences of patients with microPTC

When discussing available and possible treatment options for patients with microPTC, it is important to understand what patients' needs and preferences are, and what is most appropriate in the individual context [55]. Recently, several studies conducted a discrete choice experiment (online surveys) to characterise patients' preferences in treatment decision making in low-risk papillary thyroid cancer [73,82,83]. For example, Ahmadi *et al.* [82] showed that an excellent patient-physician communication is important for providing patients with a good understanding of the risks and benefits associated with the extent of surgery. In 2019 Pitt *et al.* [84] already described the need of a strong physician-patient relationship. McCaffery and Nickel [85] and Davies *et al.* [68] described the patient-physician relationship in terms of a traveller (patient) and their guide (physician) as an important part of SDM. The patient's experience is at the centre of decision-making: avoiding unnecessary surgery to prevent rare but significant adverse effects. Furthermore, giving information about active surveillance before the biopsy sample is taken is crucial to allow a patient to process this information in a non-anxious state [86]. Retention and stability of follow-up was the most important factor that supported patients in staying with surveillance [68]. Nickel *et al.* [72] showed that changing the terminology of small PTCs into microcarcinomas may be a strategy to reduce patients' anxiety levels and help them consider less invasive management options. Jensen *et al.* [87] characterised the attitudes and beliefs of patients and physicians about management and overtreatment of microPTC, where D'Agostino *et al.* [88] focused more on the patients' decision-making process. To achieve value-based care, explicit discussion of patients' preferences will be key [89]. Potentially, a more value-based patient-centred approach may also help to reduce unnecessary interventions that may cause harm and waste resources without providing a genuine benefit.

Statement 6: *When physicians are aware of patients' needs and preferences, they are better able to apply SDM.*

Decision support tools in patients with microPTC

SDM could be supported by the use of decision support tools or decision aids. These tools are suitable instruments to support decision making, such as decision aids (digital/paper), option grids, leaflets or flyers. Studies have shown that decision support tools generally improve patients' knowledge, and result in more realistic patient treatment expectations, in an increased active patient participation in decision-making and reduce indecisiveness [22,90]. It helps physicians to present balanced information about risks, benefits, and outcome information of the treatment options [91]. Furthermore, physicians may have some difficulty communicating the different treatment options [70]. Patients with low-risk thyroid cancer report not knowing what questions to ask, while physicians report not knowing how to elicit and incorporate patients' preferences [87,89]. For example, two qualitative studies in patients with microPTC demonstrated that they chose surgery unaware of the potential value of active surveillance [88,92]. These findings suggest that there is a need for decision support tools to implement the recommendation into practice. Recently, Brito *et al.* [70] and Pitt *et al.* [93,94] both developed a thyroid cancer treatment choice tool (paper cards). The goal of these tools is to help physicians and patients with microPTC make treatment decisions. Patients and their families can prepare by reviewing the interventions before their consultation or physicians can introduce the materials during the visit. Before these tools were implemented on broad scale, further testing is needed to determine clinical efficacy.

Statement 7: *Decision support tools could be helpful both for physicians and for patients with microPTC to communicate about the options and make treatment decisions.*

Barriers and facilitators towards implementation of SDM for patients with microPTC

As mentioned before, SDM has been recommended as an approach to increase the chance that patient's values and preferences are reflected in treatment decision-making. However, despite its widely acknowledged importance, current research indicates considerable differences between preferred and perceived level of implementation. In 2008 Légaré *et al.* [95] updated a systematic review of barriers and facilitators to implement SDM in clinical practice. The most reported barriers were lack of time and applicability due to patient characteristics, and the clinical situation. The most mentioned facilitators were provider motivation and positive impact on the clinical process and patient outcomes. Another systematic review divided several barriers in descriptive themes under two broad analytical themes: 1) how the healthcare system is organised and 2) what happens during the

healthcare consultation. They also concluded that many barriers were modifiable, and can be addressed by attitudinal changes at the level of patient, clinician/healthcare team, and the organisation [96].

More recently, several studies were published describing barriers and facilitators in SDM. A wide range of barriers and facilitators across individual, organisational, and system levels were reported. Barriers specific to the hospital setting included noisy and busy ward environments, a lack of private spaces to conduct SDM conversations, and poor physician communication [55,97,98]. The most prominent barriers to active surveillance were related to physician factors, although guideline-specific and external barriers were also observed. Beliefs about patient expectations and lack of knowledge about the guideline were also identified as barriers to offering surveillance. Guideline-specific and external barriers included the vagueness of surveillance protocols, lack of data supporting active surveillance, and societal beliefs about cancer. Facilitators of active surveillance included patients' desire to avoid surgery and SDM [99], also physicians' beliefs and attitudes have been identified in multiple studies and influence the treatment decision of low-risk microPTC patients [65,99-101].

Interestingly, implementation of active surveillance of microPTCs in Kuma hospital, Japan, was very successful. The use of an active surveillance program resulted in high retention and attendance at follow-up (both >90%) and patient worry was low. They focused on three factors: 1) delivery of information and education about microPTC and active surveillance before the biopsy is taken; 2) presentation of a choice to the patient with a clear, consistent recommendation for active surveillance as appropriate and safe, with the option to change to surgery if required or desired; and 3) regular reassessment and reassurance about the risk at each follow-up visit and emotional support provided by the physician to the patient for the choice taken. Retention and adherence do not appear to be barriers to broader implementation of this treatment option. Active surveillance programs may benefit from this specific educational and supportive approach [68,85].

Statement 8: *Several barriers and facilitators were reported in applying SDM. Many barriers are modifiable and can be addressed by attitudinal changes at the level of patient, clinician/healthcare team, and the organisation.*

Knowledge gaps and research directions

Whilst recognising the need and the benefits of a broad implementation of SDM in treatment decision-making in patients with microPTC, still important knowledge

gaps have to be resolved. Despite, a similar oncological outcome between management options, it is essential to reliably identify which patients require treatment and what is the optimal follow-up strategy. Treatment optimisation requires the ability to better predict patients with microPTC who have higher risks to progress towards macroscopic tumours and/or disseminated disease. Apart from clinical and demographic characteristics such as age or location of the tumour, molecular profiling of thyroid cancer is emerging as a promising, new tool for assessing tumour aggressiveness and adapting therapeutic approaches. Studies are warranted to determine if microPTC genotype improves our ability to select patients for an active surveillance approach or to tailor the extent of surgery. There would be the need to design a two-step and sequential study aimed at evaluating: (1) if preoperative molecular testing provides additional information that cannot be derived from thyroid nodule clinical, cytological and sonographic assessment; (2) if tailoring microPTC management based on molecular profile will affect patients' outcome. The pre-operative diagnosis should be optimised, including reliable assessment of ultrasonographic characteristics of the nodule and a complete and systematic assessment of the cervical lymph nodes. Moreover, a complete history taking and physical examination including potential risk factors for a more aggressive biological behaviour should be available. Lastly, establishing post-operative or surveillance protocols that are both safe in oncologic terms and cost-effective is essential.

One important step in application of SDM is getting a better insight into the specific needs, preferences and attitudes of patients with microPTC but also of the physicians treating these patients. A recent review by Wei *et al.* [69] indicates that the way the information is presented to patients influences their choice of treatment. As such, Nickel *et al.* found that more patients chose for a more extensive surgery when the word 'cancer' was used as opposed to other terminology such as 'papillary lesion' or 'abnormal cells' was used [72]. This knowledge can be applied to develop DAs to help both patients and physicians in better balancing the risks and benefits of each approach, and can potentially encourage the patients to choose for the more conservative alternative [69]. Also training SDM communication programs for physicians, which could be either generic or thematic, can help physicians better communicate with patients. Furthermore, proper acceptance and implementation of SDM requires a good understanding of potential facilitators and barriers towards implementation in this patient category. There are currently only a limited number of available DAs instruments that have been developed for patients with microPTC. None of these has yet been extensively and robustly assessed for clinical utility and efficacy, which limits the usability of these DAs. Moreover, particularly when

values clarification exercises are to be included in these DAs, they may not mirror correctly the views and attitudes of patients and physicians with different cultural and ethnic background.

The SDM process and the views of patients and health care providers may differ significantly in different countries and instruments developed in one country may not be interchangeably applicable for other countries. Numerous studies indicate that substantial differences exist between patients with different ethnicities and cultural backgrounds with respect to their perceptions, expectations, values and questionnaire response style. The care for the thyroid cancer patients is also differently organised in different countries and views of physicians from different disciplines and from different countries with respect to the management of these patients may vary as well. Therefore, even applying the same standardised procedure for the development of instruments to aid SDM, these instruments can be different in both content and form in different countries. The questionnaire used covered the major categories of aspects regarding attitudes and knowledge of SDM and not specifically the attitude of physicians towards a certain treatment option or the specific way they communicate these options. More research is required in order to assess the needs of patients and physicians from different cultural backgrounds and countries with respect to optimal SDM and value deliberation that could facilitate the discussion about patient values which is performed in culturally appropriate ways.

A simple translation of the tools that are being developed in one country does not encompass all differences in decision-making between countries, in order to achieve equivalence between the instruments to be used in different countries different methodological approaches could be used. Both adaptation and validation of these instruments for each country or development of the instruments separately in each country according to the same standardised procedure would be necessary. None of these methodological approaches has proven superior to the other provided they are properly applied. For pragmatic reasons, the adaptation and validation of already developed instruments is often preferred. However, to ensure equivalence, expert professionals from different disciplines and from different countries should be consulted as well as target population input by interviews and focus groups. Moreover, the clinical utility of the generated instruments should be prospectively evaluated.

EORTC ETF and its European Reference Network (ERN) partners and the scientific societies dedicated to thyroid cancer involving dedicated experts from different

disciplines managing patients with microPTC represent an ideal platform to conduct the above-mentioned studies. This platform also ensures international participation in an early stage, which enables accessibility to the resulting products for all participating countries within the framework of EORTC. Moreover, performing studies in a multinational setting will provide us a broader understanding of the patient's needs, organisational and cultural barriers and ways to overcome these barriers to facilitate uniform acceptability and implementation of SDM in different countries. The ultimate goal is to make SDM an integral part of the care for microPTC patients.

Conclusions

New management approaches with similar oncological outcome for patients with low-risk microPTC, such as active surveillance and MIT therapy have been introduced in Asia and have gradually been adopted worldwide as alternatives to TL to avoid overtreatment of these tumours. Scientific evidence is still weak including only retrospective or prospective, non-randomised observational trials, some with relatively short follow-up, that provide evidence on the outcome of the different management options. These options have not yet been broadly adopted in national or international guidelines. Whilst additional evidence on the outcome of active surveillance and MIT therapy, particularly from patient populations with different genetic backgrounds, is necessary, and although active surveillance or MIT therapy is not suitable for all microPTC patients, it is important to carefully discuss these options with the patients and to involve them in the decision process. Factors influencing the decision when all three options are deemed acceptable can include (but are not limited to) patient preference, availability of the expertise for specific MIT therapy, availability of high-quality neck ultrasonography, availability of well-balanced information, doctor-patient communication skills and decision instruments to help SDM. Although a few trials are ongoing (NCT03808779, NCT03377829, NCT 04129281, NCT01392222), future prospective research is needed to determine patients' and physicians' needs and preferences, but also potential barriers and facilitators for wide implementation of SDM in daily care of patients with microPTC.

References

1. Cabanillas ME, McFadden DG, Durante C. Thyroid cancer. *Lancet*. 2016;388(10061):2783-95.
2. McLeod DS, Sawka AM, Cooper DS. Controversies in primary treatment of low-risk papillary thyroid cancer. *Lancet*. 2013;381(9871):1046-57.
3. 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.
4. Davies L, Hoang JK. Thyroid cancer in the USA: current trends and outstanding questions. *Lancet Diabetes Endocrinol*. 2021;9(1):11-2.
5. Baloch ZW, Asa SL, Barletta JA, Ghossein RA, Juhlin CC, Jung CK, et al. Overview of the 2022 WHO Classification of Thyroid Neoplasms. *Endocr Pathol*. 2022;33(1):27-63.
6. 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.
7. Filetti S, Durante C, Hartl D, Leboulleux S, Locati LD, Newbold K, et al. Thyroid cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up†. *Ann Oncol*. 2019;30(12):1856-83.
8. Leboulleux S, Bournaud C, Chougnet CN, Zerdoud S, Al Ghuzlan A, Catargi B, et al. Thyroidectomy without Radioiodine in Patients with Low-Risk Thyroid Cancer. *N Engl J Med*. 2022;386(10):923-32.
9. Lin HW, Bhattacharyya N. Survival impact of treatment options for papillary microcarcinoma of the thyroid. *Laryngoscope*. 2009;119(10):1983-7.
10. Horiguchi K, Yoshida Y, Iwaku K, Emoto N, Kasahara T, Sato J, et al. Position paper from the Japan Thyroid Association task force on the management of low-risk papillary thyroid microcarcinoma (T1aN0M0) in adults. *Endocr J*. 2021;68(7):763-80.
11. Sugitani I, Ito Y, Takeuchi D, Nakayama H, Masaki C, Shindo H, et al. Indications and Strategy for Active Surveillance of Adult Low-Risk Papillary Thyroid Microcarcinoma: Consensus Statements from the Japan Association of Endocrine Surgery Task Force on Management for Papillary Thyroid Microcarcinoma. *Thyroid*. 2021;31(2):183-92.
12. Ito Y, Uruno T, Nakano K, Takamura Y, Miya A, Kobayashi K, et al. An observation trial without surgical treatment in patients with papillary microcarcinoma of the thyroid. *Thyroid*. 2003;13(4):381-7.
13. Cho SJ, Suh CH, Baek JH, Chung SR, Choi YJ, Chung KW, et al. Active Surveillance for Small Papillary Thyroid Cancer: A Systematic Review and Meta-Analysis. *Thyroid*. 2019;29(10):1399-408.
14. Koshkina A, Fazelzad R, Sugitani I, Miyauchi A, Thabane L, Goldstein DP, et al. Association of Patient Age With Progression of Low-risk Papillary Thyroid Carcinoma Under Active Surveillance: A Systematic Review and Meta-analysis. *JAMA Otolaryngol Head Neck Surg*. 2020;146(6):552-60.
15. Saravana-Bawan B, Bajwa A, Paterson J, McMullen T. Active surveillance of low-risk papillary thyroid cancer: A meta-analysis. *Surgery*. 2020;167(1):46-55.
16. Aygün N, İşgör A, Uludağ M. Can Active Surveillance be an Alternative to Surgery in Papillary Thyroid Microcarcinoma?: The Current Situation Worldwide. *Sisli Etfal Hastan Tip Bul*. 2018;52(4):233-43.
17. Mauri G, Hegedüs L, Bandula S, Cazzato RL, Czarniecka A, Dudeck O, et al. European Thyroid Association and Cardiovascular and Interventional Radiological Society of Europe 2021 Clinical Practice Guideline for the Use of Minimally Invasive Treatments in Malignant Thyroid Lesions. *Eur Thyroid J*. 2021;10(3):185-97.

18. Lamartina L, Durante C, Lucisano G, Grani G, Bellantone R, Lombardi CP, et al. Are Evidence-Based Guidelines Reflected in Clinical Practice? An Analysis of Prospectively Collected Data of the Italian Thyroid Cancer Observatory. *Thyroid*. 2017;27(12):1490-7.
19. Ullmann TM, Gray KD, Stefanova D, Limberg J, Buicko JL, Finnerty B, et al. The 2015 American Thyroid Association guidelines are associated with an increasing rate of hemithyroidectomy for thyroid cancer. *Surgery*. 2019;166(3):349-55.
20. Adhami M, Bhatt CR, Grodski S, Serpell J, Lee JC. Less extensive surgery for low-risk papillary thyroid cancers post 2015 American Thyroid Association guidelines in an Australian tertiary centre. *Eur J Surg Oncol*. 2021;47(11):2781-7.
21. Keij SM, van Duijn-Bakker N, Stiggelbout AM, Pieterse AH. What makes a patient ready for Shared Decision Making? A qualitative study. *Patient Educ Couns*. 2021;104(3):571-7.
22. Stacey D, Légaré F, Col NF, Bennett CL, Barry MJ, Eden KB, et al. Decision aids for people facing health treatment or screening decisions. *Cochrane Database Syst Rev*. 2014(1):Cd001431.
23. Fagerlin A, Pignone M, Abhyankar P, Col N, Feldman-Stewart D, Gavaruzzi T, et al. Clarifying values: an updated review. *BMC Med Inform Decis Mak*. 2013;13 Suppl 2(Suppl 2):S8.
24. Soares P, Póvoa AA, Melo M, Vinagre J, Máximo V, Eloy C, et al. Molecular Pathology of Non-familial Follicular Epithelial-Derived Thyroid Cancer in Adults: From RAS/BRAF-like Tumor Designations to Molecular Risk Stratification. *Endocr Pathol*. 2021;32(1):44-62.
25. Ahn HS, Kim HJ, Welch HG. Korea's thyroid-cancer "epidemic"--screening and overdiagnosis. *N Engl J Med*. 2014;371(19):1765-7.
26. Furuya-Kanamori L, Bell KJL, Clark J, Glasziou P, Doi SAR. Prevalence of Differentiated Thyroid Cancer in Autopsy Studies Over Six Decades: A Meta-Analysis. *J Clin Oncol*. 2016;34(30):3672-9.
27. Suzuki G. Communicating with residents about 10 years of scientific progress in understanding thyroid cancer risk in children after the Fukushima Dai-ichi Nuclear Power Station accident. *J Radiat Res*. 2021;62(Supplement_1):i7-i14.
28. Rosai J, LiVolsi VA, Sobrinho-Simoes M, Williams ED. Renaming papillary microcarcinoma of the thyroid gland: the Porto proposal. *Int J Surg Pathol*. 2003;11(4):249-51.
29. Pacini F, Castagna MG, Brilli L, Pentheroudakis G. Thyroid cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol*. 2012;23 Suppl 7:vii110-9.
30. Dralle H, Musholt TJ, Schabram J, Steinmüller T, Frilling A, Simon D, et al. German Association of Endocrine Surgeons practice guideline for the surgical management of malignant thyroid tumors. *Langenbecks Arch Surg*. 2013;398(3):347-75.
31. 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.
32. Rowe ME, Osorio M, Likhterov I, Urken ML. Evaluation of ultrasound reporting for thyroid cancer diagnosis and surveillance. *Head Neck*. 2017;39(9):1756-60.
33. 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.
34. Peeters M.; De Greve J.; Voorspoels N.; Andreescu C.; Decoster L.; Delpierre I.; Dequanter D.; Dignonnet A.; Dragan TDF. National expert - based practice guidelines Differentiated thyroid cancer 2020.

35. Zulewski H, Giovanella L, Bilz S, Christ E, Haldemann A, Steinert H, et al. Multidisciplinary approach for risk-oriented treatment of low-risk papillary thyroid cancer in Switzerland. *Swiss Med Wkly*. 2019;149:w14700.
36. Jarząb B, Dedecjus M, Słowińska-Klencka D, Lewiński A, Adamczewski Z, Anielski R, et al. Guidelines of Polish National Societies Diagnostics and Treatment of Thyroid Carcinoma. 2018 Update. *Endokrynol Pol*. 2018;69(1):34-74.
37. Mitchell AL, Gandhi A, Scott-Coombes D, Perros P. Management of thyroid cancer: United Kingdom National Multidisciplinary Guidelines. *J Laryngol Otol*. 2016;130(S2):S150-s60.
38. Gallardo E, Medina J, Sánchez JC, Viúdez A, Grande E, Porras I, et al. SEOM clinical guideline thyroid cancer (2019). *Clin Transl Oncol*. 2020;22(2):223-35.
39. Russ G, Bonnema SJ, Erdogan MF, Durante C, Ngu R, Leenhardt L. European Thyroid Association Guidelines for Ultrasound Malignancy Risk Stratification of Thyroid Nodules in Adults: The EU-TIRADS. *Eur Thyroid J*. 2017;6(5):225-37.
40. Chou R, Dana T, Haymart M, Leung AM, Tufano RP, Sosa JA, et al. Active Surveillance Versus Thyroid Surgery for Differentiated Thyroid Cancer: A Systematic Review. *Thyroid*. 2022;32(4):351-67.
41. Links TP, de Heide LJ, Janssen M, van Nederveen FH, van der Lugt A, Vriens M, et al. [Guideline thyroid cancer including diagnostics of the nodule]. *Ned Tijdschr Geneesk*. 2015;159:A9413.
42. Moon S, Song YS, Kim YA, Lim JA, Cho SW, Moon JH, et al. Effects of Coexistent BRAF(V600E) and TERT Promoter Mutations on Poor Clinical Outcomes in Papillary Thyroid Cancer: A Meta-Analysis. *Thyroid*. 2017;27(5):651-60.
43. Patel KN, Yip L, Lubitz CC, Grubbs EG, Miller BS, Shen W, et al. The American Association of Endocrine Surgeons Guidelines for the Definitive Surgical Management of Thyroid Disease in Adults. *Ann Surg*. 2020;271(3):e21-e93.
44. Yan L, Zhang M, Song Q, Luo Y. Ultrasound-Guided Radiofrequency Ablation Versus Thyroid Lobectomy for Low-Risk Papillary Thyroid Microcarcinoma: A Propensity-Matched Cohort Study of 884 Patients. *Thyroid*. 2021;31(11):1662-72.
45. Kwon H, Jeon MJ, Kim WG, Park S, Kim M, Song DE, et al. A comparison of lobectomy and total thyroidectomy in patients with papillary thyroid microcarcinoma: a retrospective individual risk factor-matched cohort study. *Eur J Endocrinol*. 2017;176(4):371-8.
46. Kim SK, Park I, Woo JW, Lee JH, Choe JH, Kim JH, et al. Total thyroidectomy versus lobectomy in conventional papillary thyroid microcarcinoma: Analysis of 8,676 patients at a single institution. *Surgery*. 2017;161(2):485-92.
47. Kim HJ, Cho SJ, Baek JH. Comparison of Thermal Ablation and Surgery for Low-Risk Papillary Thyroid Microcarcinoma: A Systematic Review and Meta-Analysis. *Korean J Radiol*. 2021;22(10):1730-41.
48. Kwon H, Oh HS, Kim M, Park S, Jeon MJ, Kim WG, et al. Active Surveillance for Patients With Papillary Thyroid Microcarcinoma: A Single Center's Experience in Korea. *J Clin Endocrinol Metab*. 2017;102(6):1917-25.
49. Kim HI, Jang HW, Ahn HS, Ahn S, Park SY, Oh YL, et al. High Serum TSH Level Is Associated With Progression of Papillary Thyroid Microcarcinoma During Active Surveillance. *J Clin Endocrinol Metab*. 2018;103(2):446-51.
50. 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.

51. Kim HJ, Chung SM, Kim H, Jang JY, Yang JH, Moon JS, et al. Long-Term Efficacy of Ultrasound-Guided Laser Ablation for Papillary Thyroid Microcarcinoma: Results of a 10-Year Retrospective Study. *Thyroid*. 2021;31(11):1723-9.
52. Choi Y, Jung SL. Efficacy and Safety of Thermal Ablation Techniques for the Treatment of Primary Papillary Thyroid Microcarcinoma: A Systematic Review and Meta-Analysis. *Thyroid*. 2020;30(5):720-31.
53. Ito Y, Miyauchi A, Kudo T, Higashiyama T, Masuoka H, Kihara M, et al. Kinetic Analysis of Growth Activity in Enlarging Papillary Thyroid Microcarcinomas. *Thyroid*. 2019;29(12):1765-73.
54. Politi MC, Studts JL, Hayslip JW. Shared decision making in oncology practice: what do oncologists need to know? *Oncologist*. 2012;17(1):91-100.
55. Covvey JR, Kamal KM, Gorse EE, Mehta Z, Dhumal T, Heidari E, et al. Barriers and facilitators to shared decision-making in oncology: a systematic review of the literature. *Support Care Cancer*. 2019;27(5):1613-37.
56. Kane HL, Halpern MT, Squiers LB, Treiman KA, McCormack LA. Implementing and evaluating shared decision making in oncology practice. *CA Cancer J Clin*. 2014;64(6):377-88.
57. Forner D, Noel CW, Shuman AG, Hong P, Corsten M, Rac VE, et al. Shared Decision-making in Head and Neck Surgery: A Review. *JAMA Otolaryngol Head Neck Surg*. 2020;146(9):839-44.
58. Arora NK. Interacting with cancer patients: the significance of physicians' communication behavior. *Soc Sci Med*. 2003;57(5):791-806.
59. Lohia S, Hanson M, Tuttle RM, Morris LGT. Active surveillance for patients with very low-risk thyroid cancer. *Laryngoscope Investig Otolaryngol*. 2020;5(1):175-82.
60. Ito Y, Miyauchi A. Active Surveillance as First-Line Management of Papillary Microcarcinoma. *Annu Rev Med*. 2019;70:369-79.
61. Miyauchi A, Ito Y. Conservative Surveillance Management of Low-Risk Papillary Thyroid Microcarcinoma. *Endocrinol Metab Clin North Am*. 2019;48(1):215-26.
62. Hedman C, Djärv T, Strang P, Lundgren CI. Determinants of long-term quality of life in patients with differentiated thyroid carcinoma - a population-based cohort study in Sweden. *Acta Oncol*. 2016;55(3):365-9.
63. Smulever A, Pitoia F. Active surveillance in papillary thyroid carcinoma: not easily accepted but possible in Latin America. *Arch Endocrinol Metab*. 2019;63(5):462-9.
64. Oh HS, Ha J, Kim HI, Kim TH, Kim WG, Lim DJ, et al. Active Surveillance of Low-Risk Papillary Thyroid Microcarcinoma: A Multi-Center Cohort Study in Korea. *Thyroid*. 2018;28(12):1587-94.
65. Roman BR, Brito JP, Saucke MC, Lohia S, Jensen CB, Zaborek N, et al. NATIONAL SURVEY OF ENDOCRINOLOGISTS AND SURGEONS REGARDING ACTIVE SURVEILLANCE FOR LOW-RISK PAPILLARY THYROID CANCER. *Endocr Pract*. 2021;27(1):1-7.
66. Hughes DT, Reyes-Gastelum D, Ward KC, Hamilton AS, Haymart MR. Barriers to the Use of Active Surveillance for Thyroid Cancer: Results of a Physician Survey. *Ann Surg*. 2020.
67. Sawka AM, Ghai S, Rotstein L, Irish JC, Pasternak JD, Gullane PJ, et al. A Quantitative Analysis Examining Patients' Choice of Active Surveillance or Surgery for Managing Low-Risk Papillary Thyroid Cancer. *Thyroid*. 2022;32(3):255-62.
68. Davies L, Chang CH, Sirovich B, Tuttle RM, Fukushima M, Ito Y, et al. Thyroid Cancer Active Surveillance Program Retention and Adherence in Japan. *JAMA Otolaryngol Head Neck Surg*. 2021;147(1):77-84.
69. Wei J, Thwin M, Nickel B, Glover A. Factors That Inform Individual Decision Making Between Active Surveillance, Hemithyroidectomy and Total Thyroidectomy for Low-Risk Thyroid Cancer: A Scoping Review. *Thyroid*. 2022.

70. Brito JP, Moon JH, Zeuren R, Kong SH, Kim YG, Iñiguez-Ariza NM, et al. Thyroid Cancer Treatment Choice: A Pilot Study of a Tool to Facilitate Conversations with Patients with Papillary Microcarcinomas Considering Treatment Options. *Thyroid*. 2018;28(10):1325-31.
71. Sawka AM, Ghai S, Yoannidis T, Rotstein L, Gullane PJ, Gilbert RW, et al. A Prospective Mixed-Methods Study of Decision-Making on Surgery or Active Surveillance for Low-Risk Papillary Thyroid Cancer. *Thyroid*. 2020;30(7):999-1007.
72. Nickel B, Barratt A, McGeechan K, Brito JP, Moynihan R, Howard K, et al. Effect of a Change in Papillary Thyroid Cancer Terminology on Anxiety Levels and Treatment Preferences: A Randomized Crossover Trial. *JAMA Otolaryngol Head Neck Surg*. 2018;144(10):867-74.
73. Nickel B, Howard K, Brito JP, Barratt A, Moynihan R, McCaffery K. Association of Preferences for Papillary Thyroid Cancer Treatment With Disease Terminology: A Discrete Choice Experiment. *JAMA Otolaryngol Head Neck Surg*. 2018;144(10):887-96.
74. Jeon MJ, Lee YM, Sung TY, Han M, Shin YW, Kim WG, et al. Quality of Life in Patients with Papillary Thyroid Microcarcinoma Managed by Active Surveillance or Lobectomy: A Cross-Sectional Study. *Thyroid*. 2019;29(7):956-62.
75. Bender JL, Wiljer D, Sawka AM, Tsang R, Alkazaz N, Brierley JD. Thyroid cancer survivors' perceptions of survivorship care follow-up options: a cross-sectional, mixed-methods survey. *Support Care Cancer*. 2016;24(5):2007-15.
76. Kong SH, Ryu J, Kim MJ, Cho SW, Song YS, Yi KH, et al. Longitudinal Assessment of Quality of Life According to Treatment Options in Low-Risk Papillary Thyroid Microcarcinoma Patients: Active Surveillance or Immediate Surgery (Interim Analysis of MAeSTro). *Thyroid*. 2019;29(8):1089-96.
77. Nakamura T, Miyauchi A, Ito Y, Ito M, Kudo T, Tanaka M, et al. Quality of Life in Patients with Low-Risk Papillary Thyroid Microcarcinoma: Active Surveillance Versus Immediate Surgery. *Endocr Pract*. 2020;26(12):1451-7.
78. Moon JH, Ryu CH, Cho SW, Choi JY, Chung EJ, Hah JH, et al. Effect of Initial Treatment Choice on 2-year Quality of Life in Patients with Low-risk Papillary Thyroid Microcarcinoma. *J Clin Endocrinol Metab*. 2021;106(3):724-35.
79. Min Y, Wang X, Chen H, Chen J, Xiang K, Yin G. Thermal Ablation for Papillary Thyroid Microcarcinoma: How Far We Have Come? *Cancer Manag Res*. 2020;12:13369-79.
80. Zhang M, Tufano RP, Russell JO, Zhang Y, Zhang Y, Qiao Z, et al. Ultrasound-Guided Radiofrequency Ablation Versus Surgery for Low-Risk Papillary Thyroid Microcarcinoma: Results of Over 5 Years' Follow-Up. *Thyroid*. 2020;30(3):408-17.
81. Lan Y, Luo Y, Zhang M, Jin Z, Xiao J, Yan L, et al. Quality of Life in Papillary Thyroid Microcarcinoma Patients Undergoing Radiofrequency Ablation or Surgery: A Comparative Study. *Front Endocrinol (Lausanne)*. 2020;11:249.
82. Ahmadi S, Gonzalez JM, Talbott M, Reed SD, Yang JC, Scheri RP, et al. Patient Preferences Around Extent of Surgery in Low-Risk Thyroid Cancer: A Discrete Choice Experiment. *Thyroid*. 2020;30(7):1044-52.
83. Dixon PR, Tomlinson G, Pasternak JD, Mete O, Bell CM, Sawka AM, et al. The Role of Disease Label in Patient Perceptions and Treatment Decisions in the Setting of Low-Risk Malignant Neoplasms. *JAMA Oncol*. 2019;5(6):817-23.
84. Pitt SC, Wendt E, Saucke MC, Voils CI, Orne J, Macdonald CL, et al. A Qualitative Analysis of the Preoperative Needs of Patients With Papillary Thyroid Cancer. *J Surg Res*. 2019;244:324-31.
85. McCaffery KJ, Nickel B. Clinician Be My Guide in Active Surveillance of Papillary Thyroid Microcarcinoma. *JAMA Otolaryngol Head Neck Surg*. 2021;147(1):7-8.

86. Moran TP. Anxiety and working memory capacity: A meta-analysis and narrative review. *Psychol Bull.* 2016;142(8):831-64.
87. Jensen CB, Saucke MC, Francis DO, Voils CI, Pitt SC. From Overdiagnosis to Overtreatment of Low-Risk Thyroid Cancer: A Thematic Analysis of Attitudes and Beliefs of Endocrinologists, Surgeons, and Patients. *Thyroid.* 2020;30(5):696-703.
88. D'Agostino TA, Shuk E, Maloney EK, Zeuren R, Tuttle RM, Bylund CL. Treatment decision making in early-stage papillary thyroid cancer. *Psychooncology.* 2018;27(1):61-8.
89. Doubleday AR SM, Bates MF, Pitt SC. Patient-surgeon decision-making about treatment for very low-risk thyroid cancer. *Trends in Cancer Research.* 2019;14.
90. Sawka AM, Straus S, Brierley JD, Tsang RW, Rotstein L, Rodin G, et al. Decision aid on radioactive iodine treatment for early stage papillary thyroid cancer--a randomized controlled trial. *Trials.* 2010;11:81.
91. Kunneman M, Montori VM, Castaneda-Guarderas A, Hess EP. What Is Shared Decision Making? (and What It Is Not). *Acad Emerg Med.* 2016;23(12):1320-4.
92. Nickel B, Brito JP, Moynihan R, Barratt A, Jordan S, McCaffery K. Patients' experiences of diagnosis and management of papillary thyroid microcarcinoma: a qualitative study. *BMC Cancer.* 2018;18(1):242.
93. Pitt SC, Saucke MC. Thyroid Cancer Treatment Choice Toolkit: University of Wisconsin - Madison School of Medicine and Public Health - Department of Surgery; [Available from: <https://www.hipxchange.org/ThyroidCancerTreatmentChoice>].
94. Pitt SC, Saucke MC. Novel Decision Support Interventions for Low-risk Thyroid Cancer. *JAMA Otolaryngol Head Neck Surg.* 2020;146(11):1079-81.
95. Légaré F, Ratté S, Gravel K, Graham ID. Barriers and facilitators to implementing shared decision-making in clinical practice: update of a systematic review of health professionals' perceptions. *Patient Educ Couns.* 2008;73(3):526-35.
96. Joseph-Williams N, Elwyn G, Edwards A. Knowledge is not power for patients: a systematic review and thematic synthesis of patient-reported barriers and facilitators to shared decision making. *Patient Educ Couns.* 2014;94(3):291-309.
97. Waddell A, Lennox A, Spassova G, Bragge P. Barriers and facilitators to shared decision-making in hospitals from policy to practice: a systematic review. *Implement Sci.* 2021;16(1):74.
98. Gruß I, McMullen CK. Barriers to eliciting patient goals and values in shared decision-making breast cancer surgery consultations: An ethnographic and interview study. *Psychooncology.* 2019;28(11):2233-9.
99. Jensen CB, Saucke MC, Pitt SC. Active surveillance for thyroid Cancer: a qualitative study of barriers and facilitators to implementation. *BMC Cancer.* 2021;21(1):471.
100. Hwangbo Y, Choi JY, Lee EK, Ryu CH, Cho SW, Chung EJ, et al. A Cross-Sectional Survey of Patient Treatment Choice in a Multicenter Prospective Cohort Study on Active Surveillance of Papillary Thyroid Microcarcinoma (MAeSTro). *Thyroid.* 2022;32(7):772-80.
101. McDow AD, Roman BR, Saucke MC, Jensen CB, Zaborek N, Jennings JL, et al. Factors associated with physicians' recommendations for managing low-risk papillary thyroid cancer. *Am J Surg.* 2021;222(1):111-8.
102. Wei J, Thwin M, Nickel B, Glover A. Factors That Inform Individual Decision Making Between Active Surveillance, Hemithyroidectomy and Total Thyroidectomy for Low-Risk Thyroid Cancer: A Scoping Review. *Thyroid.* 2022;32(7):807-18.



General discussion

General discussion

Shared decision making (SDM) is a collaborative process in which patients and physicians work together to make informed medical decisions that align with the patient's values and preferences. This process involves the exchange of the best available clinical evidence and active patient engagement in weighing different treatment options (1). Over the past decades, SDM has been increasingly prioritized in healthcare in the Netherlands, supported by governmental initiatives, patient organizations and health insurers. Since January 2020, the explicit use of SDM in physician-patient communication has been formally embedded in Dutch legislation, specifically within the Medical Treatment Agreement Act (Wet Geneeskundige Behandelings-overeenkomst; WGBO) (2, 3). Despite this legal foundation, the consistent integration of SDM into everyday clinical practice remains a challenge. Patient Decision Aids (PtDAs) are evidence-based tools designed to support SDM by providing structured, information and helping patients clarify what matters most to them.

This thesis evaluated the impact of a PtDA combined with SDM communication training for physicians treating patients with differentiated thyroid cancer (DTC). Three PtDAs were developed and assessed through a multicenter randomized controlled trial (RCT). In this chapter, the main findings of the study are presented. In addition, it is discussed how these results contribute to the existing literature, to outline practical implications, to consider the strengths and limitations of the research, and propose directions for future research.

Main findings

- Patients diagnosed with low-risk DTC often face the preference-sensitive choice between thyroid lobectomy (TL) and total thyroidectomy (TT). Our systematic meta-analysis of the literature (**Chapter 2**) showed comparable oncological outcomes of TL and TT (4).
- **Chapter 3** explored patients' preferences from both the patient and physician perspectives, using a qualitative design. Patients emphasized the importance of a strong physician-patient relationship and desire for comprehensive, personalized information. Physicians emphasized the provision of more general information, and focused more on the effect and benefit of the treatment.
- The COMBO study, a multicenter randomized controlled trial (**Chapter 5**) showed no additional effect of the PtDAs in trained physicians on observed SDM or secondary outcomes. The formal training of the physicians in this study potentially obviating the effect of the PtDAs.
- Positive evaluations of the PtDAs by both patients and physicians (**Chapters 4 and 5**) demonstrated that the tools were feasible to implement and valuable to support clinical decision making.
- **Chapter 6**, using a qualitative design, showed that physicians largely recognize the value of SDM and its contribution to patient-centered care (5).

Interpretation of main findings

Clinical practice in the treatment of DTC patients

In recent years, Dutch hospitals have increasingly adopted a more personalized approach to the management of patients with DTC. This trend aligns with international guidelines from Japan (6) and the United States (7). A recent nationwide retrospective study confirmed that TL and TT yield comparable oncologic outcomes in patients with low-risk DTC in the Netherlands (8). Reflecting this shift, the national guideline for DTC was recently revised to promote a more individualized and de-escalated treatment strategy (9). Despite the growing implementation of this approach in clinical practice, a general observation in other patient groups was that they were not actively involved in the decision-making process and did not perceive SDM. This lack of patient involvement may be attributed to factors related to policy, as well as patient and physician-related determinants.

Patients' and physicians' perspectives on needs and preferences for SDM in DTC

The majority of physicians reported being familiar with the concept of SDM and felt they had sufficient knowledge to apply it appropriately in clinical practice (**Chapter 6**). While most physicians stated that they discuss what matters most to their patients, exploring patients' underlying needs and preferences was the most challenging aspect of the SDM process (10, 11). Understanding patients' needs and preferences regarding the management of DTC may facilitate more comprehensive discussions about treatment options. Although clinical guidelines advocate the incorporation of patient preferences into decision making (7, 9, 12, 13), few studies have examined how well physician and patient perspectives align (14-19). **Chapter 3** explored patients' needs and preferences from both the patient and physician perspectives, using a qualitative design. Discrepancies between patient and physician preferences have also been observed in other clinical contexts and may significantly impact treatment decisions (20-22). Many of these studies have utilized Discrete Choice Experiments (DCEs), a method in which patients evaluate hypothetical scenarios to assess alignment between patient and physician values. However, methodological inconsistencies have limited their usefulness: future DCE studies should adopt standardized attributes and level to better compare perspectives across stakeholders. The observed lack of concordance between patients and physicians highlights the importance of training and encouraging physicians to actively explore patients' preferences and values – potentially supported by tools such as PtDAs.

Implementation strategies for SDM

Effective implementation of SDM requires a structured approach, tailored to barriers and facilitators for implementation found among main stakeholders (23, 24). Several initiatives have been undertaken in the Netherlands. In 2023, Santeon - a collaborative network of seven top clinical hospitals in the Netherlands - developed a roadmap aimed at facilitating the adoption of SDM. This roadmap offers a structured approach and practical tools tailored to support the initiation and integration of SDM throughout the entire care pathway. It provides step-by-step guidance and actionable strategies to address real-world barriers and promote sustainable implementation. By offering a clear framework and accessible resources, the roadmap supports healthcare professionals in embedding SDM into routine care. A critical component of this implementation strategy involves training physicians and residents in SDM practices. The Dutch Federation of University Medical Centers (NFU), in collaboration with various professional societies and the Ministry of Health, has developed tools and educational materials to support the incorporation of SDM into clinical education. Embedding communication skills training in medical curricula is expected to promote the broader uptake of SDM in clinical practice, as had been widely advocated.

Another important strategy focuses on patient engagement by preparing and prompting patients to actively participate in decision making. Physicians can encourage patients to reflect on what matters most to them. Several example questions already exist to support this process, such as the 'Three good questions' initiative (25) and 'Start a meaningful conversation' campaign (26). These question frameworks can be integrated into hospital appointment letters or provided via digital patient portals, raising awareness of SDM and empowering patients to take an active role in their treatment decisions.

Since early 2025, healthcare providers in Dutch specialist care can now explicitly register the use of SDM during clinical encounters. Previously, such conversations were recorded as standard consultations. These new registrations options have been introduced as part of the 'Appropriate Funding in Specialist Care' program led by the Dutch Healthcare Authority (NZa), which aims to ensure future-proof, high-quality, and accessible healthcare. This initiative may further incentivize physicians to adopt SDM in daily practice.

It is also crucial that national and international clinical guidelines recognize SDM and PtDAs as means to improve decision quality. In the most recent revision of the Dutch guideline for DTC, a shift toward a more personalized approach – centered

around patients' values and preferences – was evident. Notably, this updated guideline explicitly references the PtDAs developed and described in this thesis.

Implementation strategies for PtDAs

Communication tools

Several communication tools have previously been developed for patients with thyroid cancer. For instance, Sawka *et al.* created a computerized decision aid to support decision-making regarding radio-active iodine (RAI) therapy after TL in patients with early-stage papillary thyroid carcinoma (PTC) (27). Brito *et al.* developed the *Thyroid Cancer Treatment Choice* (TCTN) tool in patients with microPTC using an interactive process grounded in principles of design thinking and participatory action research (28). Additionally, Pitt and Saucke applied the IPDAS methodology in collaboration with key stakeholders to develop two complementary decision support tools for patients with low-risk thyroid cancer (29). Adequate information on the treatment strategies on DTC is essential for patients to participate in decision-making. With the development and evaluation of the PtDAs described in this thesis, we were the first to create PtDAs specifically tailored to support patients with DTC in making two critical treatment decisions (**Chapter 4**).

The PtDAs were systematically developed according to the IPDAS criteria (30) and the Ottawa Decision Support Framework (31), both of which emphasize a systematic development process. Because PtDAs aim to support patients in making informed decisions aligned with their personal values, the inclusion of an explicit values clarification method is essential (32). Patients assessed the PtDA as a usable aid and recommended the aid to other patients facing the same decision (**Chapter 5**). Two factors likely contributed to these positive evaluations. First, a comprehensive needs assessment was conducted among patients and physicians to identify key values, needs, and preferences, which informed the PtDA content. Second, the co-creation approach – engaging both patients and relevant stakeholders in the development of the PtDAs – ensured the tools were relevant and user-centered. Despite these positive evaluations, it is still a challenge to implement PtDAs in clinical practice.

Issues and concerns regarding implementation of PtDAs in routine practice

In the past years, significant progress has been made in the development of PtDAs and there is growing support for their use during clinical encounters (33). However, the implementation of PtDAs in routine practice remains limited and a coordinated national strategy is lacking. Despite the availability of various PtDAs, they are not yet systematically integrated into clinical workflows. Within the Dutch *Outcome-*

Oriented Care program (programma Uitkomstgerichte Zorg), stakeholders in the healthcare system aim to enhance SDM between patients and physicians. PtDAs are recognized as valuable tools in this process, offering structured, comprehensible, and personalized information about available treatment options. The program's objective is to ensure that PtDAs are easy to find, accessible, and user-friendly. Nevertheless, several barriers to nationwide implementation persist. Four major challenges have been identified in the implementation of PtDAs: 1) development issues, 2) quality assurance, 3) accessibility, and 4) sustainable maintenance. To overcome these barriers, a central platform is needed that offers publicly accessible PtDAs developed according to established standards, regularly updated, and readily available for use by hospitals, clinicians, and patients. In addition, structural funding is essential to support the development and ongoing maintenance of PtDAs. This includes subsidized development, free individual access – either publicly funded or reimbursed by insurers – and coverage of implementation costs within healthcare institutions. Furthermore, a clear governance structure is needed to define roles, responsibilities, and intellectual property rights among developers, professional associations, and patient advocacy groups. Unfortunately, the funding proposal outlined in the national report did not receive unanimous support. Currently, health insurers, in collaboration with stakeholders from the Outline Agreement (Hoofdlijnenakkoord, HLA), are developing an alternative funding proposal aimed at achieving broader consensus.

Another critical challenge in the implementation of PtDAs is limited health literacy (LHL). Effective use of PtDAs requires advanced cognitive and communicative competencies, and even individuals with higher education levels may experience difficulties related to LHL (34-36). An analysis of Dutch PtDAs showed that most tools meet standards for layout and general comprehensibility. However, improvements are needed regarding content quality and adherence to evidence-based strategies for risk communication (37). Adding a read-aloud option would enhance the accessibility of the PtDA, making it available to a broader range of patients. E.g., those who are illiterate, visually impaired, or blind. Translating the PtDA into various languages could contribute to reaching an international public.

Ensuring broad and sustained access to PtDAs is essential. A key objective is to promote the continued use of the PtDAs beyond the scope of the current project. Several avenues exist to support this goal. For instance, the Dutch national program *Healthcare Evaluation and Appropriate Use* (Zorgevaluatie en Gepast Gebruik, ZE&GG) is a collaborative initiative involving all stakeholders in medical specialist care. Its mission is to enhance the quality and affordability of care by identifying

and implementing effective interventions, while phasing out care that is ineffective or of low value. This program aims at improving the quality and affordability of healthcare by first evaluating which care is effective, and second implementing such effective care. PtDAs are recognized as playing a pivotal role in this process by enabling patients and healthcare professionals to make informed, preference-sensitive decisions aligned with best evidence. It is suggested in this National program that by 2028, care evaluation and appropriate use is fully integrated into routine healthcare practice.

The initial development of PtDAs is resource-intensive and typically requires external funding through grants or research programs. Nevertheless, in the Netherlands, two commercial developers have emerged as prominent players in the design, dissemination, and maintenance (updates) of PtDAs. For instance, Patient+ collaborates with Kanker.nl to ensure PtDAs are available for the broader public.

To address the dissemination of PtDAs, integrating PtDAs within electronic health records (EHR) may offer a promising alternative. Embedding PtDAs directly into EHR systems would not only reduce development costs but also enhance accessibility for both patients and physicians, facilitating real-time use during consultations. In addition to technical integration, EHR systems are critical. Patient organizations such as SchildklierNL and social media platforms can play a role in raising awareness, improving findability, and promoting the usability of PtDAs. Thus, a coordinated strategy involving PtDA developers, EHR platforms, patient advocacy groups, and digital communication channels is necessary to facilitate widespread adoption. Linking PtDAs to the most recent national guidelines for DTC (9) would help ensure consistency in the clinical information provided and promote uniformity in patient counseling. Such linking could also strengthen the uptake of PtDAs by reinforcing their relevance and legitimacy in clinical decision making.

Internationally, PtDAs are also increasingly recognized as tools that support the transformation toward more patient-centered healthcare systems. Even prior to the January 2024 update of the Cochrane Review on the effectiveness of PtDAs (32), several countries had already embedded PtDAs into their healthcare frameworks. In the United Kingdom, PtDAs are incorporated into clinical guidelines and supported across various specialties. In the Netherlands PtDAs have been added to the DTC guideline. Germany and the United States have launched large-scale initiatives, such as the “Share to Care” program and the SHAIR Collaborative have aimed to systematically integrate SDM into healthcare delivery with the backing of health insurers (38). In Denmark, national efforts involve active participation

from healthcare professionals across major institutions, such as Odense University Hospital, with strong policy-level support for patient engagement and evidence-based decision making. These international examples illustrate the importance of aligned policy, funding structures, and organizational incentives to advance the use of PtDAs and a culture of SDM in clinical practice.

Implementation strategies for SDM communication training

Communication training is important for successful implementation of SDM in clinical practice (39-42). Numerous SDM training programs for health care professionals have been developed worldwide (41). Both individual and team-based feedback on consultations have demonstrated effectiveness (43) and are widely perceived as valuable by participants (39). Our training program was based on the 'Three-Talk Model' developed by Elwyn *et al.* (44), which synthesizes several previously published SDM frameworks and consists of three core components: choice talk, option talk, and decision talk. Stiggelbout *et al.* later refined this model into four distinct steps (45) (Figure 1). Particular emphasis was placed on discussing patients' values and preferences in the training program, developed for the prospective RCT (Figure 2). In this context, values refer to 'what matters most' to patients – ranging from broad themes such as family or societal values, to treatment-specific concerns such as side effects, risks, or outcomes. These values may be directly relevant to the decision (e.g., beliefs, emotions, or perceptions regarding treatment attributes) and are derived from personal goals, worldviews, religious, or cultural norms (46). Over the past years, the Dutch Outcome Oriented Care program has prioritized SDM in education and training. The national Medical Education Framework now incorporates SDM and its associated competencies into the medical degree curriculum. Accordingly, SDM has gained more attention in undergraduate medical education, training programs, and continuing professional development – particularly through communication training and experiential learning in clinical settings. However, learning SDM mostly depends on how medical students and residents (A(N)IOS) learn from specialists during patient consultations. Greater emphasis is needed within formal training programs to ensure consistent skill development. To support this effort, interprofessional educational materials have been created.

Institutions such as the School for SDM and the Federation of Medical Specialists now offer structured communication training programs in SDM for health care professionals. Despite these encouraging developments, several barriers remain that hinder national implementation of SDM training. First, funding remains a major constraint. Hospitals often struggle to allocate the financial resources required to provide SDM training for specialists. Educators frequently have to advocate for these funds within institutional

budgets, and there is an ongoing debate about whether such training costs should be included in contractual agreements with health insurers. While individual physicians and A(N)IOS may use their personal professional development budgets, this option is not feasible for medical students. Second, time constraints pose a significant barrier. Training or retraining physicians in SDM requires dedicated time, something many clinicians lack or are unwilling to allocate. Additionally, there is a common perception that SDM prolongs consultations, which can discourage its adoption. However, evidence suggests that implementing SDM does not significantly increase consultation length (47). Third, physicians are confident they have a high level of SDM competences. Which can impede training uptake (48).

To overcome these barriers, it is essential that SDM training is fully embedded in medical education and institutional practice. Hospitals should receive support in developing educational frameworks that structurally integrate SDM into daily workflows. This may include offering mandatory (refresher) training courses, incorporating SDM discussions into morning briefings or handovers, and embedding SDM prompts into EHR systems.

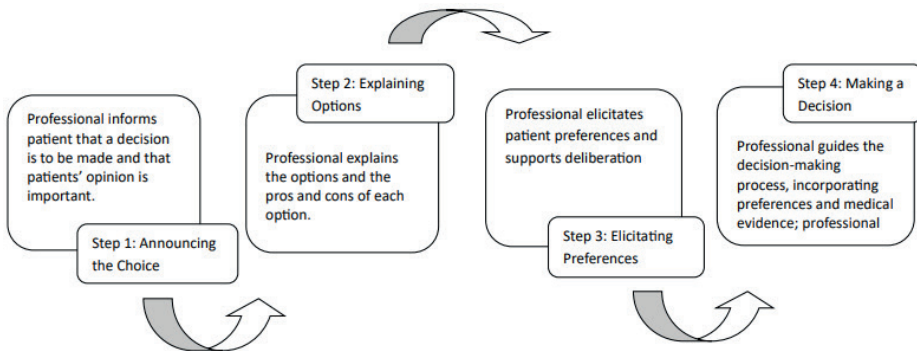


Figure 1. A 4-step approach towards SDM.

Based upon the work of Stiggelbout et al. (2015) and Elwyn et al. (2017).

Homework (30 minutes) – E-learning Session 1 (group session of 3.5 hours) – Group training by an experienced trainer – Special focus on values clarification Session 2 (individual session of 1 hour) – Audio-recording a consultation, reviewing it, and reflecting on SDM behavior.

Figure 2. SDM communication training program applied in our study.

Interpretation of trial results

The COMBO study (**Chapter 5**) showed no additional effect of the PtDAs in trained physicians on observed SDM or secondary outcomes. Some factors may explain the absence of the anticipated effect. First, the high baseline OPTION5 scores among trained physicians may have resulted in a ceiling effect (**Chapter 5**). It is plausible that the SDM training itself already enhanced observed SDM to a level where additional gains from the PtDA were minimal. The question arises what level of observed SDM is desirable. An OPTION5 total score of ≥ 75 (on a scale from 0 to 100 found in 7% of our recordings) is considered to constitute a skilled effort, characterized by substantive and deliberate patient involvement (49). Physicians who reached this threshold were particularly focused on describing treatment options and eliciting patient preferences. However, despite such high OPTION5 scores, the level of values concordance – i.e., agreement between physicians and patients on what matters most, such as the importance of avoiding side effects or maximizing survival – improved somewhat but remained low. This suggests that physicians often struggled to accurately gauge patients' values even when demonstrating high levels of SDM behaviors. Future research should explore strategies to enhance concordance by further improving value-based communication.

Second, variability in implementation logistics across participating hospitals may have contributed to the lack of effect of the PtDA. Differences in the amount and timing of information provided to patients prior to the SDM consultation may have influenced patient engagement and outcomes.

Third, disease-specific factors may play a role. These include the generally low levels of cancer-related worry and the potential familiarity with DTC among patients with advanced disease. Patients in both intervention and control groups reported a mean cancer worry score of 2 (on a 0-4 scale; **Chapter 5**). Lee *et al.* found that patients with low-risk DTC experienced comparable levels of thyroid cancer-related fear and concern regardless of whether they underwent TL or TT (50). These findings suggest that PtDAs may not significantly affect cancer-related worry in this population.

However, recent work by van de Water *et al.* (51) demonstrated that for some patients with advanced cancer, SDM can temporarily elicit negative emotions, leading to increased tension and uncertainty immediately following the consultation. Training physicians to better recognize and manage emotional responses during SDM conversations may help mitigate these short-term effects.

Despite the lack of improvement on primary and secondary outcomes in our trial, previous research has shown that, particularly in untrained physicians, PtDAs

effectively improve SDM, patients' certainty about their treatment choice, improve patient knowledge and increase patients' feeling about their personal values (32). Since in clinical practice, many physicians have not received a communication training, the use of PtDAs is therefore strongly recommended.

Methodological considerations

One of the major strengths of this thesis is the use of both qualitative (**Chapter 3 and 4**) and quantitative (**Chapter 2 and 5**) research methods. Qualitative methods were particularly appropriate for exploring patients' needs and preferences, which informed the development of the PtDAs. Subsequently, a multicenter RCT (**Chapter 5**), using quantitative methods, assessed the degree of SDM in medical specialist consultations. This assessment was based on 86 recorded real-life clinical encounters, enhancing the ecological validity of the findings. Moreover, the study included physicians from various specialties who received specific training in SDM.

Another notable strength is the structured development process of the PtDAs (**Chapter 4**). Input from patients, healthcare professionals, and patient advocates was systematically integrated throughout the development phase. This participatory approach ensured that the final PtDAs aligned with the informational needs and preferences of both patients and physicians, enhancing their relevance, comprehensibility, and utility for the target population.

To facilitate implementation beyond the study period, a collaboration was established with Patient+, an organization specialized in the development and dissemination of PtDAs. This partnership supports the sustainability of the tools, including their continued maintenance and updates. The PtDAs developed in this project were made publicly accessible via <https://www.kanker.nl/hulp-en-ondersteuning/appstore/apps/4703>, and the active involvement of the patient organization SchildklierNL further promotes their dissemination and integration into routine care.

It is important to note some methodological limitations. First, the absence of pre-training OPTION5 scores limits our ability to evaluate the effectiveness of the training. Second, the OPTION5 instrument, while widely used, includes a limited number of dimensions and is subject to inter-rater variability (49). Third, the study may have been affected by participation bias as the physicians who took part were likely to be more motivated and engaged with the topic of SDM than average.

Future perspectives

Implications for clinical practice

Adjustment of guideline(s)

It is essential that national and international clinical guidelines for patients with DTC incorporate a personalized approach and explicitly mention SDM to improve quality of decision-making. The recent revision of the national guideline reflects a shift toward a more individualized approach for DTC patients and includes SDM as an integral component. In the near future, the newly developed PtDAs will be made accessible through this guideline.

Timing of the PtDAs

PtDAs should be provided immediately following the diagnosis of DTC or upon disease progression. These tools can inform patients about available treatment options, support physicians during consultations, and actively facilitate the SDM process.

SDM training

Communication training focused on SDM should be systematically implemented in all hospitals. Such training should equip physicians with the skills necessary to engage in meaningful conversations about patients' values, needs and preferences.

International collaboration

To advance SDM and optimize treatment strategies for DTC patients, collaborative multicenter research in an international context is essential. Such efforts would facilitate the generalization of findings and the broader implementation of PtDAs. PtDAs should be translated and culturally adapted to other languages. The European Organisation for Research and Treatment of Cancer (EORTC) offers a promising platform to expand international partnerships, support large-scale studies, and promote the dissemination and use of evidence-based decision support tools across other European countries.

Implications for policy

Implementation of PtDAs

National regulations and funding mechanisms should be established to support the development and use PtDAs, ensuring open access and consistent counseling across hospitals. Healthcare insurers could play an essential role in facilitating this process.

EHR system

Integrating PtDAs into EHR systems is expected to enhance their accessibility and usability. Establishing a dedicated working group to assess integration opportunities across various EHR systems would enable systematic exploration and implementation of this approach.

Implications for future research***Enhancing SDM through training***

In this thesis, a structured SDM communication training program was developed for physicians. Adding pre-training OPTION5 scores would give us the opportunity to evaluate its effectiveness. Additional data should be collected on the feasibility and long-term effects of the training. Other questions are: does this training program enhance observed SDM among untrained physicians? What is the impact of repeated or refresher training? Which additional interventions are required to achieve a high level of SDM (OPTION5 score ≥ 75 , indicating a skilled effort), and how to improve values concordance between patients and physicians?

Developing additional PtDAs This thesis represents one of the first efforts to develop PtDAs specifically for patients with DTC. Nonetheless, other preference-sensitive decisions in DTC management could also benefit from PtDAs. For example, the decision regarding whether to administer additional RAI after TT in patients with low- and intermediate-risk DTC. Another opportunity lies in the recently proposed decision between active surveillance (AS) and minimally invasive therapies (MIT) for patients with sub-centimetric PTC. These treatment options have not yet been widely adopted in clinical practice, and the optimal role of AS and MIT as alternatives to surgery remains to be defined (5).

General conclusion

In conclusion, this thesis represents an important step toward integrating SDM into the care of patients with DTC. While both patients and physicians express a desire to engage in collaborative decision making, the implementation of SDM remains challenging. To support this process, we developed a communication training program for physicians and three PtDAs tailored to preference-sensitive decisions in DTC. Particularly in settings where formal SDM training is not yet available, the use of PtDAs may offer a valuable means to enhance patient engagement and improve the quality of decision making in DTC care.

References

1. Elwyn G, Frosch DL, Kobrin S. Implementing shared decision-making: consider all the consequences. *Implement Sci.* 2016;11:114.
2. van der Weijden T, van der Kraan J, Brand PLP, van Veenendaal H, Drenthen T, Schoon Y, et al. Shared decision-making in the Netherlands: Progress is made, but not for all. Time to become inclusive to patients. *Z Evid Fortbild Qual Gesundheitswes.* 2022;171:98-104.
3. Ubbink DT, Geerts PAF, Gosens T, Brand PLP. [Updated Dutch law demands shared decision-making]. *Ned Tijdschr Geneesk.* 2021;165.
4. Bojoga A, Koot A, Bonenkamp J, de Wilt J, Int'Hout J, Stalmeier P, et al. The Impact of the Extent of Surgery on the Long-Term Outcomes of Patients with Low-Risk Differentiated Non-Medullary Thyroid Cancer: A Systematic Meta-Analysis. *J Clin Med.* 2020;9(7).
5. Koot A, Soares P, Robenshtok E, Locati LD, de la Fouchardiere C, Luster M, et al. Position paper from the Endocrine Task Force of the European Organisation for Research and Treatment of Cancer (EORTC) on the management and shared decision making in patients with low-risk micro papillary thyroid carcinoma. *Eur J Cancer.* 2023;179:98-112.
6. Sugitani I, Kiyota N, Ito Y, Onoda N, Hiromasa T, Horiuchi K, et al. The 2024 revised clinical guidelines on the management of thyroid tumors by the Japan Association of Endocrine Surgery. *Endocr J.* 2025;72(5):545-635.
7. 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.
8. Lin JF, Rodriguez Schaap PM, Metman MJH, Nieveen van Dijkum EJM, Dickhoff C, Links TP, et al. Thyroid Lobectomy for Low-Risk 1-4 CM Papillary Thyroid Cancer is not Associated with Increased Recurrence Rates in the Dutch Population with a Restricted Diagnostic Work-Up. *World J Surg.* 2023;47(5):1211-8.
9. Dutch guideline differentiated thyroid cancer 2024 [Available from: https://richtlijndatabase.nl/richtlijn/schildklier carcinoom_2024/startpagina_-_schildklier carcinoom_2024.html].
10. Savelberg W, Smidt M, Boersma LJ, van der Weijden T. Elicitation of preferences in the second half of the shared decision making process needs attention; a qualitative study. *BMC Health Serv Res.* 2020;20(1):635.
11. Rake EA, Box ICH, Dreesens D, Meinders MJ, Kremer JAM, Aarts JWM, et al. Bringing personal perspective elicitation to the heart of shared decision-making: A scoping review. *Patient Educ Couns.* 2022;105(9):2860-70.
12. Fugazzola L, Elisei R, Fuhrer D, Jarzab B, Leboulleux S, Newbold K, et al. 2019 European Thyroid Association Guidelines for the Treatment and Follow-Up of Advanced Radioiodine-Refractory Thyroid Cancer. *Eur Thyroid J.* 2019;8(5):227-45.
13. Filetti S, Durante C, Hartl D, Leboulleux S, Locati LD, Newbold K, et al. Thyroid cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up†. *Ann Oncol.* 2019;30(12):1856-83.
14. Nickel B, Howard K, Brito JP, Barratt A, Moynihan R, McCaffery K. Association of Preferences for Papillary Thyroid Cancer Treatment With Disease Terminology: A Discrete Choice Experiment. *JAMA Otolaryngol Head Neck Surg.* 2018;144(10):887-96.
15. Ahmadi S, Gonzalez JM, Talbott M, Reed SD, Yang JC, Scheri RP, et al. Patient Preferences Around Extent of Surgery in Low-Risk Thyroid Cancer: A Discrete Choice Experiment. *Thyroid.* 2020;30(7):1044-52.

16. Dixon PR, Tomlinson G, Pasternak JD, Mete O, Bell CM, Sawka AM, et al. The Role of Disease Label in Patient Perceptions and Treatment Decisions in the Setting of Low-Risk Malignant Neoplasms. *JAMA Oncol.* 2019;5(6):817-23.
17. Pitt SC, Wendt E, Saucke MC, Voils CI, Orne J, Macdonald CL, et al. A Qualitative Analysis of the Preoperative Needs of Patients With Papillary Thyroid Cancer. *J Surg Res.* 2019;244:324-31.
18. Stalmeier PF, van Tol-Geerdink JJ, van Lin EN, Schimmel E, Huizenga H, van Daal WA, et al. Doctors' and patients' preferences for participation and treatment in curative prostate cancer radiotherapy. *J Clin Oncol.* 2007;25(21):3096-100.
19. Oostendorp LJ, Ottevanger PB, van de Wouw AJ, Honkoop AH, Los M, van der Graaf WT, et al. Patients' Preferences for Information About the Benefits and Risks of Second-Line Palliative Chemotherapy and Their Oncologist's Awareness of These Preferences. *J Cancer Educ.* 2016;31(3):443-8.
20. Mulley AG, Trimble C, Elwyn G. Stop the silent misdiagnosis: patients' preferences matter. *Bmj.* 2012;345:e6572.
21. Harrison M, Milbers K, Hudson M, Bansback N. Do patients and health care providers have discordant preferences about which aspects of treatments matter most? Evidence from a systematic review of discrete choice experiments. *BMJ Open.* 2017;7(5):e014719.
22. van der Velden NCA, Han PKJ, van Laarhoven HWM, de Vos F, Hendriks LEL, Burgers SA, et al. Prevalence and Predictors of Physician-Patient Discordance in Prognostic Perceptions in Advanced Cancer. *Oncologist.* 2023;28(8):e653-e68.
23. Flottorp SA, Oxman AD, Krause J, Musila NR, Wensing M, Godycki-Cwirko M, et al. A checklist for identifying determinants of practice: a systematic review and synthesis of frameworks and taxonomies of factors that prevent or enable improvements in healthcare professional practice. *Implement Sci.* 2013;8:35.
24. Grol R. WM. Implementatie: effectieve verbetering van de patientenzorg. Maarssen: Elsevier Gezondheidszorg 2006.
25. 3 goede vragen.
26. Begin een goed gesprek.
27. Sawka AM, Straus S, Rodin G, Thorpe KE, Ezzat S, Gafni A, et al. Decision aid on radioactive iodine treatment for early stage papillary thyroid cancer: update to study protocol with follow-up extension. *Trials.* 2015;16:302.
28. Brito JP, Moon JH, Zeuren R, Kong SH, Kim YG, Iñiguez-Ariza NM, et al. Thyroid Cancer Treatment Choice: A Pilot Study of a Tool to Facilitate Conversations with Patients with Papillary Microcarcinomas Considering Treatment Options. *Thyroid.* 2018;28(10):1325-31.
29. Pitt SC, Saucke MC. Novel Decision Support Interventions for Low-risk Thyroid Cancer. *JAMA Otolaryngol Head Neck Surg.* 2020;146(11):1079-81.
30. Coulter A, Stilwell D, Kryworuchko J, Mullen PD, Ng CJ, van der Weijden T. A systematic development process for patient decision aids. *BMC Med Inform Decis Mak.* 2013;13 Suppl 2(Suppl 2):S2.
31. Légaré F, O'Connor AC, Graham I, Saucier D, Côté L, Cauchon M, et al. Supporting patients facing difficult health care decisions: use of the Ottawa Decision Support Framework. *Can Fam Physician.* 2006;52(4):476-7.

32. Stacey D, Lewis KB, Smith M, Carley M, Volk R, Douglas EE, et al. Decision aids for people facing health treatment or screening decisions. *Cochrane Database Syst Rev*. 2024;1(1):Cd001431.
33. Rake EA, Dreesens D, Venhorst K, Meinders MJ, Geltink T, Wolswinkel JT, et al. Potential impact of encounter patient decision aids on the patient-clinician dialogue: a qualitative study on Dutch and American medical specialists' experiences. *BMJ Open*. 2022;12(2):e048146.
34. Richter R, Jansen J, Bongaerts I, Damman O, Rademakers J, van der Weijden T. Communication of benefits and harms in shared decision making with patients with limited health literacy: A systematic review of risk communication strategies. *Patient Educ Couns*. 2023;116:107944.
35. Rademakers J. KennisYnthese Gezondheidsvaardigheden Niet voor iedereen vanzelfsprekend 2014 [Available from: www.nivel.nl].
36. Berkman ND, Sheridan SL, Donahue KE, Halpern DJ, Crotty K. Low health literacy and health outcomes: an updated systematic review. *Ann Intern Med*. 2011;155(2):97-107.
37. Richter R, Jansen J, van der Kraan J, Abbaspoor W, Bongaerts I, Pouwels F, et al. How Inclusive Are Patient Decision Aids for People with Limited Health Literacy? An Analysis of Understandability Criteria and the Communication about Options and Probabilities. *Med Decis Making*. 2025;45(2):143-55.
38. Geiger F, Hacke C, Potthoff J, Scheibler F, Rueffer JU, Kuch C, et al. The effect of a scalable online training module for shared decision making based on flawed video examples - a randomized controlled trial. *Patient Educ Couns*. 2021;104(7):1568-74.
39. van Veenendaal H, Voogdt-Pruis HR, Ubbink DT, van Weele E, Koco L, Schuurman M, et al. Evaluation of a multilevel implementation program for timeout and shared decision making in breast cancer care: a mixed methods study among 11 hospital teams. *Patient Educ Couns*. 2021.
40. Légaré F, Adekpedjou R, Stacey D, Turcotte S, Kryworuchko J, Graham ID, et al. Interventions for increasing the use of shared decision making by healthcare professionals. *Cochrane Database Syst Rev*. 2018;7(7):Cd006732.
41. Diouf NT, Menear M, Robitaille H, Painchaud Guérard G, Légaré F. Training health professionals in shared decision making: Update of an international environmental scan. *Patient Educ Couns*. 2016;99(11):1753-8.
42. Henselmans I, van Laarhoven HWM, van Maarschalkerweerd P, de Haes H, Dijkgraaf MGW, Sommeijer DW, et al. Effect of a Skills Training for Oncologists and a Patient Communication Aid on Shared Decision Making About Palliative Systemic Treatment: A Randomized Clinical Trial. *Oncologist*. 2019.
43. van Veenendaal H, Voogdt-Pruis H, Ubbink DT, Hilders C. Effect of a multilevel implementation programme on shared decision-making in breast cancer care. *BJS Open*. 2021;5(2).
44. Elwyn G, Durand MA, Song J, Aarts J, Barr PJ, Berger Z, et al. A three-talk model for shared decision making: multistage consultation process. *Bmj*. 2017;359:j4891.
45. Stiggelbout AM, Pieterse AH, De Haes JC. Shared decision making: Concepts, evidence, and practice. *Patient Educ Couns*. 2015;98(10):1172-9.
46. Rocque R, Chipenda Dansokho S, Grad R, Witteman HO. What Matters to Patients and Families: A Content and Process Framework for Clarifying Preferences, Concerns, and Values. *Med Decis Making*. 2020;40(6):722-34.
47. Veenendaal HV, Chernova G, Bouman CM, Etten-Jamaludin FSV, Dieren SV, Ubbink DT. Shared decision-making and the duration of medical consultations: A systematic review and meta-analysis. *Patient Educ Couns*. 2023;107:107561.
48. Driever EM, Stiggelbout AM, Brand PLP. Shared decision making: Physicians' preferred role, usual role and their perception of its key components. *Patient Educ Couns*. 2020;103(1):77-82.

49. Elwyn G GS, Barr P. Observer OPTION-5 Manual. Measuring shared decision making by assessing recordings or transcripts of encounters from clinical settings. Manual The Dartmouth Institute for Health Policy and Clinical Practice; 2018
50. Lee S, Antunez AG, Sinco B, Saucke MC, Bushaw KJ, Dream S, et al. Cancer-related Fear and Worry in Patients with Low-Risk Thyroid Cancer: A Longitudinal Cohort Study. *J Clin Endocrinol Metab*. 2024.
51. van de Water LF, Bos-van den Hoek DW, Kuijper SC, van Laarhoven HWM, Creemers GJ, Dohmen SE, et al. Potential Adverse Outcomes of Shared Decision Making about Palliative Cancer Treatment: A Secondary Analysis of a Randomized Trial. *Med Decis Making*. 2024;44(1):89-101.



Chapter 8

Summary

Samenvatting

Summary

The aim of this thesis was to investigate whether shared decision making communication between physician and patient could be improved through patient decision aids (PtDAs).

To inform the development of patient PtDAs for differentiated thyroid cancer (DTC) surgery, we conducted a systematic meta-analysis in **Chapter 2**, to evaluate the impact of surgical extent on long-term patient outcomes. We critically assessed the management of patients with low-risk DTC, including papillary and follicular carcinoma subtypes, raising concerns about potential overtreatment in the absence of clear clinical benefit. The 2015 American Thyroid Association (ATA) guidelines propose that thyroid lobectomy (TL) could be a safe alternative to total thyroidectomy (TT) for patients with DTC up to 4cm limited to the thyroid, without evidence of metastasis (12). Based on our findings, we concluded a more conservative surgical approach, combined with appropriate follow-up, may be justified in selected cases, rather than defaulting to bilateral surgery. These findings moreover highlight the importance of shared-decision making in the management of patients with small low-risk DTC. The high degree of heterogeneity of the studies is a notable limitation.

After establishing in **Chapter 2** that treatment options for patients with low-risk DTC have similar outcomes. In **Chapter 3** we aimed to establish the factors that are important for the patients in the decision process. Two important treatment decisions for patients with DTC, which could benefit from PtDAs, were identified: 1) the extent of surgery decision in patients with low-risk DTC. Offering both TL and TT to patients involves them in the decision making process. For example, arguments for preferring TT is the concern regarding an increased risk for recurrent disease. TT also offers the possibility of radioactive iodine ablation and this facilitates follow-up by enabling the use of thyroglobulin (Tg) as a reliable tumormarker. Arguments against TT are that TL has a lower complication rate, possibly avoids iatrogenic hypothyroidism and has a shorter duration of surgery. 2) the decision to start or delay starting the treatment with tyrosine kinase inhibitors (TKIs) in patients with advanced tumors. This decision was introduced because it was identified as another clinical situation in the trajectory of patients with DTC when a critical decision between two approaches must be made. Also, for these approaches, no evidence exists supporting the superiority of one upon the other. **Chapter 3** comprised a qualitative study to identify the needs, preferences and values of patients with DTC and the physicians treating patients with DTC regarding

these two treatment decisions. The study included physician focus groups and patient focus groups discussing the above-mentioned treatment options. Two physician focus groups discussed the extent of primary surgery: one included endocrinologists and surgeons, and the other included nuclear medicine physicians treating patients with low-risk DTC. The physician focus group discussing delaying or starting TKIs included endocrinologists and oncologists treating patients with advanced radioactive iodide (RAI) refractory DTC. One patient focus group for each of the two treatment decisions took place. Interviews were audio-taped, fully transcribed verbatim, and analyzed. Several themes were identified. Patients, but not physicians, mentioned the importance of a strong doctor-patient relationship. Patients in both treatment decision groups wanted to receive more detailed information, whereas physicians preferred providing more general information. Patients in the TKI group focused on palliative care, whereas physicians focused more on the effect and benefit of TKIs. It was concluded that the themes, based on the patients' needs, preferences, and values, enabled us to improve doctor-patient communication and to develop PtDAs.

After the needs, values and preferences of the patients and physicians were identified for the abovementioned decisions, the development process of PtDAs, structured tools to facilitate SDM, was initiated as described in **Chapter 4**. PtDAs were developed using the International Patient Decision Aids Standards (IPDAS) quality criteria in an iterative process of prototype development via alpha and beta testing by patients and physicians. The information content of the PtDAs was based on the available literature, current guidelines, and patients' needs, preferences, and values. The web-based PtDAs underwent two rounds of alpha testing, revisions, and beta testing. The PtDAs have the same structure, consisting of six steps: a general introduction, the treatment options, comparing the treatment options, knowledge questions, a values clarification exercise, and saving the information. The alpha testing showed that the PtDAs were highly acceptable and usable for decision-making. Results of the beta testing in 20 patients showed that two patients did not use the PtDA; the other 18 patients considered the PtDAs readable and helpful for decision-making. All patients recommended using the PtDAs. The final version was judged to be clear, balanced, and helpful in decision-making.

In **Chapter 5**, in a prospective multicenter randomized controlled trial (RCT), the PtDAs were assessed for their effect on observed SDM in physicians who were trained in SDM. Patients with DTC were randomized into an intervention group, which received a PtDA, or in a control group, which received care as usual. Three different patient groups were included: 1) patients offered TL or TT, 2) patients

offered a totalizing thyroidectomy or follow-up, and 3) patients offered starting TKI's or delayed initiation of TKI's. In this RCT, all participating physicians received a SDM communication training consisting of an e-learning, an in-hospital group training, and individual feedback on an audio-recorded conversation with a patient, lasting in total 5 hours. The primary outcome was observed SDM process as rated by blinded observers from audio-recorded consultations with the OPTION5 instrument. Secondary outcomes included decision related outcomes, knowledge on thyroid cancer, cancer worries, trust and communication. The PtDA did not improve observed SDM compared to the Usual Care (UC) group or the patients' subjective and objective knowledge. The intervention neither affected decision related outcomes nor patients' worries on cancer or trust in their physician. However, the OPTION5 scores were high in both groups, resulting in a ceiling effect that limited the ability to detect differences in the primary and secondary outcomes. All patients recommended using the PtDA.

Recognizing the importance of SDM and its broad implementation in the care for patients with DTC is paramount. **Chapter 6** provides a position paper from the Endocrine Task Force of the European Organisation for Research and Treatment of Cancer (EORTC) on the management and SDM in patients with low-risk sub-centimetric papillary thyroid carcinoma (PTC) (previously named as micro papillary thyroid carcinoma). The incidence of DTC is increasing worldwide, mostly, as the incidental detection of sub-centimetric PTCs increased. Many cases were potentially overtreated. Several international guidelines have suggested a less aggressive approach. More recently, it has been shown that active surveillance or minimally invasive treatments (MIT) are good alternatives for the management of these patients. In this context, patient participation in the decision-making process is essential. The EORTC has undertaken the task to establish consensus based on the scientific evidence concerning, 1) the current state of diagnostic and management options in sub-centrimetric PTCs, including the current opinion of physicians about SDM, 2) the available evidence concerning patients' needs and the available decision instruments, and 3) to provide practical suggestions for implementation of SDM in this context. To improve SDM and patients' participation, knowledge gaps and research directions were highlighted.

Samenvatting

Het doel van dit proefschrift was om te onderzoeken of een communicatietraining voor artsen en keuzehulpen voor patiënten de communicatie tussen arts en patiënt zou verbeteren.

In hoofdstuk 2 deden we een systematische meta-analyse om te kijken wat het effect is van verschillende operaties bij patiënten met gedifferentieerd schildklierkanker. Vooral bij patiënten met een laag-risico tumor (papillair en folliculair carcinoom) vroegen we ons af of ze niet te zwaar behandeld worden zonder dat dit extra voordeel heeft. Volgens de richtlijn van de American Thyroid Association (ATA) uit 2015 kan een halve schildklierverwijdering (hemithyreoidectomie, HT) veilig zijn in plaats van een volledige verwijdering (totale thyreoïdectomie, TT) bij tumoren tot 4cm die beperkt zijn tot de schildklier. We concludeerden dat in goed geselecteerde patiënten een minder ingrijpende operatie in combinatie met passende follow-up, voldoende kan zijn. Dit maakt samen beslissen mogelijk. Een beperking was dat de onderzoeken die we bekeken veel van elkaar verschilden.

Nadat **Hoofdstuk 2** liet zien dat de behandelopties voor patiënten met laag-risico schildklierkarcinoom vergelijkbare resultaten hebben, stellen we in **Hoofdstuk 3** vast welke factoren belangrijk zijn voor patiënten bij het nemen van beslissingen. Twee keuzes voor patiënten met schildklierkarcinoom zijn: 1) hoeveel van de schildklier moet worden verwijderd bij laag-risico schildklierkanker en 2) of patiënten met uitgezaaide schildklierkanker wel of niet starten met tyrosine kinase remmers (TKIs). De laatste werd toegevoegd omdat dit een ander moment is in het traject van DTC-patiënten waarbij een keuze moet worden gemaakt tussen twee behandelingen. Voor beide keuzes is er geen bewijs dat de ene aanpak beter is dan de andere. In interviews en focusgroepen met artsen en patiënten kwamen we erachter dat patiënten meer waarde hechten aan een goede relatie met hun arts en aan gedetailleerde informatie. Artsen geven liever algemene informatie. Patiënten in de TKI-groep dachten meer aan kwaliteit van leven en palliatieve zorg, terwijl artsen vooral naar effect en voordeel van de medicijnen keken.

Nadat de behoeften, waarden en voorkeuren van patiënten en artsen waren vastgesteld, werd in **Hoofdstuk 4** de ontwikkeling van keuzehulpen beschreven. Keuzehulpen zijn gestructureerde hulpmiddelen die samen beslissen ondersteunen. Ze werden ontwikkeld volgens de International Patient Decision Aids Standards (IPDAS) en zijn getest in meerdere rondes met patiënten en artsen. De keuzehulpen hadden dezelfde opbouw, bestaande uit zes stappen: een algemene introductie,

de behandelopties, het vergelijken van de opties, kennis vragen, een oefening voor het verhelderen van waarden, en het opslaan van de informatie. Alle patiënten vonden de keuzehulpen duidelijk, leesbaar en behulpzaam.

In **Hoofdstuk 5** onderzochten we of de keuzehulpen echt effect hadden in de praktijk. Hiervoor deden we een randomized controlled trial (RCT) met meerdere ziekenhuizen. Artsen kregen een communicatietraining bestaande uit een e-learning, een groepstraining in het ziekenhuis en individuele feedback op een geluidsopname van een gesprek met een patiënt. De training duurde in totaal vijf uur. Vervolgens werden patiënten met schildklierkanker geloot om een keuzehulp te ontvangen of de gebruikelijke zorg. Het belangrijkste resultaat (mate van samen beslissen) werd gemeten met het OPTION5-instrument. De keuzehulp verbeterde dit niet, waarschijnlijk de scores in beide groepen al erg hoog waren (plafondeffect). Ook had de keuzehulp geen effect op andere resultaten, zoals kennis, zorgen over kanker, vertrouwen in de arts en communicatie. Alle patiënten adviseerden het gebruik van de keuzehulp.

Het erkennen van het belang van samen beslissen en de inzet ervan in de zorg voor patiënten met schildklierkanker is van groot belang. Samen beslissen is ook toepasbaar bij andere veelvoorkomende patiëntengroepen. **Hoofdstuk 6** biedt een standpuntbepaling van de Endocrine Task Force van de European Organisation for Research and Treatment of Cancer (EORTC) over de behandeling en samen beslissen bij patiënten met heel kleine (sub-centimetrische) schildkliertumoren. Deze tumoren worden steeds vaker ontdekt, vaak toevallig, en mogelijk te zwaar behandeld. Internationale richtlijnen raden al een minder agressieve aanpak aan, zoals actieve controle of minimaal invasieve behandelingen. De EORTC stelt dat samen beslissen hierbij erg belangrijk is. Er werden kennishiaten en nieuwe onderzoeksvragen benoemd om samen beslissen en patiëntparticipatie te verbeteren.



Appendices

Research Data Management

List of publications

PhD Portfolio

About the author

Acknowledgments (Dankwoord)

Research Data Management

Ethics and privacy

Medical and ethical approval

- This thesis is based on the results of research involving human participants, which were conducted in accordance with relevant national and international legislation and regulations guidelines, codes of conduct and Radboudumc policy.
- The recognized Medical Ethics Review Committee 'METC Oost-Nederland' has given approval to conduct these studies (NL
- The institutional ethical review committee CMO Radboudumc, Nijmegen, the Netherlands has given approval to conduct these studies (CMO Radboudumc dossier number: 2018-4521).

Privacy measures

- According to Dutch legislation, data collection from electronic patient files was performed by personnel with a treatment relationship with the patient AND/OR by the researcher(s) upon consent by the study participant.
- The privacy of the participants in these studies was warranted by the use of pseudonymization.
- The pseudonymization key was stored on a secured network drive that was only accessible to members of the project who needed access to it because of their role within the project.

Data collection and storage

Data collection

- Data for chapter 5 was obtained by using Castor EDC for secured online questionnaires.
- Data for chapter 5 was collected through electronic Case Report Forms (eCRF) of a prospective data collection in Castor EDC. Data were converged from health records or Castor EDC to SPSS.

Data storage

- Data from chapter 2, 4, 5 and 6 were stored and analyzed on the department server and in Castor EDC and are only accessible by project members working at the Radboudumc.
- Data from chapter 3 is analyzed in ATLAS.ti.
- Data from chapter 5 were stored and analyzed in workspace (COMBO) the Azure DRE.
- Raw data (audio-recordings) is archived in their original form in a Data Acquisition Collection (DAC) in the Radboud Data Repository*.

- Processed data and documentation are archived in a Research Documentation Collection (RDC) in the Radboud Data Repository*.
- These secure storage options safeguard the availability, integrity and confidentiality of the data.
- Paper (hardcopy) data is stored in cabinets on the department.

Data sharing according to the FAIR principles

Describe which chapters have been published

- Chapters 2, 3, 4 and 6 are published, of which all with open access.
- Chapter 5 have been submitted for publication and is currently under review.

Describe which datasets are available for reuse and published in a data repository

- Processed data and documentation from chapter 3 is published with open access in a DSC of the Radboud Data Repository*.
- The dataset from chapter 5 is published with open access in a DSC of the Radboud Data Repository*.

Describe which chapters were based on existing data

- Chapter 2 and 6 are based on existing data which was obtained from published literature.

Describe which chapters are not available for reuse

- The audio-recordings from chapter 5 are not suitable for reuse because voices can be recognized and will be archived with closed access for 15 years in a DAC of the Radboud Data Repository* after termination of the study.

Overview published and archived datasets

**The table below details where the data and research documentation for each chapter can be found on the Radboud Data Repository (RDR). All data archived as a Data Sharing Collection remain available for at least 15 years after termination of the studies.*

Chapter	RDR-DAC	RDR-DSC	NAME DATA REPOSITORY
3 and 5		DOI: 10.34973/q2h9-c060	COMBO
5	DOI: 10.34973/q2h9-c060		

List of publications

Publications in this thesis

Bojoga A*, Koot A*, Bonenkamp J, de Wilt J, Int'Hout J, Stalmeier P, Hermens R, Smit J, Ottevanger P, Netea-Maier R. The Impact of the Extent of Surgery on the Long-Term Outcomes of Patients with Low-Risk Differentiated Non-Medullary Thyroid Cancer: A Systematic Meta-Analysis. *J Clin Med.* 2020 Jul 21;9(7):2316. doi: 10.3390/jcm9072316. (*contributed equally)

Koot A, Netea-Maier R, Ottevanger P, Hermens R, Stalmeier P. Needs, Preferences, and Values during Different Treatment Decisions of Patients with Differentiated Thyroid Cancer. *J Pers Med.* 2021 Jul 20;11(7):682. doi: 10.3390/jpm11070682.

Koot A, Hermens R, Ottevanger P, Netea-Maier R, Stalmeier P; COMBO study group. Patient decision aids for patients with differentiated thyroid carcinoma: development process and alpha and beta testing. *Front Endocrinol (Lausanne).* 2023 May 31;14:1162537. doi: 10.3389/fendo.2023.1162537.

Anna Koot, Petronella Ottevanger, Rosella Hermens, Annemijn Aarts, Janneke Walraven, Han Bonenkamp, Johannes de Wilt, Grard Nieuwenhuijzen, Alexander van der Veen, Mariel Keemers, Wouter Zandee, Charlotte Blanken, Maarten van Aken, Rogier Donders, Peep Stalmeier, Romana Netea-Maier, COMBO study group, Effect of a patient decision aid on shared decision making in patients with differentiated thyroid cancer: a randomized controlled trial, *The Oncologist*, Volume 31, Issue 5, May 2026, oyag126, <https://doi.org/10.1093/oncolo/oyag126>.

Koot A, Soares P, Robenshtok E, Locati LD, de la Fouchardiere C, Luster M, Bongiovanni M, Hermens R, Ottevanger P, Geenen F, Bartès B, Rimmele H, Durante C, Nieveen-van Dijkum E, Stalmeier P, Dedecjus M, Netea-Maier R. Position paper from the Endocrine Task Force of the European Organisation for Research and Treatment of Cancer (EORTC) on the management and shared decision making in patients with low-risk micro papillary thyroid carcinoma. *Eur J Cancer.* 2023 Jan;179:98-112. doi: 10.1016/j.ejca.2022.11.005. Epub 2022 Nov 15.

Publications not in this thesis

Koot AW, Visscher AP, Huits RM. Remission of splenic marginal zone lymphoma in a patient treated for hepatitis B: a case of HBV-associated lymphoma. *Acta Clin Belg.* 2015 Aug;70(4):301-3. doi: 10.1179/2295333715Y.0000000005. Epub 2015 May 15.

Kruiswijk A, Koot AW, Richter C, Blankenberg-Sprenkels SH. Uw diagnose? *Tijdschrift voor infectieziekten.* 2016;11;178.

Koot R, van Borren M, de Boer H. Continuation of Liraglutide during Fasting is not Associated with Hypoglycaemia. *Eur J Case Rep Intern Med.* 2017 Oct 26;4(10):000712. doi: 10.12890/2017_000712.

Leentjens J, Olde Bekkink M, Koot R, Herbschleb KH, de Galan BE. Checkpointremmer geïnduceerde diabetes mellitus [Checkpoint inhibitor induced diabetes mellitus]. *Ned Tijdschr Geneeskd.* 2019 Aug 19;163:D3726. Dutch.

Myrthe M. Kuijpers, Tessa G. Steenbruggen, Bart E. Peler, Joost G. Lange, A.W.A (Rosalie) Koot, Iris M.M.J. Wakelkamp. Hirsutisme: een veelvoorkomend probleem; Wanneer moet je aan zeldzame oorzaken denken? *Ned Tijdschr Geneeskd.* 2025 Jan 20;169:D8354

PhD portfolio

Department: Health Evidence
PhD period: 01/03/2019 - 06/11/2023
PhD Supervisor(s): prof. dr. R.T. Netea-Maier
prof. dr. R.P.M.G. Hermens
PhD Co-supervisor(s): dr. P.F.M. Stalmeier
dr. P.B. Ottevanger

Training activities	Hours
Courses	
• RIHS - Introduction course for PhD candidates (2019)	15.00
• Radboudumc - Scientific integrity (2019)	20.00
• Qualitative research IQ healthcare (2019)	4.00
• RU - Qualitative Research Methods and Analysis (2019)	84.00
• RU - Statistics for PhD's by using SPSS (2019)	60.00
• Pubmed introduction (2019)	4.00
• Endnote introduction (2019)	4.00
• Radboudumc - eBROK course (2020)	42.00
• Training OPTION5 scoring (2022)	4.00
• Radboudumc - Re-registration BROK (2023)	5.00
Seminars	
• Schildklier Organisatie Nederland; schildklier week (2023)	4.00
Conferences	
• 42nd annual meeting of the European Thyroid Association (2019)	72.00
• Dutch Endocrine Meeting (2020)	48.00
• Dutch Thyroid Research Foundation (2020)	8.00
• Dutch thyroid Cancer Group (DTCG) (2021)	4.00
• American Thyroid Association (ATA) annual meeting (2021)	4.00
• 7th Young Dutch Society for Endocrinology (2021)	16.00
• Dutch Endocrine Meeting (2022)	16.00
• Dutch Thyroid Day (2022)	8.00
• 11th Annual ARPH conference (2022)	16.00
• 11th International Shared Decision Making conference (2022)	24.00
• Dutch Internal Medicine days (2022)	24.00
• 45th Annual Meeting of the European Thyroid Association (2023)	32.00
• Cancer Research Retreat (2023)	8.00
• PhD retreat (2023)	16.00
• Dutch Endocrine Meeting (2024)	16.00
• 46th Annual Meeting of the European Thyroid Association (2024)	32.00
• Dutch Endocrine Meeting (2025)	16.00

Training activities	Hours
Other	
• Board member young medical doctors Radboudumc (2021)	50.00
• EORTC EnTG meeting (2021)	4.00
• Tumorwerkgroep Schildklier carcinoom Oost (2022)	3.00
• Participation Medical Ethical Committee meetings (2022)	50.00
• Participation Radboud Endocrine Tumor Board meetings (2024)	100.00
Total hours	813.00



About the author

Rosalie Koot was born on October 16th 1986 in Houten, The Netherlands. In Nieuwegein she attended the 'Oosterlicht College' higher secondary education between 1998 and 2005 following a profile focused on nature and health. In 2003 she fell in love with Anne de Groot and they have a daughter Elin and a son Joep. In 2006 she started studying medicine at the VU Medical center in Amsterdam. She performed an internship on Aruba. Furthermore, she was a frequent volleyball player. In 2008 she obtained her Bachelor of Science degree. In 2011 she completed her medical training and in 2012 she started working as a resident at the Department of Internal Medicine at the Rijnstate Hospital in Arnhem. In 2013 she started her clinical residency in Internal Medicine, also at the Rijnstate Hospital. In 2018 she started her fellowship in endocrinology. In 2019 she interrupted her residency to commence her PhD research under the supervision of Prof. dr. R. Netea Maier, Dr. P. Stalmeier, Prof. dr. R. Hermens and Dr. P. Ottevanger. The research was funded by the KWF. The project focused on the development of patient decision aids and the communication between patients and healthcare professionals. During her PhD project she presented the results at international and national scientific conferences and attended multiple courses on endocrinology, thyroid cancer and shared decision making. In 2024 she completed her fellowship and started working as an endocrinologist at the St. Antonius Hospital in Nieuwegein/Utrecht. In October 2024 she switched to the Flevoziekenhuis in Almere.

Acknowledgements (Dankwoord)

Er is een einde gekomen aan deze intensieve maar mooie periode. Deze laatste bladzijdes wil ik gebruiken om iedereen te bedanken die betrokken is geweest bij het mogelijk maken van dit proefschrift.

Alle proefpersonen/patiënten, als eerste wil ik hen bedanken die hebben deelgenomen aan de onderzoeken die in dit proefschrift zijn beschreven. Zonder jullie was het niet mogelijk geweest om dit onderzoek te volbrengen. Het is bijzonder om te merken dat zoveel patiënten bereid waren om tijd te investeren in wetenschappelijk onderzoek.

Dr. Stalmeier, beste Peep, bedankt voor de kans die je me gaf in 2019. Ondanks dat ik bagage had, een dure kracht was en dokter, bood je me de mogelijkheid dit mooie onderzoek op te zetten. Ik denk met veel plezier terug aan onze overleg momenten bij jou op de kamer en de laatste jaren voornamelijk online. De tijd die je maakt voor overleg, het vertrouwen dat je geeft en de snelheid waarmee je artikelen kritisch bekijkt, hebben mij als jonge onderzoeker de kans gegeven mijzelf te ontwikkelen. Bedankt daarvoor. Geniet van je welverdiende pensioen.

Prof.dr. Netea-Maier, beste Romana, ontzettend dankbaar ben ik voor de fijne begeleiding. De tijd die je vrijmaakt en het enthousiasme waarmee je informatie en kennis deelt is aanstekelijk. Door jou heb ik de afgelopen jaren mogen meewerken aan bijzondere projecten en presentaties mogen geven op verschillende congressen. Heel veel dank daarvoor. Jouw benoeming tot hoogleraar is uiteraard welverdiend! Ik hoop nog lang met je te mogen samenwerken.

Prof.dr. Hermens, beste Rosella, ondanks jouw drukke agenda was het altijd mogelijk een overleg in te plannen wanneer dat nodig was. Op die momenten stuurde je bij waar nodig zonder dat je de regie over nam. Bedankt daarvoor. Ook jouw benoeming tot hoogleraar is meer dan verdiend!

Dr. Ottevanger, beste Nelleke, bedankt voor de steun en oncologische visie tijdens dit project. Jouw nuchtere kijk op veel dingen helpt om te relativiseren en door te zetten.

Mijn dank gaat uit naar de leden van de leescommissie, prof. dr. Robert Takes, prof. dr. Thera Links en Dr. Julia van Tol voor het beoordelen van het manuscript. Daarnaast dank aan allen voor het plaatsnemen in de promotiecommissie. Ik kijk ernaar uit om met jullie van gedachten te wisselen tijdens de verdediging.

Dank aan het KWF voor subsidie en dank aan SchildklierNL bij het promoten van het onderzoek en de keuzehulp bij patiënten.

Ik dank alle lokale hoofdonderzoekers en betrokken artsen uit de deelnemende ziekenhuizen. Dank voor jullie inzet bij het opzetten van de COMBO studie in jullie ziekenhuis en natuurlijk voor het includeren van de patiënten.

Dr. Stikkelbroeck, beste Nike, als opleider van de endocrinologie was jij bereid om je nek uit te steken om dit gekke schema van mij mogelijk te maken. Meerdere keren moest je hierover in overleg. Mede dankzij jouw inzet bleek het mogelijk en heb ik zowel mijn differentiatie als mijn proefschrift tot een goed einde gebracht. Hier ben ik je heel dankbaar voor.

Dr. v Veenendaal, beste Haske, bedankt voor het trainen van onze trainers, het brainstormen en de scoorders voor de OPTION5.

Dr. Donders, beste Roger, bedankt voor jouw ondersteuning in de statistiek. Een ver van mijn bed show wat jij een klein beetje dichterbij hebt laten komen.

Dr. Aarts, beste Annemijn, bedankt voor het overleg en de training in het scoren van de OPTION5.

Beste Maaïke en Ella bedankt voor het scoren van de gesprekken. Een enorme klus wat jullie heel volledig en goed hebben gedaan.

Keizer karel, beste Stefan, ontzettend bedankt voor het mooie format waarin de keuzehulpen tijdens de COMBO studie beschikbaar waren online.

Lieve vrienden en vriendinnen, dank voor alle momenten die niet met dit proefschrift of werk te maken hadden. Door de fijne vriendschappen weet je dat er nog meer is in het leven dan werk en onderzoek. Ik kijk er naar uit om na het afronden van dit proefschrift weer meer tijd met jullie door te brengen.

Lieve Bien, Fem en Ka, heerlijk om jullie hierbij te hebben. Alle feestjes, weekendjes en etentjes zorgden ervoor dat ik opgeladen weer verder kon. Het skiën en binnenkort hopelijk IJsland maken onze vriendschap extra bijzonder.

Lieve Did, Jis en El, wat gaan we al lang terug. We kunnen altijd bij elkaar terecht. Zoals we laatst nog zeiden, zo fijn altijd! Een avond is altijd te kort. Ik kan niet wachten tot ons tripje naar Zuid-Frankrijk.

El, wat te gek dat jij de omslag hebt ontworpen!!

Lieve Chiel en Marith, alle eetdates, koffiedates, vakanties en weekendjes weg maken het leven leuker! Nu na het afronden van dit proefschrift wordt het hoog tijd dat er weer een trip gepland wordt.

Lieve pap, wat was je hier graag bij geweest. En wat had ik je er graag bij gehad. Ik ken niemand die trotser zou zijn geweest op wat ik de laatste jaren heb bereikt. Ik mis je nog elke dag.

Lieve mama en Frans, wat fijn dat jullie hierbij aanwezig zijn. Zonder jullie onvoorwaardelijke steun en hulp met Elin en Joep was dit niet mogelijk geweest. Mam, ontzettend bedankt dat je echt altijd voor ons klaar staat. Nooit is iets te gek. Je staat altijd achter mijn keuzes en moedigt aan waar je kunt.

Lieve Ralph en Daan, bedankt voor de fijne weekenden weg samen met Sem. Ik kijk uit naar de nieuwe avonturen met Just erbij!

Lieve Gerda en Henk, bedankt voor jullie enorme interesse in wat ik doe. Een luisterend oor, meedenken of een kritische noot. Bijzonder dat ik dit moment met jullie kan delen. Daarnaast is ook jullie hulp met Elin en Joep onmisbaar geweest.

Lieve Anne en Bert, dank voor jullie enthousiasme en support. Wat heerlijk dat we zo dicht bij elkaar wonen, kunnen genieten van de boot en van elkaar. Pleun en Bob, ik hoop op nog heel veel boottochtjes, logeerpactijen en weekendjes weg samen.

Lieve Anne, bedankt dat jij er altijd bent. Al 24 jaar! Zonder jou was het leven een stuk minder leuk geweest. Je klaagt nooit, bent altijd optimistisch en zorgt ervoor dat mijn werk altijd door kan gaan. Je bent de liefste en de beste papa. Ik hou van jou.

Lieve Elin en Joep, mijn laatste woorden zijn voor jullie. Jullie maken het leven nog mooier! Het onderzoek is eindelijk af. Hou van jullie!

