OPTIMIZING CARE FOR PATIENTS WITH DIFFERENTIATED THYROID CANCER

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OPTIMIZING CARE FOR PATIENTS WITH DIFFERENTIATED THYROID CANCER

HET OPTIMALISEREN VAN DE ZORG VOOR PATIËNTEN MET EEN GOED GEDIFFERENTIEERD SCHILDKLIERCARCINOOM

(met een samenvatting in het Nederlands)

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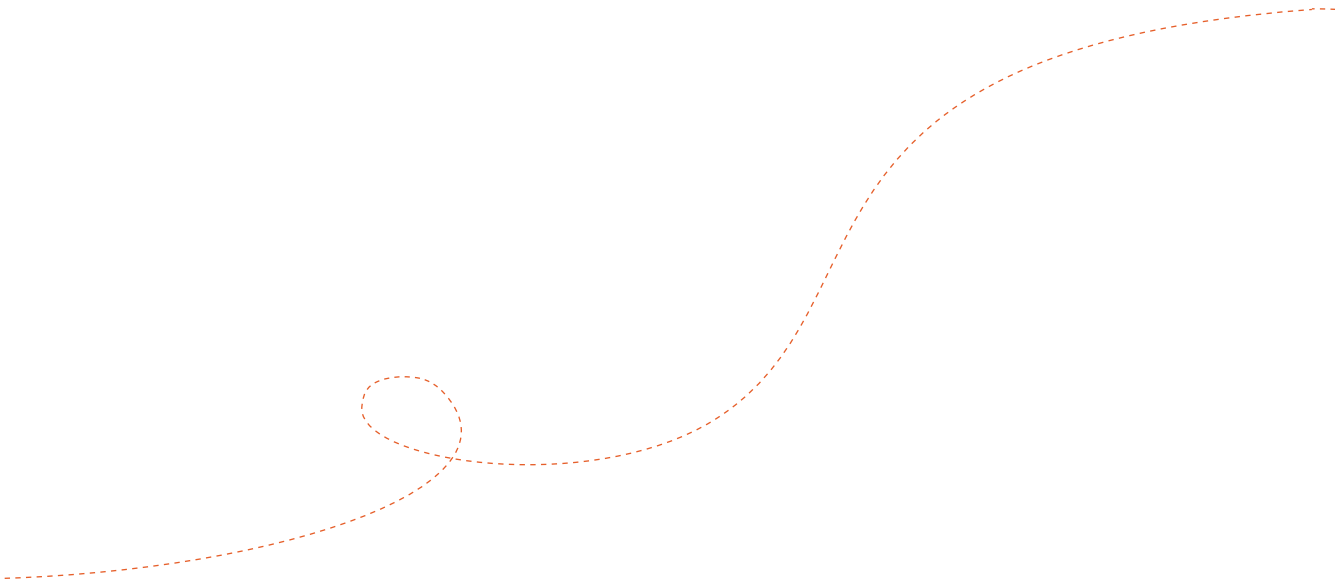
Table of contents



CHAPTER 1

General introduction and outline of the thesis

The aim of this thesis is to contribute to optimizing the care for patients with differentiated thyroid cancer (DTC) in different areas. In the diagnostic field; by evaluating the quality of FNA in our hospital and identifying factors associated with adequacy rate. In the area of customized follow-up: by investigating the use of biochemical markers and the use of diagnostic ^{131}I whole-body scan in high-risk patients. And in the prognostic area by trying to identify prognostic factors in patients with known metastatic lymph nodes.

EPIDEMIOLOGY

Differentiated thyroid cancer (DTC) is the most common type of thyroid cancer. Of the differentiated thyroid cancers, papillary cancer comprises about 85% of cases and about 12% have follicular histology, including Hürthle cell carcinomas. DTC has become increasingly prevalent over the last decades (1). Cervical lymph nodes are involved in 20–50% of patients and may be present even when the primary tumor is small and intrathyroidal. The frequency of micrometastases in cervical lymph nodes (<2mm) may approach 90% (2-9). Incidence rates in the Netherlands are 2:100.000 for men, and 4.5:100.000 for women. In 2016, 552 patients were diagnosed with differentiated thyroid cancer in the Netherlands (10).

DIAGNOSIS

Patients usually present with a palpable mass in the neck. This can be a thyroid nodule or enlarged lymph node(s). When a thyroid nodule is discovered, a complete history and physical examination focusing on the thyroid gland and adjacent cervical lymph nodes should be performed.

Clinical features suggestive for malignancy are relative rapid growth, fixation to surrounding tissue, cervical lymphadenopathy, hoarseness because of infiltration of the recurrent laryngeal nerve, inspiratory stridor or dysphagia due to compression of the trachea and esophagus. Historical factors predicting malignancy include a history of childhood head and neck radiation therapy, total body radiation, exposure to ionizing radiation in childhood or adolescence, familial thyroid carcinoma, or thyroid cancer syndrome (e.g., Cowden's disease, FAP, Carney complex, Werner syndrome/progeria), in a first degree relative (11).

With the discovery of a thyroid nodule >1 cm, a serum thyroid-stimulating hormone (TSH) level should be measured. If the serum TSH is subnormal, a radionuclide thyroid scan should be performed to document whether the nodule is hyperfunctioning ('hot'), isofunctioning ('warm') or nonfunctioning ('cold'). Cytologic evaluation is necessary for 'cold' nodules. A higher serum TSH level is associated with increased risk of malignancy in a thyroid nodule, as well as more advanced stage thyroid cancer (12-13).

Ultrasound

Diagnostic ultrasound (US) of the thyroid and cervical lymph nodes should be performed in all patients with known or suspected thyroid nodules (11). Central and lateral compartments should be evaluated for the presence of pathological lymph nodes. Preoperative US, however, identifies only half of the lymph nodes found at surgery, due to the presence of the overlying thyroid gland (14).

Fine needle aspiration

Fine needle aspiration (FNA) is the standard tool for diagnosing thyroid cancer and has led to a decrease in the number of thyroid surgeries and an increase in cancer detected during thyroid surgery (15-17). Still, a considerable percentage, up to 30% of all FNA specimens, are indeterminate and do not predict the nature of the thyroid tumor.

Thyroid FNA cytology is reported using diagnostic groups outlined in the Bethesda System for Reporting Thyroid Cytopathology. The Bethesda system recognizes six diagnostic categories and provides an estimation of cancer risk within each category based upon literature review and expert opinion. These categories and the associated risks of malignancy are (18):

1) non-diagnostic/unsatisfactory
2) benign: <1%
3) atypia of undetermined significance/follicular lesion of undetermined significance (AUS/FLUS): 5-10%
4) follicular neoplasm/suspicious for follicular neoplasm (FN/SFN), a category that also encompasses the diagnosis of Hürthle cell neoplasm/suspicious for Hürthle cell neoplasm: 20-30%
5) suspicious for malignancy: 50-75%
6) malignant: 100%

A major limitation of FNA is a high rate of non-diagnostic specimen, up to 43% (19-24). Causes of inadequate samples can be quantitative (low cellularity) or qualitative. Low cellularity may be due to a cystic component of the nodule, poor aspirating technique, or lack of experience with thyroid FNA. Qualitative problems may occur if too much blood is present or if a smear is fixated and stained inadequately. When repeated FNA remains non-diagnostic, only lobectomy offers a definitive diagnosis. A high rate of non-diagnostic specimen delays diagnosis, increases costs of the diagnostic tract, and may result in patient anxiety and discomfort (25).

To improve the quality of FNA, factors associated with adequacy rate need to be identified. Ultrasound (US)-guided FNA has been identified as a possible factor to improve adequacy rate (20-21). The two established guidelines on the management of thyroid nodules (American Thyroid Association (ATA) and the American Association of Clinical Endocrinologists (26-27), however, differed on their recommendation with respect to the use of US-guided-FNA. The American Association of Clinical Endocrinologists recommends

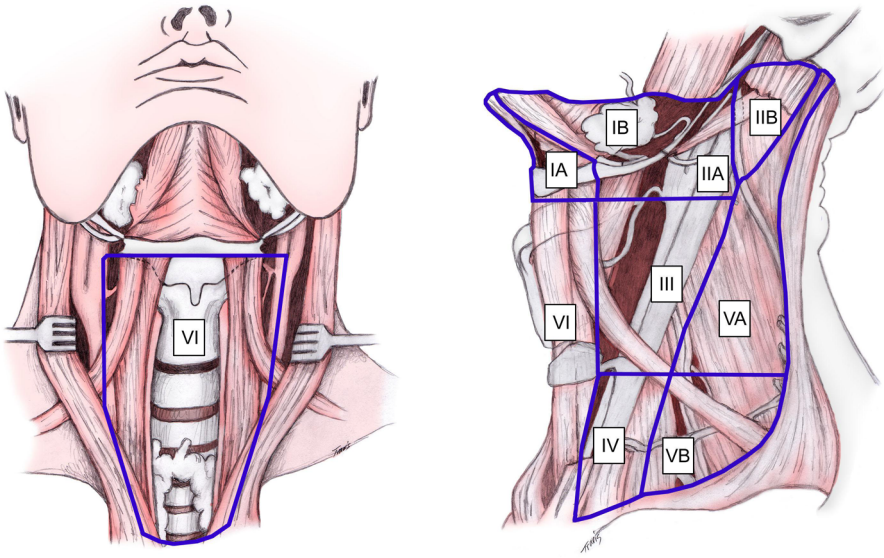


Figure 1-2. Levels of the neck (Medscape Neck Dissection Classification)

US-guided FNA for all tumors >10 mm, whereas the ATA does not favor US guidance over palpation-guided FNA. In our hospital, the US-guided FNA technique was implemented a few years earlier, without previous evaluation of the results of palpation-guided FNA. We therefore compared results of palpation- and US-guided FNA, evaluated the overall quality of all FNA samples of thyroid nodules over a 10-year period in our hospital and tried to find other factors associated with adequacy rate.
Chapter 2 describes the overall quality of FNA over a ten-year period in our hospital and compares the results between palpation- and US-guided FNA.

Staging

The TNM classification system (AJCC/UICC TNM staging) is used for all patients with DTC. Postoperative staging is used to provide prognostic information, which is of value when considering therapeutic strategy and surveillance. The TNM classification systems uses a combination of age at diagnosis, size of the primary tumor, specific tumor histology, and extrathyroidal spread of the tumor (direct extension of the tumor outside the thyroid gland, loco-regional metastases, and/or distant metastases) to stratify patients into one of several categories with different risks of death from thyroid cancer. The TNM classification is primarily used to guide initial therapeutic interventions.

Treatment

Goals of initial therapy for DTC patients are to improve overall and disease-specific survival, reduce the risk of persistent and/or recurrent disease and permit accurate disease staging and risk stratification. Postoperative risk assessment dictates subsequent disease

management and follow-up strategy. Historically treatment for DTC larger than 1 cm consists of a near-total or total thyroidectomy followed by radioactive ^{131}I ablation and TSH suppression in the Netherlands.

Radioactive iodine ablation therapy

Adjuvant radioactive ^{131}I (radioiodine) ablation treatment is used in different ways: in order to treat micro-metastases in the cervical lymph nodes and residual thyroid tissue, it can facilitate detection of recurrence with a post therapeutic whole-body scan and it may be used as therapy for recurrent disease. Total thyroidectomy followed by radioiodine ablation allows for accurate staging and risk stratification and permits accurate long-term surveillance for disease recurrence using the thyroid specific thyroglobulin (Tg) as a tumor marker.

Cervical lymph node involvement

Lymph node metastases are present in a majority of patients presenting with papillary thyroid cancer at the time of initial diagnosis and in a lesser proportion of patients with follicular thyroid cancer (28-30). The effect of the presence or absence of lymph node metastases on overall survival, if present at all, is low. Presence of lymph node metastases however does affect the risk of recurrence.

The most common site of nodal metastases is in the central compartment of the neck (level VI). Patients with clinically involved lymph nodes of the central compartment (cN1a) and patients with biopsy proven metastatic lateral lymphadenopathy (cN1b) are treated with central (level VI) and lateral compartment (II-IV/V) neck dissection.

FOLLOW-UP

The primary goal of long-term follow-up is accurate surveillance for possible recurrent disease. Until now, despite of classification systems like the AJCC TNM classification, there is a relative inability to accurately predict the risk of death or recurrence from thyroid cancer for individual patients. This may be related to the failure of current staging systems to adequately integrate the clinicopathologic features with other potentially important factors such as specific histology (well vs poorly differentiated cancer), size and location of distant metastasis, molecular profile, functional status of metastatic disease (^{131}I avid versus ^{18}F-FDG-PET avid) and effectiveness of initial therapy (completeness of resection, effectiveness of RAI).

Tg and Tg-antibodies (Tg-Ab)

Thyroglobulin is a hormone exclusively produced by thyroid tissue. It is therefore a potent tumor marker especially for patients treated with total thyroidectomy and radioactive iodine remnant ablation. In the absence of Tg-Ab serum Tg has a high sensitivity and specificity to detect thyroid cancer. When compared to other modalities used in the follow-up of DTC patients (US, diagnostic whole-body scan), recombinant human (rh)TSH stimulated Tg

measurement is the most sensitive method to detect recurrence (31). Dedifferentiation of tumors can cause tumor cells to stop producing thyroglobulin. In these patients, Tg levels are falsely low or undetectable. Additional imaging techniques should be used for these patients if recurrence is suspected.

During follow-up, it is important to detect recurrent disease without 'over-investigating' DTC patients. The timing and intensity of follow-up of patients remains largely unclear and guidelines are not explicit. The main problem is the absence of prospective trials, which are difficult to perform because survival rates are excellent and recurrences can develop many years after primary treatment.

Several authors have shown that an undetectable stimulated (either by rhTSH stimulation or after LT4 withdrawal) Tg level 9-12 months after diagnosis has a very high negative predictive value for recurrence, especially in low-risk patients (32-34). Limited evidence is available for high-risk patients. Tuttle (35) showed the same result for high-risk patients and proposed a re-staging of patients based on their response to therapy and tailor their follow-up accordingly.

In our cohort, median follow-up of all patients was very long and, moreover, it was uniform. Only a small percentage of patients were diagnosed with disease recurrence. A large portion of patients, also patients initially classified as high-risk patients were therefore 'over-investigated' during follow-up, indicating that classification of low-and high-risk should be improved. Our goal was to investigate whether stimulated-Tg levels 9-12 months after initial therapy could more accurately identify low- and high-risk patients. Also, we wanted to investigate whether repeated stimulated-Tg measurements, especially for initially classified high-risk patients, were of added value during follow-up. By doing so, we hope to contribute to a more individualized follow-up for DTC patients. **Chapter 3** describes the use of Tg as a marker for disease recurrence and as a tool for risk modification and the value of repeated Tg measurement during follow-up.

Patients with the expression of thyroglobulin-antibodies (Tg-Ab) pose a specific problem during follow-up; Tg levels cannot be accurately measured because of interference of the Tg-Ab with Tg testing. Tg levels can be falsely elevated (radioimmunic assays) or lowered (immunometric assays). Tg-Ab are present in approximately 20-25% of DTC patients. In patients without disease recurrence, but with the presence of Tg-Ab, Tg-Ab serum levels usually disappear over a median of 3 years.

Serial serum Tg-Ab quantification has been suggested as a surrogate marker for disease recurrence (36,37), while others found contradictory results (38).

A major limitation of these studies is the absence of a clear definition of a 'rising', 'declining' or 'stable' trend of Tg-Ab level. The study of Kim et al. (39) is one of the few studies that does define a rising and declining trend, and it has been incorporated in a consensus meeting regarding this subject. A rise is defined as ≥ 50% rise in concentration of measured Tg-Ab 6–12 months after remnant ablation compared to measurements during remnant ablation and a decline is defined as a ≥ 50% decline in Tg-Ab levels. However, the clinical application or relevance of this definition in DTC patients > 12 months after primary treatment had not yet been studied.

The aim of the study presented in **Chapter 4** therefore was to evaluate the outcome of patients with Tg-Ab during follow-up and to determine whether Tg-Ab trends can serve as a surrogate marker for disease recurrence in patients with well-differentiated thyroid cancer during long-term follow-up using well-defined criteria for rising, stable and declining Tg-Ab levels.

Diagnostic 131I whole-body scan (DxWBS)

Traditionally, follow-up of DTC patients consisted of periodic clinical assessment, US of the neck and performance of TSH –stimulated (either after LT4 withdrawal or after recombinant human TSH injection) Tg and Tg-Ab measurement simultaneous with diagnostic ^{131}I whole-body scintigraphy 6–12 months after initial treatment with (near)total thyroidectomy and ^{131}I remnant ablation. After 3,5,7 and 9 years this procedure was repeated. DxWBS is considered positive when uptake outside regions of physiologic uptake (oral, nasal or gastric mucosa; salivary glands; urogenital region) is observed.

Over the last decade, several authors have shown that DxWBS has a limited added value in the follow-up of low risk patients. These studies were incorporated by the American and European guidelines and DxWBS is no longer advised in the standard follow-up of low risk patients (40-41).

For high-risk patients, the value added by DxWBS to TSH-stimulated thyroglobulin measurement was largely unclear, due to limited research in a large group of high-risk patients.

The aim of the study presented in **Chapter 5** was to determine whether routine DxWBS performed 6–12 months after initial therapy offers information, additional to that provided by TSH-stimulated thyroglobulin measurements during the first year of follow-up of high-risk DTC patients.

PROGNOSIS

The prognosis of DTC patients after treatment is excellent (10-year survival >95%). But as mentioned before, disease recurrence in the lymph nodes is a relatively common problem. It has been suggested that the location of metastatic nodes (central vs lateral compartment) and the number of involved lymph nodes is of prognostic significance (42-43).

The TNM classification (44) describes the presence of positive cervical lymph nodes (CLN) as an independent risk factor for recurrence in all patients with follicular (FTC) and papillary thyroid cancer (PTC) over 45 years old. Patients are further subdivided patients with positive lymph nodes in the central compartment (level VI, N1a) and the lateral compartment (levels II-IV/V, N1b). However, the number of positive lymph nodes is not described as a prognostic factor influencing recurrence rate of DFS. Most of the research related to the location and number of positive lymph nodes has been performed by Ito et al. from Japan (45-48). They conclude that DFS of N1b patients is only significantly lower than that of N1a patients when 1) lymph nodes are larger than 3 cm; 2) 5 or more positive lymph nodes are present in the

lateral compartment; or 3) extranodal growth is present. The main problem with applying results of these studies to the European and American population is the different treatment of patients with DTC in Japan, with a much lower rate of total thyroidectomies and the limited use of ^{131}I therapy. Nonetheless, European and American guidelines are primarily based on the results of these Japanese studies (40,41).

We wanted to study the impact of the location and the number of cervical lymph node metastases on recurrence rate and DFS in patients with DTC treated in accordance with European/American standards, with (near) total thyroidectomy and postoperative ^{131}I ablation. Results of this study are presented in **Chapter 6.**

REFERENCES

1. Davies L, Welch HG 2014 Current thyroid cancer trends in the United States. JAMA Otolaryngol Head Neck Surg 140:317–322.

2. Nam-Goong IS, Kim HY, Gong G, Lee HK, Hong SJ,Kim WB, Shong YK 2004 Ultrasonography-guided fine needle aspiration of thyroid incidentaloma: correlation with pathological findings. Clin Endocrinol (Oxf) 60:21–28.

3. Chow SM, Law SC, Chan JK, Au SK, Yau S, Lau WH 2003 Papillary microcarcinoma of the thyroid—prognostic significance of lymph node metastasis and multifocality. Cancer 98:31–40.

4. Grebe SK, Hay ID 1996 Thyroid cancer nodal metastases: biologic significance and therapeutic considerations. Surg Oncol Clin N Am 5:43–63.

5. Scheumann GF, Gimm O, Wegener G, Hundeshagen H,Dralle H 1994 Prognostic significance and surgical management of locoregional lymph node metastases in papillary thyroid cancer. World J Surg 18:559–567.

6. Ito Y, Uruno T, Nakano K, Takamura Y, Miya A, Kobayashi K, Yokozawa T, Matsuzuka F, Kuma S, Kuma K, Miyauchi A 2003 An observation trial without surgical treatment in patients with papillary microcarcinoma of the thyroid. Thyroid 13:381–387.

7. Hay ID, Grant CS, van Heerden JA, Goellner JR, Ebersold JR, Bergstralh EJ 1992 Papillary thyroid microcarcinoma: a study of 535 cases observed in a 50-year period. Surgery 112:1139–1146.

8. Qubain SW, Nakano S, Baba M, Takao S, Aikou T 2002 Distribution of lymph node micrometastasis in pN0 well-differentiated thyroid carcinoma. Surgery 131:249–256.

9. Arturi F, Russo D, Giuffrida D, Ippolito A, Perrotti N, Vigneri R, Filetti S 1997 Early diagnosis by genetic analysis of differentiated thyroid cancer metastases in small lymph nodes. J Clin Endocrinol Metab 82:1638–1641.

10. Nederlandse kankerregistratie

11. Bryan R. Haugen, Erik K. Alexander, Keith C. Bible, Gerard M. Doherty, Susan J. Mandel, Yuri E. Nikiforov, Furio Pacini, Gregory W. Randolph, Anna M. Sawka, Martin Schlumberger,Kathryn G. Schuff, Steven I. Sherman, Julie Ann Sosa, David L. Steward,R. Michael Tuttle, Leonard Wartofsky 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 Volume 26, Number 1, 2016

12. Boelaert K, Horacek J, Holder RL, Watkinson JC, Sheppard MC, Franklyn JA 2006 Serum thyrotropin concentration as a novel predictor of malignancy in thyroid nodules investigated by fine-needle aspiration. J Clin Endocrinol Metab 91:4295–4301.

13. Haymart MR, Repplinger DJ, Leverson GE, Elson DF, Sippel RS, Jaume JC, Chen H 2008 Higher serum thyroid stimulating hormone level in thyroid nodule patients is associated with greater risks of differentiated thyroid cancer and advanced tumor stage. J Clin Endocrinol Metab 93:809–814.

14. Leboulleux S, Girard E, Rose M, Travagli JP, Sabbah N, Caillou B, Hartl DM, Lassau N, Baudin E, Schlumberger M 2007 Ultrasound criteria of malignancy for cervical lymph nodes in patients followed up for differentiated thyroid cancer. J Clin Endocrinol Metab 92:3590–3594.

15. Gharib H, Goellner JR. 1993 Fine-needle aspiration biopsy of the thyroid: an appraisal. Ann Intern Med ;118:282–289.

16. Hamberger B, Gharib H, Melton LJ, 3rd, Goellner JR, Zinsmeister AR 1982 Fine-needle aspiration biopsy of thyroid nodules. Impact on thyroid practice and cost of care. Am J Med. 1982;73:381–384.

17. Mittendorf EA, Tamarkin SW, McHenry CR. 2002 The results of ultrasound-guided fine-needle aspiration biopsy for evaluation of nodular thyroid disease. Surgery ;132:648–653.

18. Baloch ZW, LiVolsi VA 2008 Fine-needle aspiration of the thyroid: today and tomorrow. Best Pract Res Clin Endocrinol Metab. ;22(6):929-939.

19. Ko HM, Jhu IK, Yang SH, *et al. 2003* Clinicopathologic analysis of fine needle aspiration cytology of the thyroid. A review of 1,613 cases and correlation with histopathologic diagnoses. Acta Cytol*;* 47*:* 727–732.

20. Carmeci C, Jeffrey RB, McDougall IR, Nowels KW, Weigel RJ 1998. Ultrasound-guided fine-needle aspiration biopsy of thyroid masses. Thyroid*;* 8*:* 283–289.

21. Danese D, Sciacchitano S, Farsetti A, Andreoli M, Pontecorvi A. *1998* Diagnostic accuracy of conventional versus sonography-guided fine-needle aspiration biopsy of thyroid nodules. Thyroid*;* 8*:* 15–21.

22. Hatada T, Okada K, Ishii H, Ichii S, Utsunomiya J 1998 Evaluation of ultrasound-guided fine-needle aspiration biopsy for thyroid nodules. Am J Surg*;* 175*:* 133–136.

23. Tabaqchali MA, Hanson JM, Johnson SJ, Wadehra V, Lennard TW, Proud G. *2000* Thyroid aspiration cytology in Newcastle: A six year cytology/histology correlation study. Ann R Coll Surg Engl*;* 82*:* 149–155.

24. Morgan JL, Serpell JW, Cheng MS 2003 Fine-needle aspiration cytology of thyroid nodules: How useful is it? ANZ J Surg*;* 73*:* 480–483.

25. Borget I, Vielh P, Leboulleux S 2008 Assessment of the cost of fine-needle aspiration cytology as a diagnostic tool in patients with thyroid nodules. Am J Clin Pathol*;* 129*:* 763–771.

26. Gharib H, Papini E, Valcavi R, *et al. 2006* American Association of Clinical Endocrinologists and Associazione Medici Endocrinologi medical guidelines for clinical practice for the diagnosis and management of thyroid nodules. Endocr Pract*;* 12*:* 63–102.

27. Cooper DS, Doherty GM, Haugen BR, *et al. 2006* Management guidelines for patients with thyroid nodules and differentiated thyroid cancer. Thyroid*;* 16*:* 109–142.

28. Kouvaraki MA, Shapiro SE, Fornage BD, Edeiken-Monro BS, Sherman SI, Vassilopoulou-Sellin R, Lee JE,Evans DB 2003 Role of preoperative ultrasonography in the surgical management of patients with thyroid cancer. Surgery 134:946–954.

29. Hughes DT, White ML, Miller BS, Gauger PG, Burney RE, Doherty GM 2010 Influence of prophylactic central lymph node dissection on postoperative thyroglobulin levels and radioiodine treatment in papillary thyroid cancer. Surgery 148:1100–1106.

30. Randolph GW, Duh QY, Heller KS, LiVolsi VA, Mandel SJ, Steward DL, Tufano RP, Tuttle RM 2012 The prognostic significance of nodal metastases from papillary thyroid carcinoma can be stratified based on the size and number of metastatic lymph nodes, as well as the presence of extranodal extension. Thyroid 22:1144–1152.

31. Schlumberger M, Baudin E 1998 Serum thyroglobulin determination in the follow-up of patients with differentiated thyroid carcinoma. Eur J Endocrinol 138: 249-252.

32. Baudin E, Do Cao C, Cailleux AF, Leboulleux S, Travagli JP, et al. 2003 Positive predictive value of serum thyroglobulin levels, measured during the first year of follow-up after thyroid hormone withdrawal, in thyroid cancer patients. J Clin Endocrinol Metab 88: 1107-1111.

33. Castagna MG, Brilli L, Pilli T, Montanaro A, Cipri C, et al. 2008 Limited value of repeat recombinant human thyrotropin (rhTSH)-stimulated thyroglobulin testing in differentiated thyroid carcinoma patients with previous negative rhTSH-stimulated thyroglobulin and undetectable basal serum thyroglobulin levels. J Clin Endocrinol Metab 93: 76-81.

34. Kloos RT, Mazzaferri EL 2005 A single recombinant human thyrotropin-stimulated serum thyroglobulin measurement predicts differentiated thyroid carcinoma metastases three to five years later. J Clin Endocrinol Metab 90: 5047-5057.

35. Tuttle RM, Tala H, Shah J, Leboeuf R, Ghossein R, et al. 2010 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 20: 1341-1349.

36. Kim WG, Yoon JH, Kim WB, Kim TY, Kim EY, Kim JM, Ryu JS, Gong G, Hong SJ, Shong YK 2008 Change of serum antithyroglobulin antibody levels is useful for prediction of clinical recurrence in thyroglobulinnegative patients with differentiated thyroid carcinoma. JClin Endocrinol Metab 93:4683–4689.

37. Spencer C, Fatemi S 2013 Thyroglobulin antibody (TgAb) methods—strengths, pitfalls and clinical utility for monitoring TgAb-positive patients with differentiated thyroid cancer. Best Pract Res Clin Endocrinol Metab 27:701–712.

38. Smooke Praw S, Ro K, Levin O, et al. 2014 Thyroglobulin antibody levels do not predict disease status in papillary thyroid cancer. Clin Endocrinol (Oxf);81:271-5.

39. Yoon J, Kim W, Kim T, et al. 2008 Change of serum antithyroglobulin antibody levels is useful for prediction of clinical recurrence in thyroglobulin-negative patients with differentiated thyroid carcinoma. J Clin Endocrinol Metab ;93:4683-9.

40. Cooper DS, Doherty GM, Haugen BR, et al. 2009 Revised American Thyroid Association management guidelines for patients with thyroid nodules and differentiated thyroid cancer. Thyroid;19:1167–1214.

41. Pacini F, Schlumberger M, Dralle H, Elisei R, Smit JW, Wiersinga W 2006 European consensus for the management of patients with differentiated thyroid carcinoma of the follicular epithelium. Eur J Endocrinol.;154:787–803.

42. Deandreis D, Al Ghuzlan A, Leboulleux S, Lacroix L,Garsi JP, Talbot M, Lumbroso J, Baudin E, Caillou B, Bidart JM, Schlumberger M 2011 Do histological, immunohistochemical,and metabolic (radioiodine and fluorodeoxyglucose uptakes) patterns of metastatic thyroid cancer correlate with patient outcome? Endocr Relat Cancer 18:159–169.

43. Bardet S, Malville E, Rame JP, Babin E, Samama G, De RD, Michels JJ, Reznik Y, Henry-Amar M 2008 Macroscopic lymph-node involvement and neck dissection predict lymph-node recurrence in papillary thyroid carcinoma. Eur J Endocrinol 158:551–560.

44. Edge SB AJCC cancer staging manual (7th ed) 2010, New York, NY, Springer, 2010.

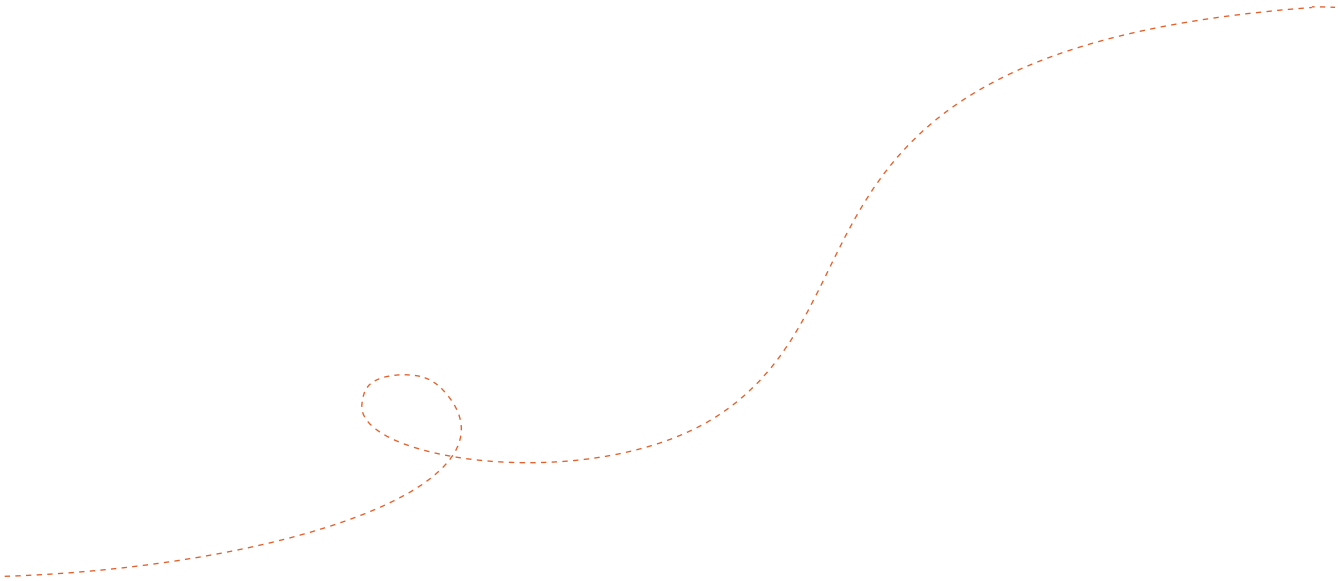
45. Ito Y, Tomoda C, Uruno T, et al. 2005 Ultrasonographically and anatomopathologically detectable node metastases in the lateral compartment as indicators of worse relapse-free survival in patients with papillary thyroid carcinoma. World J.Surg;29(7)917-920.

46. Ito Y, Miyauchi A. 2008 Lateral lymph node dissection guided by preoperative and intraoperative findings in differentiated thyroid carcinoma. World J.Surg;32(5)729-739

47. Ito Y, Fukushima M, Tomoda C, et al. 2009 Prognosis of patients with papillary thyroid carcinoma having clinically apparent metastasis to the lateral compartment. Endocr.J.;56(6)759-766.

48. Ito Y, Tomoda C, Uruno T, et al. 2004 Preoperative ultrasonographic examination for lymph node metastasis: usefulness when designing lymph node dissection for papillary microcarcinoma of the thyroid. World J. Surg.;28(5)498-501.

DIAGNOSIS



CHAPTER 2

Fine-needle aspiration of thyroid tumors: Identifying factors associated with adequacy rate in a large academic center in the Netherlands

Diagnostic Cytopathology (2010)
Diagnostic Cytopathology, Special issue (2012) 40: E21-26

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ABSTRACT

The goal of our study was to evaluate, and identify factors associated with, the adequacy rate of fine-needle aspiration (FNA) cytology of thyroid tumors to improve the quality of the procedure. We reviewed 1,611 cytological pathology reports of thyroid tumors of 871 patients between January 1998 and August 2008. The overall cytological adequacy rate was 53.9%. The freehand technique had significantly higher adequacy rates than the ultrasound (US)-guided technique ($P < 0.001$) regardless of size, tumor type, multinodularity, or location. Aspiration, performing specialist (endocrinologist versus radiologist), and size were the factors associated with adequacy rates. US-guided FNA is recommended in previous articles, but results in our clinic were in favor of freehand FNA. US guidance is a way to improve adequacy rates, but we would like to stress the importance of other factors like operator experience, education, and quality control in one's own institution before implementing techniques.

INTRODUCTION

Tumors of the thyroid are common in the general population. Four to seven percent of the general population has clinically palpable tumors. Fine-needle aspiration (FNA) cytology is the best available diagnostic procedure available for the evaluation of these tumors. The accuracy in distinguishing between benign and malignant tumors lies around 95%. This accuracy is lower in Hürthle cell and follicular neoplasm (1–4).

FNA is simple, safe, and cost-effective. The role of FNA has become more important in selecting patients for thyroid surgery. The use of FNA has resulted in a significant decrease in surgery for benign and an increase for malignant tumors (5,6). Still, a considerable percentage, up to 30% of all FNA specimens, are indeterminate and do not predict the nature of the thyroid tumor.

FNA should be considered for tumors of 1.0 cm or larger if microcalcifications are present. Furthermore, it should be considered for tumors of 1.5 cm or larger if the tumor is solid or if there are coarse calcifications within the tumor (7). Tumors smaller than 1.0 cm may be considered for FNA if the tumor is clinically suspicious or has malignant features on ultrasound (US) examination (8).

The major limitation of the procedure itself is the high rate of inadequate or "non-diagnostic" specimens, varying from 5% to 43.1% in literature (9–14). Causes of inadequate specimens can be quantitative (low cellularity) or qualitative. Low cellularity of a specimen can be due to a cystic component of the tumor, poor aspirating technique, and lack of experience with performing thyroid FNA. Qualitative problems can occur if too much blood or US gel is included in the specimen, which obscures the view. Another qualitative problem can occur if a smear is fixated and stained inadequately. The rate of non-diagnostic specimens increases costs of the diagnostic tract (15). Non-diagnostic specimens may also result in patient discomfort and a delay in diagnosis.

US is used increasingly for FNA. Recent studies show a significantly lower percentage of inadequate, non-diagnostic specimens using this technique. There are two established management guidelines on the management of thyroid tumors, one from the American Thyroid Association (ATA) and the other from the American Association of Clinical Endocrinologists (8, 16). The guidelines differ on the use of US-guided FNA. The American Association of Clinical Endocrinologists recommends US-guided FNA for all tumors >10 mm, whereas the ATA does not favor US guidance over palpation-guided FNA. One of the advantages of using US is direct visualization of the needle, thereby ensuring that tumor tissue is sampled instead of the cystic component or surrounding normal thyroid.

The goal of our study was to evaluate all FNAs performed during a 10-year period at the University Medical Center Utrecht (UMCU) and to identify factors associated with adequacy rate. Finally, we would like to make recommendations on how to further improve quality of this technique in our institution.

PATIENTS AND METHODS

Patient Selection

All consecutive patients who underwent thyroid FNA between January 1998 and August 2008 at the UMCU were included. We retrospectively reviewed the medical records and retrieved data on patient and tumor characteristics (age, gender, tumor size, type of tumor, location, solitary, or multinodular) and FNA (date, performing practitioner, previous US/computed tomography scan/magnetic resonance imaging, with or without US guidance). Cytopathological data were extracted from the database of the Pathology department of the UMCU. The size of the tumor was defined as the largest diameter measured on US. In case no previous US was performed, largest diameter on physical examination was noted.

Sampling Technique

FNA was performed either by an endocrinologist/endocrine surgeon or a radiologist and residents of both departments, sometimes under supervision. No immediate onsite cytologic assessment was performed. Endocrinologists/endocrine surgeons used a suction technique, using a 23-gauge needle attached to a 10-mL syringe. The tumor was palpated using two fingers, and the needle was inserted in the middle of the tumor. The needle tip was advanced into various positions in the tumor and moved back and forth while aspiration was performed. The collected material was placed on glass slides, smeared, and allowed to air dry.

Radiologists used a similar technique from 1998 until 2004. Radiologists used US guidance to visualize the needle and to obtain material from solid parts of the tumor while avoiding large blood vessels and cystic areas. The transducer was placed directly over the lesion in a transverse plane, followed by color Doppler to depict any large blood vessels. Radiologists used a 21-gauge needle instead of a 23-gauge needle, which was attached to a 10-mL syringe until 2005. After 2005, it was attached to a small tube. In 2005, radiologists abandoned aspiration and continued to use the non-aspirating technique. In this technique, the needle is advanced parallel to the US-transducer, into the tumor. The needle tip is carefully monitored during the procedure, and, when the needle reaches its target, the biopsy is performed. The needle is moved back and forth while being rotated along its axis. No suction is performed. Smears are prepared according to the protocol mentioned above.

Cytological Assessment

Smears were stained with Giemsa or Papanicolaou or both. Cytological analysis was performed by a core group of cytopathologists using strict cytological criteria to categorize each smear into one of the five diagnostic groups. The cytopathologists used a modified classification system in which lesions were classified into benign, indeterminate, suspicious, malignant, and non-diagnostic/inadequate (Table I).

At least three groups of 10 thyroid cells each had to be visible with a microscope to consider a specimen adequate for interpretation. Specimen with abundant colloid and/or

Table 1. Cytologic Classification Scheme

	Associated risk of malignancy (%)
Benign	<1
Follicular lesion of indeterminate significance – atypia of undetermined significance	5-10
Suspicious for neoplasm (follicular/Hurtle cell)	20-30
Suspicious for malignancy	50-75
Malignant	100
Non-diagnostic/inadequate	-

Diagnostic Terminology and Morphological Criteria for Cytological Diagnosis of Thyroid lesions used in the UMC Utrecht and associated risk of malignancy for each category (17)

macrophages with little or no follicular cells were not considered inadequate if these findings correlated with the clinical and radiologic impression of a colloid nodule or cystic lesion, which is in concordance with the Bethesda classification system (18). Smears that could not be interpreted because of quantitative or qualitative reasons (e.g., poor fixation, obscuring US gel, or blood) were classified as non-diagnostic or "inadequate."

Statistical Analysis

Data were analyzed using SPSS 15.0 (SPSS Inc. Chicago, IL). The adequacy rate for the specimens was calculated. Dichotomous variables were analyzed using the χ^2 test. Univariate and multivariate analyses were performed. A *P*-value of <0.05 was considered to be statistically significant.

RESULTS

Demographic and Tumor Features

Eight-hundred and seventy-one patients underwent 1,611 FNA of thyroid tumors. Seven-hundred and nineteen women (83%) and 152 men (17%) were included. The mean age (±SD) of patients was 51.4 (±15.1) years. The mean diameter (±SD) of the tumor was 2.8 (±1.5) cm. In 73% of the patients one or more tumors were palpable. FNA was performed under US guidance in 46% (*n* = 743) of the patients. Before FNA, in 1,187 (74%) cases, additional imaging was performed, US (*n* = 1,168), computed tomography (*n* = 15), or magnetic resonance imaging (*n* = 4).

Of the sampled tumors, 7% were cystic, 44% solid, and 20% were of the mixed type. The tumor type was unavailable in 476 (30%) of the FNA specimens. Forty-two percent of the specimens were obtained from a solitary tumor. We were unable to subtract data regarding the status of the performing specialist (e.g., intern, resident, fellow, and attending).

Cytological Adequacy

The overall cytological adequacy from 1998 to 2008 was 54% (n = 862). Adequacy rates were computed for each year (Table 2). The highest adequacy rate was achieved in 2001, with a diagnostic specimen rate of 73%. The lowest adequacy rate was seen in 2008, with only 35% of the specimens being diagnostic. Solitary tumors had higher adequacy rates than multinodular lesions (58% versus 51%, P = 0.009). Solid tumors had significantly higher adequacy rates than cystic tumors (52% versus 41%, p = 0.032). Mixed tumors had an adequacy rate of 48% (Table 3).

Size was not significantly associated with adequacy rates in multivariate analysis. However, if size was categorized, significant differences did exist. The highest adequacy rates were seen in tumors with a size between 3.5 and 4 cm (65%). A significant difference was seen if the 3.5–4 cm group (65%) was compared with the 1–1.5 cm (43%, $P \leq 0.001$) and the 0.5–1 cm groups (44%, P = 0.001; Table 4).

US-Guided FNA

Four-hundred and forty-five patients underwent 743 US-guided FNAs. Thirty-four percent of the patients had a solitary tumor. The tumor was solid in 62% of all aspirated tumors, 28% mixed, and 7% cystic. Information on the type of tumor was unavailable for the remaining ones. Tumors were palpable in 51% of the cases. Cytological adequacy was not statistically different between palpable and non-palpable tumors (44% versus 38%, P = 0.123), neither for solitary and multinodular lesions (40% versus 42%, P = 0.853).

Table 2. Percentage of Adequate FNA Specimen

	Diagnostic specimen rate %			
Year	**Overall**	**Palpation-guided FNA**	**US-guided FNA**	**P-value**
1998-2008	53.9	65.2	40.8	<0.001
1998	70.7	71.2	68.2	0.778
1999	64.1	67.3	47.6	0.85
2000	60.4	63.2	50.0	0.204
2001	73.4	75.5	66.7	0.337
2002	67.8	74.0	56.1	0.047
2003	41.6	43.5	38.5	0.513
2004	65.4	69.8	56.1	0.130
2005	49.6	68.3	34.7	<0.001
2006	44.8	65.4	37.3	<0.001
2007	38.5	59.5	32.1	0.001
2008	34.7	27.3	35.5	0.589

Table 3. Percentage of Adequate Material for Different Nodule Types

	All specimens (%)	Palpation-guided FNA (%)	US-guided FNA (%)	p-value
Solitary nodules	58.0	67.9	41.7	<0.001
Multinodular lesions	51.3	63.2	40.1	<0.001
Solid	51.7	67.4	43.4	<0.001
Mixed	47.8	63.1	38.6	<0.001
Cystic	40.6	54.5	25.5	<0.001
Nodules > 4cm	53.5	65.0	32.9	<0.001
Nodules < 4 cm	53.6	68.2	42.8	<0.001
Nodules < 1 cm	41.2	75.0	34.9	0.034

A significant difference in adequacy did exist between solid and cystic tumors (43% versus 26%, $P = 0.014$). The cytological adequacy rate was highest in tumors of 3.5–4 cm (51%). The lowest rate was seen when tumors were 4 cm or larger (33%; Table 4).

Palpation-Guided FNA

Palpation-guided FNA was performed in 426 patients, resulting in 868 biopsies. Of the aspirated tumors, 48% was solitary. In 51% of the cases, the tumor type could not be determined. For tumors that were visualized, 7% were cystic, 14% mixed, and 28% solid (Table 3).

There was no significant difference in cytological adequacy between solid and cystic lesions (67% versus 55%, $P = 0.720$). As in the US-guided group, the highest adequacy rate was seen in tumors between 3.5 and 4 cm. The lowest rate (57%) was seen in sizes between 1 and 1.5 cm (Table 4).

US-Guided Versus Palpation-Guided FNA

There was a significant difference in age ($P < 0.001$) and mean tumor size (<0.001) between US-guided and palpation-guided FNA. The mean age in the US-guided FNA group was 52.4 (SD ±15.4) versus 49 (SD ±14.6) years in the palpation-guided group. The mean size of the tumor in the US-guided group was 2.5 cm versus 3.0 cm in the palpation group. Radiologists punctured all non-palpable tumors and more patients with multiple tumors compared with endocrinologists and endocrine surgeons (65.7% versus 50.1%, $P \leq 0.001$; Table 5).

The adequacy rate was significantly higher for palpation-guided FNA compared with the US-guided FNA group (65.2% versus 41.7%, $P < 0.001$), for all tumor types and all sizes (Tables 4 and 5). When excluding the non-palpable tumors from analysis, a significant difference in adequacy rate was still observed (65% versus 44%, $P = 0.032$).

Aspirating Versus Non-aspirating FNA

We also compared results for the US-guided specimens before and after 2005, to see whether aspiration was a factor significantly related to adequacy of material obtained by radiologists. Cytological adequacy before 2005, using the aspirating technique, was 53.6%. After 2005, adequacy significantly decreased to 34.5% ($P \leq 0.001$). Comparing results of palpation-guided FNA (with aspiration) with those of the US-guided specimens taken before 2005 did not change our results. Multivariate analyses revealed that tumor type and performing specialist (endocrinologist versus radiologist) were associated with the adequacy rate.

Table 4. Percentage of Adequate FNA Material for different nodule sizes

Size (cm)	Overall	Palpation-guided	US-guided	p-value
0-0.5	0	(n=0)	0 (n=3)	-
0.5-1	43.8	75.0 (n= 8)	37.5 (n=40)	0.051
1-1.5	42.7	57.6 (n=33)	38.2 (n=89)	0.055
1.5-2	47.4	59.7 (n=72)	40.9 (n=115)	0.012
2-2.5	57.9	73.0 (n=89)	45.5 (n=99)	< 0.001
2.5-3	51.5	64.2 (n=67)	39.1 (n=64)	0.004
3-3.5	62.3	70.8 (n=113)	50.6 (n=77)	0.005
3.5-4	65.1	80.0 (n=40)	51.2 (n=43)	0.006
≥ 4	53.5	65.0 (n=157)	32.9 (n=85)	<0.001

Table 5. Palpation vs US-guided FNA

	Palpation-guided FNA	US-guided FNA	P-value
No. patients	426	445	
No. FNA-biopsies	868	743	
Mean age (+SD)	49 (14.6)	52.4 (15.4)	<0.001
Mean size nodule (+SD)	3.0 (1.45)	2.5 (1.48)	<0.001
Solitary nodules (%)	48.2	34.3	<0.001
Type of nodule (%)	Cystic: 6.5	Cystic: 6.9	0.788
	Mixed: 14.3	Mixed: 27.5	<0.001
	Solid: 28	Solid:61.5	<0.001
	Missing: 51.3	Missing: 4.2	<0.001
			<0.001
Palpable nodules (%)	100	51.3	<0.001
Imaging (%)	51.2	100	<0.001

DISCUSSION

FNA has proven to be a safe and reliable diagnostic method in distinguishing between benign and malignant thyroid tumors. However, the non-diagnostic, "unsatisfactory", or inadequate results varying from 5% to 43.1% in literature, and as high as 53.8% in our own series, remain a major problem (9–14).

As recommended by several guidelines, we reviewed all our FNA specimens to evaluate the quality of the procedure (19, 20). Surprisingly, we found that palpation-guided FNA had higher adequacy rates than US-guided FNA. This finding was independent of tumor size. Factors associated with adequacy rate were performing specialist, tumor type, and aspiration.

The overall cytological adequacy rate in our series may be lower than rates in the previously mentioned studies, but our results concerning palpation-guided FNA are similar. Comparing adequacy rates, however, is very difficult because thyroid tissue is difficult to evaluate and interobserver variety is high. No evidence-based criteria exist to assess adequacy of thyroid specimen, and various criteria are used, sometimes even among pathologists in one institute.

The adequacy rate of palpation-guided FNA was significantly higher compared with that of US-guided FNA. Most other studies reported US-guided FNA to be superior to palpation-guided in terms of adequacy rates and fewer non-diagnostic specimens. Two studies reported adequacy rates of around 68% (US-guided) versus 48% (palpation-guided), especially for tumors smaller than 2 cm, cystic tumors, and those located deep in the thyroid gland (12, 21). It has been advocated that US-guided FNA should be used for tumors smaller than 1.5 cm in diameter. Our data do not confirm this notion because results for tumors smaller than 1.5 cm were also better for freehand FNA.

We can only speculate about the reasons for the different outcomes between US-guided and palpation-guided specimens in our study. It is not possible to correct our results for some possible confounding factors. First of all, needle size could be a contributing factor. The needle sizes used in our study were 21-gauge in the US-guided and 23-gauge in the palpation-guided group. In literature, two prospective studies showed no differences in adequacy rates between needles groups (23- versus 27-gauge and 21 versus 25-gauge) (22, 23). Other studies showed an advantage for thinner needles, stating those yield a higher cellularity and cause less bloodstaining. Cappelli et al. found that using a stylet needle significantly improved the rate of diagnostic specimens in solid and complex tumors (24, 25). Because palpation-guided FNA was performed using a 23-gauge needle and US-guided FNA using a 21-gauge needle, it is unclear to which extend needle size contributed to the significant differences in adequacy rates. The same applies to aspiration technique, which was different only between endocrinologists and radiologists. Other explanations may be differences in smear technique, number of stains per patient, teaching of residents, adherence to protocol, and number of aspirations of the performing specialist and associated operator experience with FNA.

FNA is a procedure that is highly operator dependent; therefore, the differences found between freehand FNA and US-guided FNA may just represent differences in skills of the performing specialist. The number of physicians who perform FNA in the UMC Utrecht may be different from other institutions. This difference might explain our higher rate of inadequate specimens. It is recommended to keep the number of physicians performing and interpreting FNAs small to develop and maintain expertise.26 Endocrinologists strictly instruct and observe residents when they performed palpation-guided FNA. Also, the number of residents at the endocrinology department is lower, and the total number of punctures performed by a single resident, therefore, might be higher. The total number of palpation-guided punctures is similar to the punctures performed under US guidance. Furthermore, US-guided specimen taking is supposed to be more difficult to master. This causes a possible bias of our result and also might explain the lower adequacy rates for the US-guided aspirates.

Selection bias for tumors punctured under US guidance may have also caused the difference in adequacy rates. If palpation-guided biopsy were non-diagnostic, a referral for US-guided FNA was made. These tumors might present a challenge even for US-guided FNA. However, the US technique should have compensated for this.

In our series, we conclude that tumor type is a predictor of cytologic adequacy. Although we have a high percentage of missing data in this category, we still evaluated more than 800 tumors. Inclusion of cystic tumors has been suggested to lead to higher inadequacy rates. Some authors have proposed making a distinction between the cystic and solid tumors when determining adequacy rates (27, 28). Many studies have not clearly stated the rate of cystic tumors, making interpretation and comparison of results more difficult.

Cytological adequacy decreased significantly when radiologists stopped aspirating in 2005. Aspiration resulted in significantly less non-diagnostic specimen. These results are in contrast to those presented by Degirmenci et al. (24) and Romitelli et al. (29) who found a significantly higher rate of sufficient cytologic material with the non-aspirating technique. Various studies showed no difference in adequacy between the aspiration and non-aspiration techniques (30). When comparing results between the palpation-guided group and the US-guided group before 2005 (when aspiration was applied), the palpation-guided group had significantly higher adequacy rates. Aspiration, therefore, seems to be a factor that influences adequacy rate (for US-guided specimens, adequacy rates were significantly higher when using aspiration), but it also indicates that other factors that differed between the two groups contributed more to the difference in adequacy rate.

Several suggestions have been made to improve adequacy rates. Besides US guidance, another recommendation is the on-site assessment of specimens by a cytopathologist (31–34). However, other authors did not find a statistically significant difference in specimen adequacy between FNA biopsies with immediate cytological analysis and those with delayed analysis (26, 28, 32). Also, onsite interpretation is costly and time consuming. Another option would be immediate cytologic analysis by the performing specialist. These are methods that will be explored in our clinic.

When looking to the current guidelines, our results support those of the ATA, which states that US-guided FNA is not favored over palpation-guided FNA. The role of US in the diagnostic tract of a patient with a thyroid tumor is not covered in this article. US can be a valuable tool in determining whether tumors of the thyroid are eligible for FNA at all (35). In this study, adequacy rates for US-guided specimens were lower than that of published series. We do not have a clear explanation for this difference; possibly, the number of operators, operator experience and instruction, the inclusion of cystic lesions and smear technique could play a role. Also, publication bias could contribute, because institutes are more likely to submit studies with good results than disappointing outcomes.

US-guided FNA might be recommended in previous articles, but results in our clinic were in favor of freehand FNA. There are a few confounding factors that might influence our outcome (e.g., needle size, aspiration technique, and operator experience) for which we were unable to correct our results. Nevertheless, results of the palpation-guided FNAs were significantly better in our institution under the current circumstances at that time, and US guidance alone does not, therefore, predict better outcomes. We do not doubt that US guidance is a way to improve adequacy rates, but we would like to stress the importance of other factors like operator experience and expertise of the performing specialist and the importance of quality control in one's own institution, especially before and during the implementation of other techniques.

REFERENCES

1. Baloch ZW, Fleisher S, LiVolsi VA, Gupta PK. Diagnosis of "follicular neoplasm": A gray zone in thyroid fine-needle aspiration cytology. Diagn Cytopathol 2002; 26: 41–44.

2. Goldstein RE, Netterville JL, Burkey B, Johnson JE. Implications of follicular neoplasms, atypia, and lesions suspicious for malignancy diagnosed by fine-needle aspiration of thyroid nodules. Ann Surg 2002; 235: 656–662.

3. Kelman AS, Rathan A, Leibowitz J, Burstein DE, Haber RS. Thyroid cytology and the risk of malignancy in thyroid nodules: Importance of nuclear atypia in indeterminate specimens. Thyroid 2001; 11: 271–277.

4. Baloch Z, LiVolsi VA, Jain P, et al. Role of repeat fine-needle aspiration biopsy (FNAB) in the management of thyroid nodules. Diagn Cytopathol 2003; 29: 203–206.

5. Gharib H. Changing concepts in the diagnosis and management of thyroid nodules. Endocrinol Metab Clin North Am 1997; 26: 777–800.

6. Miller MC, Rubin CJ, Cunnane M, et al. Intraoperative pathologic examination: Cost effectiveness and clinical value in patients with cytologic diagnosis of cellular follicular thyroid lesion. Thyroid 2007; 17: 557–565.

7. Frates MC, Benson CB, Charboneau JW, et al. Management of thyroid nodules detected at US: Society of Radiologists in Ultrasound consensus conference statement. Ultrasound Q 2006; 22: 231–238.

8. Gharib H, Papini E, Valcavi R, et al. American Association of Clinical Endocrinologists and Associazione Medici Endocrinologi medical guidelines for clinical practice for the diagnosis and management of thyroid nodules. Endocr Pract 2006; 12: 63–102.

9. Ko HM, Jhu IK, Yang SH, et al. Clinicopathologic analysis of fine needle aspiration cytology of the thyroid. A review of 1,613 cases and correlation with histopathologic diagnoses. Acta Cytol 2003; 47: 727–732.

10. Carmeci C, Jeffrey RB, McDougall IR, Nowels KW, Weigel RJ. Ultrasound-guided fine-needle aspiration biopsy of thyroid masses. Thyroid 1998; 8: 283–289.

11. Danese D, Sciacchitano S, Farsetti A, Andreoli M, Pontecorvi A. Diagnostic accuracy of conventional versus sonography-guided fine-needle aspiration biopsy of thyroid nodules. Thyroid 1998; 8: 15–21.

12. Hatada T, Okada K, Ishii H, Ichii S, Utsunomiya J. Evaluation of ultrasound-guided fine-needle aspiration biopsy for thyroid nodules. Am J Surg 1998; 175: 133–136.

13. Tabaqchali MA, Hanson JM, Johnson SJ, Wadehra V, Lennard TW, Proud G. Thyroid aspiration cytology in Newcastle: A six year cytology/histology correlation study. Ann R Coll Surg Engl 2000; 82: 149–155.

14. Morgan JL, Serpell JW, Cheng MS. Fine-needle aspiration cytology of thyroid nodules: How useful is it? ANZ J Surg 2003; 73: 480–483.

15. Borget I, Vielh P, Leboulleux S, et al. Assessment of the cost of fine-needle aspiration cytology as a diagnostic tool in patients with thyroid nodules. Am J Clin Pathol 2008; 129: 763–771.

16. Cooper DS, Doherty GM, Haugen BR, et al. Management guidelines for patients with thyroid nodules and differentiated thyroid cancer. Thyroid 2006; 16: 109–142.

17. Baloch ZW, LiVolsi VA, Asa SL, et al. Diagnostic terminology and morphologic criteria for cytologic diagnosis of thyroid lesions: A synopsis of the National Cancer Institute Thyroid Fine-Needle Aspiration State of the Science Conference. Diagn Cytopathol 2008; 36: 425–437.

18. Theoharis CG, Schofield KM, Hammers L, Udelsman R, Chhieng DC. The Bethesda thyroid fine-needle aspiration classification system: Year 1 at an academic institution. Thyroid 2009; 19: 1215–1223.

19. Mehrotra P, Viswanathan H, Johnson SJ, Wadehra V, Richardson DL, Lennard TW. Ultrasound guidance improves the adequacy of our preoperative thyroid cytology but not its accuracy. Cytopathology 2006; 17: 137–144.

20. Carpi A, Di CG, Iervasi G, et al. Thyroid fine needle aspiration: How to improve clinicians' confidence and performance with the technique. Cancer Lett 2008; 264: 163–171.

21. Cesur M, Corapcioglu D, Bulut S, et al. Comparison of palpation-guided fine-needle aspiration biopsy to ultrasound-guided fine-needle aspiration biopsy in the evaluation of thyroid nodules. Thyroid 2006; 16: 555–561.

22. Kim MJ, Kim EK, Park SI, et al. US-guided fine-needle aspiration of thyroid nodules: Indications, techniques, results. Radiographics 2008; 28: 1869–1886.

23. Tangpricha V, Chen BJ, Swan NC, Sweeney AT, de las MA, Safer JD. Twenty-one-gauge needles provide more cellular samples than twenty-five-gauge needles in fine-needle aspiration biopsy of the thyroid but may not provide increased diagnostic accuracy. Thyroid 2001; 11: 973–976.

24. Degirmenci B, Haktanir A, Albayrak R, et al. Sonographically guided fine-needle biopsy of thyroid nodules: The effects of nodule characteristics, sampling technique, and needle size on the adequacy of cytological material. Clin Radiol 2007; 62: 798–803.

25. Cappelli C, Agabiti RE, Castellano M. Thyroid cytology: Does the needle matter? Cytopathology 2008; 19: 62–63.

26. O'Malley ME, Weir MM, Hahn PF, Misdraji J, Wood BJ, Mueller PR. US-guided fine-needle aspiration biopsy of thyroid nodules: Adequacy of cytologic material and procedure time with and without immediate cytologic analysis. Radiology 2002; 222: 383–387.

27. Kim MJ, Kim EK, Park SI, et al. US-guided fine-needle aspiration of thyroid nodules: Indications, techniques, results. Radiographics 2008; 28: 1869–1886.

28. Suen KC. Fine-needle aspiration biopsy of the thyroid. CMAJ 2002; 167: 491–495.

29. Romitelli F,Di SE,Santoro C,Iozzino M,Orsini A,Cesareo R. A comparative study of fine needle aspiration and fine needle non-aspiration biopsy on suspected thyroid nodules. Endocr Pathol 2009; 20: 108–113.

30. Kate MS, Kamal MM, Bobhate SK, Kher AV. Evaluation of fine needle capillary sampling in superficial and deep-seated lesions. An analysis of 670 cases. Acta Cytol 1998; 42: 679–684.

31. Borget I, Vielh P, Leboulleux S, et al. Assessment of the cost of fine-needle aspiration cytology as a diagnostic tool in patients with thyroid nodules. Am J Clin Pathol 2008; 129: 763–771.

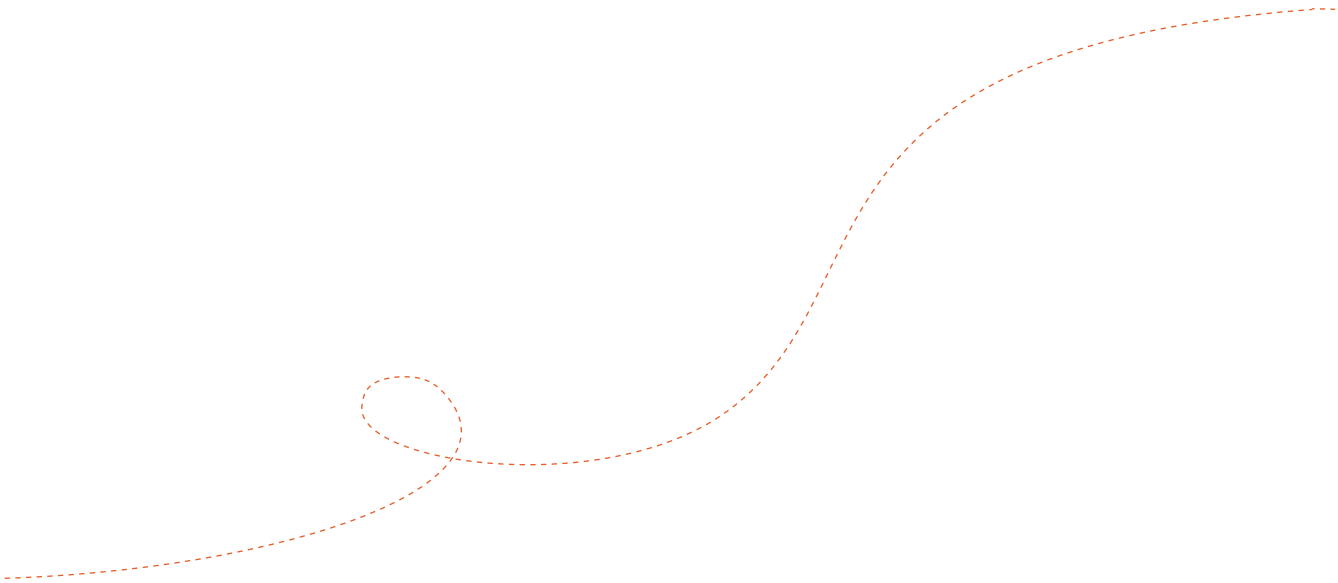
32. Eedes CR, Wang HH. Cost-effectiveness of immediate specimen adequacy assessment of thyroid fine-needle aspirations. Am J Clin Pathol 2004; 121: 64–69.

33. Ceresini G, Corcione L, Morganti S, et al. Ultrasound-guided fine-needle capillary biopsy of thyroid nodules, coupled with on-site cytologic review, improves results. Thyroid 2004; 14: 385–389.

34. Redman R, Zalaznick H, Mazzaferri EL, Massoll NA. The impact of assessing specimen adequacy and number of needle passes for fine-needle aspiration biopsy of thyroid nodules. Thyroid 2006; 16: 55–60.

35. Cooper DS, Doherty GM, Haugen BR, et al. Revised American Thyroid Association management guidelines for patients with thyroid nodules and differentiated thyroid cancer. Thyroid 2009; 19: 1167–1214.

FOLLOW-UP



CHAPTER 3

High Negative Predictive Value (NPV) Of Undetectable TSH Stimulated Tg For Disease Recurrence In Both Low- And High- Risk Differentiated Thyroid Cancer

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ABSTRACT

The extend, intensity and timing of the follow-up of differentiated thyroid cancer (DTC) patients remains unclear. Recent studies identified an undetectable TSH stimulated thyroglobulin (Tg) measurement after one year as a prognostic factor for the risk of recurrence during further follow-up, thereby further dividing patients based on risk for recurrence. Because patients experience their disease on an emotional basis rather than related to actual disease severity, follow-up should be targeted to detect recurrence without 'over-investigating' patients. The purpose of our study was to investigate the recurrence rate in high- and low-risk patients with DTC and the need for repeated (TSH stimulated) Tg measurement.

We retrospectively reviewed the medical records of 264 DTC patients with absent Tg-Ab and identified the patients with persistent/recurrent disease. Recurrence rates between patients with and without detectable TSH-stimulated thyroglobulin levels were compared. Recurrence rate was significantly higher in patients with positive stimulated Tg measurement within one year after treatment ($p<0.001$) While the negative predictive value (NPV) of an undectectable Tg was 0.97 for both high- and low-risk patients. The percentage of high-risk patients with undetectable Tg after one year is significantly lower compared to low-risk patients.

Recurrence rates for patients with undectable TSH stimulated Tg one year after initial diagnosis is very low and identical for low- and high-risk patients. Therefore it seems sensible to discharge patients from a strict specialist follow-up regime.

INTRODUCTION

The main focus in the post-surgical follow-up of patients with differentiated thyroid cancer (DTC) is the detection of persistent or recurrent disease. Because traditional treatment of DTC larger than 1 cm consists of total thyroidectomy followed by ^{131}I ablation of the remaining thyroid tissue, this follow-up can be performed using recombinant human TSH (rhTSH) stimulated thyroglobulin (Tg) measurements. Thyroglobulin is only produced by normal thyrocytes or well-differentiated thyroid cancer cells. Therefore, the presence of Tg is indicative of persistent or recurrent disease. When compared to other diagnostic modalities like ^{131}I whole-body scintigraphy (DxWBS) and ultrasound (US), serum thyroglobulin level (rhTSH stimulated or after LT-4 withdrawal) is the most sensitive method to detect disease recurrence (1). The majority of patients with DTC are initially classified as low-risk patients. Possible explanation is the increased use and sensitivity of ultrasound. Re-staging after initial therapy could be helpful in predicting recurrence more accurately. Low-risk patients with excellent response to therapy could be classified as real low-risk patients with minimal chance of recurrent disease during further follow-up. The intensity and form of the follow-up of these patients should be tailored based upon this revised risk stratification after initial therapy and the need for an intensive follow-up of the real low risk patients could be questioned. Baudin et al. (2) for example showed that the recurrence rate in low-risk patients with undetectable Tg levels at the time of performing the control WBS was only 0.6%. Several other recent studies also show a high negative predictive value of TSH stimulated Tg measurement for the risk of recurrence one year after initial therapy (3-5).

It is proposed that patients initially staged as high-risk patients could also be re-classified based on their response to therapy as shown by Tuttle et al. (5). Response to therapy is a good predictor for the risk of recurrence. While it is important to detect recurrences in an early stage it should be taken into account that the quality of life of patients with DTC could be diminished by the type and number of investigations during follow-up. DTC patients perceive their illness on an emotional basis unrelated to the actual severity of their disease status and cancer stage (6). It is therefore important to detect recurrent disease without 'over-investigating' patients.

The timing and intensity of the follow-up remains largely unclear and guidelines are not explicit. The main problem in determining a proper management protocol is the absence of prospective trials and the inability to perform a randomized study, which would take more than 35 years before results would be available. Advice about the follow-up protocol is based on retrospective series and expert opinion. Aim of our study was to investigate the recurrence rate in patients with DTC and the need for repeated (TSH stimulated) Tg measurement during further follow-up based upon the stimulated Tg level one year after initial therapy.

PATIENTS AND METHODS

We retrospectively reviewed the clinical (electronic) records of all consecutive patients with differentiated thyroid cancer evaluated at the University Medical Center Utrecht treated with (near)total thyroidectomy and ^{131}I remnant ablation from January 1994 until January 2009. Patients were further subdivided in low- and high-risk patients after initial TNM staging. We used the American Joint Committee on Cancer (AJCC) TNM version 7 criteria in determining T stage of the various tumors (7). Risk staging was done according to the European guidelines (8). Low-risk patients were defined as patients with small tumors (T1-T2), negative cervical lymph nodes (N0) and no evidence of distant metastasis at time of diagnosis. High-risk patients had large tumors (T3-T4), positive lymph nodes (N1) or distant metastasis (M1) at time of diagnosis. Patient characteristics and follow-up parameters, e.g. laboratory measurements (thyroglobulin (Tg), thyroglobulin-antibodies (Tg-Ab), total T4 and TSH), results of the ^{131}I whole-body scintigraphy after treatment (RxWBS) and low dose ^{131}I diagnostic whole-body scintigraphy during follow-up (DxWBS), were recorded. In addition, tumor characteristics, preoperative and postoperative staging and results of surgery were registered. Patients were excluded from the study for the following reasons 1) inadequate follow-up information 2) inadequate information for staging 3) age < 18 years at time of diagnosis 4) positive Tg-Ab 5) medullary and anaplastic thyroid cancer. All patients received TSH suppressive therapy and had at least two or more serum thyroglobulin and thyroglobulin-antibodies measurements during levothyroxine therapy. All patients had at least two or more thyroglobulin and thyroglobulin-antibodies measurements after levothyroxine withdrawal (until 2004) or after recombinant human TSH injection (0.9 mg im, Thyrogen: Genzyme Therapeutics). In all patients, a RxWBS and at least one DxWBS (9-12 months after initial diagnosis) were performed.

Laboratory analysis

Between 1994 and 1998 different thyroglobulin assays were used with functional sensitivities varying from 1-3 ng/ml. From 1998 onward, all thyroglobulin and thyroglobulin-antibody levels were measured using the Brahms DYNO test Tg-pluS (Brahms Diagnostica GmBH). The functional sensitivity for this assay is 0.2 ng/mL. Thyroglobulin level was judged positive whenever the value of the functional sensitivity of the test was exceeded. All thyroglobulin and thyroglobulin-antibody levels indicated in the text or in tables are TSH stimulated measurements, either by LT4 withdrawal or rhTSH injection unless indicated otherwise. TSH levels were measured simultaneously and exceeded 20 mU/l in all patients.

Follow-up

During the first year, controls were performed at least once every 6 months. Thereafter controls were performed with 6-12 month intervals. Standard follow-up of low-risk patients existed of clinical examination with or without ultrasound, TSH stimulated thyroglobulin measurement 1, 4 and 9 years after initial treatment, combined with a ^{131}I diagnostic whole-body scan. After 2008 low-risk patients with negative stimulated thyroglobulin level and a

previously negative DxWBS were no longer referred for another diagnostic whole-body scan. For high-risk patients, follow-up consisted of yearly controls including clinical examination, neck ultrasound, TSH stimulated thyroglobulin measurement and thyroglobulin measurement every 6 months. A DxWBS was performed after 1,4 and 9 years.

Persistent/Recurrent disease

Suspicion of persistent/recurrent disease was based on results of physical examination, laboratory analysis (thyroglobulin raised above functional sensitivity) and results of the DxWBS (uptake outside regions of physiological uptake). Whenever there was biochemical suspicion of disease recurrence, but normal imaging results were obtained, different strategies were followed. In some patients additional imaging like ^{18}F-FDG-PET, CT or MRI was performed. For patients with a high suspicion of recurrence, based on a high thyroglobulin or thyroglobulin-antibody level, a 'blind' therapeutic ^{131}I dose was administered followed by a RxWBS. Some patients were treated conservatively with repeated diagnostics after 6-12 months.

In order to confirm disease persistence or recurrence a positive RxWBS, anatomic substrate on additional imaging, fine-needle cytology or histology confirming DTC had to be present. When biochemical markers and imaging results were normal patients were classified as No Evidence of Disease (NED).

Statistical analysis

Statistical analysis was performed using SPSS 15.0 (Chicago, Illinois). All demographic data are shown in mean values with standard deviation (± SD) unless indicated otherwise. Percentages are rounded to the nearest integer. For statistical analysis, we used Chi-square and t-tests where appropriate. P-values smaller than 0.05 were considered statistically significant.

RESULTS

A total of 402 DTC patients were referred to the department of Nuclear Medicine for ablation therapy after total thyroidectomy and were included in our database (Figure 1).

One-hundred and sixty-eight adult patients could be classified as low-risk patients. Nine patients had positive thyroglobulin-antibodies and for 27 patients no results of laboratory analysis after one year were available and were subsequently excluded.

Two-hundred-one patients were classified as high-risk patients. For 49 patients Tg level within 12 months of follow-up were missing. Another 19 had positive thyroglobulin-antibodies and were subsequently excluded. One patient was excluded based on a definite histological diagnosis of an anaplastic carcinoma. A total of 132 patients in both groups remained for final analysis.

Demographic data, clinical features and final outcomes of the 264 low- and high-risk patients are presented in Table 1. The majority of patients were female in both groups

(76% and 68%). Mean age was 47 years for low-risk patients and 50 years for high-risk patients. These differences were not statistically significant (p=0.505) Statistically significant differences between groups were observed for mean tumor size (22 mm for low-risk and 33 mm for high-risk patients, p<0.001), recurrence rate (17% for low-risk and 41% for high-risk patients, p<0.001) and disease related mortality (0.8% vs. 5%, p=0.031). Median follow-up varied from 48 months for high-risk to 56 months for low-risk patients. Most patients (81%) had at least three TSH stimulated thyroglobulin measurement during follow-up.

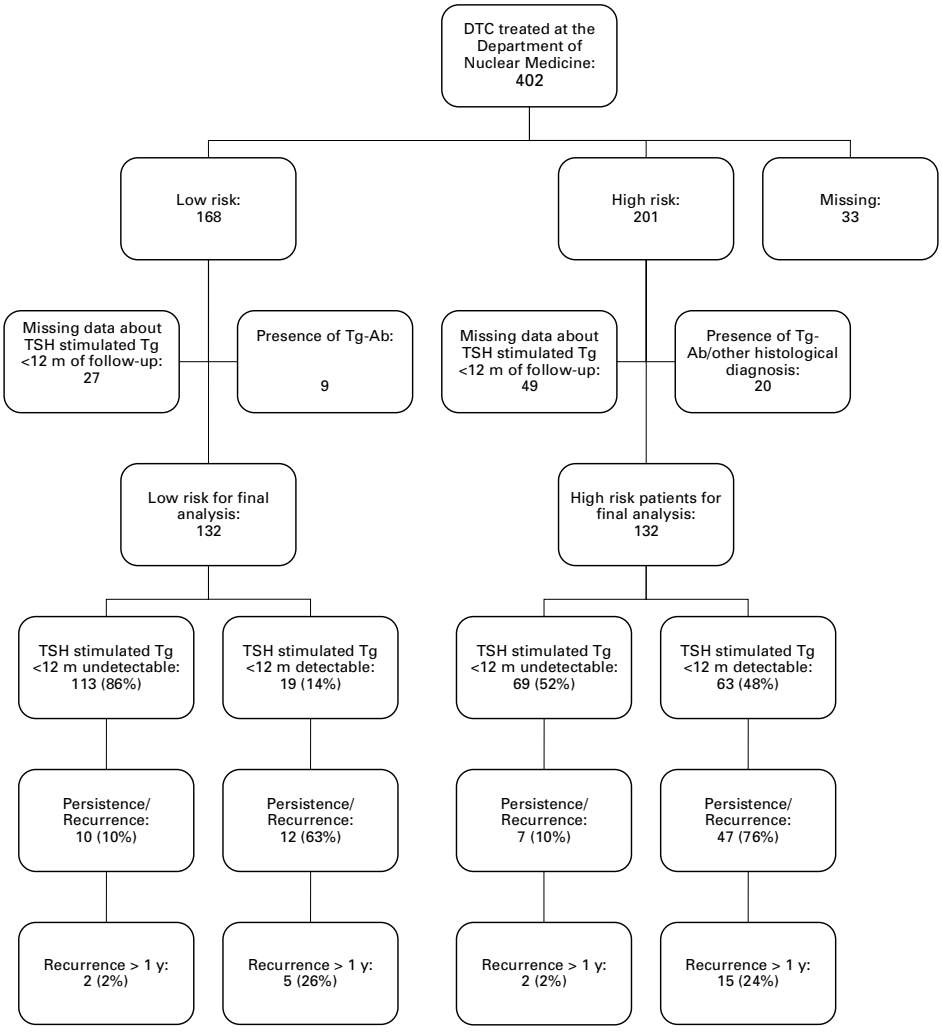


Figure 1.

Table 1. Demographic and tumor data of low-and high-risk DTC patients '98-2010

	Low-risk		**High-risk**		**p-value**
Gender	Male: n= 32	(24%)	n= 40	30%)	0.269
	Female: n= 100	(76%)	n= 92	(68%)	
Age	Median: 47 (± 15)		50 (±17)		0.505
Tumor size	Median: 22 mm (± 9.6 mm)		Mean: 33 (±22)		*<0.001*
Tumor histology	Papillary: n=95	(72%)	n =101	(77%)	0.327
	Follicular: n=23	(18%)	n=21	(24%)	
	Hurthlecell n=14	(10%)	n= 10	(8%)	
Initial presentation	Solitary nodule: n= 88	(67%)	n= 49	(37%)	
	MNG: n=20	(14%)	n= 25	(19%)	
	Non-specified diffuse swelling neck: n= 8	(6%)	n= 9	(7%)	
	Other (e.g cysts, other malignancy): n= 16	(12%)	n= 47x	(7%)	
Follow-up duration (m)	Mean: 56		Mean: 48		0.323
Recurrence	n= 23	(17%)	n= 54	(41%)	*<0.001*
Mortality rate	n= 3	(2%)	n=8	(6%)	0.159
Disease related mortality	n= 1	(0.8%)	n= 7	(5%)	0.031

Persistent/Recurrent disease

The overall persistence/recurrence rate for low-risk patients was 17%. For high-risk patients this rate was statistically significant higher with 54% (p<0.001). In both groups 78% of the patients diagnosed with recurrent/ persistent disease were diagnosed within the first year of follow-up.

Persistence/recurrence rate related to the value of the TSH stimulated Tg level within one year

Of the low-risk patients a total of 113 patients (86%) had undetectable thyroglobulin levels. The percentage of high-risk patients with undetectable thyroglobulin level was significantly lower with 52% (p<0.001). The recurrence rate for high- and low-risk patients was significantly lower for patients with undectable thyroglobulin level compared to patients with detectable thyroglobulin level (10% vs. 63% for low-(p<0.001) and 10% vs. 73% (p<0.001) for high-risk patients. Recurrence rate for patients with undetectable thyroglobulin measurement within the year was identical between high- and low-risk patients (p=0.928). The recurrence rate for patients with detectable Tg level within the year of follow-up was also not statistically different between low- and high-risk patients (p=0.408).

Table 2. Recurrence rate related to initial (rh)TSH stimulated Tg level for low- and high- risk patients

	Tg undetectable	**Tg elevated**	**p-value**
First recurrence within the year			
Low risk:	7.1%	52.7%	<0.001
High risk:	6%	66%	<0.001
First recurrence >1 year			
Low risk:	2.7%	10.5 %	0.027
High risk:	3 %	20.6%	0.001

Table 3. Recurrent/persistent disease after one year, related to (rh)TSH stimulated Tg level 6-12 months after therapy

	Undetectable Tg	**Detectable Tg**	
Recurrence > 1 year			**Low-risk:**
Low risk	2	2	Sens : 2/4=0.5
			Spec:111/127=0.87
High risk	2	15	PPV: 2/19=0.11
			NPV: 111/113=0.97
No recurrence > year			**High-risk**
Low risk	111	17	Sens: 15/17=0.88
			Spec:67/115=0.58
High risk	67	48	PPV: 15/63=0.24
			NPV: 67/69=0.97
Total			
Low risk	113	19	
High risk	69	63	

Sens = sensitivity. PPV= positive predictive value. Spec= specificity. NPV = negative predictive value

Recurrences during further follow up in patients with undetectable thyroglobulin within the first year of follow-up

The recurrence rate for patients with undetectable thyroglobulin within 12 months after treatment during further follow-up was 2% for both low- and high-risk patients.

The negative predictive value (NPV) of an undetectable Tg level for recurrence after one year was 0.97 for low- and high-risk patients (Table 3). Two high-risk patients were diagnosed with recurrent disease, while initial stimulated Tg level was undetectable.

Both patients were suspected to have recurrent disease based on a rising recombinant human-TSH stimulated-thyroglobulin level. One patient was successfully treated with a therapeutic activity of 7400 Mbq. The other patient was repeatedly treated, received external radiotherapy and is not considered disease free. Two low-risk patients developed a recurrence during further follow-up. One patient had rising recombinant human-TSH stimulated Tg level with palpable lymph nodes in the neck. The other patient had noticed a gradual increase in neck circumference. These patients were treated successfully with radioactive iodine. One patient was treated with an extra dose of 7400 MBq, the other patient was treated twice before and are both considered NED (Table 3).

DISCUSSION

There are several studies confirming a high NPV of TSH-stimulated thyroglobulin measurement (2,5,9-12). Our results are consistent with recent publications about this subject. When using the functional sensitivity of our thyroglobulin method as a cut-off value, the negative predictive value of TSH-stimulated thyroglobulin was 97% in our study. The high NPV of an undetectable thyroglobulin level was also applicable to high-risk patients. A recent report from Brassard et al. also reports this high NPV in a large prospective cohort of over 700 patients (11). Main difference with our study, besides the prospective character of their study, is the thyroglobulin method used and the cut-off value, which they calculated using ROC-curves, while we used the functional sensitivity of our test as a cut-off value. With the results of our study as an addendum to the previous reports, we conclude that the risk of recurrence is very low (~2%) in patients with undectectable TSH-stimulated thyroglobulin level 9-12 months after initial treatment. This is applicable to both low- and high-risk patients.

This is confirmed by the results of Tuttle et al. (5) who found response to therapy to be a better predictor for recurrence than initial risk staging based on tumor size and lymph node involvement. Although recurrences are infrequent in the group of patients with undetectable TSH-stimulated thyroglobulin, recurrences do occur in approximately 2% of these patients. In our study recurrences were diagnosed based on physical examination, ultrasound, TSH-stimulated thyroglobulin or other imaging studies. For all patients with rising TSH-stimulated thyroglobulin and therefore a biochemical suspicion for recurrence, thyroglobulin levels on Levothyroxine therapy were not (yet) elevated. This could be explained by the higher

sensitivity of TSH-stimulated thyroglobulin measurement.
It is questionable whether this early detection of recurrences with TSH-stimulated thyroglobulin influences survival rate, because most recurrences were small foci of disease, mostly located in the neck. Although there have been several studies investigating the predictive value of low thyroglobulin values during the follow-up of DTC patients, results have not yet been incorporated into a consensus statement or a new guideline for the follow-up. The last European consensus protocol for the follow-up of patients with DTC has been published in 2006 and the advice is comparable with the recommendations in the American guideline (10). The American guideline, published in 2009 advises annual physical examination and thyroglobulin measurement on Levothyroxine therapy (Tg-on) for low-risk patients with no evidence of disease one year after initial therapy (based on TSH-stimulated-thyroglobulin measurement, physical examination and ultrasound) (12). The obvious advantages of Tg-on measurement are that it is easily performed, cheap and less invasive for the patient. After several years of additional research, confirming that response to therapy is a good predictor of recurrence, it seems sensible to incorporate these results into a new guideline for the follow-up of DTC patients.
In concordance with Tuttle et al. we propose a re-staging 9-12 months after initial therapy based on response to therapy. Excellent responders, with a very low chance of recurrent disease could possibly be monitored less rigidly (for example with Tg-on measurement). Overall results of this less strict regime could result in lower costs for the health care system and advances in quality of life for the DTC patient. Possibly the general follow-up could be regulated by a general practitioner with specialist follow-up by referral.

REFERENCES

1. Schlumberger M, Baudin E (1998) Serum thyroglobulin determination in the follow-up of patients with differentiated thyroid carcinoma. Eur J Endocrinol 138: 249-252.

2. Baudin E, Do Cao C, Cailleux AF, Leboulleux S, Travagli JP, et al. (2003) Positive predictive value of serum thyroglobulin levels, measured during the first year of follow-up after thyroid hormone withdrawal, in thyroid cancer patients. J Clin Endocrinol Metab 88: 1107-1111.

3. Castagna MG, Brilli L, Pilli T, Montanaro A, Cipri C, et al. (2008) Limited value of repeat recombinant human thyrotropin (rhTSH)-stimulated thyroglobulin testing in differentiated thyroid carcinoma patients with previous negative rhTSH-stimulated thyroglobulin and undetectable basal serum thyroglobulin levels. J Clin Endocrinol Metab 93: 76-81.

4. Kloos RT, Mazzaferri EL (2005) A single recombinant human thyrotropin-stimulated serum thyroglobulin measurement predicts differentiated thyroid carcinoma metastases three to five years later. J Clin Endocrinol Metab 90: 5047-5057.

5. Tuttle RM, Tala H, Shah J, Leboeuf R, Ghossein R, et al. (2010) 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 20: 1341-1349.

6. Hirsch D, Ginat M, Levy S, Benbassat C, Weinstein R, et al. (2009) Illness perception in patients with differentiated epithelial cell thyroid cancer. Thyroid 19: 459-465.

7. Edge S, Byrd DR, Compton CC, Fritz AG, Greene FL et al. (2010) AJCC cancer staging manual. (7thedn). Springer, New York.

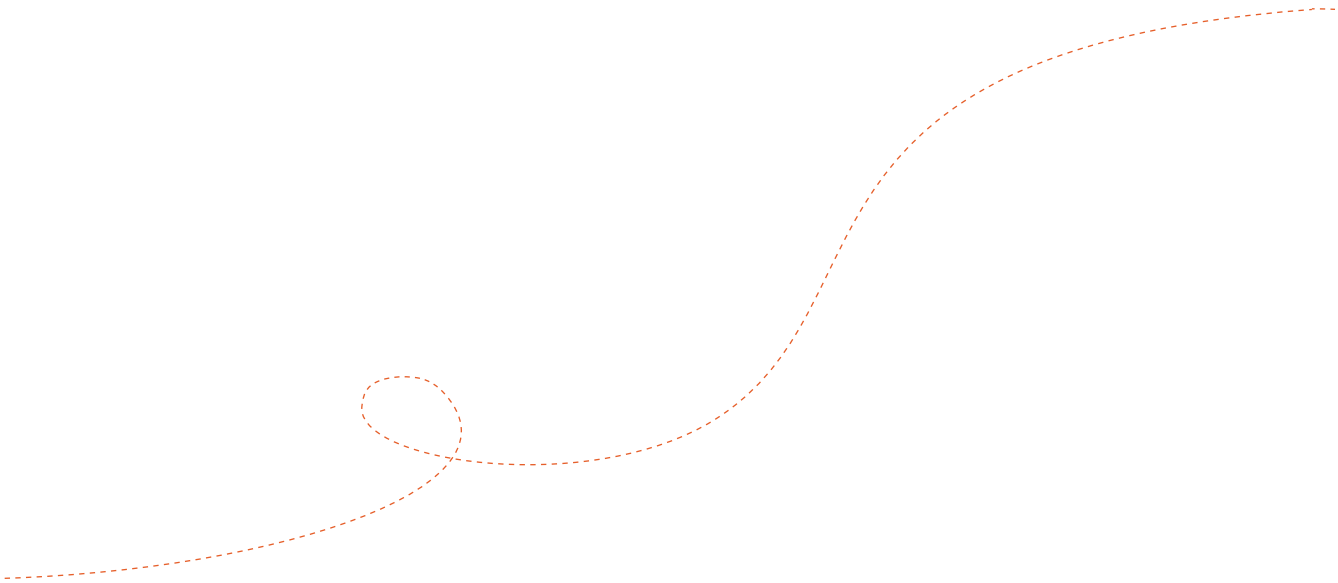
8. Pacini F, Schlumberger M, Dralle H, Elisei R, Smit JW, et al. (2006) European consensus for the management of patients with differentiated thyroid carcinoma of the follicular epithelium. Eur J Endocrinol 154: 787-803.

9. Pacini F, Molinaro E, Castagna MG, Agate L, Elisei R, et al. (2003) Recombinant human thyrotropin-stimulated serum thyroglobulin combined with neck ultrasonography has the highest sensitivity in monitoring differentiated thyroid carcinoma. J Clin Endocrinol Metab 88: 3668-3673.

10. Mazzaferri EL, Robbins RJ, Spencer CA, Braverman LE, Pacini F, et al. (2003) A consensus report of the role of serum thyroglobulin as a monitoring method for low-risk patients with papillary thyroid carcinoma. J Clin Endocrinol Metab 88: 1433-1441.

11. American Thyroid Association (ATA) Guidelines Taskforce on Thyroid Nodules and Differentiated Thyroid Cancer, Cooper DS, Doherty GM, Haugen BR, Kloos RT, et al. (2009) Revised American Thyroid Association management guidelines for patients with thyroid nodules and differentiated thyroid cancer. Thyroid 19: 1167-1214.

12. Brassard M, Borget I, Edet-Sanson A, Giraudet AL, Mundler O, et al. (2011) Long-term follow-up of patients with papillary and follicular thyroid cancer: a prospective study on 715 patients. J Clin Endocrinol Metab 96: 1352-1359.



CHAPTER 4

Follow-up of DTC patients with thyroglobulin-antibodies: Rising Tg-Ab trend is a risk factor for recurrence

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ABSTRACT

Differentiated thyroid cancer is the most common endocrine malignancy. Recurrences (5-20%) are the main reason for follow-up. Thyroglobulin (Tg) has proven to be an excellent disease marker, but thyroglobulin-antibodies (Tg-Ab) may interfere with Tg measurement, leading to over- or underestimation.

It is proposed that Tg-Ab trend can be used as a marker for disease recurrence, yet few studies define trend and have a long-term follow-up. The objective of our study was to investigate the value of a well-defined Tg-Ab trend as a surrogate marker for disease recurrence during long term follow-up.

We retrospectively studied patients treated at the Nuclear Department of the University Medical Center Utrecht from 1998-2010 and the Netherlands Cancer Institute from 2000-2009. All patients with Tg-Ab 12 months after treatment were included.

The definition of a rise was a >50% increase of Tg-Ab value in a 2-year time period. A decline as >50% decrease of Tg-Ab value.

Twenty-five patients were included. None of the patients with declining or stable Tg-Ab without a concomitant rise in Tg developed a recurrence. Four patients were diagnosed with recurrence. Three of these patients had a rising Tg-Ab trend, in two of these patients Tg was undetectable.

Tg-Ab trend can be used as a crude surrogate marker for long term follow-up of Tg-Ab patients. A rising trend in Tg-Ab warrants further investigation to detect recurrent disease. Stable or declining Tg-Ab levels do not seem to reflect a risk for recurrence.

INTRODUCTION

Differentiated thyroid cancer (DTC) is the most common endocrine malignancy. Survival rates are excellent; however, recurrences occur in 5-20 percent of the patients (1). Recurrences are the main reason for follow-up. The thyroid specific thyroglobulin (Tg) is the primary tumor marker for detecting recurrences and, combined with ultrasound of the neck, the current gold standard for follow-up of DTC patients. However, 20-25% of DTC patients also have thyroglobulin-antibodies (Tg-Ab) present (2,3). These antibodies interfere with Tg measurements by over- or underestimating Tg values, depending on the test used (4). Immunoradiometric assays (IRMA) are considered to be consistently more sensitive than radioimmunoassays (RIA) and usually give an underestimation of Tg level, whereas RIAs can also overestimate Tg level (5). So, any sample with a positive Tg-Ab result is unreliable for measuring serum Tg concentrations and the value of the otherwise excellent tumor marker is of limited use in these patients (6). Consequently, Tg-Ab positivity poses a dilemma in follow-up of a significant proportion of DTC patients. Some authors have suggested that Tg-Ab can be used as a surrogate marker, especially in case of de novo appearance more than one year after diagnosis (6-10) while others found contradictory results (11).

A major limitation of these studies is the absence of a clear definition of 'trend'. The study of Kim et al. (12) is one of the few studies that does define trend, and it has been incorporated in a consensus meeting regarding this subject. Their definition of trend was: a $\geq$50% rise in concentration of measured Tg-Ab 6-12 months after remnant ablation compared to measurements during remnant ablation. A decline was defined as a $\geq$50% decline in Tg-Ab levels. However, the clinical application of this definition in patients at 12 months after primary treatment has not yet been studied.

This study was designed to determine whether Tg-Ab trends can serve as a surrogate marker for disease recurrence in patients with well-differentiated thyroid cancer during long term follow-up using the definitions as proposed by Kim et al. as mentioned before.

PATIENTS AND METHODS

We retrospectively reviewed all patients treated for DTC at the department of Nuclear Medicine of the UMC Utrecht (Utrecht, the Netherlands) between January 1998 and August 2010, and all patients treated at the Department of Nuclear Medicine of the Netherlands Cancer Institute (Amsterdam, the Netherlands) between 2000 to 2009. All patients with detectable Tg-Ab 12 months after primary treatment were included in this study.

Patients were treated with (near)total thyroidectomy, additional lymph node dissection on indication and postoperative $I^{131}I$ radioactive ablation (RAI) with doses varying from 3700-7400 MBq. Patient characteristics and follow-up parameters, e.g. laboratory measurements (Tg and Tg-Ab levels) and results of all imaging modalities were recorded. In addition, tumor characteristics, preoperative and postoperative staging and results of

surgery were registered. Furthermore, data regarding disease status during follow-up and duration of follow-up were recorded.
Exclusion criteria were age under 18 years, missing data regarding stage of disease, missing follow-up information within the year after treatment, missing laboratory measurements and/or distant metastases at time of presentation. Patients with distant metastases were excluded because these patients are not suitable for follow-up with Tg and/or Tg-Ab alone and therefore a different follow-up protocol applied for these patients.

Laboratory measurement
In the UMC Utrecht, Tg and Tg-Ab levels were measured using the Brahms DYNOtest Tg-pluS and the BRAHMS anti-Tg RIA- kit (Brahms Diagnostica GmBH, Berlin, Germany). This Tg method is a high-sensitivity IRMA. Until 2002, the functional sensitivity, defined as the lowest Tg-level than can be measured with a variation less than 20%, for this assay was 1.0 µg/L for Tg and 20 U/ml for Tg-Ab. From 2002 onward the functional sensitivity for this assay was 0.2 µg/L, and 20 U/mL for the Tg-Ab assay. In the Netherlands Cancer institute Tg-Ab levels were assessed by a competitive electrochemiluminescence immunoassay whereby serum Tg-Ab competes for biotinylated human-Tg with ruthenium-labeled Tg-Ab. The Tg-TgAb complexes form and bind streptavidin-coated microparticles and are magnetically captured onto the surface of an electrode. Tg levels were measured by a sandwich immunoassay (Cobas6000, Roche Diagnostic GmBH, D-68298 Mannheim).
The functional sensitivity of this assay for Tg was 0.1 µg/L and 22 U/mL for Tg-Ab. In both centers Tg and Tg-Ab levels were judged positive when patients had a value above the functional sensitivity. TSH levels were measured simultaneously and exceeded 20 mU/L in all patients. All Tg and Tg-Ab levels indicated in the text or tables are TSH stimulated measurements, either by LT4 withdrawal after recombinant human-TSH (rhTSH) stimulation.

Tg-Ab trend
For Tg-Ab trend analysis we divided the follow-up in periods of 24 months starting from 12 months after primary treatment. Within each period patients were divided into four groups according to changes in Tg-Ab concentration. Tg-Ab trend was recorded as increasing when, in one of these periods of 24 months, Tg-Ab levels increased with >50%. When Tg-Ab levels declined >50% or normalized to undetectable value the trend was recorded as decreasing, and as undetectable, when Tg-Ab levels were below the detection limit. Tg-Ab trend was recorded as stable when Tg-Ab levels were elevated, but fluctuations were less than 50%.

Recurrent and suspicion of recurrent disease
Recurrences can occur in patients that have been judged as free of disease, frequently described as 'no evidence of disease' (NED). A recurrence had to be proven by cytology, histology or positive post-^{131}I therapy scan. Patients were defined as 'suspicion of

recurrence' when a therapeutic dose of ^{131}I was given because, biochemical markers were rising but no substrate was found using imaging techniques or suspicious lesions were found at physical examination.

Imaging modalities

Neck ultrasound was performed at least yearly. In order to provide an anatomic substrate for patients with detectable Tg and/or Tg-Ab additional imaging modalities where used, including ^{131}I radioiodine diagnostic whole-body scintigraphy (DxWBS), post-therapy scintigraphy (RxWBS), MRI, CT, ^{124}I and ^{18}F-FDG PET CT scanning.

Risk classification

The 2015 ATA risk classification was used (13). Patients with distant metastases (M1) were excluded from analysis. For TNM-classification and stage grouping we used the 7th edition of the American Joint Committee on Cancer (AJCC) TNM-classification (13).

Statistical analysis

Statistical analysis was performed using SPSS 23.0 (Chicago, Illinois, USA). All demographic data are shown in mean values with standard deviation (±SD) unless indicated otherwise.

RESULTS

In total 443 patients were treated for differentiated thyroid cancer in both hospitals (Figure 1). A total of 64 (14%) patients had positive Tg-Ab levels at time of diagnosis. One patient died within the year after primary treatment as a result of metastatic thyroid cancer. Twenty-nine patients (7%) had positive Tg-Ab 12 months after primary treatment. Four patients were excluded, two due to pulmonary metastasis, one due to persistent disease diagnosed within one year after primary treatment and one due to non-radical tumor resection without subsequent radioiodine.

As a result, 25 patients were included. Baseline characteristics are shown in Table 1. Most patients were female (76%). The majority of tumors were of papillary origin (88%). The mean follow-up period was 96 months (SD 77.5, range 25-296). Nine-teen patients (76%) had no evidence of disease during the entire follow-up period, four patients (16%) had a recurrence, and two patients (8%) had the suspicion of recurrent disease.

Tg-Ab trends during follow up are shown in Table 2. Descriptive case presentations of the patients with recurrent or suspicion of recurrent disease (n=6) are presented in Table 3. A plot of these six cases is shown in Figure 2.

Tg-Ab trend

12-36 months follow-up (n=25)

Eleven patients had a declining trend of Tg-Ab levels. One of these patients (case no. 1) was diagnosed with suspicion of recurrence based on a palpable lesion in the neck detected

31 months after primary treatment. The year before Tg-Ab trend was declining to zero, Tg levels were undetectable and DxWBS was normal. Additional CT showed no lesions indicating metastasis and fine needle aspiration of the palpable lesion showed no malignant cells. Nonetheless, based on the high clinical suspicion, lymph node extirpation was performed, revealing a follicular proliferation; therefore, recurrent disease was not confirmed. During further follow-up (248 months) Tg-Ab and Tg levels remained undetectable and no recurrences were diagnosed.

Seven patients had an increasing trend of Tg-Ab levels. Two of these patients were diagnosed with recurrent disease (cases no. 2 and 3) and one with suspicion of recurrent disease (case no. 4). In all three cases Tg levels were undetectable. In case no. 2 ^{18}F-FDG PET-CT was performed due to increasing Tg-Ab levels, showing a pathologic lymph node

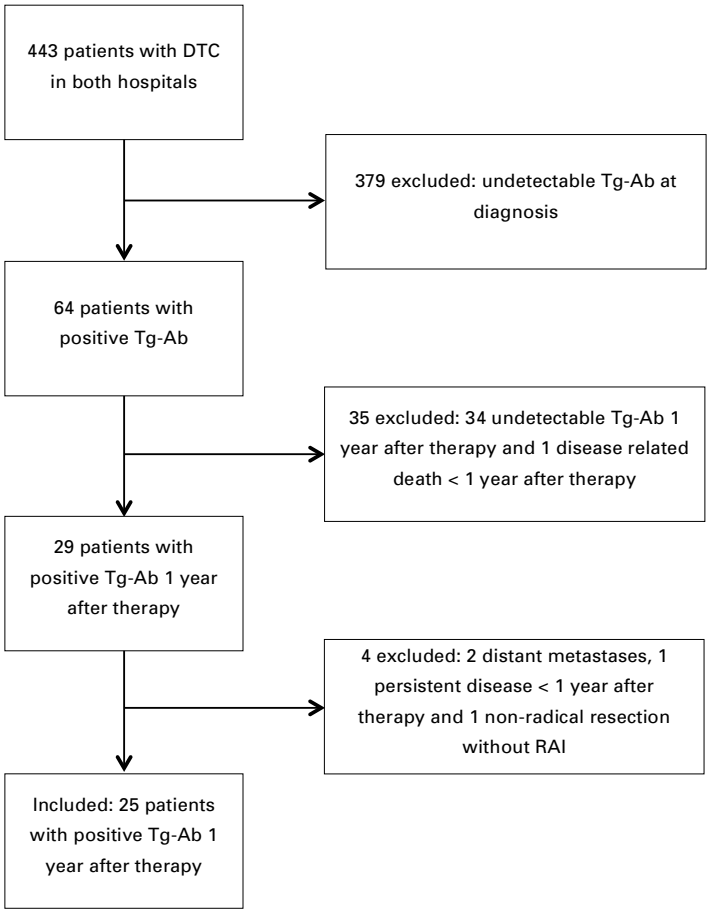


Figure 1. Flow-chart of patient selection
Abbreviations: DTC = differentiated thyroid cancer; Tg-Ab = thyroglobulin-antibodies

Table 1. Baseline characteristics of patients with positive Tg-Ab (n=25) at one year after primary treatment.

Variable	Number (percentage) or mean ±SD (range)
Gender	
Male	6 (24.0%)
Female	19 (76.0%)
Mean age	43.3 ± 13.4 (25-82)
Histological subtype	
PTC	22 (88.0%)
FTC	3 (12.0%)
T Classification (7th)	
Tmissing	1 (4.0%)
T1a	3 (12.0%)
T1b	8 (32.0%)
T2	9 (36.0%)
T3	3 (12.0%)
T4a	1 (4.0%)
N Classification (7th)	
N0	11 (44.0%)
N1a	7 (28.0%)
N1b	5 (20.0%)
N1a/N1b	2 (8.0%)
TNM Stage (7th)	
I	16 (64.0%)
II	3 (12.0%)
III	3 (12.0%)
IV	3 (12.0%)
Risk classification	
Low risk	10 (40.0%)
Intermediate risk	10 (40.0%)
High risk	5 (20.0%)
Mean follow-up in months	95.9 ± 77.5 (25-296)

Abbreviations: Tg-Ab = thyroglobulin-antibodies; PTC = papillary thyroid cancer; FTC = follicular thyroid cancer

in the neck; histology after resection confirmed metastasis of PTC. During follow-up Tg-Ab and Tg levels remained undetectable and no further recurrence was diagnosed. Case no. 3 presented with a palpable lesion in the neck. Ultrasound and additional CT showed four suspicious lesions. Fine needle aspiration showed papillary thyroid metastasis. This was

confirmed histologically after additional lymph node dissection, revealing four metastatic lymph nodes. During subsequent follow-up Tg-Ab levels remained detectable with a persistent stable trend while Tg levels remained undetectable. No other recurrence was found. Case no. 4 was suspected of having recurrence based on increasing Tg-Ab trend with undetectable Tg levels and suspicious uptake on DxWBS 27 months after primary treatment. The patient was treated with a high dose ^{131}I radioiodine therapy. The post-therapy scan did not show any uptake. Further follow-up revealed no recurrences.
One patient with increasing Tg-Ab trend was dismissed from follow-up 27 months after primary treatment based on undetectable Tg levels and normal DxWBS.
Seven patients had a persistent stable Tg-Ab trend. None of these patients developed recurrent or suspicion of recurrent disease.

36-60 months follow-up (n=21)
Eight patients had declining trends of Tg-Ab levels. Of these eight patients, four declined to zero, one was dismissed from further follow-up. Forty-four months after treatment one patient with declining Tg-Ab trend (case no. 5) was diagnosed with recurrent disease based on a simultaneously rising Tg level and a palpable lesion in the neck. In this patient, the Tg-Ab trend had been declining since primary treatment. The patient was treated with ^{131}I therapy. Post-therapy scintigraphy showed uptake in a suspicious lesion in the neck thereby confirming recurrent disease.
Two patients had an increasing trend and ten patients a persistent stable Tg-Ab trend. No events occurred in both groups and from the persistent stable group six patients were dismissed from follow-up. During this period Tg-Ab levels of one patient remained undetectable.

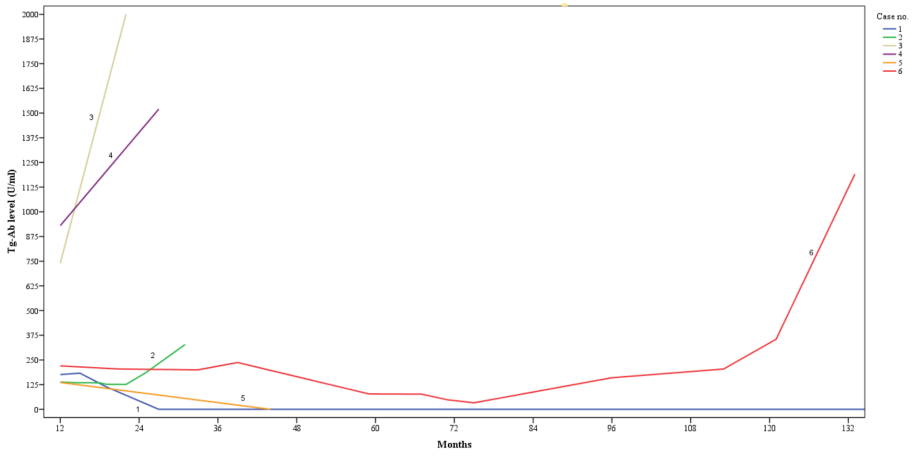


Figure 2. Disease-free survival

Table 2. Trend analyses of Tg-Ab levels and corresponding disease status during different periods of follow-up.

Period of follow-up in months	Tg-Ab trend	n=	NED	Recurrent disease	Suspicion of recurrent disease
12–36 (n=25)	Declining	11	10	-	1
	Increasing	7	4	2	1
	Stable	7	7	-	-
	Undetectable	-	-	-	-
36–60 (n=21)	Declining	8	7	1	-
	Increasing	2	2	-	-
	Stable	10	10	-	-
	Undetectable	1	1	-	-
60–84 (n=13)	Declining	4	4	-	-
	Increasing	2	2	-	-
	Stable	4	4	-	-
	Undetectable	3	3	-	-
84–108 (n=10)	Declining	-	-	-	-
	Increasing	2	2	-	-
	Stable	4	4	-	-
	Undetectable	4	4	-	-
108–132 (n=6)	Declining	1	1	-	-
	Increasing	1	1	-	-
	Stable	1	1	-	-
	Undetectable	3	3	-	-
132–156 (n=6)	Declining	1	1	-	-
	Increasing	1	-	1	-
	Stable	-	-	-	-
	Undetectable	4	4	-	-
> 156 (n=5)	Declining	-	-	-	-
	Increasing	-	-	-	-
	Stable	1*	1	-	-
	Undetectable	4**	4	-	-

* Case with persistent stable between 156-180, declining between 180-204 and persistent stable between 204-296 with NED until follow-up was ended at 296 months after primary treatment.
** All 4 cases had undetectable Tg-Ab levels and NED until follow-up was ended at 161, 196, 248 and 258 months after primary treatment.
Abbreviations: Tg-Ab = thyroglobulin-antibodies; NED = no evidence of disease

60-132 months follow-up (n=13)

No events occurred during this period and seven patients were dismissed from follow-up, four due to persistent stable trend and three due to undetectable trend.

132-156 months follow-up (n=6)

One patient (case no. 6) had an increasing Tg-Ab trend and was diagnosed with recurrence 133 months after primary treatment. Besides rising Tg-Ab levels, Tg levels were rising and a palpable lesion in the neck was found during physical examination. Lymph node extirpation confirmed solitary PTC metastasis and the patient was treated additionally with radioiodine

Table 3. Descriptive case presentation of all patients (n=6) with recurrent, persistent or suspicion of recurrent disease.

Case	Gender	Age	Histology	TNM	Risk classification	Event type	Months after initial treatment	Tg-Ab trend	Tg level	Detection	Treatment and results
1	Female	25	PTC	T1N1M0	Intermediate	Suspicion of recurrence	31	Declining	< 1	Palpable lesion, on CT not suspect for metastasis. FNAC showed no malignant cells	Lymph node extirpation showing follicular proliferation. Further FU(248months) without recurrence.
2	Female	48	PTC	T2N1M0	Intermediate	Recurrence	31	Rising	< 1	Positive lymph node on FDG-PET	Lymph node extirpation showing PTC metastasis
3	Male	65	PTC	T2N0M0	Low	Recurrence	22	Rising	<0.2	Palpable lesion suspect on ultrasound and CT. FNAC showed PTC metastasis. No uptake on DxWBS and I-124 PET.	Additional lymph node dissection showing 4 with PTC metastasis
4	Male	82	PTC	TxN2M0	Intermediate	Suspicion of recurrence	27	Rising	0.2	Uptake on DxWBS	131I therapy with no uptake on post-therapy scan
5	Female	37	PTC	T4N0M0	High	Recurrence	44	Declining	20	Rising Tg level and palpable lesion. Negative DxWBS	131I therapy with uptake in a suspicious lesion on post-therapy scan
6	Female	60	PTC	T2N1M0	High	Recurrence	133	Rising	3.3	Palpable lesion with biopsy showing PTC metastasis. CT showing lymph node and pulmonary metastasis	Lymph node extirpation showing PTC metastasis

Abbreviations: Tg-Ab = thyroglobulin-antibodies; Tg = Thyroglobulin; PTC = papillary thyroid cancer; FNAC = fine needle aspiration cytology; DxWBS = Diagnostic Radioiodine Whole-Body-Scintigraphy

therapy; the post-therapy scintigraphy also showed uptake in a pulmonary metastasis. Tg-Ab trend analysis for this patient showed a rise of less than 50% from 84 months onwards, with an increasing trend of more than 50% from 120 months after primary treatment. No cases were dismissed follow-up during this follow-up period.

>156 months follow-up (n=5)
No events occurred.

Total of Tg-Ab trends and corresponding events
Over the total follow-up period, 25 declining trends were recorded. One of the patients with a declining trend (but with a simultaneous rise of Tg level) was diagnosed with recurrence. One patient underwent extensive evaluation and operation because of suspicion of recurrence based on a palpable lesion in the neck; that turned out to be a follicular proliferation.
Fifteen increasing trends were registered and three patients were diagnosed with recurrences (one patient had a simultaneous increase of Tg, two had an undetectable Tg level) and 1 suspicion of recurrent disease (post-therapy ^{131}I scan showed no uptake).
No recurrences occurred, or suspicion of recurrence was raised, in 32 stable and 31 undetectable trends (Table 4).

Table 4. Cumulative trend analysis of Tg-Ab levels and corresponding disease status.

Tg-Ab trend	n=	NED	Recurrent disease	Suspicion of recurrent disease
Declining	25	23	1	1
Increasing	15	11	3	1
Stable	32	32	-	-
Undetectable	31	31	-	-

Abbreviations: Tg-Ab = thyroglobulin-antibodies; NED = no evidence of disease

DISCUSSION

This study evaluates the use of the trend of Tg-Ab level as a marker for disease status during the follow-up of DTC patients with detectable Tg-Ab levels 12 months after primary treatment using predefined definitions for trends in Tg-Ab levels. The current study shows that in patients with declining or stable Tg-Ab levels, the risk of recurrence is negligible. In these cases, no further imaging is warranted. However, in patients with declining or undetectable Tg-Ab levels, with a simultaneous rise of Tg, additional imaging is indicated to search for recurrence. In case of rising Tg-ab levels, we recommend that the treating physician should actively try to diagnose recurrence, although one should be aware that in the majority of the patients no recurrence will be found.

Of the patients with detectable Tg-Ab 12 months after primary treatment, four (15%) were diagnosed with a recurrence during further follow-up. Three of the four recurrences occurred during the first three years after initial therapy. One patient had a recurrence after 133 months precipitated by rising Tg-Ab and Tg-levels. Three out of four patients showed a rise in Tg-Ab before recurrence was confirmed, while the other patient had a declining Tg-Ab level, with a simultaneous rise of Tg level. In our cohort, no patients were diagnosed with recurrent disease when Tg-Ab levels were stable or undetectable.

Our data are in concordance with the published clinical position statement by Verburg, et al. on Tg-Ab positive patients. They state that changes in serum TgAb levels can be used as an imprecise surrogate marker and that the trend is of greater value than the absolute level (14). Most studies report a low recurrence rate in patients with Tg-Ab levels that eventually become negative (3,6). By some authors it is proposed that Tg-Ab persistence longer than 3 years after initial treatment may suggest recurrence or persistent disease (15). Our study does not support these results. The mere presence of Tg-Ab, in some patients as long as 156 months after primary treatment, was not found to be a predictor for recurrence.

If Tg-Ab levels are rising, additional diagnostic modalities as US of the neck, DxWBS, ^{18}F-FDG and ^{124}I PET/CT can be used for further evaluation (9,16-22). This also applies to patients with rising Tg even in the presence of Tg-Ab.

A limitation of our study is the relatively small number of patients. However, it is similar to the number of patients presented in other studies investigating Tg-Ab positive patients (12,23,24). The number of patients in clinical practice is also low. Statistical significance could not be assessed due to the limited number of events and it therefore limits the strength of our conclusion.

The retrospective nature of our study could introduce detection bias. Selective additional investigation could have been performed in patients with rising Tg-Ab level.

Main strengths of our study are the long follow-up period and the use of a well-defined definition for trend, making the reliability and reproducibility of our data more robust.

CONCLUSION

The trend in Tg-Ab levels can be used as a crude surrogate marker for Tg. In patients with declining or stable Tg-Ab levels, without a simultaneous rise of Tg, the risk of recurrence is negligible. In contrast, a rising Tg-Ab trend >50% in a 2-year time period in patients without detectable Tg warrants the need for additional diagnostic work-up to detect possible recurrent disease.

REFERENCES

1. Schlumberger MJ. Papillary and follicular thyroid carcinoma. N Engl J Med 1998;338:297-306.

2. Ringel M, Nabhan F. Approach to follow-up of the patient with differentiated thyroid cancer and positive anti-thyroglobulin antibodies. J Clin Endocrinol Metab 2013;98:3104-10.

3. Pacini F, Mariotti S, Formica N, et al. Thyroid autoantibodies in thyroid cancer: incidence and relationship with tumour outcome. Acta Endocrinol 1988;119:373-80.

4. Spencer CA, Bergoglio LM, Kazarosyan M, et al. Clinical impact of thyroglobulin (Tg) and Tg autoantibody method differences on the management of patients with differentiated thyroid carcinomas. J Clin Endocrinol Metab 2005;90:5566-75.

5. Giovanella L, Clark P, Chiovato L, et al. Thyroglobulin measurement using highly sensitive assays in patients with differentiated thyroid cancer: a clinical position paper. Eur J Endocrinol 2014;171:R33-46.

6. Spencer CA, Takeuchi M, Kazarosyan M, et al. Serum thyroglobulin autoantibodies: prevalence, influence on serum thyroglobulin measurement, and prognostic significance in patients with differentiated thyroid carcinoma. J Clin Endocrinol Metab 1998;83:1121-7.

7. Chung J, Park YJ, Kim TY, et al. Clinical significance of elevated level of serum antithyroglobulin antibody in patients with differentiated thyroid cancer after thyroid ablation. Clin Endocrinol (Oxf) 2002;57:215-21.

8. Görges R, Maniecki M, Jentzen W, et al. Development and clinical impact of thyroglobulin antibodies in patients with differentiated thyroid carcinoma during the first 3 years after thyroidectomy. Eur J Endocrinol 2005;153:49-55.

9. Seo J, Lee S, Ahn B, et al. Recurrence detection in differentiated thyroid cancer patients with elevated serum level of antithyroglobulin antibody: special emphasis on using (18)F-FDG PET/CT. Clin Endocrinol (Oxf) 2010;72:558-63.

10. Hsieh C, Wang P. Sequential changes of serum antithyroglobulin antibody levels are a good predictor of disease activity in thyroglobulin-negative patients with papillary thyroid carcinoma. Thyroid 2014;24:488-93.

11. Smooke Praw S, Ro K, Levin O, et al. Thyroglobulin antibody levels do not predict disease status in papillary thyroid cancer. Clin Endocrinol (Oxf) 2014;81:271-5.

12. Yoon J, Kim W, Kim T, et al. Change of serum antithyroglobulin antibody levels is useful for prediction of clinical recurrence in thyroglobulin-negative patients with differentiated thyroid carcinoma. J Clin Endocrinol Metab 2008;93:4683-9.

13. Haugen B, Alexander E, Bible K, 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.

14. Verburg F, Luster M, Cupini C, et al. Implications of thyroglobulin antibody positivity in patients with differentiated thyroid cancer: a clinical position statement. Thyroid 2013;23:1211-25.

15. Chiovato L, Latrofa F, Braverman L, et al. Disappearance of humoral thyroid autoimmunity after complete removal of thyroid antigens. Ann Intern Med 2003;139:346-51.

16. Cooper D, Doherty G, Haugen B, et al. Revised American Thyroid Association management guidelines for patients with thyroid nodules and differentiated thyroid cancer. Thyroid 2009;19:1167-214.

17. Pacini F, Castagna MG, Brilli L, et al. Thyroid cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2010;21 Suppl 5:v214-9.

18. Pacini F, Schlumberger M, Dralle H, et al. European consensus for the management of patients with differentiated thyroid carcinoma of the follicular epithelium. Eur J Endocrinol 2006;154:787-803

19. Pitoia F, Ward L, Wohllk N, et al. Recommendations of the Latin American Thyroid Society on diagnosis and management of differentiated thyroid cancer. Arq Bras Endocrinol Metabol 2009;53:884-7.

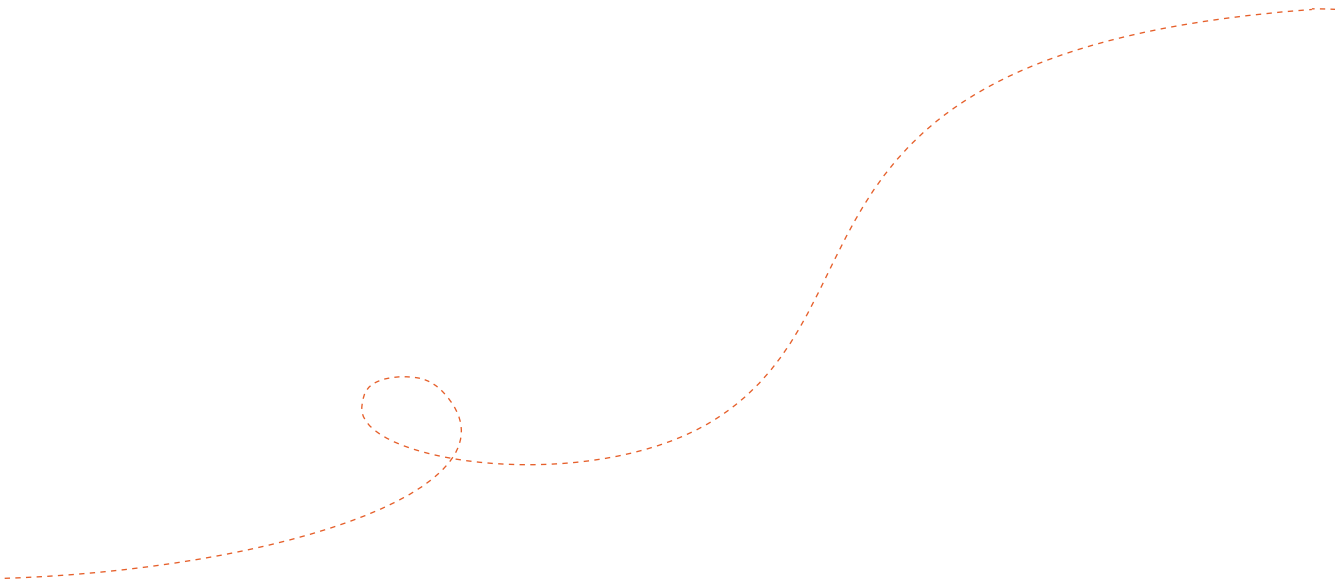
20. Gharib H, Papini E, Valcavi R, et al. American Association of Clinical Endocrinologists and Associazione Medici Endocrinologi medical guidelines for clinical practice for the diagnosis and management of thyroid nodules. Endocr Pract 2006;12:63-102.

21. Freudenberg L, Jentzen W, Stahl A, et al. Clinical applications of 124I-PET/CT in patients with differentiated thyroid cancer. Eur J Nucl Med Mol Imaging 2011;38 Suppl 1:S48-56.

22. Van Nostrand D, Khorjekar G, O'Neil J, et al. Recombinant human thyroid-stimulating hormone versus thyroid hormone withdrawal in the identification of metastasis in differentiated thyroid cancer with 131I planar whole-body imaging and 124I PET. J Nucl Med 2012;53:359-62.

23. Ozkan E, Soydal C, Araz M, et al. The additive clinical value of 18F-FDG PET/CT in defining the recurrence of disease in patients with differentiated thyroid cancer who have isolated increased antithyroglobulin antibody levels. Clin Nucl Med 2012;37:755-8.

24. Pacini F, Molinaro E, Castagna MG, et al. Recombinant human thyrotropin-stimulated serum thyroglobulin combined with neck ultrasonography has the highest sensitivity in monitoring differentiated thyroid carcinoma. J Clin Endocrinol Metab 2003;88:3668-73.



CHAPTER 5

The role of routine diagnostic radioiodine whole-body scintigraphy in patients with high- risk differentiated thyroid cancer

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ABSTRACT

Follow-up diagnostic radioiodine whole-body scintigraphy (DxWBS) is still advised for high-risk patients with differentiated thyroid cancer. The aim of this study was to evaluate the additional value of DxWBS to stimulated thyroglobulin measurement in high-risk patients. The results of DxWBS and thyroglobulin measurements performed 6–12 months after surgery and radioiodine thyroid remnant ablation in patients with differentiated thyroid cancer were retrospectively evaluated for 112 patients with high-risk features for recurrence (R3/T4 and N1).

One patient had an undetectable thyroglobulin level, with DxWBS results suggestive of cervical recurrence. DxWBS was found to be false-positive. Of the patients with detectable thyroglobulin levels, the DxWBS results were negative in 65 and positive in only 8. The 6 patients positive for thyroglobulin antibody had negative DxWBS results. The remaining patients had an undetectable thyroglobulin level and negative DxWBS results.

Because undetectable stimulated thyroglobulin levels have a negative predictive value of 100%, DxWBS offers no information additional to recombinant human thyroid-stimulating hormone–stimulated thyroglobulin measurements in patients with high-risk differentiated thyroid cancer.

INTRODUCTION

Differentiated thyroid carcinoma is a common malignancy with excellent survival rates (1,2). Lifelong follow-up of patients is important because recurrences regularly occur (3–6). Traditionally, follow-up consisted of periodic assessment of thyroglobulin and thyroglobulin antibody levels and performance of thyroid-stimulating hormone (TSH)–stimulated thyroglobulin measurement simultaneous with diagnostic radioiodine whole-body scintigraphy (DxWBS) 6–12 months after initial treatment with near-total thyroidectomy and ^{131}I remnant ablation.

For low-risk patients, however, the use of follow-up DxWBS is no longer recommended by either the American or the European guidelines (3,7). For high-risk patients, the value added by DxWBS to TSH-stimulated thyroglobulin measurement is largely unclear, because no studies evaluating this value have been performed in a large group of well-defined high-risk patients. The aim of our study was to determine whether routine DxWBS performed 6–12 months after initial therapy offers information additional to that provided by TSH-stimulated thyroglobulin measurement during the first year of follow-up of differentiated thyroid carcinoma patients with predetermined high-risk features.

PATIENTS AND METHODS

From January 1998 until January 2009, all consecutive patients who had undergone surgery for thyroid carcinoma and had been referred to the Department of Nuclear Medicine for ^{131}I ablation were retrospectively studied. Patient characteristics and follow-up parameters, such as laboratory measurements and the results of DxWBS, were recorded. In addition, tumor characteristics, preoperative and postoperative staging, and the results of surgery were registered. Follow-up data such as disease recurrence, duration of follow-up, and laboratory measurements (thyroglobulin and thyroglobulin antibody) were also considered. DxWBS 1 year after initial treatment was judged positive if uptake outside regions of physiologic uptake—such as the oral, nasal, or gastric mucosa; the salivary glands; or the urogenital region—or uptake classified as thyroid remnant was observed.

High- versus low-risk patients

The American and European guidelines differ in the definition of high- versus low-risk patients. In addition, the American guideline identifies intermediate-risk patients (3,7).

In our study, we used the American Joint Committee on Cancer (AJCC) TNM version 7 classification in determining the T stage of the various tumors (8).

For this study, we defined high-risk patients as patients with T3 or T4 tumors or positive cervical lymph nodes (N1). We did not include age as a predictor of low- or high-risk disease, because the treatment protocol is independent of age. This definition is in concordance with the European guideline. Patients with distant metastasis (M1) were excluded from analysis.

Diagnostic Whole-Body Scintigraphy

Until December 2004, all patients referred for DxWBS 6-12 months after initial therapy were withdrawn from LT4 medication 4 weeks before administration of 370 MBq ^{131}I. From January 2005 onward, patients received intramuscular injections with 0.9 mg recombinant human TSH (rhTSH) on two consecutive days followed by administration of 370 MBq of ^{131}I on day 3, obviating LT4-withdrawal. Blood samples were taken to measure thyroglobulin levels and thyroglobulin-antibody on days 3 and 5. The serum TSH level was measured on day 3. One week after administration of ^{131}I, DxWBS was performed with a dual –head gamma camera (MCD; Philips Medical Systems) fitted with high-energy collimators. Ten-minute spot views on a 256x256 matrix were obtained with a 15% energy window centered on a 364-keV photopeak of the head, neck, thorax and abdomen.

Laboratory analysis

Thyroglobulin and thyroglobulin-antibody levels were measured using the DYNOtest thyroglobulin-pluS (Brahms Diagnostica GmBH) The functional sensitivity, defined as the lowest thyroglobulin level that can be measured with a variation of less than 20%, for this assay is 0.2 ng/mL. TSH levels were measured simultaneously and exceeded 20mU/L in all patients.

All thyroglobulin and thyroglobulin antibody levels indicated in the text or tables are TSH-stimulated measurements, either by LT4 withdrawal or recombinant human TSH injection.

Statistical analysis

Statistical analysis was performed using SPSS 13.0 (Chicago, Illinois) All demographic data are shown as mean values ±SD unless indicated otherwise. For statistical analysis, we used Chi-square and t-tests where appropriate. P-values less than 0.05 were considered statistically significant.

RESULTS

Patient characteristics

From January 1998 until January 2009, 402 patients were treated with ^{131}I ablation therapy after resection of differentiated thyroid carcinoma in the University Medical Center Utrecht, The Netherlands. Two hundred eleven patients were excluded from analysis because they were classified as low-risk patients on the basis of tumor size and lymph node status (T1/T2N0); 20 of the remaining high-risk patients had metastatic disease at the time of diagnosis and were therefore excluded. Another 59 patients were not included in the final analyses either because information about thyroglobulin level or DxWBS was missing (n = 56) or because they were treated with a blind therapeutic dose and post-therapeutic scintigraphy was performed (n = 3).

As a result, 112 high-risk patients remained for final analysis. Most of these patients were female (70% vs. 30%). The median age was 48 y (range, 20–83 y) (Table 1).

Table 1. Patient and Tumor Characteristics of 112 high-risk DTC patients

Characterics	Result
Sex (n)	
Male	35 (31%)
Female	77 (69%)
Median age ± SD (y)	48 ± 16
Median tumor size ± SD (mm)	30 ± 20
Tumor histology (n)	
Papillary	91 (81%)
Follicular	21 (19%)
Hürthle cell	8 (7%)
^{131}I ablation dosage	
3700 mBq	40 (36%)
5550 mBq	63 (56%)
7400 mBq	9 (8%)
TNM stage at time of diagnosis (n)	
I	54 (48%)
II	-
III	24 (21%)
IV	26 (23%)
Missing	8 (7%)
T and N stage (n)	
T1N1	22
T2N1	23
T3N0	31
T4N0	14
T3N1	10
T4N1	3
TxN1	9

Tumor characteristics

Median tumor size in these patients was 30 mm (±20mm, with a range of 3-90 mm). Most patients were treated for papillary carcinoma 81% (n=91) (Table 1).

TNM stage

TNM stage according to the 2010 TNM criteria at the time of diagnosis was stage I in most patients (48 %). In 8 patients (7%), the TNM stage was unknown because of missing information about the primary tumor size (Table 1). Specified information on the T and N stages of the tumor is also shown in Table 1.

DxWBS and thyroglobulin measurement

The results are summarized in Table 2.

Most patients had a thyroglobulin value above the lower detection limit of 0.2 ng/mL (66%). Only 8 patients had a thyroglobulin value above 0.2 ng/mL in combination with positive DxWBS results.

All these patients were diagnosed with disease recurrence. In 6 patients, only neck recurrence was observed. The other 2 patients were diagnosed with a distant metastasis to the skull (1 patient) or to the lung and brain (1 patient).

In 31 patients (30%), thyroglobulin measurements were below 0.2 ng/mL, no thyroglobulin antibody was found, and DxWBS showed no signs of recurrent or metastatic disease. Six patients (5%) had undetectable thyroglobulin measurements in the presence of thyroglobulin antibody. None of these patients had DxWBS results suggestive of cervical node metastases.

Of the patients with an undetectable thyroglobulin level and no detectable thyroglobulin antibody, 1 had DxWBS findings suggestive of cervical node metastases. Additional imaging using neck ultrasound, ^{18}F-FDG PET, and MRI found no evidence of cervical recurrence. DxWBS performed 1 year later showed no uptake, and thyroglobulin levels remained undetectable, without the presence of thyroglobulin antibody.

The negative predictive value of stimulated thyroglobulin levels less than 0.2 ng/mL for disease recurrence in our group was therefore 100%.

Table 2. Results of DxWBS 6-12 months after initial therapy combined with Tg level measurements of High-Risk DTC patients

	Thyroglobulin level			
	<0.2 ng.ml	>0.2 ng/ml	<0.2 nl/ml, TgAb +	Total
DxWBS result				
Negative	32 (29%)	65 (58%)	6 (5%)	103
Positive	1 (1%)	8 (7%)	0 (0%)	9
Total	**33**	**73**	**6**	**112**

DISCUSSION

The European and the American guidelines have different definitions of high-risk differentiated thyroid cancer, and neither guideline stages into groups according to the AJCC cancer staging manual (8). The authors of the American guideline introduce a 3-level stratification system because the AJCC cancer staging manual was developed to predict death, not recurrence (9). The authors of the European guideline do not state why they choose to introduce their own definition of high-risk differentiated thyroid cancer.

The American and European guidelines do not give clear advice on the use of DxWBS. The recently published American guideline states that DxWBS may be of value in the follow-up of high- or intermediate-risk patients. This recommendation is based on expert opinion and does not specifically say when or when not to perform DxWBS (3). The European consensus statement states that DxWBS is indicated by some authors in the follow-up of high-risk patients or when post-ablation scintigraphy is poorly informative or discloses suggestive uptake (10,11). Routine DxWBS is advised for patients positive for thyroglobulin antibody (7). Our study indicated that routine DxWBS added no diagnostic value to stimulated thyroglobulin level measurement in a large population of patients with high-risk differentiated thyroid carcinoma.

The literature about this subject is limited, and most studies have evaluated low- and high-risk patients together. Only the study by Verburg et al. analyzed high-risk patients separately, but the high-risk group contained only 44 patients and lacked a clear formulation of high-risk criteria. Still, the authors concluded that routine DxWBS might be omitted in high-risk patients just as in low-risk patients (12). Other studies have found that in their study population, which also included high-risk patients, DxWBS had no value additional to that provided by stimulated thyroglobulin measurement (12–17).

Robbins et al. strongly advocate the routine performance of DxWBS in the follow-up of all differentiated thyroid carcinoma patients. The authors concluded that thyroglobulin measurement alone is insufficient to detect all recurrences or metastases and that DxWBS detected the recurrences or metastases missed by thyroglobulin measurement, therefore complementing the thyroglobulin measurement (18).

DxWBS can have a role in patients with thyroglobulin antibody present. Because of thyroglobulin antibody interference in immunometric tests, thyroglobulin levels are unreliable in the presence of these antibodies (19).

In patients with detectable thyroglobulin (>2 ng/mL), further diagnostic imaging is required. In these patients, DxWBS is one of the tools that can be used to detect recurrent or metastatic disease. Other options include blind therapeutic activities, which are the administration of ^{131}I without previous visualization of the anatomic substrate. Post-therapeutic scintigraphy is more sensitive, but DxWBS delivers a far lower radiation burden to the patient. Approximately 40% of post-therapeutic scans are negative and will not reveal thyroglobulin-producing lesions (20). Other imaging modalities, such as ^{18}F-FDG PET, ^{124}I PET, CT, and MRI, can be used in an attempt to localize recurrent or metastatic differentiated thyroid carcinoma in patients in whom disease is suspected on the basis of the thyroglobulin level.

REFERENCES

1. Sampson E, Brierley JD,Le LW, Rotstein L, Tsang RW. Clinical management and outcome of papillary and follicular (differentiated) thyroid cancer presenting with distant metastasis at diagnosis. Cancer. 2007;110:1451–1456.

2. Sciuto R, Romano L, Rea S, Marandino F, Sperduti I, Maini CL Natural history and clinical outcome of differentiated thyroid carcinoma: a retrospective analysis of 1503 patients treated at a single institution. Ann Oncol. 2009;20:1728–1735.

3. Cooper DS,Doherty GM, Haugen BR, et al. Revised American Thyroid Association management guidelines for patients with thyroid nodules and differentiated thyroid cancer. Thyroid. 2009;19:1167–1214.

4. Mazzaferri EL, Jhiang SM. Long-term impact of initial surgical and medical therapy on papillary and follicular thyroid cancer. Am J Med. 1994;97:418–428.

5. Pacini F, Cetani F, Miccoli P, et al. Outcome of 309 patients with metastatic differentiated thyroid carcinoma treated with radioiodine. World J Surg. 1994;18:600–604.

6. Mazzaferri EL, Kloos RT Clinical review 128: current approaches to primary therapy for papillary and follicular thyroid cancer. J Clin Endocrinol Metab. 2001;86:1447–1463.

7. Pacini F, Schlumberger M, Dralle H, Elisei R, Smit JW, Wiersinga W. European consensus for the management of patients with differentiated thyroid carcinoma of the follicular epithelium. Eur J Endocrinol. 2006;154:787–803.

8. Edge SB, Byrd DR, Compton CC, Fritz AG, Greene FL, Trotti A, eds. AJCC Cancer Staging Manual. 7th ed. New York, NY: Springer; 2010.

9. Eustatia-Rutten CF, Corssmit EP, Biermasz NR, Pereira AM, Romijn JA, Smit JW. Survival and death causes in differentiated thyroid carcinoma. J Clin Endocrinol Metab. 2006;91:313–319.

10. Schlumberger M, Berg G, Cohen O, et al. Follow-up of low-risk patients with differentiated thyroid carcinoma: a European perspective. Eur J Endocrinol. 2004;150:105–112.

11. Mazzaferri EL, Robbins RJ, Spencer CA, et al. A consensus report of the role of serum thyroglobulin as a monitoring method for low-risk patients with papillary thyroid carcinoma. J Clin Endocrinol Metab. 2003;88:1433–1441.

12. Verburg FA, de Keizer B, de Klerk JM, Lentjes EG, Lips CJ, van Isselt JW. Value of diagnostic radioiodine scintigraphy and thyroglobulin measurements after rhTSH injection. Nuklearmedizin. 2009;48:26–29.

13. Huang SH, Wang PW, Huang YE, et al. Sequential follow-up of serum thyroglobulin and whole body scan in thyroid cancer patients without initial metastasis. Thyroid. 2006;16:1273–1278.

14. Cailleux AF, Baudin E, Travagli JP, Ricard M, Schlumberger M. Is diagnostic iodine-131 scanning useful after total thyroid ablation for differentiated thyroid cancer? J Clin Endocrinol Metab. 2000;85:175–178.

15. Pacini F, Capezzone M, Elisei R, Ceccarelli C, Taddei D, Pinchera A. Diagnostic 131-iodine whole-body scan may be avoided in thyroid cancer patients who have undetectable stimulated serum Tg levels after initial treatment. J Clin Endocrinol Metab. 2002;87:1499–1501.

16. Taylor H, Hyer S, Vini L, Pratt B, Cook G, Harmer C. Diagnostic 131I whole body scanning after thyroidectomy and ablation for differentiated thyroid cancer. Eur J Endocrinol. 2004;150:649–653.

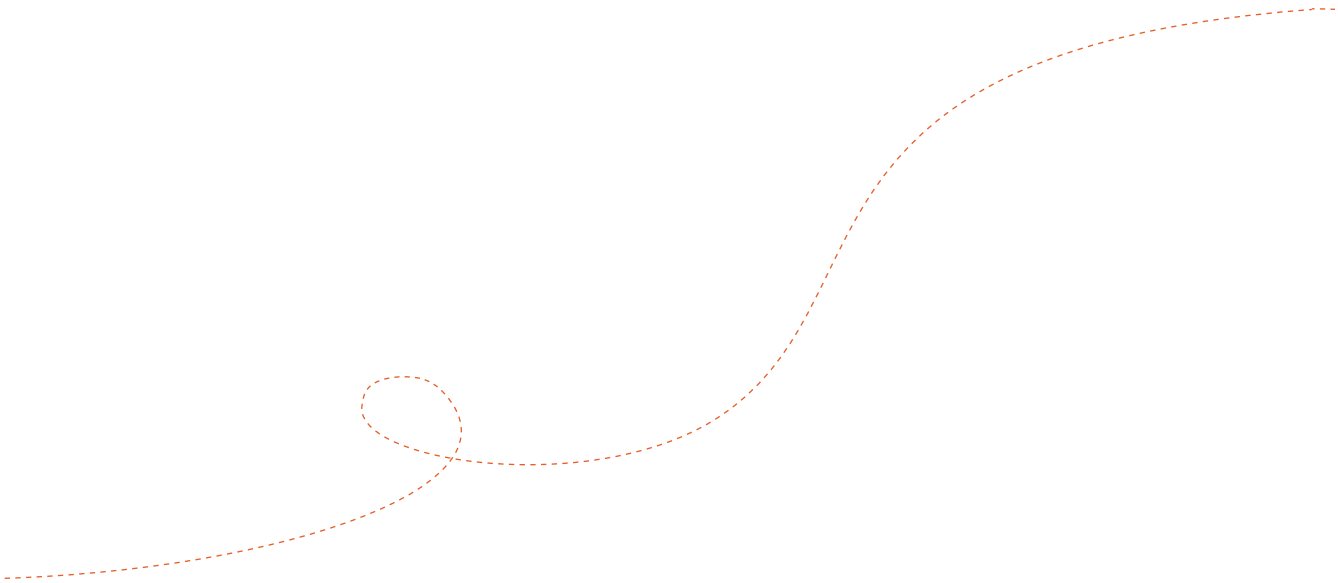
17. David A, Blotta A, Bondanelli M, et al. Serum thyroglobulin concentrations and 131I whole-body scan results in patients with differentiated thyroid carcinoma after administration of recombinant human thyroid-stimulating hormone. J Nucl Med. 2001;42:1470–1475.

18. Robbins RJ, Chon JT, Fleisher M, Larson SM, Tuttle RM. Is the serum thyroglobulin response to recombinant human thyrotropin sufficient, by itself, to monitor for residual thyroid carcinoma? J Clin Endocrinol Metab. 2002;87:3242–3247.

19. Spencer CA, Takeuchi M, Kazarosyan M, et al. Serum thyroglobulin autoantibodies: prevalence, influence on serum thyroglobulin measurement, and prognostic significance in patients with differentiated thyroid carcinoma. J Clin Endocrinol Metab. 1998;83:1121–1127.

20. Ma C, Kuang A, Xie J. Radioiodine therapy for differentiated thyroid carcinoma with thyroglobulin positive and radioactive iodine negative metastases. Cochrane Database Syst Rev. 2009;(1):CD006988

PROGNOSIS



CHAPTER 6

Not the number but the location of lymph nodes matters for recurrence rate and disease-free survival in patients with differentiated thyroid cancer

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ABSTRACT

Several Japanese studies have focused on identifying prognostic factors in patients with positive lymph nodes in order to predict recurrence rate and disease-free survival (DFS). However, different treatment protocol is followed in Japan compared to the European and American approach. This study was designed to investigate whether the number and/or location of lymph nodes predicts prognosis in patients with differentiated thyroid cancer (DTC) treated with (near)total thyroidectomy, lymph node dissection and postoperative radioactive iodine ablation.

All 402 patients who were treated at the Department of Nuclear Medicine between 1998 and 2010 for DTC were reviewed. Patients were treated with (near)total thyroidectomy, lymph node dissection on indication and postoperative ^{131}I ablation. Median follow-up was 49 months (range 10-240 months) Outcome measures were recurrence rate and disease-free survival.

Ninety-seven patients had proven lymph node metastases. Recurrence rate was significantly higher in patients with positive lymph nodes in the lateral compartment vs. patients with lymph node metastasis in the central compartment (60 versus 30%, p=0.007) Disease-free survival and mean time to recurrence were also significantly shorter (30 versus 52 months, p=0.035 and 7 versus 44 months, p=0.004, respectively). The number of lymph nodes and extranodal growth were not significantly associated with the outcome measures used.

The location of positive lymph nodes was significantly correlated with the risk of recurrence and shorter disease-free survival. Hence, the TNM criteria are useful in subdividing patients based on risk of recurrence and DFS.

INTRODUCTION

Differentiated thyroid cancer (DTC) is the most common type of thyroid malignancies. The disease-related mortality for DTC is very low, but spread to the regional lymph nodes frequently occurs, especially in patients with papillary thyroid cancer (1,2).
The TNM classification (3) describes the presence of positive cervical lymph nodes (CLN) as an independent risk factor for recurrence in all patients with follicular (FTC) and papillary thyroid cancer (PTC) over 45 years old. The disease-related mortality however, is not influenced by this parameter. The TNM classification further subdivides patients with positive lymph nodes into N1a, ie. positive nodes in the central compartment (level VI) and N1b patients, ie. with positive nodes in the lateral compartment (levels II-IV/V). N1b status is in patients with DTC is thereby implied to result in worse disease-free survival (DFS). Most of the research focused on disease-free survival and recurrence rate related to the location and number of positive lymph nodes has been done by Ito et al. from Japan. (4-7) One of their most recent publications implicates that DFS of N1b patients is only significantly lower than that of N1a patients when 1) lymph nodes are larger than 3 cm 2) 5 or more positive lymph nodes are present in the lateral compartment, or 3) extranodal growth is present (5). The main problem of applying results of these studies to the European and American population is the different treatment of patients with DTC in Japan, with a much lower rate of total thyroidectomies and the limited use of radioactive ^{131}I therapy. However, European and American guidelines are primarily based on the results of these Japanese studies (8,9). The purpose of this study was to investigate the impact of the location and the number of cervical lymph node metastases on recurrence rate and DFS in patients with DTC treated in accordance with European/American standards, with (near) total thyroidectomy and postoperative ^{131}I ablation.

PATIENTS AND METHODS

We performed a retrospective study in the University Medical Center Utrecht. All patients referred to our Nuclear Medicine department for ^{131}I ablation therapy after surgical treatment for DTC between January 1998 and April 2010 were reviewed (Figure 1).
Low-risk patients were defined as patients with small tumors (T1-T2) without the presence of lymph node metastasis (N0). All other patients were defined as high-risk patients, this staging is in concordance with the 7th edition of the American Joint Committee on Cancer (AJCC) TNM staging criteria. Patients were staged after their initial surgery. Patients were excluded from analysis when distant metastasis were present or when the number of positive lymph nodes could not be retracted from clinical records.

Initial treatment
Patients were treated according to the known extent of disease at time of diagnosis. All patients were treated by (near)total thyroidectomy followed by ^{131}I radioiodine remnant

ablation. All patients received an ablative dosage varying from 3700 to 7400 mBq, 4- 6 weeks after thyroid resection. Patients were not substituted with levothyroxine in the weeks ahead of ablation therapy to raise endogenous TSH production. Treatment traditionally consists of surgery followed by radioiodine ablation for every patient treated for DTC, regardless of size, extension or lymph node involvement in the Netherlands. Only dosages vary from 3700MBq for low-risk patients to 7400MBq for patients with large tumors and lymph node involvement and patients with distant metastasis. Preoperative examination consisted of ultrasound of the neck and thorough physical examination. If enlarged lymph nodes were detected, lymph node dissection was

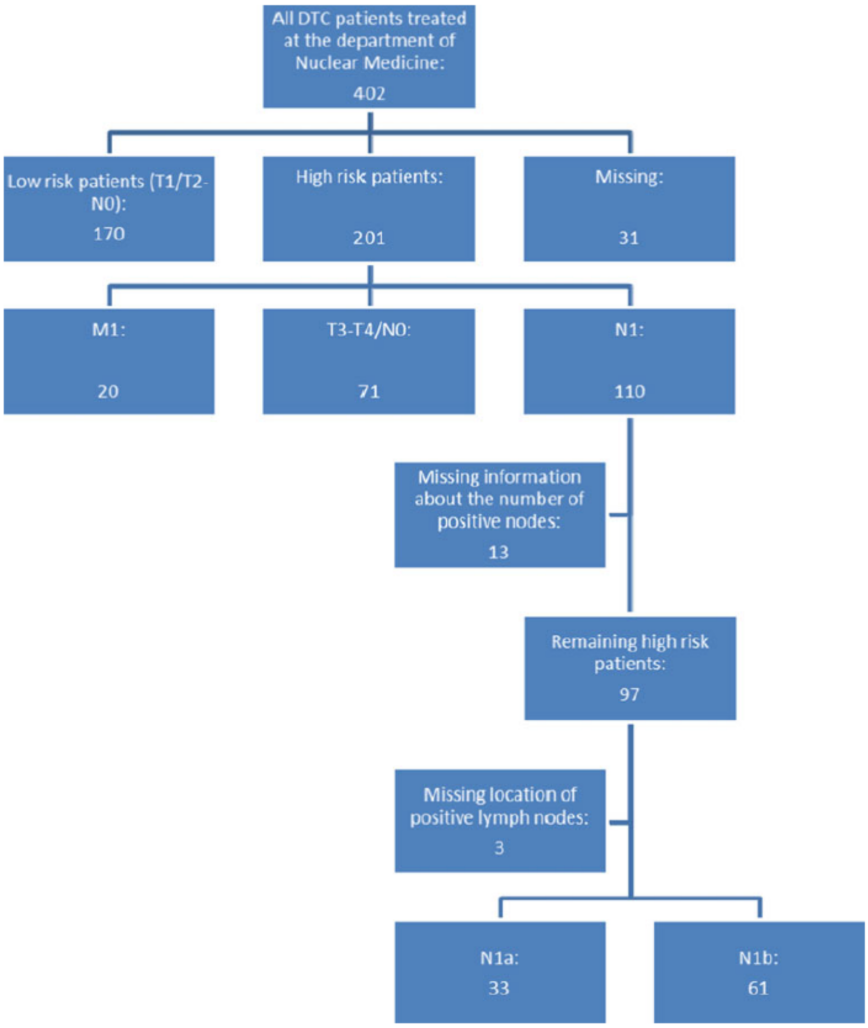


Figure 1. Flowchart

performed. Lymph node dissection was also performed bases on operative findings suggestive of lymph node spread. All patients who were treated with lateral lymph node resection also had central neck dissection.

Laboratory analysis and diagnostic whole-body scan

Blood samples were obtained at various moments during follow-up. On the day of administration of the ablative dosage, blood samples were obtained to measure the levels of thyroid stimulating hormone (TSH), thyroid hormone, thyroglobulin (Tg) and thyroglobulin-antibodies (Tg-Ab).

Every 6 months Tg level and Tg-Ab were measured without TSH stimulation and ultrasound of the neck was performed to screen for recurrent disease. TSH stimulated specimen (either by LT4 withdrawal or after using intramuscular recombinant human TSH (rhTSH) injections) were drawn at least after 1,4 and 9 years with the simultaneous performance of a diagnostic whole-body scan using 370 mBq radioactive ^{131}I).

Tg and Tg-Ab levels were measured using the DYNOtest Tg-pluS (Brahms Diagnostica GmBH). The functional sensitivity for this assay is 0.2ng/mL.

Additional treatment

Based on findings during follow-up examination, some patients received additional treatment. Additional treatment included central (level VI) and/or lateral neck dissection (levels II-V), administration of therapeutic dosages of ^{131}I and external radiotherapy.

Measures of outcome

For this study, we defined three major measures of outcome: recurrence of disease, disease-free survival and mean time to recurrence. Patients were diagnosed with disease recurrence whenever one of the following features was present: cytological/histological evidence of newly developed disease, rising Tg or Tg-Ab levels in patients with previously undetectable levels or detectable Tg/Tg-Ab levels combined with positive ultrasound (cervical lymphadenopathy), diagnostic whole-body or post therapy scintigraphy, or ^{18}F-FDG-PET. Patients with already detectable Tg level, neck ultrasound suspicious for lymph node recurrence, or uptake on a post-ablation scan within 9-12 months after therapy are referred to as patients with disease persistence. Whenever one of these features remained positive during total follow-up a patient was diagnosed as never free of disease. DFS was defined as the time in months without evidence of disease recurrence. Mean time to recurrence was calculated for all the patients diagnosed with recurrent disease.

Statistical analysis

Statistical analysis was performed using SPSS for Windows 15.0 (SPSS, Chicago, IL, USA). For numeric variables, Pearson's chi-squared test was used, whereas continuous variables were compared using ANOVA. The Kaplan-Meier curve was used to compare DFS rates. A p-value <0.05 was considered to be statistically significant.

RESULTS

As shown in the flowchart a total of 402 patients with DTC were reviewed.
A total of 97 patients (24%) had a known number of positive lymph nodes at time of initial diagnosis without the presence of distant disease and were available for analysis. Median follow-up was 49 months (range 10 – 240 months). Eighty-five percent of the patients with N1b status also had lymph node involvement of the central compartment. Patient characteristics are summarized in Table 1.
Forty-five patients (46%) were diagnosed with recurrent disease. Most recurrences were of lymphatic origin with the involvement of regional and/or distant lymph nodes (83%). One third of the patients were treated with additional neck dissection, while the remaining patients were treated with one or more additional therapeutic dosages of ^{131}I. Five patients were additionally treated with external radiotherapy.
The number of positive lymph nodes was not significantly related to the risk of recurrence, DFS or time until recurrence for the whole group (Table 2). When analyzing only the group of patients with N1b status, the number of lymph nodes also did not significantly influence recurrence rate (p=0.308).

Table 1. Patient characteristics of high-risk patients N1M) (n=97)

Gender	
M	38% (n=37)
F	62% (n=60)
Mean age (±SD)	48 yr (±17)
Histology	
Papillary	96%
Follicular	4%
N-stage	
1a	34% (n=33)
1b	63% (n=61)
No. of lymph nodes	
1-4	66% (n=66)
5-9	18% (n=17)
10-14	7% (n=7)
15-19	2% (n=2)
20-24	4% (n=4)
≥ 25	1% (n=1)
Mean preablative TSH (±SD)	92 (±41)
Median follow-up (m)	49
Recurrence rate	46% (n=45)
Disease-related mortality	4% (n=4)

Table 2 Recurrence rate and DFS related to the number of positive lymph nodes

No. of positive lymph nodes	Total patients	Recurrence rate	P value	Mean DFS (mo)	P value	Mean time to recurrence (mo)	P value
<5	66	50%	0.879	37	0.85	16	0.428
>5	31	51%		36		7	
<10	83	47%	0.145	37	0.764	15	0.494
>10	14	69%		33		6	
<15	90	49%	0.414	38	0.306	14	0.711
>15	7	67%		18		7	

The only factor that significantly influenced recurrence rate and DFS in multivariate analysis was the presence of positive lymph nodes in the lateral compartment.

Thirty percent of the patients with positive central lymph nodes developed recurrent disease compared with 60% of the patients with positive lateral lymph nodes (p=0.007). The mean disease-free survival for N1a patients was 52 months versus 30 months for N1b patients (p=0.035). Also, the mean time to recurrence was significantly shorter in patients with positive nodes of the lateral compartment (7 vs. 44 months, p= 0.004, respectively). This difference also applied for patients with N1b status without the presence of central lymph nodes (p=0.023)

All disease related deaths (n=4) were observed in the patients with N1b status, however this was not statistically significant (p=0.139), possibly due to the low number of patients. Results are shown in table 3; Figure 2.

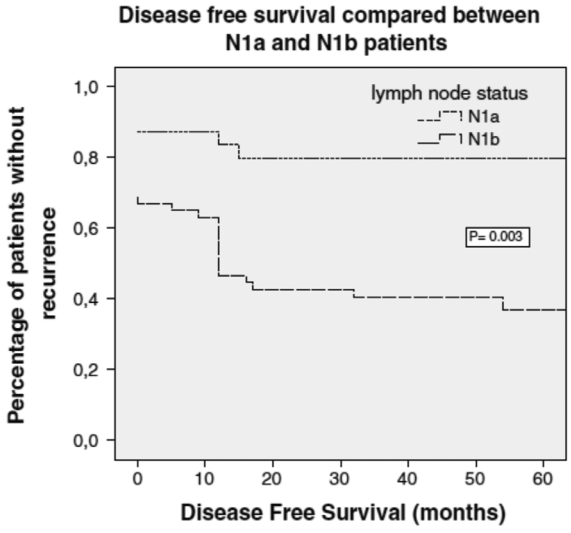


Figure 2.

Table 3. Recurrence rate and DFS related to N stage

N stage	Total patients	Recurrence rate	P valule	Mean DFS (mo)	P value	Mean time to recurrence	P value
N1a	33	30	0.007	52	0.035	44	0.004
N1b	66	60		30		7	

DISCUSSION

The presence of lymph node spread at the time of diagnosis predicts a higher risk of recurrent disease for patients with DTC. We found that the location of the lymph nodes significantly influences recurrence rate, time to recurrence and disease-free survival. Patients with clinically evident lymph nodes of the lateral compartment have a significantly higher recurrence rate compared to patients with positive central lymph nodes.

Our research addresses the clinical implication of lymph node involvement in a European patient group. Most studies focusing on this subject are from Asia, and especially Japan, where treatment strategy of patients is substantially different from the European method, whereas European and American treatment strategy is quite similar.

Results of our study can be used to further specify treatment and follow-up recommendations for the European and American population.

Furthermore, results of Asian studies are similar, which might indicate that treatment can be performed adequately in different ways for DTC patients.

We also showed that N1b status, in the large majority of cases, can be considered as more advanced disease compared to patients with only lymph node spread to the central compartment. Yet, at the same time our research shows that patients with the solitary involvement of lateral lymph nodes have a higher recurrence rate and shorter DFS.

Our results are in concordance with the findings of the Japanese studies, which found that the presence of clinically evident positive lymph nodes in the lateral compartment was a predictor of higher recurrence rate and shorter DFS (5,10,11).

The number of positive lymph nodes or the presence of extranodal growth did not contribute significantly to a worse DFS or higher recurrence rate in our study. This is in contradiction with the results of Ito et al., who found that the number (> 5 positive nodes) and the presence of extranodal growth did significantly influence DFS. The study of Lee et al. also investigated the prognostic significance of the number of positive nodes, but only in N1a patients; their preliminary results suggest that more than 5 positive lymph nodes in the central compartment may affect recurrence rate and DFS (12). Analysis of our N1a- and N1b-positive patients did not show a significant correlation between the number of lymph nodes and disease recurrence (p=0.549, p=0.308). Age and extranodal growth also did not show a significant correlation with recurrence rate (p=0.165, p=0.549). Size of the metastatic nodes has also been indicated as a prognostic factor by Ito et al. and Sugitani

et al. (13). Our data missed information about the size of positive lymph nodes and therefore could not be analyzed regarding this parameter.

Different explanations could exist for the different findings between our study and the studies performed in Asia. The main difference between our study population and the Japanese population is the nature of the treatment of thyroid cancer. Whereas routine ablation of the thyroid remnant is performed in Europe and the United States, it is not frequently used in Japan and other Asian countries. The Japanese guidelines on the treatment and follow-up of thyroid cancer also differ on various other points from the American and European guidelines (14).

Therefore, the results of Asian studies, especially about prognostic significance, follow-up and treatment are sometimes difficult to generalize to the European and American population.

The use of routine ablation therapy in western countries might be responsible for the different outcomes in respect to the prognostic significance of the number and growth type of positive lymph nodes between our study and the Japanese studies. The ablation therapy might compensate for a higher number of lymph nodes and the presence of extranodal growth in our patients, neutralizing it as a significant prognostic factor. The ablation dosages used in our study varied, but the current opinion in our institution is that low ablation dosages are just as effective higher dosages.

It is quite possible that the number of lymph nodes and the presence of extranodal growth do influence recurrence rate and DFS in the western population, but that our study population was too small to achieve statistical significance for these factors. Japanese treatment and especially lymph node resection, is performed more often and usually more aggressive due to the less frequent use of radioactive iodine. More information about the lymph nodes is therefore collected and more variables can be analyzed.

Limitations of our study include its retrospective nature. Randomized and prospective studies are, however, almost impossible to perform because of the large number of patients that should be included and the long follow-up period. In addition, a median follow-up of 49 months for high risk patients may be considered relatively short, as recurrences can occur after 10 years. Even though most recurrences are identified in an early stage of disease (mean time of recurrence in our study was 14 months) studies with longer follow-up are necessary in order to support our findings. Our study however, did analyze all patients treated in an academic hospital over the course of more than 12 years.

With this study, we confirm the adequacy of the 7th edition of the AJCC TNM staging manual concerning the subdivision of patients based on lymph node status (N1a versus N1b). Other factors such as the number of positive lymph nodes or the presence of extranodal growth could not be confirmed as prognostic factors that significantly influenced recurrence rate and DFS in our study population.

REFERENCES

1. Baek SK Jung KY, Kang SM, et al. Clinical risk factors associated with cervical lymph node recurrence in papillary thyroid carcinoma. Thyroid 2010;20(2)147-152.

2. Jonklaas J, Sarlis NJ, Litofsky D, et al. Outcomes of patients with differentiated thyroid carcinoma following initial therapy. Thyroid 2006;16(12)1229-1242.

3. Edge SB AJCC cancer staging manual (7th ed) 2010, New York, NY, Springer, 2010.

4. Ito Y, Tomoda C, Uruno T, et al. Ultrasonographically and anatomopathologically detectable node metastases in the lateral compartment as indicators of worse relapse-free survival in patients with papillary thyroid carcinoma. World J.Surg. 2005;29(7)917-920.

5. Ito Y, Miyauchi A. Lateral lymph node dissection guided by preoperative and intraoperative findings in differentiated thyroid carcinoma. World J.Surg. 2008;32(5)729-739.

6. Ito Y, Fukushima M, Tomoda C, et al. Prognosis of patients with papillary thyroid carcinoma having clinically apparent metastasis to the lateral compartment. Endocr.J. 2009;56(6)759-766.

7. Ito Y, Tomoda C, Uruno T, et al. Preoperative ultrasonographic examination for lymph node metastasis: usefulness when designing lymph node dissection for papillary microcarcinoma of the thyroid. World J.Surg. 2004;28(5)498-501.

8. Pacini F, Schlumberger M, Dralle H, et al. European consensus for the management of patients with differentiated thyroid carcinoma of the follicular epithelium. Eur J Endocrinol. 2006;154(6)787-803

9. Cooper DS, Doherty GM, Haugen BR, et al. Revised American Thyroid Association management guidelines for patients with thyroid nodules and differentiated thyroid cancer. Thyroid 2009;19(11)1167-1214.

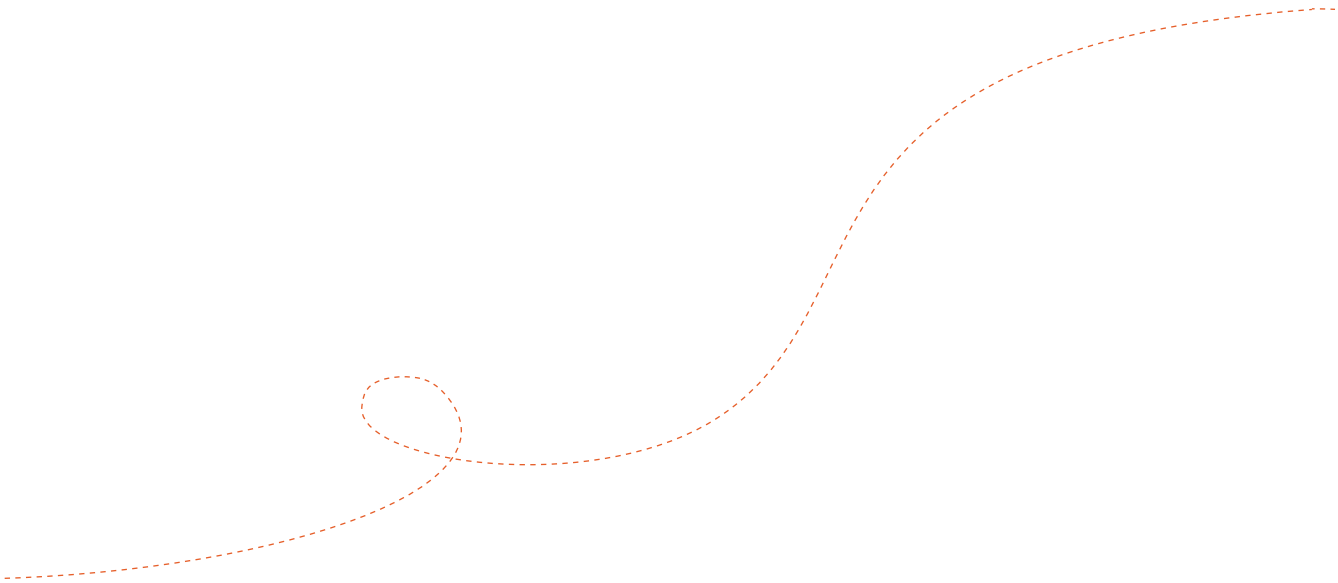
10. Ito Y, Higashiyama T, Takamura Y, et al. Risk factors for recurrence to the lymph node in papillary thyroid carcinoma patients without preoperatively detectable lateral node metastasis: validity of prophylactic modified radical neck dissection. World J.Surg. 2007;31(11)2085-2091.

11. Ito Y, Miyauchi A, Jikuzono T, et al. Risk factors contributing to a poor prognosis of papillary thyroid carcinoma: validity of UICC/AJCC TNM classification and stage grouping. World J.Surg. 2007;31(4)838-848.

12. Lee YS, Lim YS, Lee JC, et al. Clinical implication of the number of central lymph node metastasis in papillary thyroid carcinoma: preliminary report. World J.Surg. 2010;34(11)2558-2563.

13. Sugitani I, Kasai N, Fujimoto Y, et al. A novel classification system for patients with PTC: addition of the new variables of large (3 cm or greater) nodal metastases and reclassification during the follow-up period. Surgery 2004;135(2)139-148.

14. Takami H, Ito Y, Okamoto T, et al. Therapeutic strategy for differentiated thyroid carcinoma in Japan based on a newly established guideline managed by Japanese Society of Thyroid Surgeons and Japanese Association of Endocrine Surgeons. World J.Surg. 2011;35(1)111-121.



CHAPTER 7

General discussion and future perspectives

The major subjects discussed in this thesis relate to the approach of patients with thyroid nodules, prognostic factors influencing outcome and proper follow-up strategy for patients with differentiated thyroid cancer.

DIAGNOSIS OF DIFFERENTIATED THYROID CANCER

The role of fine needle aspiration in diagnosing thyroid cancer

Chapter 2 focused on Fine Needle Aspiration (FNA) as a tool to diagnose thyroid cancer. FNA remains the cornerstone of thyroid nodule evaluation. However, non-diagnostic FNA leads to repeat FNA or diagnostic lobectomy, leading to patient anxiety (1). Moreover, repeat FNA delays diagnosis and thus definitive care for patients with thyroid cancer.
The authors of the Bethesda System for Reporting Thyroid Cytopathology state in their guideline that ideally a maximum of 10% of FNAs should be non-diagnostic. This is in sharp contrast with reported non-diagnostic rates of up to 34% in current literature. Our study reports an overall non-diagnostic rate of 54%. While ultrasound(US)-guided FNA was thought to reduce non-diagnostic aspirates, little difference was found compared with palpation-guided FNA. Other factors that could influence adequacy rates are operator experience, aspiration technique, size and vascularization of the nodule, type and size of the needle and the number of needle passes (2-7). Rapid onsite adequacy assessment (ROSAA) whereby the FNA sample is assessed for adequacy by a cytopathologist on-site, providing immediate feedback, has also been suggested in literature as a way to improve adequacy rate (3, 8, 9). After our study was performed, a subsequent study was conducted in our hospital, introducing ROSAA. This resulted in better adequacy rates, however the percentage of non-diagnostic aspirates still exceeded the suggested 10% (10).
It is possible that published adequacy rates in other studies are subject to publication bias, leaving studies with higher non-diagnostic rates unpublished. High non-diagnostic rates might also go unnoticed in centers where own performance is not documented. Our study outlines the importance of critically assessing local performance and evaluating results, especially when a change of technique has been implemented.
There are other possible strategies of interest that could possibly reduce the number of non-diagnostic aspirates: core needle biopsy (CNB) and molecular testing. Meta-analyses on CNB versus repeat FNA after initial non-diagnostic aspirates show a significantly lower non-diagnostic rate of 1.4% for CNB versus 34.2% for FNA. The relative risk for a non-diagnostic aspirate for CNB is four times lower.
A study evaluating CNB as a primary method to evaluate thyroid nodules showed a significantly lower non-diagnostic rate in the CNB group compared to patients that underwent FNA (5.2% vs 12.1%) The complication rate was similar as were patient comfort and tolerability between techniques (11-12). Molecular testing is another method suggested by the members of the Endocrine Society and American Thyroid Association (ATA) as a tool to decrease the number of non-diagnostic tests. However, this seems to be especially

applicable for aspirates with undetermined significance. Whether aspirates with low cellularity or bloody aspirates are suited for molecular testing is unclear. Future studies are needed to evaluate this (13).

Prognosis and follow-up

Accurate surveillance for possible recurrence is a major goal of long-term follow-up. Tests with high specificity and negative predictive value allow identification of patients unlikely to experience disease recurrence. Less aggressive follow-up strategies can be used in these patients that are safe and more cost-effective. On the other hand, patients with a higher risk of recurrence are monitored more aggressively, because it is believed that early detection of recurrence offers the best opportunity for effective treatment (28).

Re-staging

In **Chapter 3** we have shown that an undetectable level of stimulated-Tg 9-12 months after therapy has a very high negative predictive value for recurrence for both low- AND high-risk patients. High-risk patients can have a low risk of recurrence when they their response to therapy was excellent. These results are supported by several other authors (14-27). Initial risk staging is useful in determining treatment and early diagnostic follow-up strategy. However, it is important to recognize that risk of recurrence and disease-specific mortality can change over time as a function of clinical course and response to therapy and does not only reflect tumor biology.

Re-evaluation of risk category has therefore been proposed, making the classification of low- and high-risk patients a dynamic process, also based on response to therapy. This re-classification, also called 'Ongoing Risk Stratification' or 'Delayed Risk Stratification' allows for modulation of the subsequent follow-up, excluding a significant number of especially intermediate and high-risk patient from unnecessary intensive work-up.

The clinical application of this dynamic classification system is dependent on the availability of high-quality biochemical testing methods and appropriate interpretation of functional imaging and therefore only useful in countries with high standard of care. The system proposed by and initially validated by Tuttle et al. (14) describes four groups:

- Patients with excellent response to therapy; no biochemical or structural evidence of disease
- Biochemical incomplete response: abnormal Tg or rising Tg antibody level in the absence of localizable disease
- Structural incomplete response: persistent or newly identified loco-regional or distant metastases
- Indeterminate response; non-specific biochemical or structural findings that cannot be confidently classified as either benign or malignant. For example, patients with stable or declining Tg-antibodies without structural evidence of disease.

This new stratification system still lacks published prospective data utilizing this system and validation in specific groups, for example patients not treated with remnant ablation or total thyroidectomy. Further research is needed to validate the system in patients treated

with total thyroidectomy but without remnant ablation and in patients treated with less than total thyroidectomy. Studies focusing on what type of functional imaging should be used to rule out disease recurrence/residual disease in patients with a biochemical incomplete response are also needed.

The latest ATA guideline, published in 2015, acknowledges the importance of re-classifying patients based on response to therapy and the proposed classification of Tuttle et al. is incorporated in the new guideline (28). 'Delayed Risk Stratification' is incorporated in the latest revision of the Dutch guideline as well (29).

Biochemical markers

In **Chapter 3 and 4** we have discussed the importance of TSH-stimulated Tg and Tg-Ab measurements in the follow-up of patients with differentiated thyroid cancer (DTC) patients. Stimulated Tg, in the absence of Tg-Ab, is an excellent tumor marker and undetectable Tg levels have been shown to reflect excellent response to therapy (15,30,31).

The follow-up strategy of patients with Tg-Ab remains a challenge for physicians. The ATA guideline does not provide a clear advice on the follow-up of patients with Tg-Ab, apart from recognizing that declining Tg-Ab levels are a good prognostic sign, while rising antibody levels in the absence of Tg significantly increase the risk of recurrence. The Dutch guideline proposes that additional imaging with ^{18}F-FDG-PET CT or an additional therapeutic dose ^{131}I be considered in patients with stable and rising Tg-Ab levels. In our study, no recurrences were diagnosed in patients with stable Tg-Ab levels and this is supported by several other authors (32-37). Additional imaging with ^{18}F-FDG-PET-CT or the administration of a therapeutic dose should, in our opinion, be reserved for patients with rising Tg-Ab levels.

Because the interference of Tg-Ab remains a problem in current methodologies for both the measurement of Tg and Tg-Ab, new strategies are being developed to deal with Tg-Ab. For example, a pilot study has been conducted evaluating the role of circulating epithelial cells as a tumor marker in patients with papillary thyroid cancer with serum Tg-Ab. Results of the study are promising and confirm that these epithelial cells could be a potential biomarker in identifying recurrence (38).

Another method under investigation is improving diagnostic performance of high-sensitivity Tg assays. Giovanella et al. claim that by lowering the threshold for Tg, in case of Tg-Ab presence, patients can reliably be followed using only Tg measurement (39).

Imaging

Imaging is an important aspect of the surveillance strategy for DTC patients.

In **Chapter 5** we have shown that in absence of Tg and Tg-Ab, in combination with a negative ultrasound of the neck, diagnostic ^{131}I whole-body scintigraphy has no added value for low- AND high-risk DTC patients (patients with distant metastasis excluded).

The ATA and Dutch guidelines still recommend diagnostic ^{131}I whole-body scintigraphy (DxWBS) for high-risk patients. The American guideline subdivides patients not only in low-or high risk, but adds a third category: intermediate-risk patients. These are patients

with aggressive histology, minor extrathyroidal extension, vascular invasion or >5 involved lymph nodes varying up to 3 cm in diameter. High-risk patients are defined as patients with gross extrathyroidal extension, incomplete tumor resection, distant metastases or lymph nodes larger than 3 cm. The Dutch guideline only recognizes low- and high- risk patients. The patients belonging to the intermediate category in the ATA guideline would be classified as high-risk patients in the Dutch classification system. The Dutch guideline is therefore somewhat more liberal in the use of DxWBS compared to the American one.
In our opinion, the strategy regarding the use of DxWBS should not be based on initial risk stratification, but should be combined with the re-classification of patients based on their response to therapy as discussed previously. In that case, high-risk patients are patients with a clinical or biochemical suspicion of recurrence/persistence and an anatomic substrate can possibly be located using DxWBS. If DxWBS shows no uptake, additional imaging is warranted. Using this strategy, many previously diagnosed intermediate or high-risk patients will not be 'over-investigated' with a DxWBS.
Of note, DxWBS is one of many tools to detect recurrent or metastatic disease in DTC patients.
Other imaging techniques that might be useful in the detection of persistent or recurrent disease during follow-up of DTC patients include:

Cervical ultrasonography
US of the neck is the most important imaging technique during follow-up of DTC patients. It is easily performed and very well tolerated by patients. It is highly sensitive in detecting cervical lymph node metastases in patients with DTC (40-42). It is used to evaluate the thyroid bed and the lymph node compartments. It is performed 6-12 months after initial therapy and can be periodically performed thereafter, based on the patient's risk of recurrence. Neck US can detect metastases as small as 2–3 mm in diameter (in patients in whom serum Tg may be low or undetectable), but benefit of their early discovery (<8–10 mm) has not been demonstrated and has no diagnostic consequences.

SPECT-CT and PET-CT
The application of radioactive ^{131}I (radioiodine) has become more targeted, based on evidence of the indolent behavior of a majority of tumors. Clinicians are in need of a diagnostic method which identifies patients that benefit from therapeutic interventions like radioiodine and thereby optimizes the therapeutic benefits and limits both radiation-related risks and healthcare costs.
DxWBS has traditionally been an important contributor to decision- making about potential ^{131}I therapy.
Whole-body scintigraphy includes planar images or images using a dual-head SPECT gamma camera of the whole body and spot images of the neck, mediastinum and any abnormal focus of radioiodine uptake. It may be performed after a diagnostic or therapeutic activity of radioiodine. It is often difficult to differentiate uptake in normal thyroid tissue or cervical lymph nodes because of the lack of anatomical landmarks on planar images. Diagnostic

^{123}I and low dose ^{131}I scintigraphy is known to underestimate the disease burden compared to ^{131}I post-treatment scans, especially in patients that have been previously treated with radioiodine (43-44).
Hybrid cameras combine a dual-head SPECT gamma camera with a CT-scan. This allows a combination of functional and anatomical imaging. Whole-body SPECT/CT performed after administration of a diagnostic or therapeutic activity of ^{131}I is associated with an increased number of patients with a diagnosis of metastatic lymph nodes and a decreased frequency of equivocal findings (45-50).
Moreover, CT provides information on non-iodine avid lesions. The SPECT-CT changed treatment management of up to a third of patients (24-36%) by decreasing the rate of equivocal findings. It avoids the need for further imaging with contrast CT. Therefore, whenever a diagnostic scan is indicated a SPECT-CT should be considered.
The use of ^{124}I, a positron emitting tomography tracer, in combination with CT (PET-CT) has made it possible to detect and image thyroid cancer lesions with high sensitivity and resolution. It can not only be used to localize disease, but also as a dosimetric tool. It permits an accurate measurement of the volume and uptake of ^{124}I and therefore is a highly sensitive imaging modality for detection of radioiodine avid metastatic DTC. Sensitivity has been reported to be higher compared to planar whole-body scintigraphy, it has not yet been compared with SPECT-CT in a large series. However, ^{124}I PET-CT also detects many lesions that are not visualized on the posttreatment ^{131}I scan, indicating that their iodine avidity may not be sufficient to achieve a specific activity that would deliver effective ^{131}I treatment to lesions identified. Therefore, it cannot be used as a tool to identify patients amenable to ^{131}I ablation therapy (51). Another disadvantage of PET-CT is its availability, it has not been widely available for clinical use. It is used primarily as a research tool (52).

^{18}F-FDG-PET CT

For patients with biochemical suspicion of disease, but with negative US and ^{131}I imaging ^{18}F-FDG-PET CT could be considered. It has a high sensitivity and specificity for non ^{131}I avid lesions. Factors influencing sensitivity are tumor dedifferentiation (higher sensitivity in tumors with aggressive histological subtypes, including poorly differentiated cancer) and tumor burden. ^{18}F-FDG uptake is a major negative predictive factor for response to radioiodine treatment and a prognostic factor for survival (53-54).
For patients with a low stimulated-Tg serum level the sensitivity of ^{18}F-FDG-PET CT is low. False positive lesions can also be observed with ^{18}F-FDG-PET imaging. The number varies from 0-39%, this indicates the need for FNA of lesions detected by ^{18}F-FDG-PET CT. Neck US has a higher sensitivity for detection of small metastatic lymph nodes, while ^{18}F-FDG-PET CT is more sensitive for the retropharyngeal and retro-clavicular areas (55).

CT and MRI

Diagnostic CT and/or MRI are mainly used when widely distributed recurrent nodal disease is present, or metastatic disease is suspected. It can complement neck US for the detection of macrometastases in het central compartment, mediastinum and area behind the trachea.

It is the most sensitive tool for detection of micrometasases in the lungs. It is useful for pre-operative work-up prior to revision surgery and can complement ^{18}F-FDG-PET CT and/or radioiodine imaging to evaluate the extent of locally recurrent invasive disease and the relationship with vessels.
MRI is superior in delineating lesions from the aerodigestive tract and is often used as a second-line imaging technique (56).
In conclusion, DxWBS should not be used as routine diagnostic work-up in the follow-up of low- or high-risk patients. It should be preserved as a first line imaging procedure for patients who have clinical or biochemical suspicion of recurrence/persistence after initial treatment. When the DxWBS is negative, other imaging procedures, such as SPECT-CT, ^{18}F-FDG-PET CT or CT may be considered in order to possibly find an anatomic substrate.

Prognostic factors in patients with lymph node metastases
In **Chapter 6** we have focused on the number and location of lymph node metastases and found that the location of lymph nodes metastases was of prognostic significance. We did not find a statistically significant prognostic effect of the number of lymph nodes. These findings are in concordance with the AJCC TNM classification that differentiates patients based on the location of nodal metastases (central versus lateral compartment).
Clinically apparent nodal disease (cN1), is associated with higher rates of persistent disease, higher recurrence rates and shorter disease-free survival, but contradicting results exist when looking at the number and location of nodal metastases.
The most recent ATA guidelines, published in 2015 (28), claim that a higher number of lymph node metastases and extranodal growth are related to a higher recurrence rate, based on the work by Leboulleux et al. (57) They were one of the first who studied whether the number of involved lymph nodes was prognostic. A cohort of 148 patients were studied, all treated with total thyroidectomy, central neck dissection, ipsilateral dissection of level III/IV and radioiodine remnant ablation. A large number of lymph node metastases (>10) was associated with a higher rate of residual disease. However, the number of lymph nodes was not statistically significant related to recurrence rate in a multivariate analysis. The results of this study do not support the conclusion that the number of lymph nodes is related to a higher recurrence rate. Extranodal extension in more than three lymph nodes was the only factor associated with a higher recurrence rate. There was no prognostic significant difference between patients with lymph node metastases in the central or lateral compartment. Although this study is frequently cited, not only by the ATA task force, the proposed relationship between number of affected nodes and recurrence has not been demonstrated in multivariate analysis (58).
The only studies showing a statistically significant effect of the number of nodal metastases on recurrence and disease-free survival are several Asian studies. In a study by Ito et al. (59), disease-free survival was only reduced in patients with metastases in the lateral compartment (N1b) if lymph nodes were larger than 3 cm, if extranodal growth was found, or if more than 5 clinically apparent lymph nodes were present. In multivariate analyses, an effect on cause-specific survival was found in patients with large metastases > 3cm

and extranodal extension. Subgroup analyses differentiating patients based on age revealed that for patients older than 55 years size was statistically significant influencing disease-free survival, while for younger patients (<55) more than 5 metastatic nodes in the lateral compartment was an individual prognostic factor for disease-free survival. Similarly, Sugitani et al. (60) demonstrated that the risk of recurrence was significantly higher in patients with more than 5 nodal metastases (19 vs 5%), this was independent of age and location. Disease-free survival in patients with more than 5 lymph nodes in the lateral compartment was associated with significantly worse disease-free survival. These findings are supported by the recent study of Wei et al. (61).

In conclusion, size, nodal metastases in the lateral compartment and extranodal growth are frequently described as prognostic factors for disease recurrence (57-59, 62). The studies reporting lymph node number as an independent prognostic factor have been performed in Asia. Whether the results of the Asian studies are applicable to the Western population is questionable. Treatment protocols differ; lymph node dissection is performed more frequently and aggressively, while ablation therapy is barely used in Asia. Our study has shown no prognostic difference for patients with more than 5 lymph nodes.

There is little evidence available from European or American studies regarding the number of lymph nodes as a prognostic factor for recurrence. In our opinion, there is no convincing evidence indicating that the number of lymph nodes has a significant influence on disease-free survival or recurrence rate in patients treated with (near)total thyroidectomy and radioiodine remnant ablation. More research in a large cohort of patients is needed.

Lack of prospective studies and randomized controlled trials

Limitations of our studies include their retrospective nature. This is a well-known problem for research concerning DTC patients. The good prognosis and low disease-related mortality in DTC patients, as well as the possibility of recurrent disease many years after initial diagnosis, makes it difficult to perform good quality randomized or prospective research. Follow-up of these patients has to be sufficiently long (decades) in order to obtain reliable results and large numbers of patients have to be included. When reliable results are finally available it is quite possible that therapeutic or diagnostic strategy have changed in the meantime. The retrospective nature of research in these patients seems to be inevitable, however, quality of the research might be optimized by analyzing large numbers of patients. To enlarge patient numbers, national and/or international collaborative efforts would have to be sought for future studies. Fortunately, our group has been involved in several such endeavors.

FUTURE PERSPECTIVES ON OPTIMIZING CARE FOR DTC PATIENTS

Treatment

While previous guidelines have advised total thyroidectomy as initial treatment for DTC patients, the most recent guideline states that in properly selected low- to intermediate risk patients (unifocal tumors <4cm, no extrathyroidal extension, no lymph node metastases) initial surgery has little impact on disease-specific survival (63-67). Some of these studies have demonstrated a lower risk of loco-regional disease recurrence following thyroidectomy. This is not surprising considering the fact that papillary thyroid cancer is often multifocal. However, with proper patient selection, recurrence rates of less than 4% and completion thyroidectomy rates of less than 10% can be achieved. The recurrences that occur during follow-up are readily detected and treated without impact on survival (67, 68).

Therefore, for tumors between 1-4 cm either a (near)total thyroidectomy or a lobectomy may be chosen as initial treatment. Recurrence rate is lower in patients treated with total thyroidectomy, but salvage therapy seems to be quite effective in the few patients with recurrence after lobectomy. Because of the more selective use of radioiodine and a greater reliance on neck US during follow-up thyroidectomy does not have to be performed only to facilitate remnant ablation and follow-up. Patient specific criteria for recommending a bilateral procedure followed by radioiodine ablation in low risk patients are age >45 years, contralateral thyroid nodules, a history of head and neck irradiation and familial DTC.

A conservative approach is suggested for patients with papillary microcarcinomas of the thyroid by Ito and Sugitani et al. (69,70). These studies from Japan propose active surveillance rather than primary operation for properly selected low risk patients with papillary microcarcinomas. Results originate from studies that have been performed in two large centers in Japan and outcomes are similar.

Patients with papillary thyroid carcinoma with low risk features (no clinically evident metastases, local invasion or cytologic evidence of aggressive disease) were observed with an average follow-up of 74 months. Three-hundred-forty patients were actively followed; 6% of the patients showed tumor enlargement on US at 5-year follow-up and 16 % at 10-year follow-up. 1% and 3% showed lymph node enlargement after 5 and 10 years respectively. Ultimately 109 patients underwent surgery and none of these patients developed a recurrence after delayed surgery. The study by Sugitani et al. (70) confirms that delayed surgery does not affect outcome. Their study results were even more favorable. Three-hundred low risk patients were followed with active surveillance. They found that 7% of the tumors had increased in size, 90% was unchanged and 3% had decreased. No patients developed extrathyroidal invasion or distant metastases during follow-up. Three patients (1%) who developed lymph node metastases and 9 patients (4%) in whom tumor size increased eventually underwent surgery after 1-12 years of follow-up. The conservative approach for patients with low risk DTC and papillary thyroid microcarcinomas has some advantages. With remaining lobe(s) present, patients may not need lifelong exogenous thyroid hormone replacement therapy. It might also be a favorable

approach for patients with comorbid conditions that are at high surgical risk; patients with an expected short remaining life span or patients with conditions that need to be addressed prior to surgery.

Up to date there are no clinical features or molecular markers that can reliably identify patients with papillary microcarcinomas at risk of developing recurrent disease or disease progression. Even well-known cancer oncogenes (BRAF) are not able to identify microcarcinomas that will progress and spread outside of the thyroid.

However, a more conservative approach also poses new dilemmas. Most research, including our own, has focused on patients treated by (near)total thyroidectomy and radioiodine remnant ablation. It is questionable whether biochemical markers or neck ultrasound will be useful in reliably detecting disease progression in the follow-up of these patients. More research is needed to identify risk factors that favor surgical resection over active surveillance. How active surveillance should be performed in order to most accurately detect disease progression and what specific indications for surgery should be need to be studied.

Another topic of interest is the timing of radioiodine remnant ablation after surgery. In current day practice radioiodine ablation is performed 4-6 weeks after surgery. Primarily this was done because patients needed to be withdrawn from levothyroxine prior to ablation. However, nowadays radioiodine therapy is given after rh-TSH stimulation. Emmanouilidis et al. (71) showed that the use of rh-TSH to stimulate radioiodine uptake after thyroidectomy is as efficient as a period of withholding thyroid hormones and showed a reduction in sick leave time and shortening of the hospital stay. Fast track radioiodine ablation one week after surgery could possibly result in better quality of life, while treatment is safe and effective.

Studies examining quality of life, costs and feasibility are needed.

REFERENCES

1. Redman R, Zalaznick H, Mazzaferri EL, Massoll NA The impact of assessing specimen adequacy and number of needle passes for fine-needle aspiration biopsy of thyroid nodules. Thyroid. 2006 Jan;16(1):55-60.

2. Cengic I, Tureli D, Ahiskali R, Bugdayci O, Aydin H, Aribal E: Thyroid fine needle aspiration biopsy: do we really need an on-site cytopathologist? Eur J Radiol 2014;83:680–683.

3. Ghofrani M, Beckman D, Rimm DL: The value of onsite adequacy assessment of thyroid fine-needle aspirations is a function of operator experience. Cancer 2006;108:110–113.

4. De Fiori E, Rampinelli C, Turco F, Bonello L, Bellomi M: Role of operator experience in ultrasound-guided fine-needle aspiration biopsy of the thyroid. Radiol Med 2010;115:612– 618.

5. Cappelli C, Pirola I, Gandossi E, De Martino E, Agosti B, Castellano M: Fine-needle aspiration cytology of thyroid nodule: does the needle matter? South Med J 2009;102:498–501.

6. Karadeniz Cakmak G, Emre AU, Tascilar O, Gultekin FA, Ozdamar SO, Comert M: Diagnostic adequacy of surgeon-performed ultrasound-guided fine needle aspiration biopsy of thyroid nodules. J Surg Oncol 2013;107:206– 210.

7. Sidiropoulos N, Dumont LJ, Golding AC, Quinlisk FL, Gonzalez JL, Padmanabhan V: Quality improvement by standardization of procurement and processing of thyroid fine- needle aspirates in the absence of on-site cytological evaluation. Thyroid 2009; 19:1049– 1052.

8. Breeze J, Poller DN, Gibson D, Tilley EA, Cooke L, Soar E, et al: Rapid on-site assessment of specimens by biomedical scientists improves the quality of head and neck fine needle aspiration cytology. Cytopathology 2014;25:316–321.

9. Zhu W, Michael CW: How important is on- site adequacy assessment for thyroid FNA? An evaluation of 883 cases. Diagn Cytopathol 2007;35:183–186.

10. de Koster EJ, Kist JW, Vriens MR, Borel Rinkes IH, Valk GD, de Keizer B. Thyroid Ultrasound-Guided Fine-Needle Aspiration: The Positive Influence of On-Site Adequacy Assessment and Number of Needle Passes on Diagnostic Cytology Rate. Acta Cytol. 2016;60(1):39-45.

11. Baek JH, Kim KW, Sung TY, Kim TY, Song DE, Choi YJ, Lee JH. The role of core-needle biopsy for thyroid nodules with initially nondiagnostic fine-needle aspiration results: a systematic review and meta-analysis. Endocr Pract. 2016; Jun;22(6):679-88.

12. Wolinski K, Stangierski A, Ruchala M. Comparison of diagnostic yield of core-needle and fine-needle aspiration biopsies of thyroid lesions: Systematic review and meta-analysis Eur Radiol. 2017; 27(1): 431–436.

13. Brito JP, Castro MR, Dean DS, Fatourechi V, Stan M. Survey of current approaches to non-diagnostic fine-needle aspiration from solid thyroid nodules Endocrine 2015 Aug;49(3):745-51.

14. Tuttle RM, Tala H, Shah J, Leboeuf R, Ghossein R, Gonen M, Brokhin M, Omry G, Fagin JA, Shaha A. 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; 20:1341–1349.

15. Vaisman F, Momesso D, Bulzico DA, Pessoa CH, Dias F, Corbo R, Vaisman M, Tuttle RM. Spontaneous remission in thyroid cancer patients after biochemical incomplete response to initial therapy. Clin Endocrinol (Oxf) 2012;77:132–138.

16. Castagna MG, Maino F, Cipri C, Belardini V, Theo- doropoulou A, Cevenini G, Pacini F 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; 165:441–446.

17. Berger F, Friedrich U, Knesewitsch P, Hahn K. Diagnostic 131I whole-body scintigraphy 1 year after thyroablative therapy in patients with differentiated thyroid cancer: correlation of results to the individual risk profile and long-term follow-up. Eur J Nucl Med Mol Imaging 2011; 38:451–458.

18. Malandrino P, Latina A, Marescalco S, Spadaro A, Re- galbuto C, Fulco RA, Scollo C, Vigneri R, Pellegriti G. Risk-adapted management of differentiated thyroid cancer assessed by a sensitive measurement of basal serum thyroglobulin. J Clin Endocrinol Metab 2011; 96:1703– 1709.

19. Soyluk O, Boztepe H, Aral F, Alagol F, Ozbey NC. Papillary thyroid carcinoma patients assessed to be at low or intermediary risk after primary treatment are at greater risk of long term recurrence if they are thyroglobulin antibody positive or do not have distinctly low thyroglobulin at initial assessment. Thyroid 2011; 21:1301– 1308.

20. Castagna MG, Brilli L, Pilli T, Montanaro A, Cipri C, Fioravanti C, Sestini F, Capezzone M, Pacini F. Limited value of repeat recombinant human thyrotropin (rhTSH)-stimulated thyroglobulin testing in differentiated thyroid carcinoma patients with previous negative rhTSH- stimulated thyroglobulin and undetectable basal serum thyroglobulin levels. J Clin Endocrinol Metab 2008; 93:76–81.

21. Kloos RT Thyroid cancer recurrence in patients clinically free of disease with undetectable or very low serum thyroglobulin values. J Clin Endocrinol Metab 2010; 95:5241–5248.

22. Rosario PW, Furtado MS, Mineiro Filho AF, Lacerda RX, Calsolari MR. Value of repeat stimulated thy- roglobulin testing in patients with differentiated thyroid carcinoma considered to be free of disease in the first year after ablation. Thyroid 2012; 22:482–486.

23. Brassard M, Borget I, Edet-Sanson A, Giraudet AL, Mundler O, Toubeau M, Bonichon F, Borson-Chazot F, Leenhardt L, Schvartz C, Dejax C, Brenot-Rossi I, Toubert ME, Torlontano M, Benhamou E, Schlumberger M. Long-term follow-up of patients with papillary and follicular thyroid cancer: a prospective study on 715 patients. J Clin Endocrinol Metab 201; 96:1352–1359.

24. Klubo-Gwiezdzinska J, Burman KD, Van Nostrand D, Wartofsky L. Does an undetectable rhTSH-stimulated Tg level 12 months after initial treatment of thyroid cancer indicate remission? Clin Endocrinol (Oxf) 2011;74:111– 117.

25. Crocetti U, Durante C, Attard M, Maniglia A, Tumino S, Bruno R, Bonfitto N, Dicembrino F, Varraso A, Meringolo D, Filetti S, Trischitta V, Torlontano M. Predictive value of recombinant human TSH stimulation and neck ultrasonography in differentiated thyroid cancer patients. Thyroid 2008; 18:1049–105.

26. Verburg FA, Stokkel MP, Duren C, Verkooijen RB, Mader U, van Isselt JW, Marlowe RJ, Smit JW, Reiners C, Luster M. No survival difference after successful (131)I ablation between patients with initially low-risk and high-risk differentiated thyroid cancer. Eur J Nucl Med Mol Imaging 2010; 37:276–283.

27. Giovanella L, Maffioli M, Ceriani L, De PD, Spriano G. Unstimulated high sensitive thyroglobulin mea- surement predicts outcome of differentiated thyroid carcinoma. Clin Chem Lab Med 2009; 47:1001–1004.

28. Haugen BR, Alexander EK, Bible KC, et al. 2015 American Thyroid Association Management Guidelines for Adult Patients with Thyroid Nodules and Differentiated Thyroid Cancer: the American Thyroid Association Guidelines Task Force on Thyroid Nodules and Differentiated Thyroid Cancer. Thyroid 2016;26:1–133.

29. https://richtlijnendatabase.nl/richtlijn/schildkliercarcinoom/follow_up/follow_up_niet_laag_risico.html.

30. Baudin E, Do CC, Cailleux AF, Leboulleux S, Travagli JP, Schlumberger M Positive predictive value of serum thyroglobulin levels, measured during the first year of follow-up after thyroid hormone withdrawal, in thyroid cancer patients. J Clin Endocrinol Metab 2003; 88:1107-1111.

31. Mazzaferri EL, Robbins RJ, Spencer CA, Braverman LE, Pacini F, Wartofsky L, Haugen BR, Sherman SI, Cooper DS, Braunstein GD, Lee S, Davies TF, Arafah BM, Ladenson PW, Pinchera A A consensus report of the role of serum thyroglobulin as a monitoring method for low-risk patients with papillary thyroid carcinoma. J Clin Endocrinol Metab 2003; 88:1433-1441.

32. Spencer CA, Takeuchi M, Kazarosyan M, Wan CC, Guttler TB, Singer PA, Fatemi S, LoPresti JS, Nicologg JT Serum thyroglobulin autoantibodies: prevalence, influence on serum thyroglobulin measurement, and prognostic significance in patients with differentiated thyroid carcinoma. J Clin Endocrinol Metab 1998; 83:1121-1127.

33. Chung JK, Park YJ, Kim TY, Kim SK, Park DJ, Lee DS, Cho BY Clinical significance of elevated level of serum antithyroglobulin antibody in patients with differentiated thyroid cancer after thyroid ablation. Clin Endocrinol (Oxf) 2002; 57:215-221.

34. Gorges R, Maniecki M, Jentzen W, Sheu SN, Mann K, Bockisch A, Janssen OE Developmend and clinical impact of thyroglobulin antibodies in patients with differentiated thyroid carcinomoa during the first 3 years after thyroidectomy. Eur J Endocrinol 2005; 153:49-55.

35. Seo JH, Lee SW, Ahn BC, Lee J Recurrence detection in differentiated thyroid cancer patients with elevated serum level of antithyroglobulin antibody: special emphasis on using (18)F-FDG PET/CT. Clin Endocrinol (Oxf) 2010; 72:558-563.

36. Adil A, Jafri RA, Wagar A, Abbasi SA, Matiul H, As-ghar AH, Jilani A, Naz I Frequency and clinical importance of anti-Tg auto-antibodies (ATG). J Coll Physicians Surg Pak 2003;13:504-506.

37. Kim WG, Yoon JH, Kim WB, Kim TY, Kim EY, Kim JM, Ryu JS, Gong G, Hong SJ, Shong YK Change of serum antithyroglobulin antibody levels is useful for prediction of clinica recurrence in thyrogloglobulin-negatieve patients with differentiated thyroid carcinoma. J Clin Endocrinol Metab 2009; 93:4683-4689.

38. Li YR, Tsenf CP, Lin HC, Chen YA, Liou MJ, Lin JD. Circulating epithelial cells as potential biomarkers for detection of recurrence in patients of papillary thyroid carcinoma with positive serum anti-thyroglobulin antibody Clin Chim Acta 2017;477: 74-80.

39. Giovanella L, Imperiali M, Verburg FA, Trimboli P. Early post-treatment risk stratification of differentiated thyroid cancer: comparison of three high-sensitive Tg assays Eur J Endocrinol. 2018 Jan;178(1):77-84.

40. Kouvaraki MA, Shapiro SE, Fornage BD, Edeiken- Monro BS, Sherman SI, Vassilopoulou-Sellin R, Lee JE, Evans DB. Role of preoperative ultrasonography in the surgical management of patients with thyroid cancer. Surgery 2003; 134:946–954.

41. Torlontano M, Crocetti U, Augello G, D'Aloiso L, Bonfitto N, Varraso A, Dicembrino F, Modoni S, Frus- ciante V, Di GA, Bruno R, Filetti S, Trischitta V. Comparative evaluation of recombinant human thyrotropin-stimulated thyroglobulin levels, 131I whole- body scintigraphy, and neck ultrasonography in the follow-up of patients with papillary thyroid micro- carcinoma who have not undergone radioiodine therapy. J Clin Endocrinol Metab 2006; 91:60–63.

42. Pacini F, Molinaro E, Castagna MG, Agate L, Elisei R, Ceccarelli C, Lippi F, Taddei D, Grasso L, Pinchera A. Recombinant human thyrotropin-stimulated serum thyroglobulin combined with neck ultrasonography has the highest sensitivity in monitoring differentiated thyroid carcinoma. J Clin Endocrinol Metab 2003 88:3668–3673.

43. Bravo, P.E., Goudarzi, B., Rana, U. Clinical significance of discordant findings between pre-therapy (123)I and post-therapy (131)I whole body scan in patients with thyroid cancer. International Journal of Clinical and Experimental Medicine 2013; 6: 320–333.

44. Schoelwer, M.J., Zimmerman, D., Shore, R.M. et al. The use of 123I in diagnostic radioactive iodine scans in children with differentiated thyroid carcinoma. Thyroid 2015; 25: 935–941.

45. Kohlfuerst S, Igerc I, Lobnig M, Gallowitsch HJ, Gomez-Segovia I, Matschnig S, Mayr J, Mikosch P, Beheshti M, Lind P. Posttherapeutic (131)I SPECT- CT offers high diagnostic accuracy when the findings on conventional planar imaging are inconclusive and allows a tailored patient treatment regimen. Eur J Nucl Med Mol Imaging 2009; 36:886–893.

46. Grewal RK, Tuttle RM, Fox J, Borkar S, Chou JF, Gonen M, Strauss HW, Larson SM, Schoder H The effect of posttherapy 131I SPECT/CT on risk classification and management of patients with differentiated thyroid cancer. J Nucl Med 2010; 51:1361–1367.

47. Aide N, Heutte N, Rame JP, Rousseau E, Loiseau C, Henry-Amar M, Bardet S. Clinical relevance of single-photon emission computed tomography/computed tomography of the neck and thorax in postablation (131)I scintigraphy for thyroid cancer. J Clin Endocrinol Metab 2009; 94:2075–2084.

48. Schmidt D, Szikszai A, Linke R, Bautz W, Kuwert T. Impact of 131I SPECT/spiral CT on nodal staging of differentiated thyroid carcinoma at the first radioablation. J Nucl Med 2009; 50:18–23.

49. Jeong SY, Lee SW, Kim HW, Song BI, Ahn BC, Lee J. Clinical applications of SPECT/CT after first I-131 ablation in patients with differentiated thyroid cancer. Clin Endocrinol (Oxf)2014; 81:445–451.

50. Tharp K, Israel O, Hausmann J, Bettman L, Martin WH, Daitzchman M, Sandler MP, Delbeke D. Impact of 131I-SPECT/CT images obtained with an integrated system in the follow-up of patients with thyroid carcinoma. Eur J Nucl Med Mol Imaging 2004; 31:1435–1442.

51. Kist, J.W., de Keizer, B., van der Vlies, M. et al. 124I PET/CT to predict the outcome of blind 131I Treatment in Patients with Biochemical Recurrence of Differentiated Thyroid Cancer: Results of a Multicenter Diagnostic Cohort Study (THYROPET). Journal of Nuclear Medicine 2016; 57: 701–707.

52. Santhanam P, Taieb D, Solnes L, Marashdeh W and Ladenson PW. Utility of I-124 PET/CT in identifying radioiodine avid lesions in differentiated thyroid cancer: a systematic review and meta-analysis Clinical Endocrinology 2017; 86: 645-651.

53. Robbins RJ, Wan Q, Grewal RK, Reibke R, Gonen M, Strauss HW, Tuttle RM, Drucker W, Larson SM. Real-time prognosis for metastatic thyroid carcinoma based on 2-[18F]fluoro-2-deoxy-D-glucose-positron emission tomography scanning. J Clin Endocrinol Metab 2006; 91:498–505.

54. Deandreis D, Al Ghuzlan A, Leboulleux S, Lacroix L, Garsi JP, Talbot M, Lumbroso J, Baudin E, Caillou B, Bidart JM, Schlumberger M. Do histological, immunohistochemical, and metabolic (radioiodine and fluorodeoxyglucose uptakes) patterns of metastatic thyroid cancer correlate with patient outcome? Endocr Relat Cancer 2011 18:159–169.

55. Leboulleux S, Schroeder PR, Busaidy NL, Auperin A, Corone C, Jacene HA, Ewertz ME, Bournaud C, Wahl RL, Sherman SI, Ladenson PW, Schlumberger M. Assessment of the incremental value of recombinant thyrotropin stimulation before 2-[18F]-fluoro-2-deoxy- D-glucose positron emission tomography/computed tomography imaging to localize residual differentiated thyroid cancer. J Clin Endocrinol Metab 2009; 94:1310– 1316.

56. Wang JC, Takashima S, Takayama F, Kawakami S, Saito A, Matsushita T, Matsuba H, Kobayashi S. Tracheal invasion by thyroid carcinoma: prediction using MR imaging. AJR Am J Roentgenol 177:929–936. Wang J, Takashima S, Matsushita T, Takayama F, Kobayashi T, Kadoya M Esophageal invasion by thyroid carcinomas: prediction using magnetic resonance imaging. J Comput Assist Tomogr 2001; 27:18–25.

57. Leboulleux S, Rubino C, Baudin E, Caillou B, Hartl DM, Bidart JM, Travagli JP, Schlumberger M. Prognostic factors for persistent or recurrent disease of papillary thyroid carcinoma with neck lymph node me- tastases and/or tumor extension beyond the thyroid capsule at initial diagnosis. J Clin Endocrinol Metab 2005; 90:5723–5729.

58. Randolph GW, Duh QY, Heller KS, LiVolsi VA, Mandel SJ, Steward DL, Tufano RP, Tuttle RM. The prognostic significance of nodal metastases from papillary thyroid carcinoma can be stratified based on the size and number of metastatic lymph nodes, as well as the presence of extranodal extension. Thyroid 2012;22:1144–1152.

59. Ito Y, Fukushima M, Tomoda C. Prognosis of patients with papillary thyroid carcinoma having clinically apparent metastasis to the lateral compartment. Endocr J 2009;56:759–766.

60. Sugitani I, Kasai N, Fujimoto Y et al. A novel classification system for patients with PTC: addition of the new variables of large (3 cm or greater) nodal metastases and reclassification during the follow-up period. Surgery 2004; 135(2):139–148.

61. Wei WJ, Lu ZW, Wen D et al. The Positive Lymph Node Number and Postoperative N-Staging Used to Estimate Survival in Patients with Differentiated Thyroid Cancer: Results from the Surveillance, Epidemiology, and End Results Dataset (1988–2008) World Journal of Surgery 2017.

62. Bardet S, Malville E, Rame JP, Babin E, Samama G, De RD, Michels JJ, Reznik Y, Henry-Amar M. Mac- roscopic lymphnode involvement and neck dissection predict lymph-node recurrence in papillary thyroid car- cinoma. Eur J Endocrinol 2008; 158:551–560.

63. Matsuzu K, Sugino K, Masudo K, Nagahama M, Kita- gawa W, Shibuya H, Ohkuwa K, Uruno T, Suzuki A, Magoshi S, Akaishi J, Masaki C, Kawano M, Suganuma N, Rino Y, Masuda M, Kameyama K, Takami H, Ito K Thyroid lobectomy for papillary thyroid cancer: long-term follow-up study of 1,088 cases. World J Surg 2014; 38:68–79.

64. 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; 33:645–649.

65. Mendelsohn AH, Elashoff DA, Abemayor E, St John MA Surgery for papillary thyroid carcinoma: is lobectomy enough? Arch Otolaryngol Head Neck Surg 2010; 136:1055–1061.

66. Haigh PI, Urbach DR, Rotstein LE 2005 Extent of thyroidectomy is not a major determinant of survival in low- or high-risk papillary thyroid cancer. Ann Surg Oncol 2010; 12:81–89.

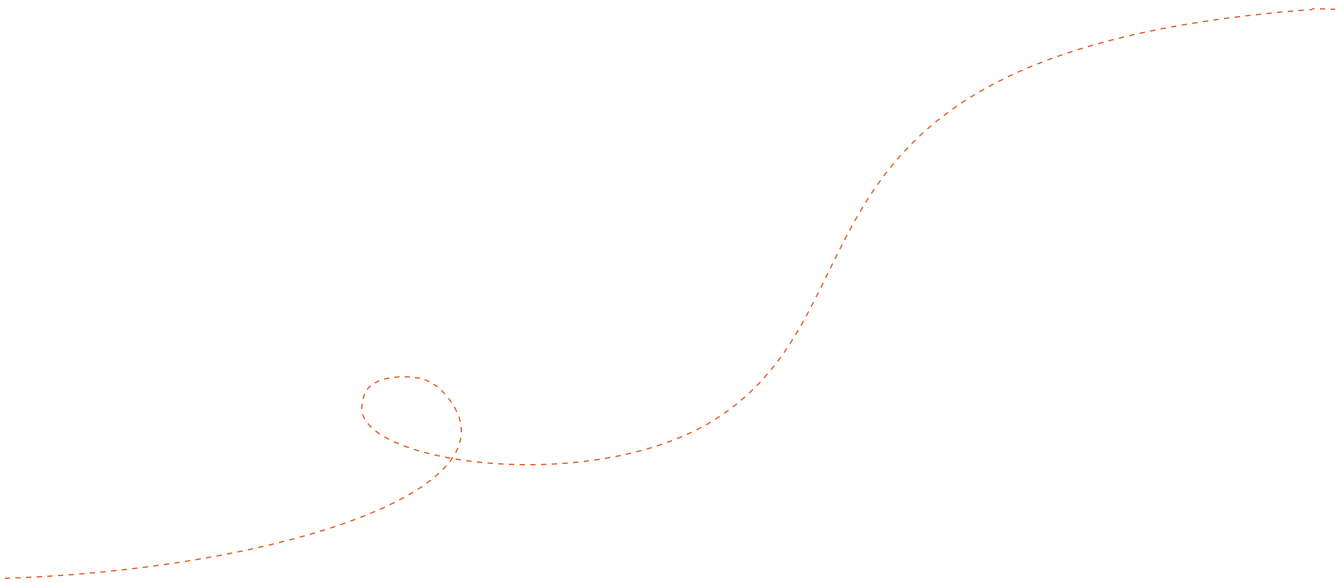
67. Nixon IJ, Ganly I, Patel SG, Palmer FL, Whitcher MM, Tuttle RM, Shaha A, Shah JP Thyroid lobectomy for treatment of well differentiated intrathyroid malignancy. Surgery 2012; 151:571–579.

68. Vaisman F, Shaha A, Fish S, Michael TR 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 (Oxf) 2011; 75:112–119.

69. Ito Y, Miyauchi A, Inoue H, Fukushima M, Kihara M, Higashiyama T, Tomoda C, Takamura Y, Kobayashi K, Miya A. An observational trial for papillary thyroid microcarcinoma in Japanese patients. World J Surg 2010; 34: 28–35.

70. Sugitani I, Toda K, Yamada K, Yamamoto N, Ikenaga M, Fujimoto Y Three distinctly different kinds of papillary thyroid microcarcinoma should be recognized: our treatment strategies and outcomes. World J Surg 2010; 34: 1222–1231.

71. Emmanouilidis N, Muller JA, Jager MD, Kaaden S, Helfritz GA, Guner Z, Kespohl H, Knitsch W, Knapp WH, Klempnauer J, Scheumann GFW Surgery and radioablation therapy combined: introducing a 1-week-condensed procedure bonding total thyroidectomy and radiablation therapy with recombinant human TSH. Eur J Endocrinol 2009; 161: 763-769.



CHAPTER 8

Summary

This thesis incorporates different studies regarding the diagnosis, follow-up and prognosis of patients with differentiated thyroid cancer.
Differentiated thyroid cancer (DTC) is the most common type of thyroid cancer, and the most common endocrine malignancy. Papillary cancer comprises around 85% of the cases, while 12% of the tumors are of follicular origin. DTC has become increasingly prevalent over the last decades. Survival rates are excellent, but recurrences occur in 5-20 percent of the patients. Recurrences are the main reason for follow-up.

DIAGNOSIS

Patients usually present with a palpable mass in the neck. Clinical features suggestive for malignancy are relative rapid growth, fixation to surrounding tissue, cervical lymphadenopathy, hoarseness, inspiratory stridor of dysphagia.
Diagnostic ultrasound of the thyroid and cervical lymph nodes should be performed in all patients with suspected thyroid nodules.
Fine needle aspiration is the standard tool, and still the cornerstone, for diagnosing cancer. Unfortunately, a considerable percentage of FNA specimen are indeterminate and do not predict the nature of the thyroid nodule. **Chapter two** focused on identifying factors associated with the adequacy rate of fine needle aspiration cytology. Fine needle aspirates are difficult to interpret and a sufficient number of cells are needed to properly classify the cytology of a thyroid nodule in one of the six categories of the Bethesda system. If an insufficient amount of cells is harvested, or bloody aspirates are obtained, specimen is classified as non-diagnostic/inadequate for diagnosis. These non-diagnostic aspirates delay definitive diagnosis and cause patient anxiety.
Ultrasound guidance is proposed to reduce the number of inadequate specimen, and several studies had shown a beneficial effect on adequacy rates. The rate of non-diagnostic FNA specimen was high in our hospital. Ultrasound guidance was implemented, but unfortunately, did not improve the results. Other factors associated with better results are on-site assessment of aspirates, operator experience, education, vascularization, needle size and number of needle passes. In order to improve results, quality control of diagnostic procedures like FNA, at one's own institution is essential before and after implementing new techniques.

Treatment for DTC larger than 1 cm consists of a near-total thyroidectomy followed by radioactive ablation with I-131 in the Netherlands. The goal of initial therapy for DTC patients are to improve overall and disease-specific survival, reduce the risk of persistent and/or recurrent disease and permit accurate disease staging and risk stratification.

FOLLOW-UP

The goal of follow-up is accurate surveillance for recurrent disease. There is a relative inability to accurately predict the risk of recurrence from thyroid cancer for the individual patient. Thyroglobulin (Tg) is a hormone produced exclusively by thyroid tissue and therefore used a tumor marker, especially for patients treated by total thyroidectomy followed by remnant ablation. It is the most sensitive method to detect recurrence. However, in the presence of thyroglobulin-antibodies (Tg-Ab) (in 20-25% of the patients), the Tg values can be falsely lowered of elevated.

Chapter 3 and 4 are related to these biochemical markers in DTC.
Chapter 3 focused on the postsurgical (including RAI ablation) follow-up of patients with DTC. Patients with undetectable Tg one year after initial treatment had a very low recurrence rate. Recurrence rate was comparable for low- and high-risk patients with an undetectable Tg level after one year. The negative predictive value of undetectable serum Tg one year after surgical and postoperative radioactive ablation treatment is very high for both low and high-risk patients (NPV 97%).

With comparable recurrence rate for low- and high-risk patients who've had an excellent response to therapy, based on the stimulated Tg level one year after treatment, we support the idea that response to therapy is a better predictor of recurrence than initial risk staging. We argue that a dynamic classification system is more appropriate; using not only tumor size and lymph node involvement, but also response to therapy to classify DTC patients. The follow-up regime of the patients with an excellent response to therapy could possibly be less frequent and rigid. This could result in a better quality of life and lower costs for the healthcare system.

In **Chapter 4** the results of our patients with Tg-Ab are described. Some authors have proposed to use Tg-Ab as a surrogate tumor marker. We studied this hypothesis in our patient group over a period of twelve years. In our cohort, the risk of recurrence was negligible for patients with declining or stable Tg-Ab level in patients with an undectectable Tg level.
Our results do not support the claim that Tg-Ab persistence for more than 3 years is an indicator for disease recurrence. In case of rising Tg-Ab levels, the treating physician should actively try to diagnose recurrent disease. In the majority of patients however, no recurrence will be detected.

In **Chapter 5** additional imaging with a diagnostic radioactive iodine (I-131) whole body scan is discussed (DxWBS). This procedure was routinely and regularly performed in all DTC patients during follow-up in the last decades. At the time of our research, DxWBS was no longer recommended as a routine diagnostic procedure for low-risk patients. For high-risk patients, the added value of DxWBS was unclear because of limited available

research. Our study therefore specifically focused on high risk patients. Results of our study showed that the routine performance of a DxWBS, in addition to Tg measurement and ultrasound of the neck, had limited diagnostic value. The DxWBS is however, useful as a detection tool in patients with biochemical suspicion of recurrence.

PROGNOSIS

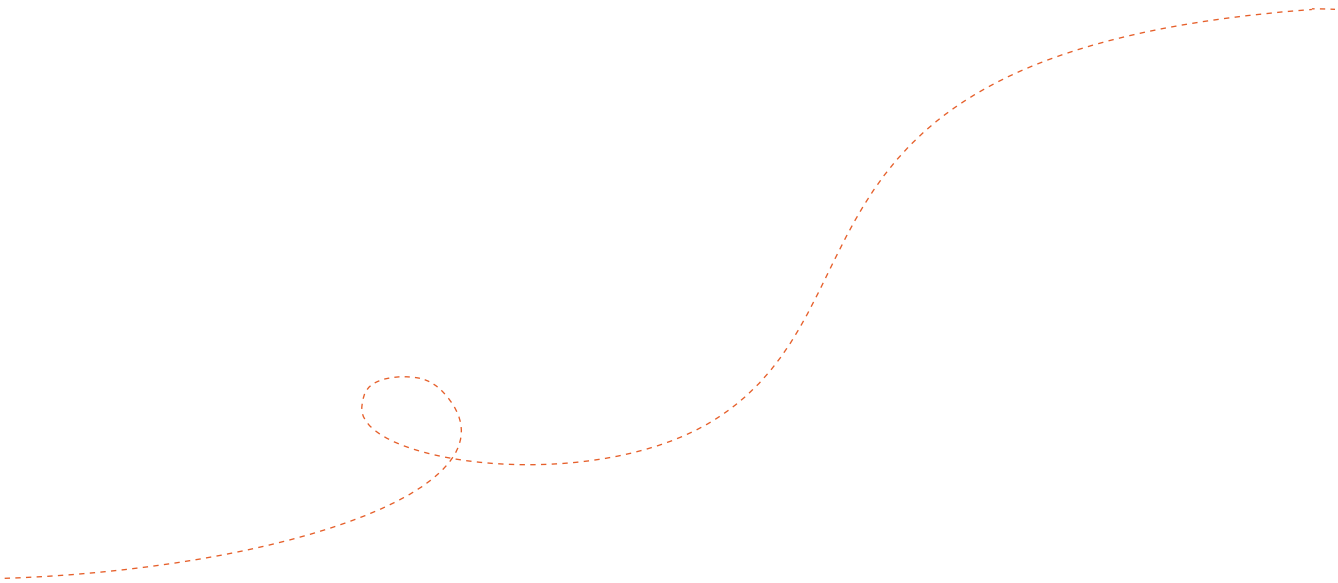
The TNM classification system is used for all patients with DTC. Postoperative staging is used to provide prognostic information, which is of value when considering therapeutic strategy and surveillance. The TNM system uses a combination of age, size of the tumor, tumor histology, and extrathyroidal spread to stratify patients into one of several categories with different risks from death from thyroid cancer. It is primarily used to guide initial therapeutic interventions.

In a large number of DTC patients (20-50%) the cervical lymph nodes are involved. The role of the number and location of lymph node metastasis is discussed in **Chapter 6**. In the search for prognostic factors influencing recurrence rate and disease-free survival we investigated whether the number of lymph node metastasis and/or the location (central vs lateral compartment) had prognostic significance. Most research related to the location of positive lymph nodes has been done by Ito et al. from Japan. They found that the number of lymph nodes in the lateral compartment (>5) had prognostic significance. The difficulty of applying these results to European and American guidelines lies in the different treatment of DTC patient in Japan. In contradiction to western common practice, total thyroidectomy is less frequently performed and the use of radioactive I-131 is very limited in Japan and other Asian countries.

Hence, we investigated whether the number and/ or location of lymph nodes effected disease free survival and recurrence rate in patients treated according to western standards with (near)total thyroidectomy, lymph node resection followed by radioactive ablation.

The only factor that significantly influenced recurrence rate and disease-free survival in our study was the presence of lymph node metastasis in the lateral compartment. Analysis of N1a- and N1b-positive patients did not show a significant correlation between the number of lymph nodes or disease recurrence. With this study, we confirmed the adequacy of the seventh edition of the AJCC Cancer Staging Manual concerning the subdivision of patients based on location of cervical lymph node metastases (N1a vs. N1b).

APPENDIX



Nederlandse samenvatting

List of publications

Curriculum Vitae

Dankwoord

NEDERLANDSE SAMENVATTING

De onderwerpen die in dit proefschrift worden behandeld variëren van het verbeteren van de diagnostiek tot het optimaliseren van de follow-up en de identificatie van prognostische factoren voor patiënten met een gedifferentieerd schildkliercarcinoom.

Het goed gedifferentieerde schildkliercarcinoom is de meest voorkomende vorm van schildklierkanker (~97%) en de meest voorkomende endocriene maligniteit. Patiënten met een papillair schildkliercarcinoom vormen de grootste groep (~85%) gevolgd door patiënten met een folliculair schildkliercarcinoom (~12%). Patiënten met een goed gedifferentieerd schildkliercarcinoom hebben een uitstekende overlevingskans, echter recidieven treden in zo'n 5-20% van de patiënten op. Detectie van deze recidieven is dan ook een van de belangrijkste doelen tijdens de follow-up.

DIAGNOSE

Patiënten presenteren zich meestal met een palpabele massa in de hals. Kenmerken die suggestief zijn voor een maligniteit zijn: relatief snelle groei, fixatie aan het omliggende weefsel, lymfadenopathie van de halsklieren, heesheid, inspiratoire stridor en dysfagie.

Alle patiënten met een zwelling in de schildklier moeten geëvalueerd worden middels een echografie van de schildklier en de lymfeklieren in de hals. De gouden standaard voor het stellen van de diagnose is het dunne naald biopt. Cytologisch materiaal van de schildklier is moeilijk te interpreteren en er moeten voldoende cellen zijn geaspireerd om het materiaal in te delen in een van de zes categorieën van de Bethesda classificatie, die de verschillende typen cellen indeelt op basis van de kans op een maligniteit.
Het belangrijkste nadeel van het dunne naald biopt is, dat een aanzienlijk percentage van de preparaten een onvoldoende hoeveelheid kwalitatief goede cellen bevat om een uitspraak te doen over de aard van de schildkliernodus. Deze preparaten worden niet-diagnostisch of inadequaat genoemd. Deze niet-diagnostische preparaten vertragen het stellen van een definitieve diagnose en kunnen leiden tot onrust bij de patiënt. In **hoofdstuk 2** hebben we ons gericht op het beoordelen van de kwaliteit van het dunne naald biopt en de identificatie van factoren die hierbij een rol kunnen spelen.

Het percentage niet-diagnostische preparaten in ons ziekenhuis bleek erg hoog te liggen. Omdat er verschillende studies waren die een gunstig effect van echogeleide aspiratie lieten zien in het verminderen van het aantal niet-diagnostische preparaten, werd deze methode ingevoerd. De resultaten bleken in ons ziekenhuis echter niet te verbeteren na de invoering van de echogeleide puncties. Andere factoren die geassocieerd zijn met een betere kwaliteit zijn directe cytologische beoordeling tijdens de punctie, ervaring van de specialist die de punctie uitvoert, vascularisatie van de afwijking, dikte van de naald en het

aantal aspiratiepogingen per keer. Om de kwaliteit van de diagnostische procedure te verbeteren, is kwaliteitscontrole van de procedure, voor en na de implementatie van een nieuwe techniek of verandering van het protocol essentieel.

De behandeling van het schildkliercarcinoom (>1 cm) bestaat uit een totale resectie van de schildklier (totale thyroidectomie), gevolgd door ablatie met radioactief jodium. Het doel van de behandeling is het verbeteren van de overleving, de kans op blijvende ziekte of een recidief verminderen, en de follow-up te vergemakkelijken. Een ander doel is de identificatie van laag- en hoog-risico patiënten.

FOLLOW-UP

Het doel van de follow-up van patiënten met een goed gedifferentieerd schildkliercarcinoom is de detectie van recidieven. Hierbij is het belangrijk om recidieven vroegtijdig op te sporen om ze snel te kunnen behandelen. Echter, het is ook belangrijk om zorgvuldig om te gaan met aanvullend onderzoek en dit pas te initiëren als patiënten een reëel kans hebben op een recidief.

Thyreoglobuline (Tg) is een hormoon wat uitsluitend door de schildklier wordt geproduceerd en wordt daarom gebruikt als tumormarker voor patiënten die behandeld zijn met een totale thyroidectomie, gevolgd door ablatie van het resterende weefsel met radioactief jodium. Het is de meest sensitieve methode om een recidief te diagnosticeren. Er zijn echter ook patiënten (20-25% van de patiënten met een goed gedifferentieerd schildkliercarcinoom) die antistoffen maken tegen Tg; thyreoglobuline-antistoffen (Tg-Ab). De aanwezigheid van deze antistoffen beïnvloeden de testen die de Tg concentratie meten. Wanneer er Tg-Ab in het bloed aanwezig zijn is de waarde van Tg niet betrouwbaar vast te stellen. De Tg waarde kan foutief verlaagd of verhoogd zijn, afhankelijk van welke meetmethode wordt gebruikt. Voor deze patiënten kan Tg derhalve niet als tumormarker worden gebruikt.

Hoofdstuk 3 en 4 richten zich op deze biochemische markers.
In **hoofdstuk 3** bestuderen we de Tg waardes van patiënten die behandeld zijn met een operatie (totale thyroidectomie) en ablatie met radioactief jodium. Patiënten met een niet-detecteerbare concentratie van Tg, een jaar na de initiële behandeling, bleken een zeer lage kans op een recidief te hebben. Dit gold ook voor de patiënten die geclassificeerd waren als hoog-risico. De negatief voorspellende waarde van een negatief Tg, 1 jaar na de primaire behandeling, was 97% voor zowel laag- als hoog-risico patiënten.
De lage waarde van het Tg na een jaar weerspiegelt de respons op de therapie. Patiënten met een onmeetbaar lage concentratie hebben een goede respons op de therapie gehad. Met dit onderzoek hebben we laten zien dat de respons op therapie een betrouwbaardere voorspeller is van een recidief is dan de initiële risico classificatie. We vinden dat de risico classificatie een dynamisch proces hoort te zijn, waarbij ook de respons op de therapie

meegenomen dient te worden. Het follow-up regime van patiënten met een uitstekende respons op de therapie, ook als deze primair als hoog-risico patiënt is geclassificeerd, zou minder strict kunnen zijn. Dit zou tot een verbetering van de kwaliteit van leven voor de patiënt, en lagere kosten voor het zorgstelsel kunnen leiden.

Hoofdstuk 4 beschrijft de resultaten van het onderzoek van de patiënten met Tg-Ab. Sommige studies laten zien dat de Tg-Ab waarden als, een minder nauwkeurige, tumormarker gebruikt kunnen worden. Het nadeel van de gepubliceerde studies is dat zij niet duidelijk aangeven wanneer zij vinden dat er een stijgende of een dalende trend van Tg-Ab bestaat. In onze studie hanteerden we daarom duidelijke definities van een stijgende en dalende trend. In onze onderzoekspopulatie werden geen recidieven gediagnosticeerd bij patiënten met een stabiele of dalende Tg-Ab concentratie. Ook voor patiënten waarbij langdurig Tg-Ab werden aangetoond was er geen verhoogde kans op een recidief. Alleen bij een klein percentage van de patiënten met een stijgende Tg-Ab trend werd een recidief gevonden. Ons advies naar aanleiding van de studie is derhalve om, in het geval van een stijgende Tg-Ab trend, aanvullend onderzoek te verrichten op zoek naar een mogelijk recidief. Het is echter goed om te beseffen dat in het merendeel van de patiënten geen recidief zal worden aangetoond.

Hoofdstuk 5 gaat over de toepassing van de diagnostische 'whole-body' scintigrafie in de follow-up van patiënten met een gedifferentieerd schildkliercarcinoom. Dit is een onderzoek waarbij patiënten radioactief jodium krijgen toegediend waarna een opname van het lichaam wordt gemaakt waarbij de weefsels die het jodium hebben opgenomen zichtbaar kunnen worden gemaakt. Omdat schildkliercellen jodium opnemen is het mogelijk om eventueel aanwezige schildkliercellen in beeld te brengen. Dit onderzoek was jaren standaard onderdeel van de follow-up van patiënten met een schildkliercarcinoom en werd om het jaar verricht. Met de toegenomen gevoeligheid van de Tg bepaling, was het de vraag of zo'n diagnostisch scintigrafie nog wel een toegevoegde waarde had in de follow-up van alle patiënten. Er waren al studies gepubliceerd die een beperkte toegevoegde waarde van de diagnostische scan voor laag-risico patiënten liet zien. Maar, naar de toepassing bij hoog-risico patiënten was nog weinig onderzoek gedaan. Derhalve richtte ons onderzoek zich specifiek op de toegevoegde waarde van de diagnostische scan in de follow-up van hoog-risico patiënten. Onze resultaten lieten zien dat het standaard verrichten van een diagnostische scan bij hoog-risico patiënten van zeer beperkte aanvullende waarde is. De diagnostische scintigrafie zou gereserveerd moeten worden voor patiënten met een klinische of biochemische verdenking op een recidief.

PROGNOSE

De TNM-classificatie wordt gebruikt voor alle patiënten met een gedifferentieerd schildkliercarcinoom.
Postoperatieve stadiering wordt onder andere gebruikt om de therapeutische en follow-up strategie te bepalen. Tumorgrootte en tumoruitbreiding, de aanwezigheid van uitzaaiingen in de lymfeklieren, metastasen op afstand en de leeftijd van de patiënt zijn factoren die gebruikt worden om patiënten in te verschillende risicocategorieën die elk een andere kans op overlijden reflecteren.

In een groot percentage van de patiënten met een gedifferentieerd schildkliercarcinoom (~20-50%) zijn de cervicale lymfeklieren aangedaan. De aanwezigheid van lymfekliermetastasen bij patiënten met een gedifferentieerd schildkliercarcinoom is een onafhankelijke voorspeller voor het optreden van een recidief.
Hoofdstuk 6 heeft betrekking op het aantal en de locatie van de halskliermetastasen.
Er zijn studies die laten zien dat de locatie van de lymfekliermetastasen (centraal versus lateraal) en het aantal lymfekliermetastasen (>5) van prognostisch belang is. Echter, deze studies zijn voornamelijk uitgevoerd in Japan. Omdat in Japan de behandeling van het schildkliercarcinoom wezenlijk anders is (minder operaties, nauwelijks gebruik van ablatie met radioactief jodium) wilden wij kijken of de resultaten van deze studies ook toepasbaar zijn op de patienten die behandeld worden volgens de Westerse inzichten. Met onze studie hebben we gekeken of het aantal positieve halsklieren een effect heeft op de ziektevrije overleving en de kans op een recidief voor patiënten behandeld met een totale thyroidectomie en postoperatieve ablatie met radioactief jodium.
De enige factor die een significant effect had op de ziektevrije overleving en de kans op recidief was de aanwezigheid van lymfekliermetastasen in het laterale compartiment van de hals. Er werd geen significant verband gevonden tussen het aantal lymfeklieren en de kans op recidief. Onze resultaten zijn in overeenstemming met de TNM-classificatie, die onderscheid maakt tussen patiënten met lymfeklier metastasen in het centrale (N1a) of laterale (N1b) compartiment, maar het aantal lymfeklieren niet meeneemt als prognostische factor.

LIST OF PUBLICATIONS

SGA de Meer, JM Schreinemakers, PM Zelissen, G Stapper, DM Sie-Go, IHM Borel-Rinkes, MR Vriens. Fine needle aspiration of thyroid tumors: Identifying factors associated with adequacy rate in a large academic center in the Netherlands *Diagnostic Cytopathology 2010*

SGA de Meer, MR Vriens, PMJ Zelissen, IHM Borel Rinkes, B de Keizer. The role of routine diagnostic radioiodine whole body scan in patients with high risk differentiated thyroid cancer. *Journal of Nuclear Medicine 2011; 52: 56-59*

SGA de Meer, MR Vriens, PMJ Zelissen, IHM Borel Rinkes, B de Keizer. Reply: Utility of Diagnostic Whole-Body Iodine Scanning in High-Risk Differentiated Thyroid Carcinoma. *Journal of Nuclear Medicine 2012: 53: 662-663*

SGA de Meer, M. Dauwan, B de Keizer, GD Valk, IHM Borel Rinkes, MR Vriens. Not the number but the location of lymph nodes matters for recurrence rate and disease-free survival in patients with differentiated thyroid cancer. *World Journal of Surgery 2012; 36: 1262-1267*

SGA de Meer, JM Schreinemakers, PM Zelissen, G Stapper, DM Sie-Go, IHM Borel-Rinkes, MR Vriens. Fine needle aspiration of thyroid tumors: Identifying factors associated with adequacy rate in a large academic center in the Netherlands *Diagnostic Cytopathology, Special issue 2012: 40: E21-26*

Schouten N, Elshof JW, Simmermacher RK, van Dalen T, **de Meer SG**, Clevers GJ, Davids PH, Verleisdonk EJ, Westers P, Burgmans JP. Selecting patients during the " learning curve" of endoscopic Totally Extraperitoneal (TEP) hernia repair. *Hernia 2013: 17: 737-743*

SGA de Meer, MR Vriens, GD Valk, IHM Borel Rinkes, B de Keizer. High Negative Predictive Value (NPV) Of Undetectable TSH Stimulated Tg For Disease Recurrence In Both Low- And High- Risk Differentiated Thyroid Cancer. *Journal of Thyroid Disorders and Therapy 2014: 3: 149*

SGA de Meer, WMCM Vorselaars, JW Kist, MPM Stokkel, B de Keizer, GD Valk, IHM Borel Rinkes , MR Vriens. Follow-up of DTC patients with thyroglobulin-antibodies: rising Tg-Ab trend is a risk factor for recurrence. *Endocrine Research 2017: 42; 302-310*

SGA de Meer. De geluxeerde vinger op het voetbalveld, wat te doen? *Ned Tijdschrift Geneeskd 2017; 161*

CURRICULUM VITAE

Sijbrigje Grietje Anna (Siegrid) de Meer was born in Hilversum, The Netherlands, on the 8th of March 1985, as the second daughter of Dirk and Jane-lies de Meer. She graduated with honors from high school in 2003 (VWO+, Erfgooierscollege, Huizen). After high school, she entered medical school at the University of Utrecht. In 2004, she obtained her 'propadeuse' with honors. During her studies, Siegrid did an extracurricular elective at the University Teaching Hospital in Lusaka, Zambia, at the department of Infectious diseases. During her study, she participated in a research project at the department of Surgery under supervision of Prof. dr. M.R. Vriens and Prof. dr. I.H.M. Borel Rinkes and completed an elective clinical rotation at the department of Surgical Oncology under the supervision of Prof. dr. I.H.M. Borel Rinkes.

She worked at the Anatomy department as a student teacher.

After obtaining her medical degree in 2009, Siegrid started working at the department of Surgery at the University Medical Center Utrecht as a tutor of medical interns, also participating as a teacher in the medical curriculum at the University of Utrecht. At that time, she got the opportunity to start as a PhD-student (under supervision of Prof. Dr. M.R. Vriens, Prof. dr. I.H.M. Borel Rinkes and Dr. B. de Keizer) which eventually resulted in this thesis.

In 2011, she started working as a surgical resident (ANIOS) at the Diakonessen hospital in Utrecht under supervision of dr. G.J. Clevers.

In January 2012, she started her clinical training at the department of Surgery at the Twee Steden Hospital in Tilburg (dr. M.S. Ibelings) and the Elisabeth Hospital in Tilburg (Dr. P.W.H.E. Vriens), nowadays fused as the ETZ Hospital.

She started her Traumasurgery training at the Diakonessen Hospital in Utrecht (Dr. T. Van Dalen and Dr. E.J. Verleisdonk), and the University Medical Center Utrecht (Prof. Dr. M.R. Vriens, Prof. Dr. L.P.H. Leenen). She is currently completing her training at the Meander Medical Center (Dr. E.C.J. Consten, Dr. T.K. Timmers) and will finish her training in December 2018.

Siegrid lives with Pim and their son, Ben, in Zeist.

DANKWOORD

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'Een student gaat pas slapen als alle sterren zijn geteld' …dat liedje zal nooit meer hetzelfde zijn.
En…je had me bijna om.

Beste stafleden, arts-assistenten, verpleegkundigen, gipsverbandmeesters en poli-dames uit het Diakonessenhuis,
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Tijdens het keuzevak 'de hand' is onze vriendschap ontstaan. Heidi, co-schappen lopen in Zambia was niet hetzelfde geweest zonder jou. Jij durft alles. Door jou durfde ik meer… We komen jullie graag een keer opzoeken in Noorwegen!
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