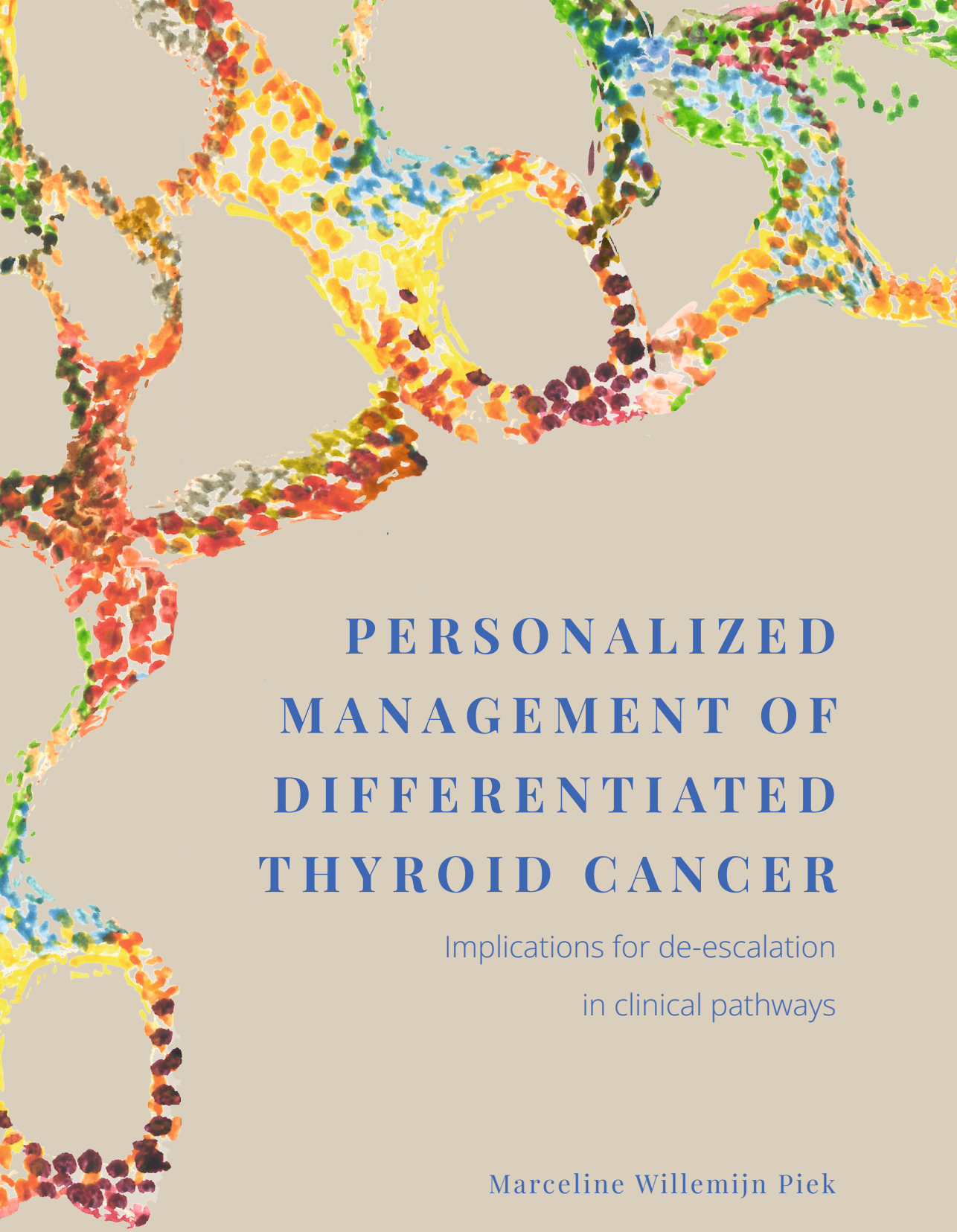

PERSONALIZED MANAGEMENT OF DIFFERENTIATED THYROID CANCER

Implications for de-escalation in clinical pathways

Marceline Willemijn Piek

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“All that glitters is not gold”

William Shakespeare

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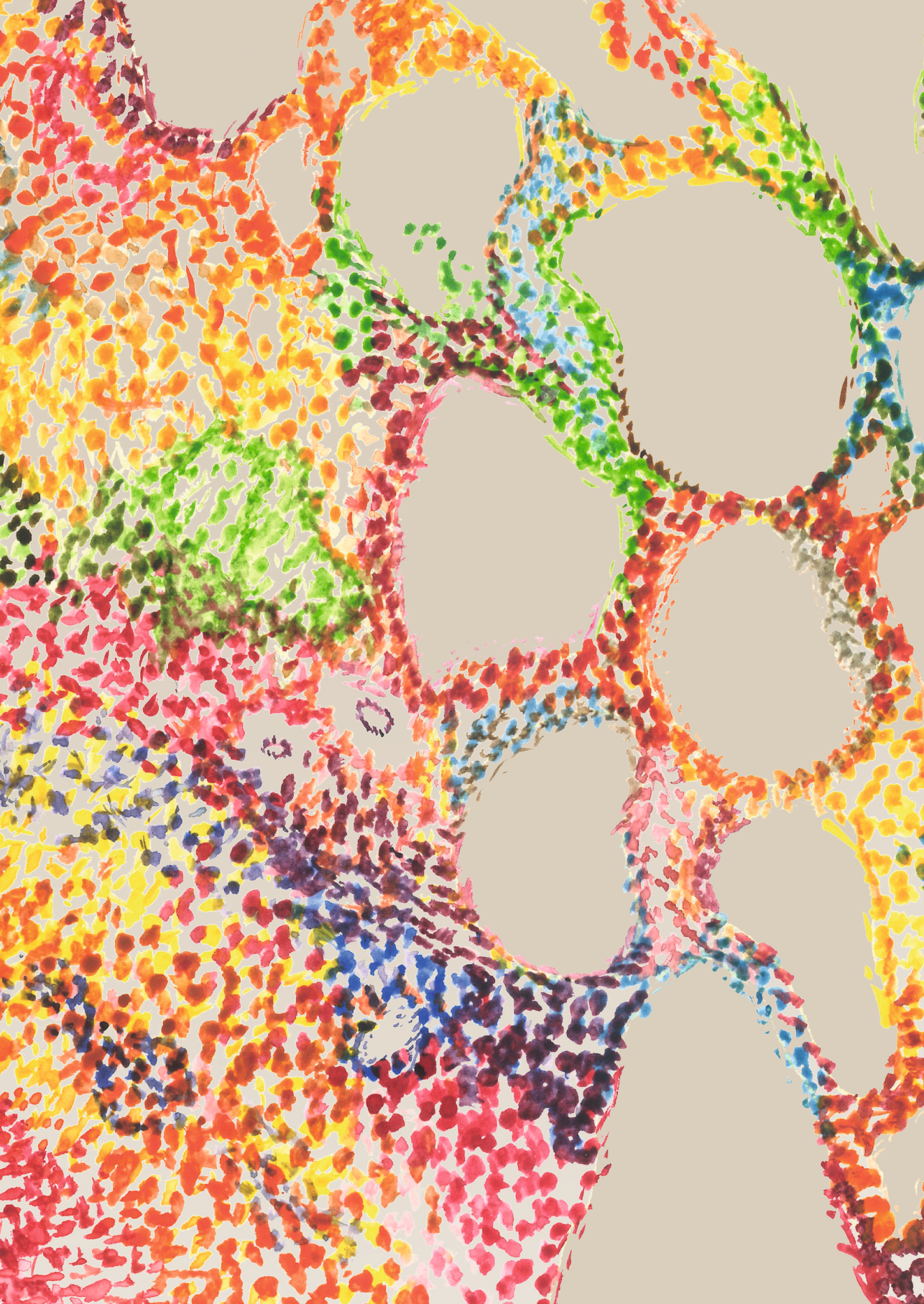

1 CHAPTER

Introduction and outline of the thesis

INTRODUCTION

The global incidence of thyroid cancer (TC) is increasing. In the Netherlands, the overall incidence of TC has significantly risen from 340 new cases in 1990 to 900 new cases in 2021 (1). This increase cannot be solely attributed to population growth and aging. The introduction and widespread use of advanced diagnostic techniques may contribute to the higher detection rates of TC (2). Exogenous factors such as radiation exposure, high iodine intake, Western lifestyle and environmental pollutants as well as endogenous factors like high thyroid-stimulating hormone (TSH) levels or obesity are potential etiological factors for TC (3).

Thyroid cancer can be classified into differentiated and undifferentiated histological subtypes including papillary (PTC), follicular (FTC), medullary (MTC) and anaplastic thyroid cancer (ATC) (4). The most common type is papillary thyroid cancer, accounting for 70-90% of well-differentiated thyroid malignancies (DTC) (5).

Thyroid cancer is the seventh most common malignancy in women and is 2.9 times more prevalent in women than in men (6). The rate of early detection of papillary thyroid cancer (tumor ≤ 2 cm) is more than four times higher in women than in men (7). In females, the incidence rate sharply rises at the beginning of the reproductive years, peaking at 40-49 years, while in men, the peak occurs at 60-69 years (6). Fluctuations in sex hormones during a woman's menstrual cycle have been associated with the risk of thyroid cancer, particularly in younger women (8). However, the evidence regarding the role of hormones and the influence of the menstrual or reproductive cycles in thyroid cancer in women remains inconclusive (6).

Primary staging and treatment

Primary staging and treatment of differentiated thyroid cancer (DTC) involve multiple staging systems, with the American Joint Committee on Cancer (AJCC) Tumor Node Metastasis (TNM) system being widely used. Patients over 55 years of age are upstaged using the AJCC staging system (9).

After detecting a thyroid nodule, ultrasound (US) imaging is used to determine the need for fine needle aspiration cytology (FNAC). The Thyroid Imaging Reporting and Data System (TIRADS) is used to assess the risk of malignancy for thyroid nodules on ultrasound imaging (10). The Bethesda System for Reporting Thyroid Cytopathology is the standard for interpreting FNAC specimens (11). The 2017 Bethesda system consists of six different categories: (I) non-diagnostic or unsatisfactory; (II) benign; (III) atypia of undetermined significance (AUS) or follicular lesion of undetermined significance

(FLUS); (IV) follicular neoplasm or suspicious for a follicular neoplasm; (V) suspicious for malignancy; and (VI) malignant. Despite the benefits of FNAC, some cytopathology reports describe “atypical” or “indeterminate” which are difficult to interpret and confuse management (11). Well-differentiated thyroid cancers, including PTC and FTC, have the best overall prognosis with appropriate treatment (12). The aim of the treatment is to improve the overall- and disease-specific survival and minimize treatment-related morbidity. Surgical resection plays a crucial role in the treatment of DTC with the initial procedure being thyroid lobectomy for tumors < 1 cm without extra thyroidal extension and metastatic lymph nodes. Total thyroidectomy is required for primary thyroid carcinoma > 1 cm with a neck dissection for regional or distant metastases (14). However, total thyroidectomy may not offer a survival benefit for tumors sized 1-4 cm, especially among young patients (15). Revised guidelines suggest that the initial surgical procedure can be either a total thyroidectomy or a hemithyroidectomy for thyroid cancer > 1 cm and < 4 cm with the goal of de-escalation (16). Postoperative treatment with radioactive iodine (RAI) is administered to some patients to minimize the risk of disease recurrence and metastases if all normal thyroid tissue is removed (17). The use of adjuvant neck/thyroid external radiation therapy in DTC patients remains controversial (18).

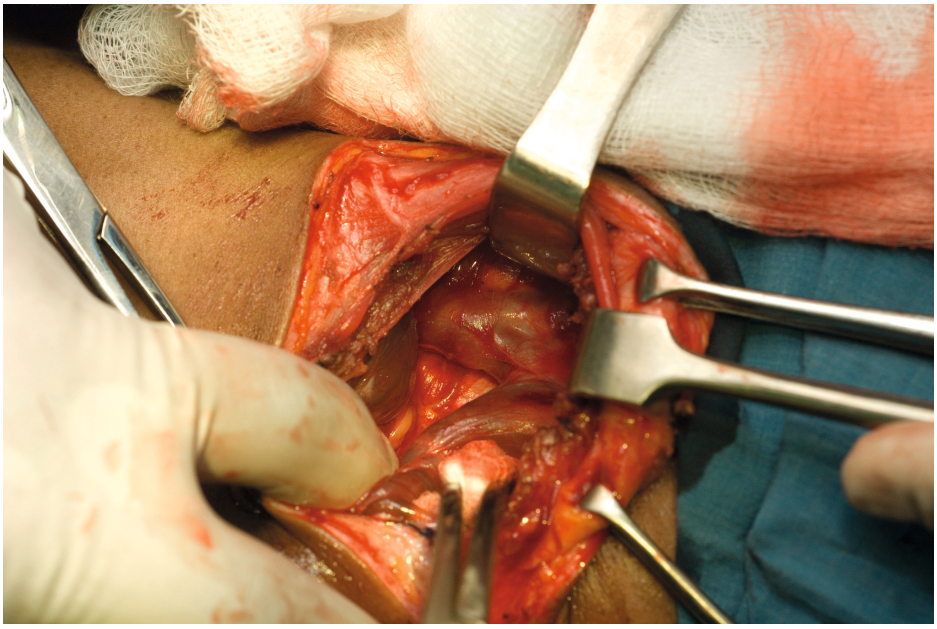

Figure 1 Thyroid surgery

Following initial treatment, the long-term objectives for differentiated thyroid cancer (DTC) patients are to maintain adequate thyroxine levels and detect possible recurrences. The follow-up of DTC patients involves combining neck ultrasound (US) imaging with serum thyroglobulin (Tg) checks for patients who underwent total thyroidectomy and radioactive iodine (RAI) and when necessary, a 131-Iodine total body scan after thyroid-stimulating hormone (TSH) stimulation (19). Surveillance of low-risk DTC patients can be discontinued after five years since the recurrence rates in this group are low (20). It seems reasonable to reduce the frequency of follow-up in patients with low-risk papillary thyroid carcinoma without vascular invasion after hemithyroidectomy (21). Patients at a higher risk of recurrence require long-term follow-up because recurrences have been reported several decades after initial therapy (22). The majority of DTC patients have a favorable prognosis with an overall 10-year survival rate ranging from 80% to 95% (23). In patients with papillary thyroid carcinoma (PTC), the disease-specific 5-year survival rate is generally above 97% (24). Survival rates strongly depend on the age at presentation with patients under 40 years having the most favorable prognosis (25). Larger DTC tumors (> 4 cm) have a relatively less favorable prognosis (26).

The revised DTC guidelines

The American Thyroid Association (ATA) Thyroid Nodules and Differentiated Thyroid Cancer guidelines were published in 2006 (27) and revised in 2009 (28). Due to the

substantial growth of literature in this field, the guidelines were updated in 2015 (16). The primary aim of the new ATA guidelines was to minimize potential harm from over-treatment in low-risk patients with regards to disease-specific mortality and morbidity, while appropriately treating those patients at higher risk. In other words, the objective was to avoid extensive treatment whenever possible and safe (de-escalation) and recommend it to patients who would clearly benefit from surgery and adjuvant treatment (possible escalation). Other organizations, such as the American Association of Clinical Endocrinologists, Associazione Medici Endocrinologi, European Thyroid Association, British Thyroid Association, Royal College of Physicians, and the National Comprehensive Cancer Network have also developed clinical practice guidelines (29-31). With the increasing incidence of incidentally detected small tumors, there has been a shift towards a thoughtful, evidence-based treatment de-escalation approach. The main goal is to improve risk stratification of well-differentiated thyroid cancers since not all detected diseases pose a threat to health or survival (32). This approach also allows patients to avoid extensive treatment while preserving their quality of life. An example of this new approach is the reduction in aggressive surgery for the treatment of low-risk patients (33, 34). Despite the clear shift towards a more conservative approach in the diagnosis and treatment of DTCs, controversies still exist in the field leading to variations in clinical practice across different geographic regions. The research presented in this thesis aims to provide clarification on the application of the topics covered in the DTC guidelines.

Incidental thyroid nodules

The rising incidence of thyroid cancer (TC) can be partially attributed to the widespread diagnosis of thyroid nodules in asymptomatic patients (35, 36). A thyroid incidentaloma refers to an unexpected, asymptomatic thyroid tumor discovered during the evaluation of an unrelated condition (37). The prevalence of occult thyroid nodules may vary between 20% and 76% in asymptomatic individuals (38-40). The increased detection of occult thyroid nodules is partly due to incidental findings on imaging studies (41). The prevalence rates of thyroid incidentalomas are 67% with ultrasound (US) imaging, 15% with computed tomography (CT) or magnetic resonance imaging (MRI) of the neck and 1-2% with 18F-fluoro-2-deoxyglucose positron emission tomography/computed tomography (^{18}F-FDG-PET/CT) scans (42). The uptake of the radioactive agent ^{18}F-FDG in the thyroid gland can be focal or diffuse. Focal ^{18}F-FDG uptake in the thyroid gland is incidentally detected in 1%-2% of patients, while an additional 2% of patients has diffuse thyroidal uptake (43, 44). Focal thyroidal ^{18}F-FDG uptake is associated with the highest risk of malignancy, ranging from 28% to 42% (45, 46). The radioactive agent prostate-specific membrane antigen (PSMA) has also been detected in the thyroid gland on PET/CT scans leading to PSMA PET/CT thyroid incidentalomas (47). Current clinical guidelines advocate for a more conservative management approach for thyroid nod-

ules as an alternative to fine-needle aspiration cytology (FNAC) in selected patients (16, 48, 49). The American Thyroid Association guidelines suggest performing FNAC in all thyroid nodules > 1 cm as they have a greater potential to develop clinically significant cancers (16). The Dutch guidelines suggest that patients with a thyroid incidentaloma on US, CT, or MRI should not undergo routine further diagnostic testing due to the low probability of thyroid cancer. However, additional evaluation with US and FNAC is recommended for patients with an ^{18}F-FDG-PET/CT thyroid incidentaloma, given the relatively high probability of malignancy, unless it is deemed clinically irrelevant due to the patient's comorbidities (16). The existence of various guidelines on this topic highlights the need for uniformity in the diagnosis, treatment and follow-up of thyroid nodules (50). Furthermore, guidelines may not always provide the best personalized treatment recommendations, especially for patients with a history of another cancer or significant comorbidities. Overdiagnosis is costly and may lead to potential iatrogenic harms by unnecessarily exposing patients to the burden associated with active management (51).

Differentiated thyroid cancer as (second) primary tumor

The long-term health perspective of this population becomes crucial as the population of cancer survivors continues to expand. Cancer survivors may face an increased risk of developing second or multiple primary cancers (52). The detection of a primary cancer followed by another primary cancer in a patient appears to have increased during recent decades (53). An European study demonstrated that thyroid cancer patients have an elevated risk of up to 27% for a second primary malignancy compared to the cancer rates in the general population (54). The most common second primary cancer among patients with papillary thyroid cancer is breast cancer (55, 56). One hypothesis is that the treatment given for thyroid cancer, such as radioactive iodine (RAI), may subsequently increase the risk of other types of cancer (56).

The risk of developing thyroid cancer as a second primary malignancy is elevated in both breast cancer patients and survivors of Hodgkin's disease (57, 58). Most patients treated for Hodgkin's disease undergo radiation therapy in the head/neck region, which is a known risk factor for the development of thyroid cancer (59). The increased rate of second primary thyroid malignancies may also be attributed to the ability to detect cancers in the preclinical stage during follow-up imaging of the primary cancer. However, a true increase in incidence is also possible as indicated by the observation that the occurrence of large tumors has also risen, while gender differences are present (3).

Adolescents and young adults

Adolescents and young adults (AYAs) present a unique set of clinical challenges in terms of treatment and management. AYAs are individuals between 15 and 39 years old and constitute a significant proportion of incident thyroid cancer cases (60). Thyroid cancer has been steadily increasing among AYAs since 1990, particularly in females (61). Managing thyroid cancer in AYAs poses challenges due to the unknown side effects of treatment in this specific age group. Their survival is often accompanied by difficulties such as physical impairments, concerns about recurrence, disruptions to life plans and uncertainty regarding employment and insurance (62). Radioactive iodine (RAI) therapy is commonly administered after total thyroidectomy to treat persistent or metastatic residual thyroid cancer and prevent disease recurrence (16). The proportion of AYAs with differentiated thyroid cancer receiving postoperative RAI therapy is higher compared to older patients (63). The disease-specific survival rate is approximately 98% for AYAs with thyroid cancer (64). This suggests that there is potential for treatment de-escalation. Therefore, it is important to consider the side effects of RAI, including gonadal dysfunction and the development of second primary malignancies. Radioactive iodine affects male fertility and the risk of persistent gonadal dysfunction increases with repeated or high cumulative RAI activities (65). Men receiving cumulative RAI activities ≥ 400 mCi should be counseled about the potential risks of infertility [Recommendation 90] (16). The effects of RAI on fertility in female AYA patients have been examined only in small retrospective studies but remain somewhat unclear.

AIMS AND OUTLINE OF THIS THESIS

The increasing incidence of differentiated thyroid cancer (DTC) and the favorable oncological outcomes have generated growing interest in de-escalating treatment strategies. The management of DTC has shifted from a "one size fits all" approach, which included total thyroidectomy, radioactive iodine therapy and thyroid-stimulating hormone (TSH) suppression to more personalized strategies. Advances in knowledge have enabled the de-escalation of thyroid surgery and radioactive iodine therapy in patients diagnosed with low-risk well-differentiated thyroid cancer. The evolving field of personalized cancer care involves identifying "at-risk" patients and applying individualized therapies. The favorable prognosis of DTC makes it challenging to determine diagnostic and therapeutic strategies due to the low incidence and the requirement for long-term follow-up. This thesis aims to enhance knowledge regarding the personalized management of DTC. Although extensive research has already been conducted, several challenges remain. The extent to which treatment and follow-up can be limited without increasing the risk of cancer-related death is demonstrated in selected cohorts. Risk stratification guided by refined data collection becomes a crucial step toward achieving the goal of personalized DTC management. The findings of this thesis can be used to implement guideline recommendations in daily clinical practice.

This thesis is divided into two parts. **Part I** focuses on evaluating the optimization of care for incidentally discovered thyroid nodules through imaging techniques in oncological patients. In **Chapter 2**, we explore the organization of care for ^{18}F-FDG-PET/CT thyroid incidentaloma in a tertiary oncological referral hospital. The incidence, treatment and outcomes of these patients are analyzed. In **Chapter 3**, we investigate the use of radiomics analysis for classifying the malignancy risk of thyroid incidentalomas based on ^{18}F-FDG-PET/CT scans. In **Chapter 4**, we examine the organization of care for PSMA PET thyroid incidentaloma and analyze the incidence, treatment and outcomes in both a tertiary oncological referral hospital and an academic hospital. Additionally, in **Chapter 5**, we assess how the incidence of PSMA PET thyroid incidentaloma depends on the analysis method and tracer used.

Part II focuses on optimizing care in the treatment of thyroid cancer. In **Chapter 6**, we investigate the association between differentiated thyroid cancer and breast cancer in the Netherlands. In **Chapter 7**, we examine the risk of differentiated thyroid cancer in adolescents and young adults treated for Hodgkin's disease in the Netherlands. Adolescents and Young Adults often receive adjuvant radioactive iodine therapy. In **Chapter 8**, we investigate the effect of radioactive iodine therapy on ovarian function and fertility in female thyroid cancer patients.

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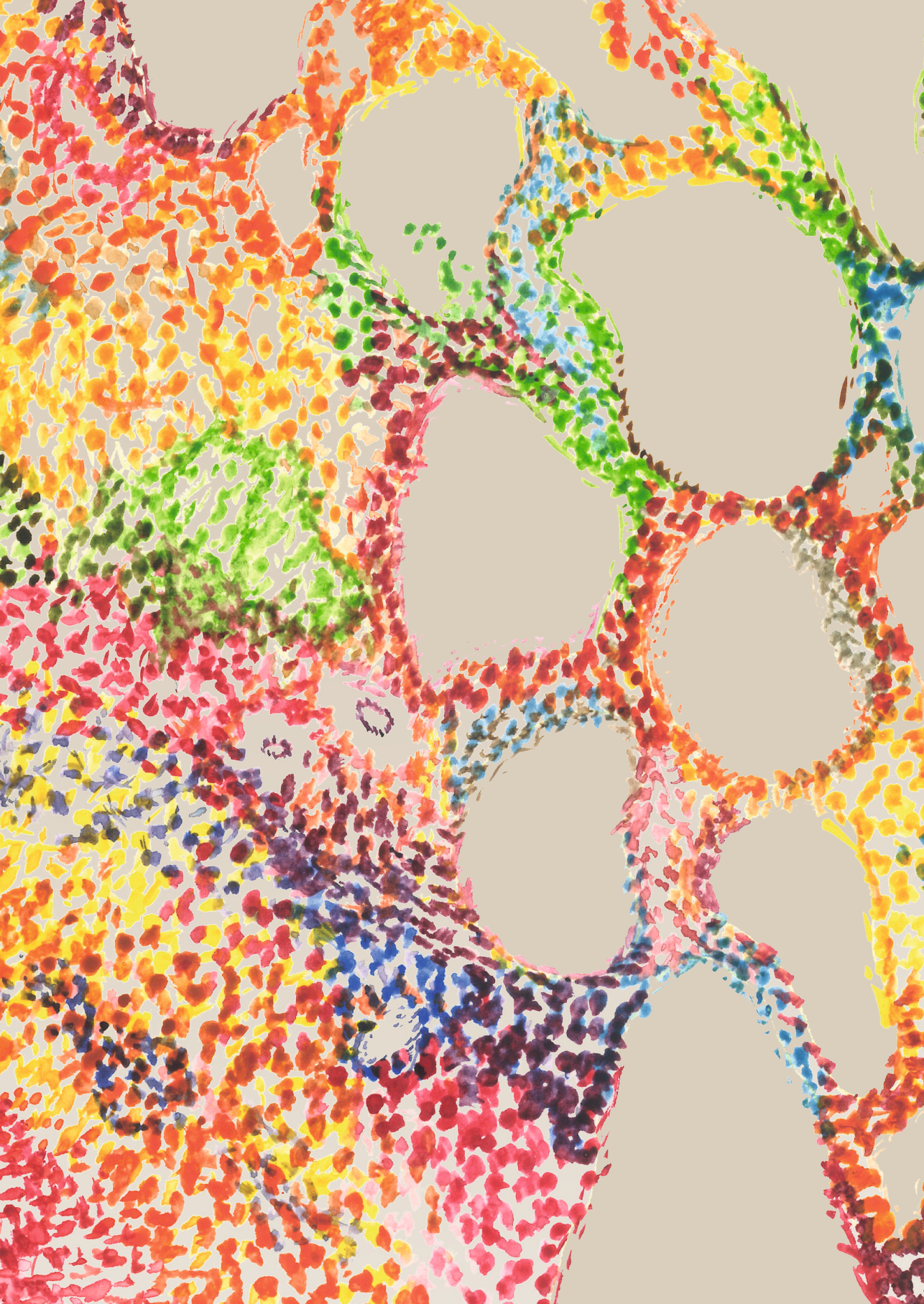
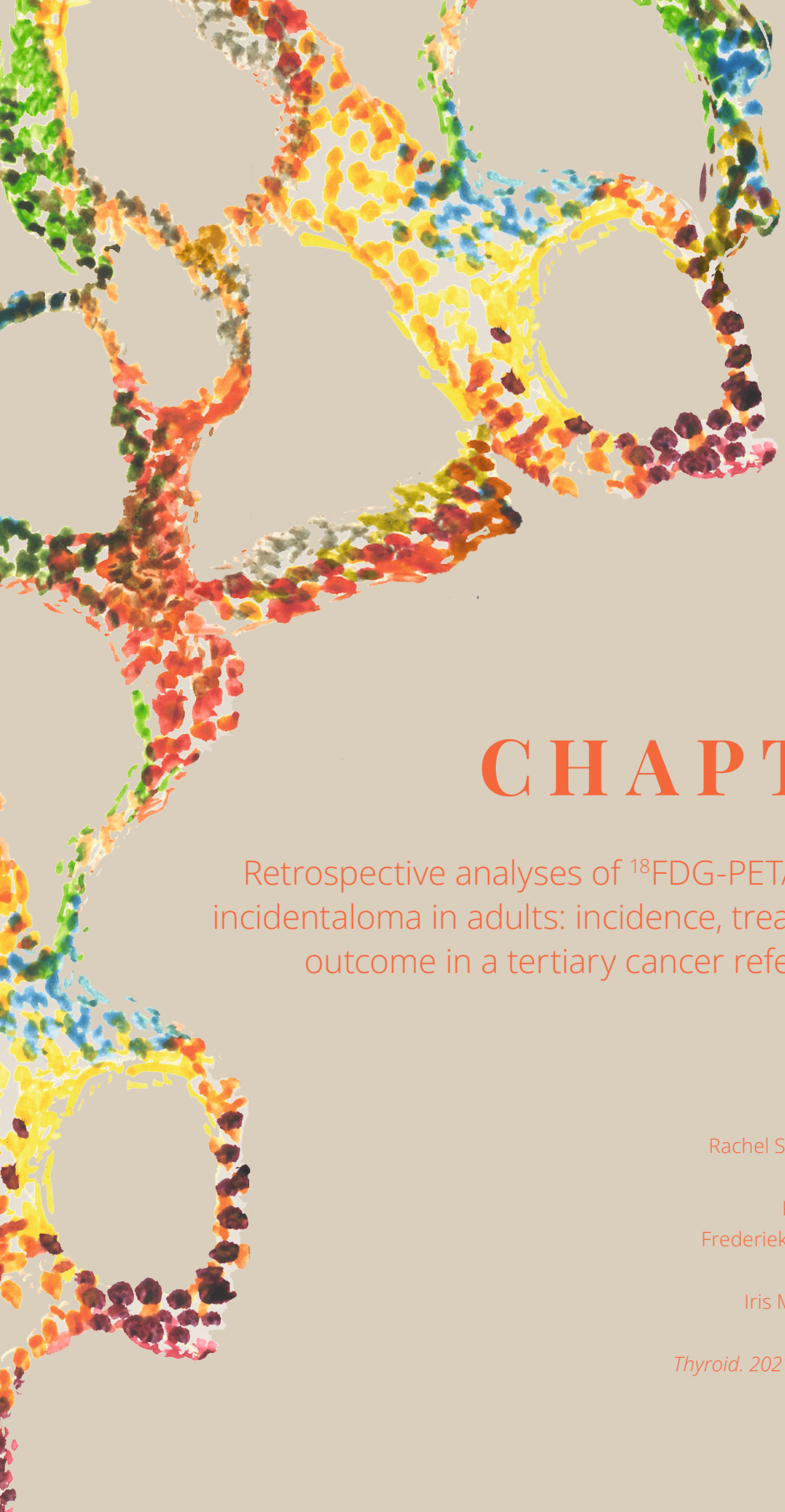
PART I

The optimization of care of thyroid nodules incidentally discovered by imaging techniques in oncological patients





2 CHAPTER

Retrospective analyses of ^{18}FDG-PET/CT thyroid incidentaloma in adults: incidence, treatment and outcome in a tertiary cancer referral center

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ABSTRACT

A thyroid incidentaloma (TI) is an unexpected, asymptomatic thyroid tumor discovered during the investigation of an unrelated condition. The aim of the present study is to examine the incidence of 18Fluorodeoxyglucose (^{18}FDG)-positron emission tomography (PET) TI, the associated management strategies and the outcomes in a tertiary cancer referral center. This study involves a retrospective cohort study of 1003 patients with TI found on ^{18}FDG-PET/CT scans performed between January 2010 and January 2020. All patients were diagnosed with a non-thyroid malignancy. The Kaplan-Meier method was used for survival analyses in patients concerning an underlying malignancy, with a prevalence of 5% or higher in this cohort. Logistic- and cox regression analyses were performed to analyze predictors of thyroid malignancy and mortality. A propensity score weighted method was used to control for baseline differences between the intervention (additional TI diagnostics) and control (no TI diagnostics) group. FDG-positive TI occurred in 1.9% (1003/52693) of the oncologic ^{18}FDG-PET/CT scans performed in our center. Thyroid surgery was performed in 47 patients (6%) and a thyroid malignancy was detected in 31 of them, which is 66% of those who had an operation and 4% of all patients. During the follow-up (median 6 years), 334 deaths (42%) related to different types of cancer (38%) or other causes (4%) were observed. One patient died from medullary thyroid cancer. In multivariate analysis adjusted for age, gender and the type- and stage of nonthyroidal malignancy, were independent predictors of survival ($p < .05$). The incidence of TI in this tertiary cancer referral center was comparable to current literature. Further thyroid work-up was performed in less than half of the patients and only a minority of patients underwent thyroid surgery. Since only one patient died from thyroid cancer, the strategy to withhold from thyroid diagnostics and treatment seems valid for most TI. Active thyroid treatment might benefit a subgroup of patients in whom the primary non-thyroid malignancy is successfully treated or presumably stable. A wait-and-see policy with ultrasound follow-up could be an alternative strategy. These considerations should be part of the shared decision making in cancer patients with a TI.

INTRODUCTION

^{18}Fluorodeoxyglucose (^{18}FDG)-Positron Emission Tomography / Computed Tomography (PET/CT) is a widely used imaging tool in the work-up for tailored treatment of several types of cancer. The increased use of ^{18}FDG-PET/CT scans leads to more incidental findings, so called incidentalomas. These additional findings are often depicted in the colon, thyroid gland and ovaries (1,2). ^{18}FDG-PET thyroid incidentalomas (TIs) are defined as unexpected thyroid lesions on ^{18}FDG-PET/CT scans, made for non-thyroid diseases. Data from previous studies show that the prevalence of TI detected by ^{18}FDG-PET/CT scans ranged from 0.1 to 4.3% (3-6). The FDG-uptake pattern in the thyroid can be divided in a limited enhancement (focal) or a more diffuse uptake. Focal hypermetabolic TIs are at higher risk for malignancy (up to 30%) when compared to diffuse thyroid uptake (3-8). Most malignant TI comprise of differentiated thyroid cancer (DTC) (9). The increase in number of ^{18}FDG-PET/CT scans might be a contributing factor to the worldwide ongoing growing detection rate of DTC (10).

There is yet much to learn about the clinical relevance of TI in patients with underlying malignancies. The 2015 American Thyroid Association (ATA) guideline recommends investigation of thyroid nodules 1 cm or larger with ultrasound with or without fine-needle aspiration cytology (FNAC) in patients without relevant comorbidities (11, 12). The predominant indication for a ^{18}FDG-PET/CT scan in cancer patients is staging of the primary malignancy. Therefore, this specific population has relevant comorbidities influencing prognosis. The strategy to actively pursue all TI of 1 cm and above in this population may lead to overtreatment of thyroid nodules that might never become clinically relevant. Moreover, DTC is associated with an estimated survival of 95-98% (13). The clinical impact of an asymptomatic thyroid malignancy in the context of an active nonthyroidal malignancy is unknown and there is a need for guidelines in the management of TI in cancer patients. The aim of the present study was to examine the incidence of ^{18}FDG-PET TI in a tertiary cancer referral center over a 10-year period of time. We also describe the different treatment strategies and the results of these different approaches in ^{18}FDG-PET TIs patients with a nonthyroid primary cancer. This study also aimed at identifying predictors of thyroid malignancy and at analyzing survival for cancer patients with a ^{18}FDG-PET TI.

METHODS

This study is approved by the Institutional Review Board (IRB) from the Antoni van Leeuwenhoek Hospital (AvL), a tertiary oncological referral hospital in Amsterdam, The Netherlands (IRBd19178). It involves a retrospective cohort study of ^{18}FDG-PET/CT scans that were performed in this cancer center between January 2010 and January 2020. The ^{18}FDG-PET/CT scans were performed in the AvL hospital for diagnosis, staging or treatment response measurement for a known or suspected (non-thyroidal) malignancy according to the European Association of Nuclear Medicine (EANM)-guidelines for ^{18}FDG-PET/CT scans (14). The decision to perform ultrasound and FNAC was dependent upon the physician's preference and the patient's risk factors for thyroid cancer, anxiety, comorbidities, life expectancy and other relevant considerations. The ATA guidelines to refrain from FNAC in thyroid nodules <1 cm unless there was cervical lymphadenopathy or another finding associated with a higher cancer risk was used and since 2017 the The Thyroid Imaging Reporting and Data System (TIRADS) was used (15). The TI sizes in the ultrasound examination reports were re-evaluated by a specialized radiologist (C. Lange).

The FNAC results were analyzed by dedicated pathologists based on the Bethesda System for Thyroid Cytopathology (16). Clinical and pathological staging was reported according to the TNM classification criteria by the American Joint Committee on Cancer (AJCC). The reports from the Department of Nuclear Medicine were selected anonymously and retrospectively by screening for the word "thyroid". The reports were than manually screened by author M.W.P. to verify the presence of FDG uptake in the thyroid gland. Patients with known thyroid cancer or thyroid disease and non-avid thyroid nodules were excluded. All patients with focal- or diffuse FDG uptake in the thyroid gland primarily depicted by ^{18}FDG-PET/CT scans were included in this study. We retrospectively reviewed medical records of the included patients and collected the primary malignancy type and stage, FDG avidity, extent of thyroid investigation, treatment and follow-up.

Statistical analysis

Baseline values of continuous variables are reported as mean ± standard deviation or median with interquartile range (IQR, 25th-75th percentile) and baseline categorical variables were presented as frequencies and percentages. Differences between the two groups were tested with the Pearson's chi-square test. All statistical tests were two-tailed, and a value of $p \leq 0.05$ was considered statistically significant.

In univariate analysis, individual variables and their association with TI final pathology results were analyzed by using adjusted odds ratios. Multivariate Cox regression models or patients survival were created based on the variables assessed in the univariate analysis, with stepwise removal of factors with a p-value < 0.01. A p-value of 0.05 was taken to indicate statistical significance.

The Kaplan-Meier method was used to estimate overall survival (OS). The OS was measured from the date of the ^{18}FDG-avid TI to the date of death from any cause, censoring patients who were still alive at the date of last contact. The main diagnoses that occurred ≥ 5% in this cohort (breast cancer, lung cancer, melanoma, colon cancer, head- and neck cancer and urothelial cancer) were included in the analysis to increase the strength of the association. The OS was compared across the aforementioned groups using the log-rank test.

Propensity score weighting was used to control for the baseline differences between the treatment groups to compare cancer-related mortality. This analysis was performed post hoc. Two groups were created: patients who underwent additional diagnostics for TI (intervention) versus patients who had no TI diagnostics (control). Additional diagnostics consisted of an ultrasound and FNAC. The included patients had focal FDG uptake on ^{18}FDG-PET/CT. The propensity score was calculated using logistic regression. Baseline covariates which differed between the intervention- and control group were included in the analysis: age, the stage and type of primary non-thyroidal malignancy that occurred ≥ 5% in this cohort of patients. The occurrence of a local-, regional- or distant recurrence or a second primary tumor during follow-up were also included in the analysis because this affected the performance of TI diagnostic tests. Patients with missing data were excluded from this analysis. Propensity weights were then calculated using the propensity scores. To allow weighted estimates, each intervention patient received a weight of $\frac{1}{\mathrm{ps}}$ and each control patient received a weight of $\frac{1}{1-ps}$, where ps is the propensity score. Propensity scores were then utilized for inverse propensity score weighted adjustment in the final cox proportional hazards model (17). Analyses were performed in SPSS (version 25.0) and R (version 4.0.3).

RESULTS

Patient selection

Between 2010 and 2020, a total of '52.693' ^{18}FDG-PET/CT scans were performed in this center of which 3928 (7.5%) nuclear medicine scan reports included the word "thyroid". After exclusion of duplicates and triplicates, 1424 patients (2.7%) with increased uptake of ^{18}F-FDG in the thyroid gland were found. Based on the exclusion criteria for this report, we excluded 421 patients and included 1003 (1.9%) patients in this study, that is, FDG-positive TI occurred in 1.9% (1003/52693) of oncologic ^{18}FDG-PET/CT scans that were performed in this cancer center. The process for patient selection is presented in **Figure 1**.

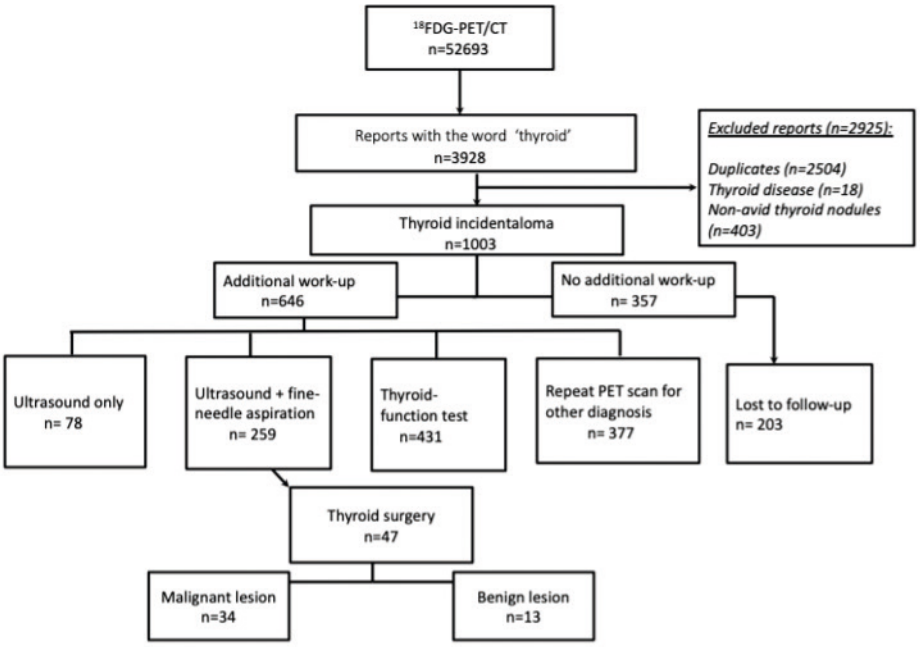

Figure 1 Flowchart of patient-selection.

^{18}FDG-PET/CT TI investigation and treatment

Two-hundred and three patients (20%) were referred to our center for PET imaging only and were subsequently treated in a different hospital. We included these patients in the initial work-up concerning PET/CT and laboratory data (N= 1003) but excluded them from the thyroid management analysis (N= 800). Baseline characteristics are described in **Table 1.**

Table 1 Clinical characteristics and [18]FDG-PET/CT data.

Variable	N = 1003 (%)
Women	723 (72%)
Age years, mean (±SD)	67 (±13.1)
Men	281 (28%)
Age years, mean (±SD)	73 (±11.6)
Indication for FDG-PET	
Breast cancer	239 (24%)
Non-small cell lung cancer	157 (16%)
Melanoma	130 (13%)
Colon cancer	77 (8%)
Head-neck cancer	57 (6%)
Urothelial cancer	49 (5%)
Other primary cancer diagnoses	294 (<5%)
Lymphoma, anal, gynecological, esophageal, gastric, prostate and skin cancer, sarcoma, NET tumor	*1-5%*
Penile, brain, thymoma, hematological, cholangio and pancreatic cancer, GIST tumor, Schwannoma	*<1%*
FDG thyroid uptake	
Focal	626 (62%)
Diffuse	377 (38%)
SUV_{max} (%ID/g)	
Median (IQR)	5.1 (3.7-7.2)
Distribution FDG-uptake	
Right lobe	299 (30%)
Left lobe	271 (27%)
Isthmus	27 (3%)
Both lobes	298 (30%)
Not described	108 (11%)
Suspected lymph nodes	61 ((6%)
Level I	9 (0.9%)
Level II	25 (3%)
Level III	13 (1%)
Level IV	4 (0.4%)
Level VI	3 (0.3%)
Mediastinal	7 (0.7%)
Thyroid function test results	431 (43%)
Euthyroid	303 (30%)
Hypothyroid	5 (0.5%)
Subclinical hypothyroid	96 (10%)
Subclinical hyperthyroid	27 (3%)

Of 800 patients that were treated in our center, subsequent evaluation by ultrasound was performed in 337 (42%) patients (**Table 2**). FNAC was done in 259 (77%) of the 337 patients who underwent ultrasound. In this study population, 47 patients (6%) received surgery, most frequently (75%) a hemithyroidectomy. The median age of the patients who had an operation was 65.6 (55.8-73.8) years and the median tumor dimension of the TI was 1.25 (0.8-2.3) cm. The final pathology report showed a thyroid malignancy in 31 patients, which is 67% of those who had an operation and 4% of all patients who were treated for a nonthyroid primary cancer in our hospital. In **Figure 2**, the final pathology results are shown per Bethesda classification. The predictive factors analyzed for the final pathology results are shown in **Table 3** (N=47 patients). Univariable analysis showed that none of these independent covariates were statistically significant predictors of TI being malignant on pathology.

Table 2 Thyroid incidentalomas investigation and treatment.

Variable	***N = 800*** ***Number of patients (%)***
Number of ultrasounds	
US size thyroid nodule (cm) *	
< 0.5	337 (42%)
<1	12 (4%)
1-2	64 (19%)
2-3	135 (40%)
3-4	54 (16%)
> 4	22 (7%)
Size not mentioned	10 (3%)
US distribution thyroid nodule*	40 (12%)
Right lobe	110 (33%)
Left lobe	117 (35%)
Isthmus	18 (5%)
Both lobes	52 (15%)
Suspected lymph nodes*	45 (13%)
Level I	4 (1%)
Level II	21 (6%)
Level III	11 (3%)
Level IV	5 (1%)
Level V	1 (0.3%)
Level VI	2 (0.6%)

Table 2 Continued

Variable	*N = 800* *Number of patients (%)*
Cytology thyroid incidentalomas	
Number of punctures	259 (32%)
1	183 (71%)
2	49 (19%)
3	17 (7%)
> 4	10 (4%)
BETHESDA classification**	
Category I	46 (19%)
Category II	135 (52%)
Category III	12 (5%)
Category IV	11 (4%)
Category V	17 (7%)
Category VI	38 (15%)
Thyroid surgery***	48 (6%)
Hemithyroidectomy	36 (75%)
Total thyroidectomy	8 (17%)
Isthmus resection	2 (4%)
Parathyroidectomy	1 (2%)
Surgery planned	1 (2%)
Neck dissection****	4 (0.4%)
Modified radical neck dissection	2 (50%)
Lateral neck dissection (levels II-V)	2 (50%)
PA thyroid surgery***	
Papillary thyroid carcinoma	26 (54%)
Follicular thyroid carcinoma	4 (8%)
Medullary thyroid carcinoma	1 (2%)
Metastasis different cancer	3 (6%)
Thyroid adenoma	8 (17%)
Thyroiditis	1 (2%)
Parathyroid adenoma	1 (2%)
Hurtle cell metaplasia	3 (6%)
PA neck dissection****	
Metastasis thyroid cancer	2 (50%)
Metastasis different cancer (melanoma)	1 (25%)
Non-malignant	1 (25%)

US= ultrasound, * = Percentage of patients who underwent ultrasound, ** Percentage of patients who underwent FNAC, *** Percentage of patients who underwent thyroid surgery, **** Percentage of patient who underwent a neck dissection

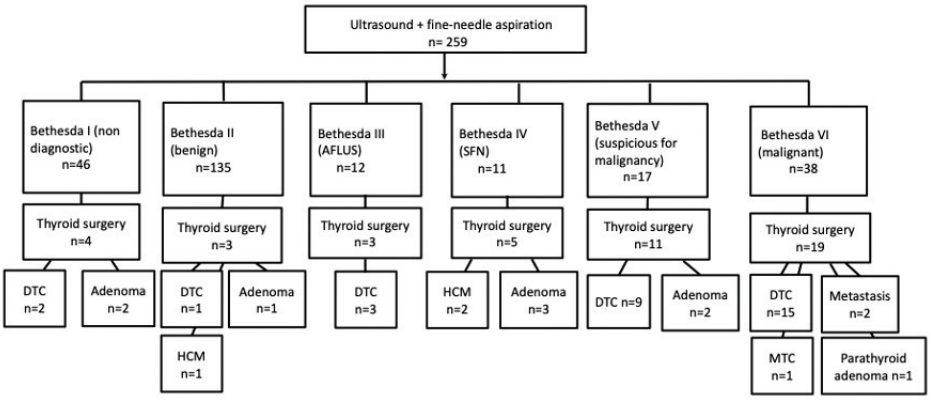

Figure 2 Flowchart of pathology results after thyroid surgery stratified by Bethesda classification. AFLUS, atypical follicular lesion of undetermined significance; DTC, differentiated thyroid carcinoma, HCM, hurtle cell metaplasia, MTC, medullary thyroid carcinoma; SFN, suspicious for follicular neoplasm.

Table 3 Results of univariable logistic regression model to predict thyroid malignancy (n=47).

Predictor	Coefficient (β)	AOR (95% CI)	*p-value*
Age (yrs)	0.036	1.04 (0.98-1.09)	0.18
Male gender	0.33	1.39 (0.31-6.14)	0.67
Tumor size TI (cm)	0.36	1.43 (0.85-2.39)	0.18
Thyroid function			
Subclinical hyperthyroid		1.0 (Ref)	
Subclinical hypothyroid	-0.14	0.87 (0.46-1.64)	0.67
Euthyroid	1.051	2.89 (0.16-5.13)	0.47
SUV_{max}	0.03	1.03 (0.89-4.17)	0.71
FDG uptake			
Focal uptake		1.0 (Ref)	
Diffuse uptake	-1.11	0.33 (0.09-1.11)	0.07

AOR = adjusted odds ratio; TI = thyroid incidentaloma

Follow-up and survival

The median follow-up was 6 years (range 4-8 years). During follow-up, 21% of patients received treatment for recurrent disease of their primary cancer diagnosis, 13% of patients for a secondary non-thyroid type of cancer and 24% of the study patients had no cancer-related event after the TI finding. After the total follow-up period, 334 patients (42%) had died. In 300 patients (38%), the cause of death was related to their primary cancer and in 33 patients (4%) to a non-cancer related event. One patient, who had the PET scan to identify a neuroendocrine tumor, had a medullary thyroid carcinoma and died of this 21 months after diagnosis. Kaplan Meier analyses showed significant differences in OS between different subgroups categorized by the nonthyroid primary cancer (log-rank $p < 0.0005$) (**Figure 3**). Patients with lung cancer and urothelial cancer had the lowest OS (median survival time: 35 months) followed by patients with colon cancer (median survival time: 42 months). Five-year survival rates in these groups (lung-, urothelial- and colon cancer) were lowest at 31.1%, 33.2% and 36.6% respectively. Patients with breast cancer had the most favorable prognosis with a 5-year survival rate of 72.3%.

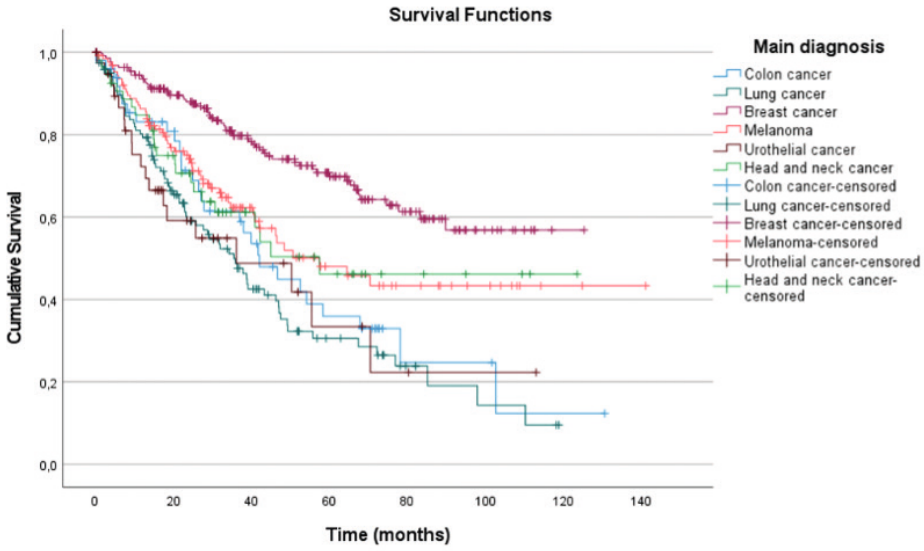

Figure 3 Kaplan-Meier analysis of OS comparing different subgroups based on the main cancer diagnosis with a study prevalence of ≥5% of the patient cohort (*n* = 606). Patients were censored due to loss to follow-up. OS, overall survival.

Univariate and multivariate Cox regression analyses were used to examine the relationship between patient survival and multiple prognostic variables. TI characteristics (Bethesda classification, tumor dimension, and final pathology results) were not predictive for patient survival in univariate analysis. The following predictive factors for patient survival were included in a multivariate analysis (**Table 4**): age, male sex, the AJCC stage and the type of nonthyroidal primary malignancy (≥ 5% of the patient cohort), distant metastases of the primary tumor, and a second primary nonthyroidal tumor during follow-up. In multivariate analysis, these factors remained important determinants of survival.

Table 4 Results of multivariable cox regression model to predict mortality (n=800).

Predictor	Coefficient (β)	HR (95% CI)	*p-value*
Age (yrs)	0.02	1.02 (1.01-1.03)	< 0.001
Male gender	0.73	2.08 (1.67-2.59)	< 0.001
Main diagnosis	-0.10	0.90 (0.84-0.97)	< 0.005
AJCC stage main diagnosis	0.31	1.46 (1.26-1.68)	< 0.001
Distant recurrence[a]	1.21	3.35 (2.59-4.32)	<0.001
Second primary non-thyroidal tumor	0.48	1.61 (1.09-2.39)	0.01

AJCC; American Joint Committee on Cancer; CI, confidence interval, HR, hazard ratio
a Recurrence of the primary non-thyroidal malignancy

Comparison of TI treatment strategy groups

In the studied patient cohort, there appear to be substantial differences in the patients who underwent subsequent ultrasound imaging and FNAC of the ^{18}FDG-PET TI (intervention group) compared with those who did not (control group). Therefore, a propensity score analysis was performed to balance prognostic variables and compare patient survival between these two groups. A total of 539 patients were included in the propensity score analysis, and 464 patients were excluded due to missing data in any of the covariates. The baseline characteristics of the propensity-weighted population in the intervention and control group are displayed in **Table 5**. It shows significant differences in the distributions of age, main diagnosis and AJCC stage ($p \leq 0.05$). The nonthyroidal primary malignancies with a worse prognosis (**Figure 3**) were predominant in the control group.

Before the propensity score weighting, there was a significant patient survival advantage in the TI intervention group compared with the control group (unadjusted hazard ratio [HR] 0.57; confidence interval [95% CI 0.42-0.78], $p < 0.001$). When comparisons of the patient survival among the intervention and control group were made wit the PSW adjustment, there was no significant difference between the two groups (adjusted HR, 0.77 [95% CI 0.56-1.07], $p = 0.13$).

Table 5 Patient characteristics of propensity weighted population (n=539).

	Intervention (n=169) (%)	**Control (n=370) (%)**	***p-value***
Demographics			
Age years, mean (±SD)	67 ±12.9	64.4±13.2	0.03
Female gender	129 (76)	283 (76)	0.97
Main diagnoses (≥ 5%)			0.01
Colon cancer	9 (5)	30 (8)	
Non-small cell lung cancer	15 (9)	89 (24)	
Breast cancer	77 (45)	128 (35)	
Melanoma	39 (23)	74 (20)	
Urothelial cancer	10 (6)	26 (7)	
Head-neck cancer	19 (11)	23 (6)	
AJCC stage *			0.05
Stage 1	20 (12)	49 (13)	
Stage 2	60 (36)	91 (25)	
Stage 3	52 (31)	120 (32)	
Stage 4	37 (22)	110 (30)	

* AJCC stage of the non-thyroidal primary malignancy

DISCUSSION

This study shows that TIs were found in 1.9% of the ^{18}FDG-PET/CT scans that were done in this tertiary cancer referral center from 2010 to 2020. In total, 42% of the patients with known follow-up data (n=800) underwent additional ultrasound and 32% of the patients also underwent FNAC. Our study population showed no significant predictors for TI cytology- and final pathology results. In 47 patients (6%), thyroid surgery was performed. The majority of the patients who had an operation (66%) had a histologically proven thyroid cancer. Our study population showed no significant predictors for TI malignant pathology results. In 38% of the analyzed patients, the cause of death was related to their non-thyroid primary cancer, in 4% to a non-cancer related event and one patient (0.1%) died from medullary thyroid cancer. The primary nonthyroidal malignancies were predictive for patient survival and differed between the TI treatment groups. These factors were corrected for by propensity-weighted analysis, which resulted in no significant difference in patient survival between the TI intervention and control groups.

The incidence of ^{18}FDG-PET/CT TIs in literature (2-3%) is comparable to the current study result (1.9%) (18, 19). The FNAC analyses showed a Bethesda V or VI classification in 21% of the patients subjected to an ultrasound and biopsy, which is lower compared to previous studies (26%-50%) (20). The under-investigation may have led to a lower malignancy rate compared to other populations described in literature. The most frequent malignant histological subtype was papillary thyroid carcinoma (53%), which is comparable to previous studies (21-24). The incidence of TI increases in western countries and has been described in a number of previous studies analyzing different diagnostic modalities. The current literature revealed four systematic reviews concerning ^{18}FDG-PET TI (21-24). Most of the reviewed studies were retrospective in nature and included a small number of patients with TIs. Two reviews concluded that focal hypermetabolic thyroid nodules were associated with a higher prevalence of malignancy (21,22). The general advice extracted from available literature is that healthcare insitutions should make their own TI management strategies with the aim to avoid unnecessary investigations and surgery (23,24).

In our center, different types of management strategies were applied. The prognosis of most patients was dependent upon the underlying malignancy type. Pattison et al. focused on the clinical relevance of investigating ^{18}FDG-avid TI in cancer patients. They emphasized the perspective of a broader clinical context prior to investigation of ^{18}FDG-avid TIs (25). The amount of FDG-uptake in the index malignancy and the disease stage of the primary non-thyroid malignancy were all statistically significant predictors of mortality (25). These results are consistent with our study observations, although the

amount of FDG-uptake in the index malignancy was not verified. The overall mortality in patients with ^{18}FDG-avid TI undergoing ^{18}FDG-PET/CT in this tertiary cancer referral center was relatively high (42%). This is probably due to the fact that the study was performed in a tertiary oncology referral center. In 38% of the analyzed patients, the cause of death was related to their non-thyroid primary cancer, in 4% to a non-cancer related event and one patient (0.1%) died from medullary thyroid cancer. Stratification for type of primary non-thyroidal malignancy showed a poor prognosis for lung, urothelial and colon cancer patients whereas breast cancer patients had a favorable survival outcome. The nonthyroidal primary malignancies with an unfavorable prognosis were predominant in the control group. This strongly suggests that physicians in our cancer center select their patients for further ^{18}FDG-avid TI diagnostic work-up and possible treatment based on the expected survival of their main oncological diagnosis. The propensity-weighted analysis implies that the decision to not perform additional TI diagnostic tests does not harm patient survival and is a safe strategy in our patient population.

Strengths and limitations

The strengths of this study include the comprehensive assessment of the relevance of performing TI diagnostics in cancer patients. Further, the large size of 800 patients and long duration of follow-up add to the validity of this study. A limitation of this study is the retrospective nature and the exclusion of 20% of the patients due to lack of follow-up data. However, the retrospective nature of the study did enable us to have a long follow-up period of a rare pathology. The post hoc analyses should be considered hypothesis-generating and require independent validation. Another limitation is that the decision to perform further investigation of a TI was made by the physician responsible for the primary nonthyroid cancer care. This also led to a lack of ultrasound evaluation in a large proportion of patients. The group of patients without additional ultrasound investigation is likely to harbor possible thyroid malignancies, but follow-up data show that these possible missed malignancies did not become clinically relevant. Furthermore, a minority of patients underwent thyroid surgery and therefore had a final histological diagnosis available. Although FNAC has a high sensitivity, it is possible hat malignancies were missed (26).

CONCLUSION

In conclusion, the incidence of TI in this tertiary cancer referral center was comparable to current literature. Further thyroid diagnostic analyses was performed in less than half of the patients and only a minority of patients underwent thyroid surgery. Our current study did not identify relevant clinical predictors to select cancer patients with an ^{18}FDG-avid TI for further diagnostic work-up or surgery other than the type of the primary non-thyroidal malignancy and its associated survival. Since only one patient died from thyroid cancer, the strategy to withhold from thyroid diagnostic workup and treatment seems valid for a large group of patients with a ^{18}FDG-avid TI and a nonthyroid cancer diagnosis. In the presence of a treatable underlying malignancy, a full diagnostic workup according to the recent ATA guidelines and, if indicated, followed by surgery can be discussed in these patients (27). Thus, actively pursuing a TI might benefit a subgroup of patients in whom the primary non-thyroid malignancy or disease is successfully treated or presumably stable. A wait-and-see policy with ultrasound follow-up could be an alternative strategy. These considerations should be part of the shared decision making in cancer patients with a TI.

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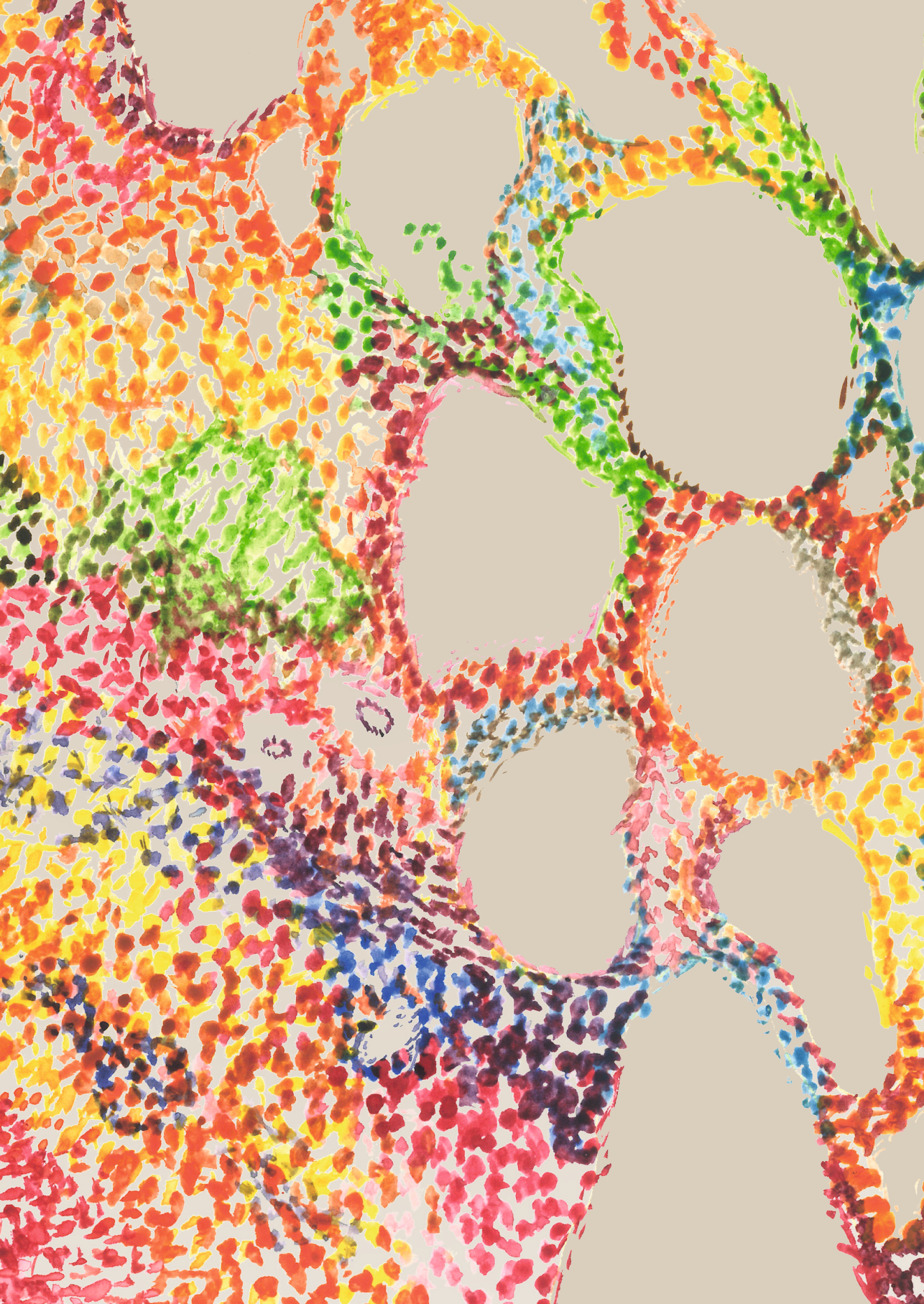

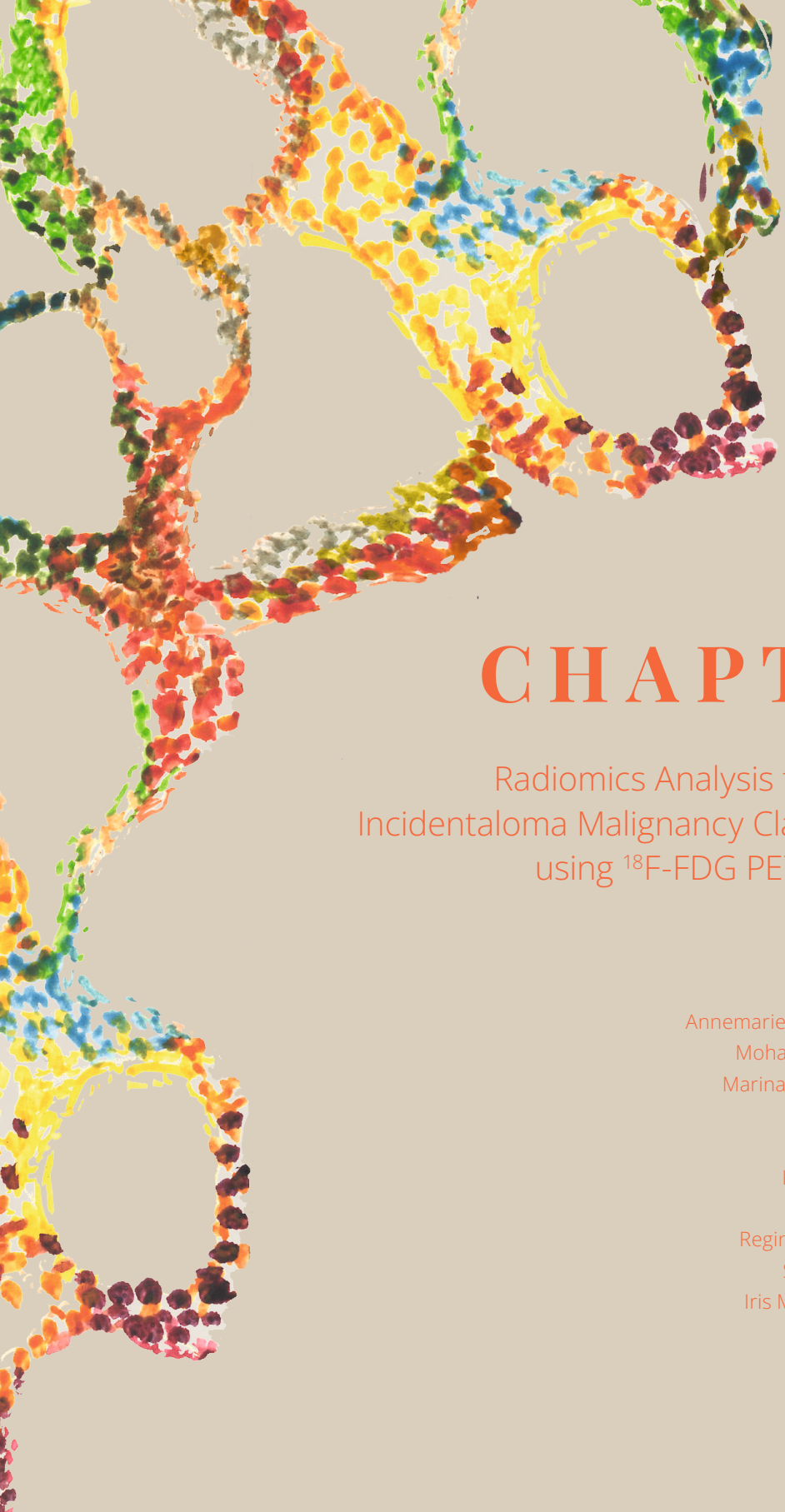

3 CHAPTER

Radiomics Analysis for Thyroid Incidentaloma Malignancy Classification using ^{18}F-FDG PET/CT Scans

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ABSTRACT

Thyroid incidentalomas (TIs) are thyroid lesions incidentally detected on fluorodeoxy-D-glucose (^{18}F-FDG) positron emission tomography/computed tomography (PET/CT) scans performed for other purposes. This study aims to investigate the role of non-invasive PET/CT-derived radiomic features in characterizing ^{18}F-FDG PET/CT TIs and distinguishing between benign and malignant thyroid lesions in oncological patients. We conducted a screening of all patients with incidental focal thyroid uptake described in their ^{18}F-FDG PET/CT reports (N=1424) and included those who underwent thyroid ultrasound and thyroid surgery at our tertiary oncological referral hospital (N=46). Radiomic features were extracted from regions of interest (ROIs) in both PET and CT images, preprocessed, and the final sets of features were used to predict the malignancy risk of TIs. The TIs were graded using the Thyroid Imaging, Reporting, and Data System (TIRADS) by the American College of Radiology. Histopathological postoperative results served as the reference standard. Univariate analysis was performed using features from each modality individually and in combination. The predictive ability of radiomic features was compared to that of the TIRADS.

Among the 46 included patients (16 males, 30 females; mean age ± SD: 66 ± 12 years), 36 patients (78%) had malignant thyroid lesions, while 10 patients (22%) had benign lesions. The highest area under the curve (AUC) of 0.86 (95% CI: 0.71-0.98, $p<0.05$) was achieved by combining the Run Length Non-Uniformity (RLN) radiomic feature extracted from PET and CT cubical regions of interest (CROIs). This performance was comparable to that of the TIRADS ultrasound-guided classification system (AUC: 0.84, 95% CI: 0.74-0.91, $p<0.05$) in discriminating between benign- and malignant thyroid nodules. The difference in AUCs between RLN and the TIRADS system was not statistically significant in our cohort. The results of this study demonstrate the potential predictive ability of ^{18}F-FDG PET/CT-derived radiomic features in distinguishing between benign- and malignant thyroid nodules. Further studies with larger cohorts and deep learning-based methods should be conducted to obtain more robust results.

INTRODUCTION

Fluorine-18-fluorodeoxy-D-glucose positron emission tomography/computed tomography (^{18}F-FDG PET/CT) thyroid incidentalomas (TIs) are unexpected thyroid lesions discovered on ^{18}F-FDG PET/CT scans for non-thyroidal purposes (1). TIs are reported in 1.5%-2% of oncologic ^{18}F-FDG PET/CT scans and up to 30% of focal TIs are malignant (2-6).

The 2015 American Thyroid Association (ATA) guidelines suggest additional work-up of focal TIs when clinically relevant for the patient (3). The prognosis of cancer patients is often determined by the primary malignancy outside the thyroid. Therefore, it is crucial to avoid unnecessary work-up of TIs that could lead to discomfort and delays in the diagnosis or treatment of the underlying malignancy (4). Risk-stratification of focal thyroidal ^{18}F-FDG-uptake is essential to guide clinicians and patients.

Currently, initial management of thyroid nodules relies on ultrasonographic characteristics and thyroid function testing. The American College of Radiology Thyroid Imaging Reporting and Data System (ACR-TIRADS) is a valuable tool for stratifying thyroid nodules for further cytological evaluation (7). A previous study have shown excellent performance of ACR-TIRADS in the risk stratification of thyroid nodules (8). Ultrasound-guided fine-needle aspiration cytology (FNAC) is the most sensitive and specific preoperative indicator of thyroid malignancy (9). However, a significant percentage of thyroid FNACs (20-25%) yield indeterminate cytology results and require repeat FNACs or even diagnostic surgery (10). These diagnostic procedures impose risks and anxiety on patients and consume time and resources (11). Moreover, previous studies have indicated that only a limited percentage of indeterminate cytology results are confirmed as thyroid malignancies, ranging from 19.8% to 36.2% (2, 5, 12-14). Therefore, for the majority of TI patients, surgery appears to be unnecessary and should be reserved for selected cases (4).

In recent years, there has been a growing interest in non-invasive techniques, such as radiomics, for distinguishing between benign- and malignant ^{18}F-FDG PET/CT thyroid incidentalomas (TIs) (15). The extraction and analysis of radiomic features from routine ^{18}F-FDG PET/CT imaging hold the potential to differentiate between benign- and malignant TIs, thereby avoiding unnecessary additional diagnostic procedures. Several recent studies have explored the role of radiomics in discriminating between benign- and malignant TIs (16-21). Some studies have suggested the potential utility of combining radiomics with PET-derived clinical parameters (16, 17). However, a robust non-invasive radiomic biomarker that can reliably differentiate between benign- and

malignant TIs has yet to be identified. This study aims to investigate the role of radiomic features extracted from PET and CT imaging, both individually and in combination, in discriminating between benign- and malignant thyroid nodules in oncological patients. The predictive performance of radiomic features will be compared to that of the ACR-TIRADS ultrasound categories, which is a validated system for stratifying the risk of malignancy in thyroid nodules (8).

MATERIALS AND METHODS

Study Cohort

A retrospective search was conducted in databases for all patients who had undergone a ^{18}F-FDG PET/CT scan for non-thyroidal oncological indications between 2010 and 2022. The acquisition and reporting of ^{18}F-FDG PET/CT scans were performed according to the protocol outlined by the European Association of Nuclear Medicine (EANM) (22). All ^{18}F-FDG PET/CT scans with the word "thyroid" in the report were automatically selected. The reports were then manually screened by the author MP to verify the presence of ^{18}F-FDG uptake in the thyroid gland. Patients with known thyroid cancer or thyroid disease and non-avid thyroid nodules were excluded. All patients with focal ^{18}F-FDG uptake in the thyroid gland primarily depicted by ^{18}F-FDG PET/CT scans were included in this study. Additional inclusion criteria were the presence of an ultrasound examination and a definitive histopathological diagnosis.

The decision to perform ultrasound (US) was influenced by various factors, including the estimated risk of a relevant (second) malignancy, the preferences of the physician and the patient comorbidities, life expectancy and other relevant considerations. The evaluation of US images was routinely conducted using the ACR-TIRADS system (3, 23). The decision to perform US-guided fine needle aspiration cytology (FNAC) was primarily based on the ACR-TIRADS recommendation provided by the ATA (23). However, in certain cases, the decision was also made through shared decision making with the patient. The FNAC samples obtained were analyzed by two experienced pathologists who had received training in thyroid cytology. These pathologists strictly adhered to the Bethesda Classification System when reporting on the cytology of thyroid nodules (24). Additionally, the thyroid nodules of the study patients underwent a retrospective reassessment on US to determine their composition, echogenicity, shape, margin, and presence of echogenic foci. This reassessment was performed by a different radiologist (ABR) from the one who had initially reported on the US findings.

DATA PREPROCESSING AND ANALYSIS

Cubical region of interest (CROI)-based analysis

The ITK-Snap software (25) was utilized to extract cubical regions of interest (CROIs) around thyroid incidentalomas (TIs) exhibiting high ^{18}F-FDG uptake on whole-body CT-based attenuation correction (CTAC) PET scans. Corresponding CROIs were also extracted from the corresponding low-dose CT scans (**Figure 1**). PET scans were SUV corrected, PET and CT scans and the corresponding CROIs were then resampled into 4mm and 1mm isotropic voxel size, respectively.

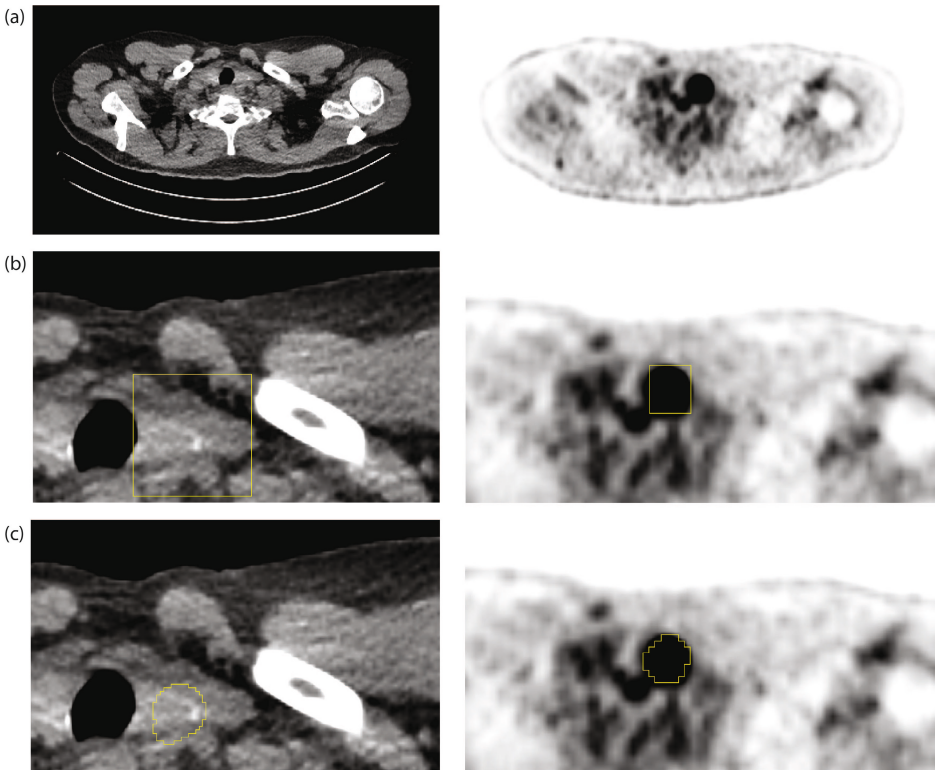

Figure 1 An example of (a) low dose CT and CT-based attenuation correction ^{18}F-FDG PET scans showing (b) the cubical regions of interest (CROIs) and (c) the volumetric segmentations.

Radiomic features, known as quantitative radiographic phenotyping features, were computed from the CROIs indicated on the ^{18}F-FDG PET and CT scans (26). A total of 77 features were extracted from various categories including statistical first-order features, second-order textural features derived from Gray Level Co-occurrence Matrix (GLCM), Gray Level Run Length Matrix (GLRLM), Neighboring Gray Tone Difference

Matrix (NGTDM), and Gray Level Dependence Matrix (GLDM). Detailed explanations of the included radiomic features can be found in the PyRadiomics documentation and the work by Griethuysen et al (26). In addition to radiomic features, the US-based TIRADS malignancy classification score was included as an additional feature in the analysis.

The feature preprocessing and selection pipeline involved standardization of the features to zero mean and unit variance. Next, features with zero variance and high pairwise correlation (Spearman's correlation: $r > 0.95$, $p < 0.05$) were removed. The feature that exhibited the lowest correlation with the label was eliminated. Subsequently, the selected features were individually assessed for their correlation with the malignancy risk of TIs compared to the pathological diagnosis.

Volumetric segmentation-based analysis

To assess the influence of thyroid nodule shape and size on the malignancy classification of thyroid incidentalomas (TIs), two radiologists (MAA and MHH) generated volumetric segmentations of the thyroid nodules on ^{18}F-FDG PET and CT imaging using the 3D Slicer software (27) (**Figure 1**). MHH, with 4 years of radiological experience, and MAA, with 9 years of radiological experience, carefully reviewed and revised the segmentations to ensure consistency and uniformity.

In addition to the previously mentioned radiomic features, which included first-order, GLCM, GLRLM, NGTDM, and GLDM features, additional radiomic features related to shape and the Gray Level Size Zone Matrix (GLSZM) were extracted (total of n=107 features). These features were derived from the manual segmentations of the PET and CT scans. The feature preprocessing, selection and analysis pipeline, as described in section 2.2.1, were followed in a similar manner for the analysis based on the segmentations.

Combining PET and CT imaging

In addition to the analysis of individual PET and CT scans, the anatomical and metabolic information from both modalities was combined at two distinct levels: image-level fusion, PET+CT (KLD-based) and feature-level fusion, PET+CT (PCA-based). The PET+CT (KLD-based) fusion technique integrates PET and CT scans at the image-level by averaging the normalized PET and CT images employing a parameter obtained through a minimum Kullback-Leibler Divergence (KLD) criterion, as described in the study conducted by Mu et al. (28). On the other hand, PET+CT (PCA-based) fusion combines textural radiomic features extracted from both PET and CT imaging modalities using principal component analysis (PCA) (29). Analysis was repeated similarly using radiomics features extracted from the combined PET/CT imaging.

Statistical Analysis

In the univariate analysis, the correlation between the selected radiomic features, along with the TIRADS system and the malignancy of thyroid incidentalomas (TIs) was assessed using the area under the receiver operating curve (ROC-AUC). Given the relatively modest sample size of the study, confidence intervals were determined using 1000-times bootstrapping through repeated sampling with replacement. To ensure comparability of results, AUCs below 0.5 were inverted and marked with an asterisk (*), indicating a negative correlation between the features and the pathological malignancy diagnosis.

The Mann-Whitney U test was performed to compare the diagnostic test results, radiomic features and TIRADS classification between the benign- and malignant groups. The Chi-square test was used for categorical blood-based parameters. Furthermore, the statistical significance was adjusted for multiple testing in the radiomics and TIRADS analysis using the Benjamini/Hochberg procedure. P-values below 0.05 were considered statistically significant. Additionally, the significance of the difference between the AUCs of the TIRADS classification and the best-performing radiomic feature was calculated using the Hanley and McNeil method (30). All analyses were conducted using Python (v3.7) and the following libraries: PyRadiomics (v3.0.1) (28), Scikit Learn (v1.0.1) (31), and SciPy (v1.7.1).

RESULTS

Study Cohort

Among the entire cohort of patients who had focal thyroidal ^{18}F-FDG uptake on their PET/CT scans (n=1424), we identified 46 patients (16 males and 30 females) who had focal ^{18}F-FDG uptake and underwent US and thyroid surgery at our institution. The analyzed cohort's characteristics are presented in **Figure 2**. For patients with Bethesda I, II, and III cytology results, diagnostic thyroid lobectomies were performed based on the preferences of the physician and/or the patient, following repeated inconclusive FNACs. The majority of the included patients (N=36, 78%) were diagnosed with a malignant lesion after surgical intervention, while a subset had a benign lesion (N=10, 22%). The clinical and blood-based parameters of the cohort are summarized in **Table 1**. Eight patients with a thyroid nodule size < 1 cm were included. No significant differences were observed between the malignant- and benign groups in terms of thyroid nodule size, thyroid function tests or SUV_{max} values. Notably, one patient diagnosed with medullary thyroid cancer exhibited abnormal calcitonin (hCT) levels.

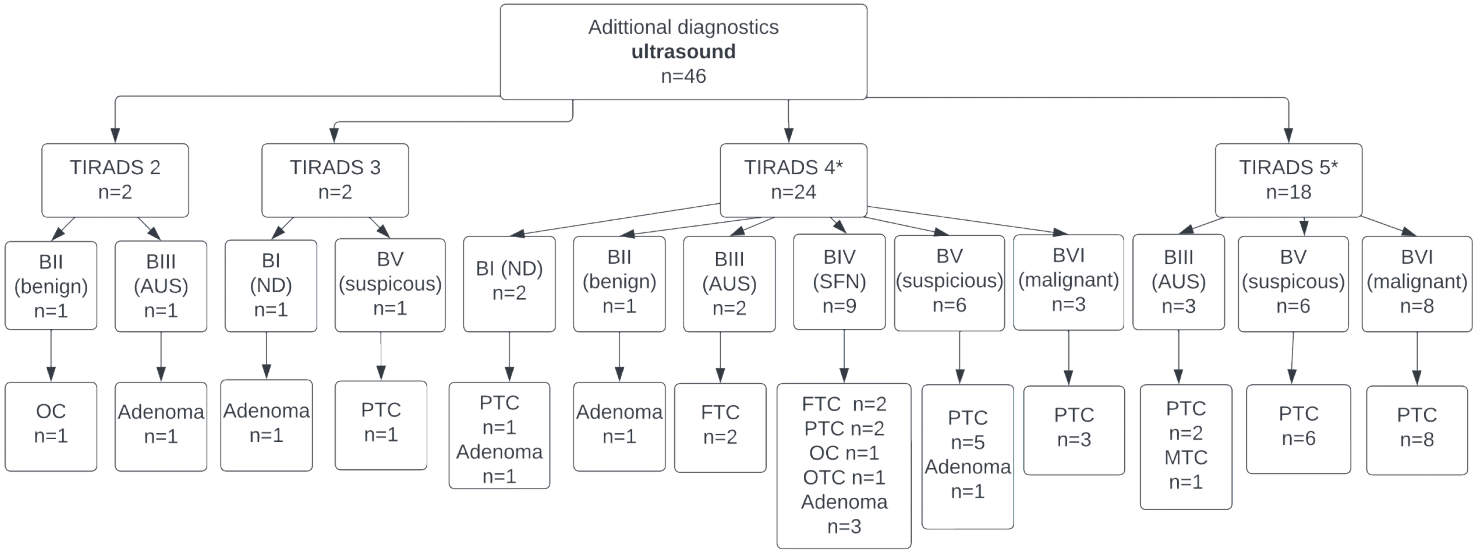

Figure 2 Flowchart of the ACR-TIRADS, Bethesda results, and final pathology results (N=46).
B, Bethesda; AUS, atypia of undetermined significance; ND, non-diagnostic; suspicious, suspicious for malignancy; SFN, suspicious for follicular neoplasm; OC, oncocytic change; PTC, papillary thyroid cancer; FTC, follicular thyroid cancer; OTC, oncocytic thyroid cancer; MTC, medullary thyroid cancer. * Bethesda classification was unknown in 2 patients.

Table 1 Summary of diagnostic test results.

Parameters	Benign nodule	Malignant nodule	Overall	*p*-value
Nodule size in mm (median (IQR))	13 (9-36)	15 (8-24)	15 (9-24)	0.76
Blood-based parameters				
Thyroid stimulating hormone (mIU/L) (mean ± SD)	1.8 ± 0.9	1.8 ± 1.5	1.8 ± 1.4	0.42
Anti-thyroglobulin antibodies[a]	Positive = 1 Negative = 1	Positive = 3 Negative = 19	Positive = 4 Negative = 20	0.31
Semiquantative ^{18}F-FDG PET/CT parameters				
SUV_{max} (mean ± SD)	18.2 ± 26.7	9.1 ± 7.6	10.9 ± 13.7	0.07

a. Available in 24/46 patients

Comparison of the performance between radiomic features derived from cubical regions of interest (CROIs) and volumetric segmentations, and TIRADS

A total of 24 radiomic features from PET, 50 features from CT and 37 features from the combination of PET+CT (KLD-based), as well as 45 features from PET+CT (PCA-based), were selected for analysis in the CROI-based approach. Additionally, a total of 27 features from PET, 44 features from CT, 29 features from PET+CT (KLD-based) and 46 features from PET+CT (PCA-based) were included in the segmentation-based analysis. Detailed information on the most significant radiomic features extracted from CROIs and volumetric segmentations of PET and CT imaging, along with the TIRADS classification of the 46 patients, can be found in **Table 2**.

Table 2 Comparison of the correlation of TI malignancy with the TIRADS classification and PET/CT radiomic features.

Analysis	Modality	Significant features	Category	AUC	95% CI	*p*	Adjusted *p*
CROI derived radiomics	PET	Run Entropy	GLRLM	0.31 (0.69*)	(0.58- 0.81)*	0.027	n.s.
		Run Length Non-Uniformity (RLN)	GLRLM	0.27 (0.73*)	(0.62- 0.83)*	0.006	n.s.
		Run Length Non-Uniformity Normalized (RLNN)	GLRLM	0.69	(0.57- 0.80)	0.029	n.s.
	CT	Sum Entropy	GLCM	0.72	(0.49- 91)	0.042	n.s.
		Dependence Non-Uniformity	GLDM	0.83	(0.69- 93)	0.002	n.s.
		Run Length Non-Uniformity (RLN)	GLRLM	0.80	(0.66- 91)	0.005	n.s.
	PET+CT (KLD-based)	Large Dependence Low Gray Level Emphasis (LDLGLE)	GLDM	0.26 (0.74*)	(0.57- 0.88)*	0.026	n.s.
		Run Length Non-Uniformity (RLN)	GLRLM	0.27 (0.73*)	(0.55- 0.88)*	0.032	n.s.
	PET+CT (PCA-based)	Sum Entropy	GLCM	0.28 (0.72*)	(0.49- 0.91)*	0.037	n.s.
		Dependence Non-Uniformity	GLDM	0.76	(0.54- 0.94)*	0.013	n.s.
		Gray Level Non-Uniformity	GLRLM	0.71	(0.49- 0.89)*	0.05	n.s.
		Run Length Non-Uniformity (RLN)	**GLRLM**	0.12 (0.88*)	(0.75- 0.97)*	<0.001	0.01
		Run Variance	GLRLM	0.23 (0.77*)	(0.57- 0.93)*	0.011	n.s.

Table 2 Continued

Analysis	Modality	Significant features	Category	AUC	95% CI	*p*	Adjusted *p*
Segmentation derived radiomics	PET	Dependence Non-Uniformity (DN)	GLDM	0.28 (0.72 *)	(0.52- 0.89) *	0.042	n.s.
	CT	Minor Axis Length	Shape	0.27 (0.73 *)	(0.54- 0.89) *	0.032	n.s.
		90 Percentile	First order	0.74	(0.58- 0.87)	0.023	n.s.
		Mean	First order	0.71	(0.54- 0.85)	0.05	n.s.
		Root Mean Squared	First order	0.74	(0.59- 0.87)	0.021	n.s.
		Large Area High Gray Level Emphasis (LAHGLE)	GLSZM	0.28 (0.72 *)	(0.53- 0.89) *	0.037	n.s.
	PET+CT (KLD-based)	No significant features					
	PET+CT (PCA-based)	Dependence Non-Uniformity	GLDM	0.29 (0.71 *)	(0.50- 0.90) *	0.047	n.s.
		Small Dependence Low Gray Level Emphasis	GLDM	0.71	(0.51- 0.88)	0.05	n.s.
-	Ultrasound	TIRADS	-	0.84	(0.74- 0.91)	<0.001	<0.05[a]

Radiomic features were derived from cubical region of interests (CROI) and volumetric segmentations of PET, CT, and PET+CT imaging in n=46 patients. The table summarizes only the statistically significant features before multiple testing correction.

* A flipped AUC, resembling negative correlation

[a] TIRADS was included as a feature in both types of analysis of radiomic features (CROI-derived and segmentation-derived) from PET, CT and PET+CT (KLD-based) and PET+CT (PCA-based), showing different *p*-values after multiple testing correction (*p*: 0.020, 0.010, 0.015, and 0.010, respectively) in CROI-based analysis and (*p*: 0.010, 0.018, 0.012 and 0.019, respectively) in segmentation-based analysis.

The highest AUC of 0.88* (p= 0.01) was achieved by combining the CT and PET-derived GLRLM feature called run length non-uniformity (RLN) in the CROI-based PET+CT (PCA-based) analysis. Additionally, AUCs of 0.73* (p= 0.077) and 0.80 (p= 0.084) were obtained when RLN was derived individually from PET and CT, respectively, in the CROI-based analysis. **Table 3** provides a detailed summary of the feature values for RLN in benign- and malignant TIs.

Table 3 A summary of the TIRADS classification categories and the best performing radiomic feature.

Type	TIRADS CLASSIFICATION	Malignant nodule (n=36)	Benign nodule (n=10)
TIRADS	TIRADS 2	0	2
	TIRADS 3	1	1
	TIRADS 4	17	7
	TIRADS 5	18	0
Radiomics	**Run Length Non-Uniformity (RLN) feature**	**Median values (95% CI)**	**Median values (95% CI)**
CROI-based analysis	PET	41.64 (5.97 - 41.64)	41.64 (41.64 - 103.43)
	CT	34206.20 (10151.34 - 54531.07)	27403.95 (13957.44 - 35450.24)
	PET+CT (PCA-based)	0.27 (0 - 0.54)	0.35 (0.26 - 1)
	PET+CT (KLD-based)	39.65 (3.81 - 53.62)	40.67 (38.07 - 64.09)
Volumetric segmentation-based analysis	PET	9.34 (2.84 - 36.12)	13.54 (4.09 - 483.04)
	CT	537.31 (85.89 - 17342.05)	2302.56 (122.52 - 60906.22)
	PET+CT (PCA-based)	0.01 (0 - 0.16)	0.03 (0 - 1)
	PET+CT (KLD-based)	9.49 (2.84 - 31)	13.54 (4.09 - 59.37)

The median values (95% CI) of the best performing radiomic feature, run length non-uniformity (RLN), alongside TIRADS categories are summarized across malignant and benign TIs of n=46 patients

In the segmentation-based analysis, the RLN feature was not selected during the feature selection step for all modalities. However, individual evaluation of this feature derived from segmentations of PET, CT and PET+CT (PCA-based) modalities yielded AUCs of 0.65*, 0.68*, and 0.66*, respectively, without reaching statistical significance.

The TIRADS system demonstrated a competitive performance compared to the RLN feature derived from CROIs of PET+CT imaging with an AUC of 0.84 ($p< 0.05$) in both PET, CT, and PET+CT analyses.

The AUCs of the TIRADS system (AUC: 0.84) and the best-performing RLN feature from the combined PET+CT analysis (AUC: 0.88*) were statistically compared and no significant difference was observed.

DISCUSSION

Our study aimed to evaluate the potential of radiomic features in distinguishing between benign- and malignant thyroid incidentalomas (TIs) using ^{18}F-FDG PET/CT scans. In this modest cohort of 46 patients, we observed that the run length non-uniformity (RLN) radiomic feature, derived from CROIs of PET and CT imaging and combined using PCA, exhibited promise by displaying a negative correlation with malignancy with an AUC of 0.88* (95% CI: 0.75*-0.97*, p=0.01). When comparing the RLN feature extracted from CROIs of individual PET or CT imaging, we observed AUCs of 0.73* and 0.80, respectively. These results indicate that the combined RLN feature, derived from both modalities, showed a higher correlation than the individual modalities. RLN quantifies the heterogeneity of run lengths in the image, where run lengths represent consecutive pixels with the same value. In the CROI-based analysis of PET+CT (PCA-based), malignant TIs showed slightly lower RLN values compared to benign TIs, indicating more homogeneity among run lengths in malignant TIs. Furthermore, the combined RLN feature demonstrated competitive performance with the TIRADS classification, achieving an AUC of 0.84 (95% CI: 0.74-0.91, p=0.01). The difference in AUCs between the combined RLN feature (inverted AUC to indicate negative correlation) and TIRADS was not statistically significant ($p=0.6$).

Previous studies have provided insights into the predictive role of PET-derived clinical parameters and radiomics in assessing thyroid incidentalomas (TIs) on ^{18}F-FDG PET/CT scans (16-21). Kim et al. investigated the standard uptake value (SUV) measurements in distinguishing thyroid malignancy from benign disease (30). In line with our findings, they found no significant difference in maximum SUV between benign- and malignant thyroid nodules. Sollini et al. conducted a study that identified several SUV-based, histogram-based, and grey-level co-occurrence matrix (GLCM) based parameters as potentially significant predictors of final TI diagnosis using ROC analysis (21). Skewness, metabolic tumor volume (MTV), and total lesion glycolysis (TLG) yielded an area under the curve (AUC) of 0.66, which was lower than the AUCs we observed (21). They also reported that SUV_{max} could discriminate between benign- and malignant thyroid

nodules in their cohort (21). Another study by Aksu et al. demonstrated that combining grey-level run length matrix (GLRLM) based run length non-uniformity (RLN) and SUV_{max} showed superior discriminatory power (AUC=0.849) in predicting TI pathological outcome compared to SUV_{max} (AUC=*0.758, 95% CI: 0.61-0.90, p=0.004*) or RLN alone (AUC=*0.827, 95% CI: 0.70-0.96, p<0.001*) (16). This AUC for RLN aligns with the AUC we obtained in our study. Aksu et al. also reported an AUC of 0.731 when evaluating the combination model on an unseen test set (16), which we did not have access to for further evaluation.

The analysis based on volumetric segmentations revealed that the inclusion of additional radiomic features related to shape and size did not contribute to the differentiation of TIs in our study cohort. Furthermore, the radiomic features derived from volumetric segmentations did not yield similar results compared to the CROI-based analysis. Specifically, the RLN feature, which was the most effective in the CROI-based analysis, was not among the selected features after removing correlated features in the volumetric analysis. Moreover, when individually evaluated, RLN did not exhibit the same predictive ability as observed in the CROI-based analysis (*of 0.65*, 0.68*, and 0.66* for PET, CT and combined PET+CT, respectively, p=n.s.*). This discrepancy could be attributed to potential radiological biases or the fact that CROIs had a wider region surrounding the nodules indicating that the peritumoral region might have played a role in capturing certain differences between benign- and malignant TIs in our cohort. In contrast, Ceriani et al. conducted an analysis using radiomic features derived from volumetric segmentations. They found that shape sphericity was the most reliable predictor for classifying TIs in their univariate analysis (17). Further analysis should be conducted on larger cohorts to draw definitive conclusions regarding the impact of nodule shape and size on the malignancy classification of TIs.

The findings of this study highlight the ongoing challenge in accurately differentiating benign- and malignant TIs on ^{18}F-FDG PET/CT scans using the currently available diagnostic tools such as laboratory tests, ultrasonography and fine-needle aspiration cytology (FNAC). In our study, laboratory tests were found to be non-discriminatory in the evaluation of thyroid nodules. The ACR-TIRADS score, which provides a standardized protocol for radiologists, is widely utilized to stratify thyroid nodules for cytological evaluation and remains the most commonly used ultrasound (US) based system in clinical practice (31). Previous studies have reported an AUC of 0.875 and 0.88 in the discrimination of malignant nodules using the ACR-TIRADS system, which is consistent with the performance in our study (AUC of 0.84) (8, 32). In the present study, only thyroid lesions with confirmed histopathological diagnosis through surgery were included, which may have introduced selection bias. Fine needle aspiration cytology

(FNAC) samples were not utilized as the gold standard due to challenges in interpreting certain samples (33). Within our cohort, a proportion of patients exhibited non-diagnostic (Bethesda I) (7%), indeterminate (Bethesda III) (14%), or suspicious for follicular neoplasm (Bethesda IV) (20%) cytology results. These rates align with findings from a meta-analysis by Bongiovanni et al., which reported percentages of 12.9%, 9.6%, and 10.1% for Bethesda I, Bethesda III and Bethesda IV cytology results, respectively (34).

Approximately 15% to 30% of FNACs yield indeterminate thyroid cytopathology results, creating a situation where watchful waiting may be inadequate, but thyroid surgery may be too aggressive (35, 36). Diagnostic thyroid lobectomy is considered for nodules with repeated indeterminate FNAC results (37). These diagnostic procedures and associated uncertainties impose additional stress on patients who are already undergoing treatment for other types of cancer. The use of radiomic features derived from ^{18}F-FDG PET/CT scans for categorizing TIs could assist physicians in making clinical decisions. Since ^{18}F-FDG PET/CT imaging is routinely used in current oncological practice, incorporating radiomics provides an opportunity to enhance cancer treatment decision-making at minimal additional costs.

Strengths and limitations

Our study has demonstrated the potential of non-invasive ^{18}F-FDG PET/CT radiomics as a predictive tool for classifying the malignancy risk of TIs. However, it is important to acknowledge certain limitations in our study. The inclusion of patients may have been influenced by biases stemming from the variability in ultrasonography referral and FNAC. Additionally, the sample size in our study was relatively modest as data was obtained from a single center. Conducting larger-scale multicenter follow-up studies would enable the development and validation of more robust algorithms. Access to larger datasets would not only allow for a more objective evaluation of performance, such as through a separate validation cohort, but would also facilitate the utilization and assessment of more advanced deep-learning techniques for automatic detection, imaging segmentation and malignancy classification of TIs on ^{18}F-FDG PET/CT scans. Furthermore, integrating additional diagnostic data, such as PET-based clinical parameters and clinical information, with ^{18}F-FDG PET/CT imaging could potentially enhance the automated diagnosis of TIs.

CONCLUSION

Our study aimed to investigate the application of radiomics in distinguishing between benign- and malignant thyroid nodules identified through ^{18}F-FDG PET/CT imaging. We identified the most correlated radiomic feature, RLN, derived from PET and CT cubical regions of interest (CROI) using PCA. Our findings demonstrated that this radiomic feature, combined from PET and CT imaging, has potential diagnostic capability comparable to that of the established TIRADS malignancy risk stratification system used in ultrasound imaging. The incorporation of ^{18}F-FDG PET/CT radiomics in the future holds promise for reducing unnecessary diagnostic procedures such as ultrasound, fine needle aspiration cytology (FNAC) and surgery for selected patients. However, further research involving larger cohorts, external validation and advanced AI-based data analysis techniques is necessary to assess the clinical value and reliability of ^{18}F-FDG PET/CT radiomics in routine clinical practice.

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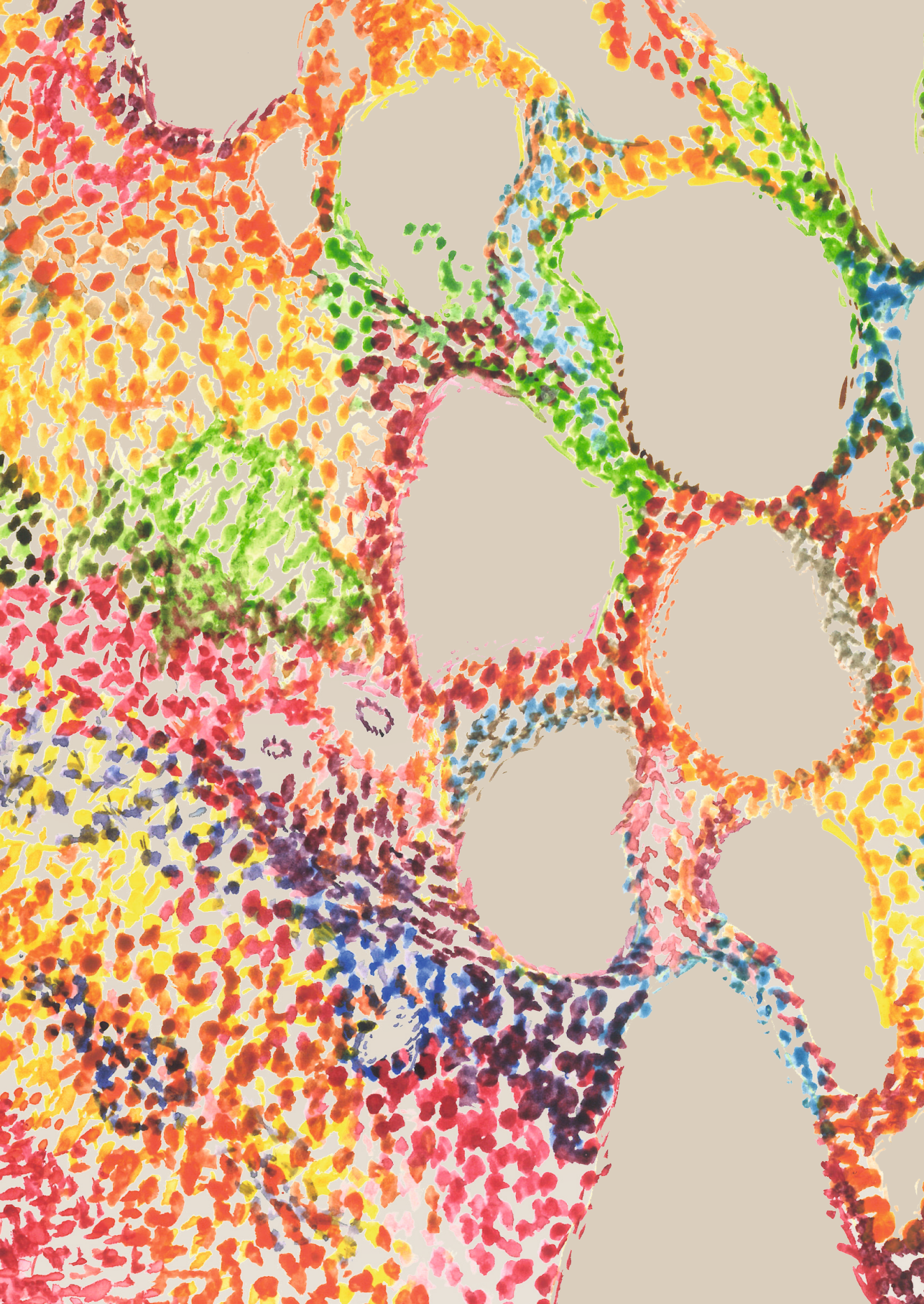

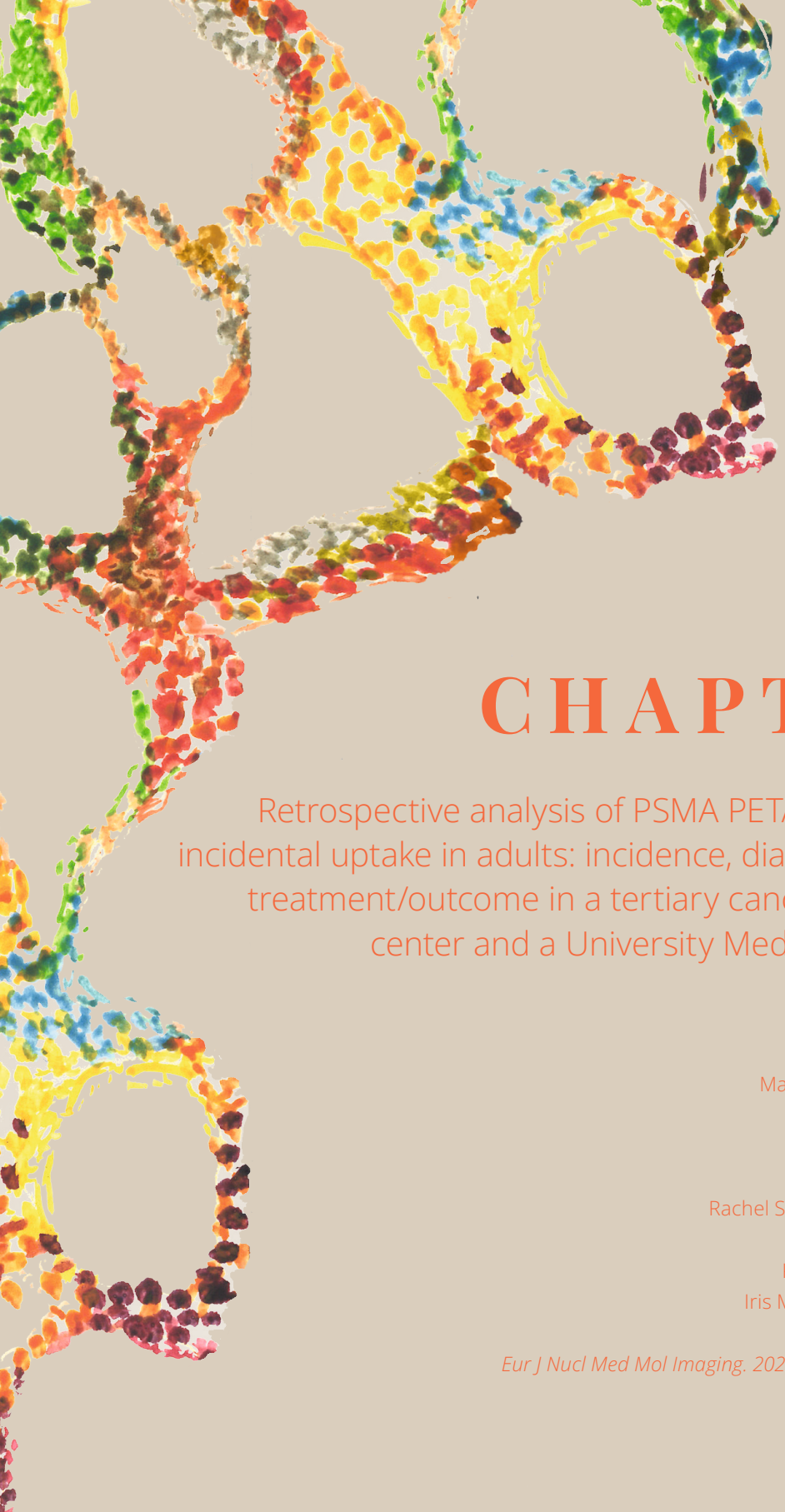

4 CHAPTER

Retrospective analysis of PSMA PET/CT thyroid incidental uptake in adults: incidence, diagnosis and treatment/outcome in a tertiary cancer referral center and a University Medical Center

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ABSTRACT

A prostate-specific membrane antigen (PSMA) thyroid incidentaloma (PTI) is an unexpected, PSMA-avid thyroid lesion, newly detected during the investigation of an unrelated condition using PSMA PET/CT. The aim of this study is to examine the incidence and clinical significance of PTI and the associated management strategies since the implementation of the PSMA PET/CT scan. This study involves a retrospective cohort study of 61 PTI cases depicted on PSMA PET/CT scans performed between January 2016 and July 2021, almost exclusively for (re)staging prostate cancer. The medical records of the included cases were retrospectively reviewed and data of the PSMA PET/CT scans, primary malignancy, thyroid diagnostics, treatment and follow-up were collected. PTI was reported in 1.1% of the patients who underwent oncologic PSMA PET/CT scans included in this study. Two PTI cases had a histologically proven thyroid cancer, one a benign thyroid lesion and one a metastasis of a renal cell carcinoma. In none of the cases in whom any form of further thyroid workup was withheld, the PTI became clinically relevant during follow-up (median 1.8 years (1.1-3.3)). Six patients (10%) died due to their primary cancer. The incidence of thyroid incidentalomas on PSMA PET/CT was low (1.1%) in this large, two-center experience. Less than half of the PTI cases were analyzed and the risk of malignancy, despite being low, was not negligible. The clinical outcome was good using a standard diagnostic workup for PTI, while the prognosis of the patient was determined by the primary malignancy. The consideration to analyze and treat PTI cases should be part of the shared decision making in cancer patients.

INTRODUCTION

The incidence of many types of cancer has increased over the past decade and oncologists strive to improve tailor-made treatment options (1). Imaging is an important part of staging cancer and essential to provide patient specific treatment. The role of positron emission tomography/computed tomography (PET/CT) has expanded in oncology and is performed as a routine investigation in a number of common cancers (2, 3). An incidentaloma is an unexpected finding on imaging not related to the original diagnostic inquiry (4). With the rising number of performed scans, the incidence of incidentalomas increases too.

Prostate carcinoma (PCa) is the most common malignancy in men worldwide with annual age-adjusted rates of 59.3 per 100.000 in Europe (5). Diagnosis and treatment response in prostate cancer is challenging because the clinical course of the disease is often heterogeneous (6). Prostate-specific membrane antigen (PSMA) is a transmembrane protein with significantly increased expression in prostate cancer cells compared to normal prostate tissue (7). PET/CT targeting the PSMA receptor (PSMA PET/CT) plays an increasingly important role in the detection and staging of primary and recurrent PCa (8, 9). PSMA is also expressed in tumor associated neovasculature of a wide spectrum of malignant neoplasms, including various thyroid carcinomas (10-17). As a result, PSMA may be used as target for nuclear imaging and therapy in different advanced tumors such as thyroid, prostate, head and neck and breast cancer (18-24). PSMA expression was observed in differentiated thyroid cancer (DTC) as well as in undifferentiated (anaplastic) thyroid cancer (14,17). The expression of PSMA was seen more frequently in DTC with distant metastases (100%) compared to DTC with lymph node metastases only (67%) (14). The expanding use of PSMA PET/CT has led to the identification of PSMA incidentalomas, also depicted in the thyroid gland (25-27). PSMA thyroid incidentaloma (PTI) is defined as an unexpected PSMA-avid thyroid lesion, newly detected on PSMA PET/CT. The clinical significance of PTIs has not been investigated extensively.

The aim of this study is to evaluate the incidence and clinical significance of PTIs revealed by PSMA targeting PET/CT in a tertiary cancer referral center and a University Medical Center. The intention was to describe the different possible management strategies, the results and the clinical relevance of these different approaches to PTIs in patients with a non-thyroid primary cancer.

METHODS

Ethical

This study was approved by the Institutional Review Board from the Netherlands Cancer Institute-Antoni van Leeuwenhoek (NCI-AvL) Hospital and the University Medical Center Utrecht (UMCU) (IRBd21-019).

Imaging

All cases scanned between January 2016 and July 2021 with PSMA PET/CT in the NCI-AvL or UMCU or referred with an externally performed PSMA targeting PET/CT (using either ^{68}Ga-PSMA-11, ^{18}F-PSMA-1007 or ^{18}F-DCFPyl as tracer) were identified from the medical records. A total of 4061, 192 and 1181 patients underwent ^{68}Ga-PSMA, ^{18}F-PSMA-1007 and ^{18}F-DCFPyL PET/CT scans, respectively. The incidence of PTI was calculated using the data from the scans performed in our hospitals and the data from the externally performed scans. The PSMA targeting PET/CTs had been performed for diagnosis, staging or treatment response measurements for a known or suspected non-thyroidal malignancy, almost exclusively PCa. The imaging reports were searched for the word "thyroid". The reports were then manually screened by authors M.W.P. and L.H.d.V. to assess whether focal or diffuse PSMA uptake in the thyroid gland was reported. Diffuse uptake was defined as PSMA uptake in the whole thyroid gland, whereas focal uptake was defined as PSMA uptake in well circumscribed areas of the thyroid gland. Cases with known thyroid disease or thyroid cancer were excluded. Medical records of included cases were reviewed and data on the primary malignancy, tumor stage, PSMA avidity, extent of thyroid investigation, treatment and follow-up was collected.

Analyses/evaluation of thyroid nodules

The initial PSMA PET/CT scans were analyzed by specialized nuclear medicine physicians according to the European Association of Nuclear Medicine (EANM) guidelines (28). The Thyroid Imaging Reporting and Data System (TIRADS) published in 2017 served as a guidance for ultrasound analysis (29). ACR-TIRADS scores were determined for 19 patients by a specialized radiologist. In 3 patients the ultrasonograhy images were performed externally and therefore not available for this analysis. In most cases the American Thyroid Association guidelines (ATA) were followed to refrain from fine-needle aspiration cytology (FNAC) in thyroid nodules <1 cm unless there was cervical lymph-adenopathy or another finding associated with a higher cancer risk (30). FNAC results were analyzed by dedicated pathologists based on the Bethesda System for Thyroid Cytopathology (31). Clinical and pathological staging was reported according to the 8th edition TNM classification by the American Joint Committee on Cancer (AJCC).

Statistical analysis

Baseline values of continuous variables were visually checked for normality with histograms, q-q plots and the Shapiro-Wilk normality test. For normally distributed numeric data, the mean and standard deviation were reported. Non-normally distributed numeric data were reported as median with interquartile range (IQR, 25th-75th percentile). For categorical data frequencies and percentages were reported. All statistical tests were two-tailed, and a value of $p \leq 0.05$ was considered statistically significant. Statistical analysis was conducted using R software, version 4.0.3.

RESULTS

Incidence of PSMA PET/CT thyroid incidentalomas

A total of 5434 patients underwent PSMA PET/CT of which 61 PTIs (1.1%) were identified. Hereof, ^{68}Ga-PSMA PET/CT was performed in 4061 patients, of which 37 had a PTI (0.9%). One hundred and ninety-two patients underwent ^{18}F-PSMA-1007 PET/CT scan, of which 15 PTIs (7.8%) were identified. ^{18}F-DCFPyL PET/CT was performed in 1181 patients, of which 9 PTIs (0.8%) were included. The process for patient selection is presented in **Figure 1**. Eleven cases with a known thyroid nodule were excluded from PTI analysis. The majority of these patients (4/11) had a multinodular goiter that was diagnosed earlier. Two patients had a thyroid nodule that was previously detected on FDG PET/CT, of which one was benign and one was a papillary thyroid carcinoma (PTC). Five patients had no cytology results available.

Management strategies

The median age of all PTI cases (N=61) was 71.0 years (IQR 68-75) and 98% were male (**Table 1**). Imaging was performed due to PCa in most patients (98%) and parotid cancer in one female patient. The PSMA PET/CT scans showed focal PSMA uptake in the thyroid gland in 70% of PTI cases (**Figure 3a**). One case also had uptake in cervical lymph nodes (level VI). Laboratory testing including thyroid stimulating hormone (TSH), T4 levels was performed in 21% of cases and most of them were euthyroid.

Subsequent evaluation by ultrasound was performed in 25 (25/61) PTI cases (**Table 2**). Five of these cases (5/25) had an advanced stage of PCa with lymph node metastasis or distant metastasis at the time of initial diagnosis. The majority of cases (20/25) who received ultrasound for PTI had a less advanced PCa stage (N0, M0). Consequently, the odds of receiving additional PTI diagnostics was decreased (odds ratio 0.24; 95% CI: 0.05-0.86; $p = 0.01$) for the patients with an advanced stage of PCa compared to the patients with a less advanced stage of PCa.

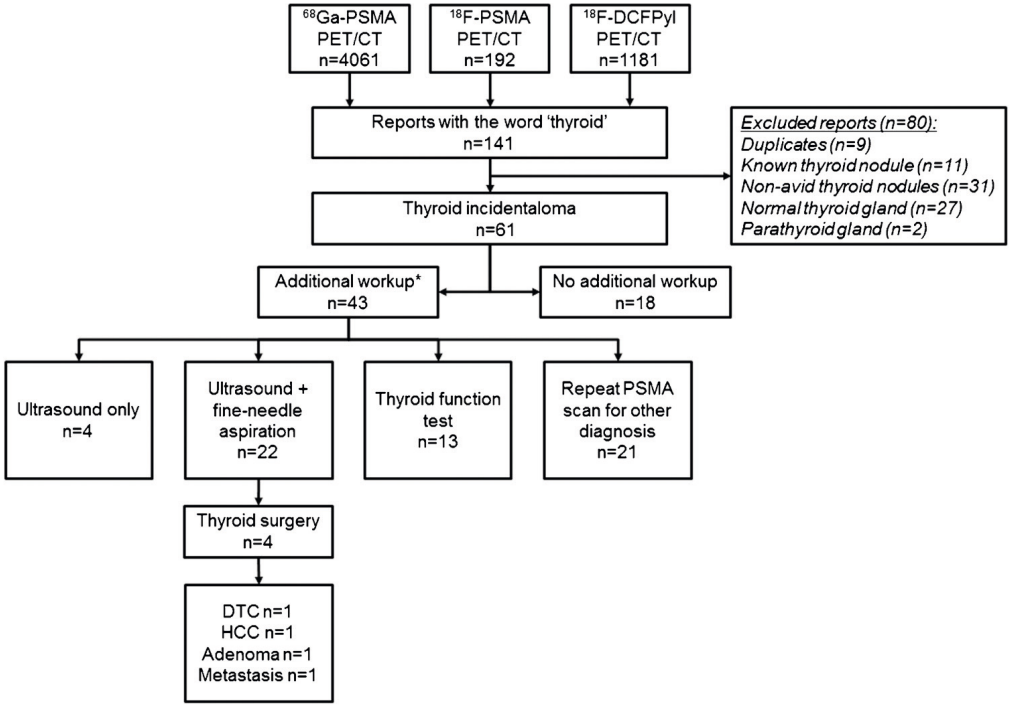

Figure 1 Flowchart of patient-selection.

PSMA = Prostate-specific membrane antigen
PET/CT = Positron emission tomography/computed tomography
DTC = Differentiated thyroid carcinoma, HCC = Hurthle cell carcinoma
* 18 patients received a combination of ultrasound, thyroid function test and/or a repeated PSMA scan for other diagnosis.

Table 1 Clinical characteristics and PSMA PET/CT data.

Variable	N = 61 (%)
Women	1 (2)
Age in years	67
Men	60 (98)
Age in years, median (IQR)	71 (68-75)
PSMA tracer/thyroid uptake	
^{68}Ga-PSMA-11	
Focal uptake	25 (41)
Diffuse uptake	12 (20)
^{18}F-DCFPyl	
Focal uptake	7 (11)
Diffuse uptake	2 (3)
^{18}F-PSMA-1007	
Focal uptake	11 (18)
Diffuse uptake	4 (7)
Indication for PSMA PET/CT	
Staging prostate cancer	60 (98)
Staging salivary gland cancer	1 (2)
AJCC stage prostate cancer (primary malignancy)	
Stage I	8 (13)
Stage IIa	4 (7)
Stage IIb	4 (7)
Stage IIc	7 (12)
Stage IIIa	5 (8)
Stage IIIb	7 (12)
Stage IIIc	2 (3)
Stage IVa	12 (20)
Stage IVb	11 (18)
AJCC stage head-neck cancer (primary malignancy)	
Stage III	1 (2)
Distribution PSMA uptake	
Right lobe	26 (43)
Left lobe	25 (41)
Both lobes	10 (16)
Suspected lymph nodes	
Level VI	1 (2)
Thyroid function test results	13 (22)
Euthyroid	12 (20)
Subclinical hyperthyroidic	1 (2)

PSMA = Prostate-specific membrane antigen
PET/CT = Positron emission tomography/computed tomography

Figure 3 Images PTI

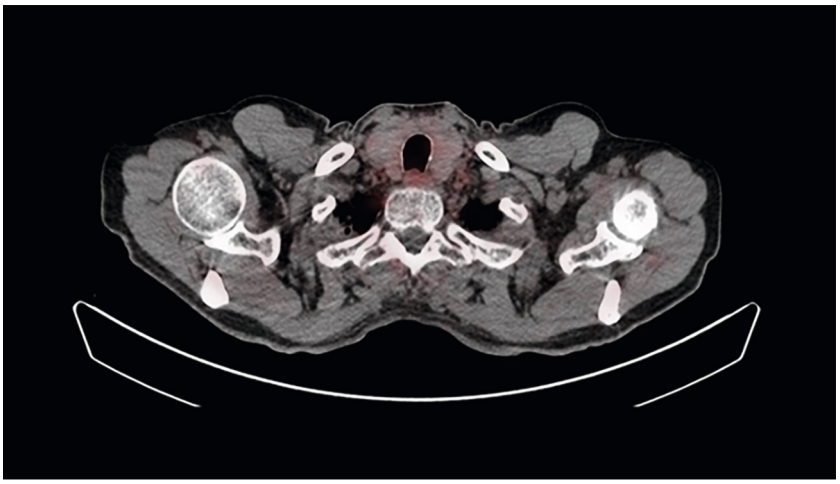

Figure 3a Thyroid without PSMA uptake on 68Ga-PSMA PET/CT fused image.

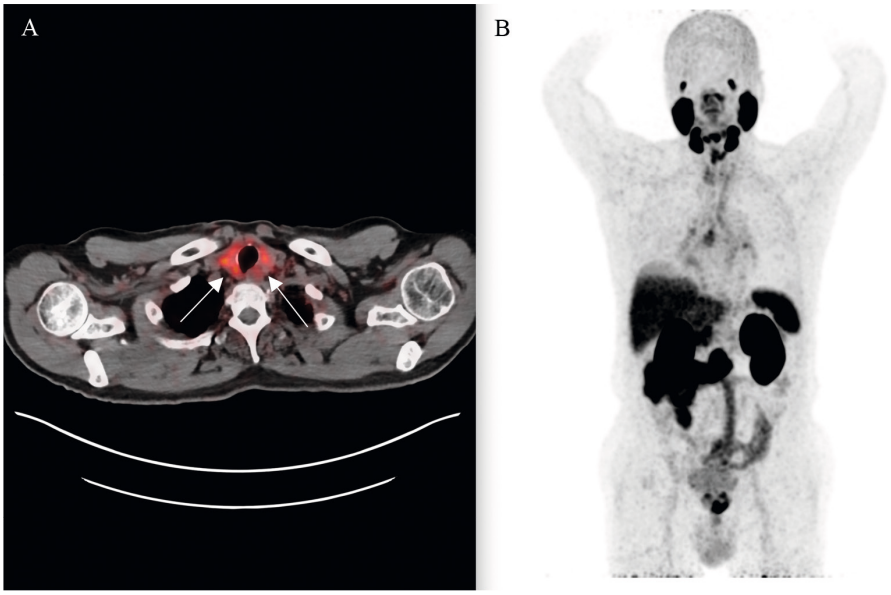

Figure 3b Diffuse thyroidal PSMA uptake on both sides on A) ^{68}Ga-PSMA PET/CT fused image and B) ^{68}Ga-PSMA PET/CT maximum intensity projection (MIP) image.

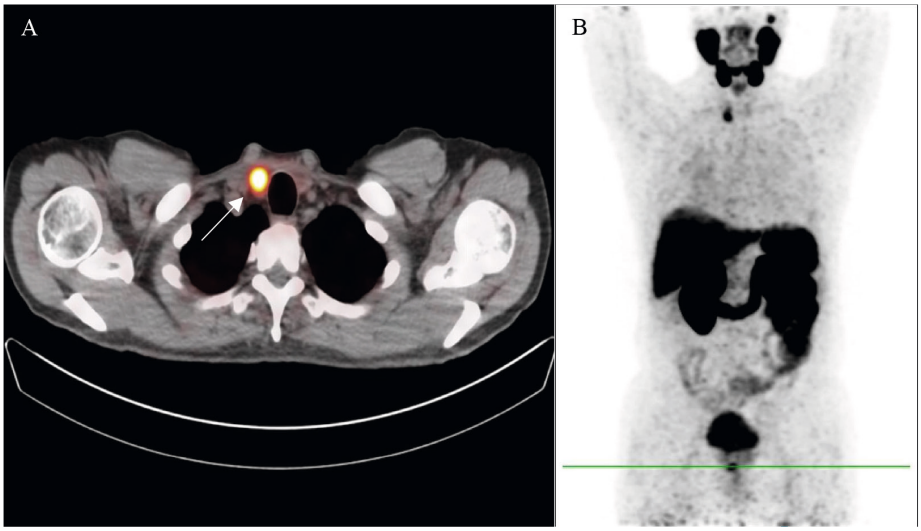

Figure 3c Focal thyroid PSMA uptake on the right side on A) ^{68}Ga-PSMA PET/CT fused image and B) ^{68}Ga-PSMA PET/CT maximum intensity projection (MIP) image.

PTI = PSMA thyroid incidentaloma, PSMA = Prostate-specific membrane antigen, PET/CT = Positron emission tomography/computed tomography.
PTI = PSMA thyroid incidentaloma

Table 2 Work-up characteristics and treatment of PSMA thyroid incidentalomas.

Variable	N = 61 (%)
Repeated PSMA PET/CT result[a]	21 (34)
No uptake	7 (33)
Less uptake	2 (10)
Same uptake	0 (0)
More uptake	14 (67)
Number of US	
US size thyroid nodule (cm)[b]	
<0.5	25 (41)
<1	2 (8)
1-2	8 (32)
2-3	6 (24)
3-4	1 (4)
Size not mentioned	3 (12)
US distribution thyroid nodule[b]	
Left lobe	5 (20)
Right lobe	9 (36)
Both lobes	7 (28)
Not mentioned	7 (28)
Suspected lymph nodes on US[b]	2 (8)
Level IV	1 (2)
Cytology thyroid incidentalomas	
Number of punctures	22 (36)
1	12 (57)
2	5 (24)
3	4 (19)
Bethesda classification (final) *,[c]	
Category I	0 (0)
Category II	14 (64)
Category III	2 (10)
Category IV	3 (14)
Category V	0 (0)
Category VI	1 (5)
Thyroid surgery[d]	4 (7)
Hemithyroidectomy	2 (50)
Total thyroidectomy	2 (50)
Neck dissection[d]	1 (2)
Lateral neck dissection (levels II-V)	1 (100)

Table 2 Continued

Variable	N = 61 (%)
PA thyroid surgery[d]	
Follicular thyroid carcinoma	1 (25)
Hurthle cell thyroid carcinoma	1 (25)
Thyroid adenoma	1 (25)
Metastasis different cancer	1 (25)
PA neck dissection[e]	
Metastasis different cancer	1 (100)

[a] = Percentage of patients with repeated PSMA PET/CT scan [b] = Percentage of patients who underwent ultrasound, [c] = Percentage of patients who underwent FNAC, [d] = Percentage of patients who underwent thyroid surgery, [e] = Percentage of patients who underwent neck dissection
* Two Bethesda result were not described in the pathology reports
PSMA = Prostate-specific membrane antigen
PET/CT = Positron emission tomography/computed tomography
US= ultrasound

Ten cases (10/25) who were additionally imaged by ultrasound had PSMA-avid thyroid nodules larger than 1 cm. In one case, ultrasound depicted both a thyroid lesion and pathological regional lymph nodes, as was also seen on PSMA PET/CT. ACR-TIRADS classifications were scored retrospectively in 19 patients in which ultrasonopgraphy images were available. Of the 19 cases, 3 nodes were considered benign (TIRADS 2) and 3 nodes probably benign (TIRADS 3). Six nodes were indeterminate for malignancy (TIRADS 4) and 7 nodes were suspicious for malignancy (TIRADS 5). In **Figure 2** the TIRADS categories, final Bethesda results and final pathology results are shown for 19 patients in which the ultrasonography images were scored. The probability of a benign FNAC (Bethesda II) was 100% in TIRADS category 2, while in the other categories (TIRADS 3, 4, 5) it was 66.7, 33.3 and 57.1% respectively. The probability of a malignant FNAC (Bethesda VI) for TIRADS 3, 4 and 5 was 0, 16.7 and 0% respectively.

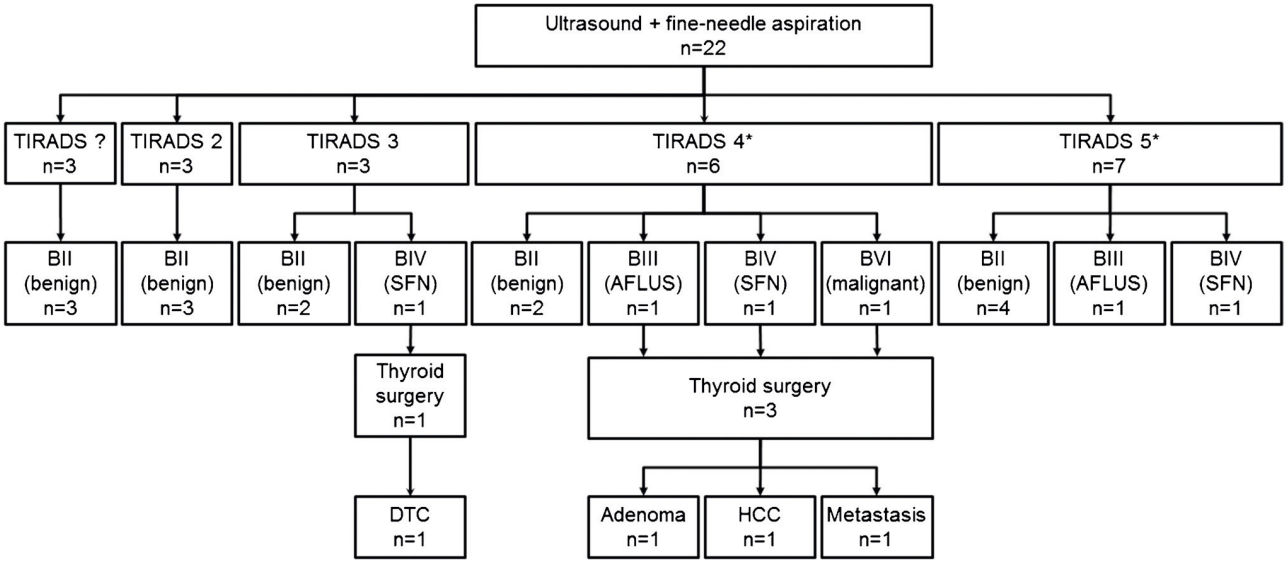

Figure 2 Flowchart of the ACR-TIRADS, Bethesda results and final pathology results (N=19).

AFLUS = atypical follicular lesion of undetermined significance, SFN = suspicious for follicular neoplasm, DTC = differentiated thyroid carcinoma, HCC = Hurthle cell carcinoma

* In 3 patients the ultrasonography images were not available for analysis

** Bethesda pathology results were missing in 2 patients.

In total, FNAC was performed in 22 of the 25 (88%) cases who underwent ultrasonography. In 3 cases, the thyroid gland showed multinodular disease with no defined nodules and therefore FNAC was not indicated. Bethesda II, III, IV and VI was reported in 14 (64%), 2 (9%), 3 (14%) and 1 (5%) case(s), respectively. In 2 cases (9%), Bethesda results were not described.

In this study population, 4 patients (7%) received thyroid surgery due to a Bethesda III, IV or VI cytology score. One patient with a Bethesda IV score had a FNA cytology result with a difficult distinction between thyroid- and parathyroid tissue. This patient had the final diagnosis of primary hyperparathyroidism and received no thyroid surgery. Two patients with a Bethesda III and IV score respectively underwent a hemithyroidectomy for a 3.6 cm and 1.9 cm thyroid nodule in the right lobe. The pathology result showed a thyroid adenoma and a papillary thyroid carcinoma, respectively. Two other patients with a Bethesda IV and VI score with multiple thyroid nodules in both lobes underwent a total thyroidectomy. Pathological examination showed a Hurthle cell carcinoma of 5.6 cm and a thyroid metastasis from renal carcinoma of 6.2 cm with lymph node metastasis.

Follow-up

The median follow-up for the total cohort of PTI cases was 1.8 years (IQR 1.1-3.3). During follow-up, 11 (18%) PTI cases had no cancer related event after the PSMA PET/CT scan, 44 (67%) PTI cases were treated for recurrent PCa , and 3 (5%) for a different cancer type (head- and neck cancer, neuroendocrine tumor). There were no thyroid disease related events in the group of PTI cases without additional thyroid imaging. Six (10%) patients died after a median follow-up period of 2.6 years (IQR 1.7-3.6) due to progression of disseminated PCa.

DISCUSSION

This study showed that PTIs were found in 0.9%, 8% and 0.8% of patients who underwent ^{68}Ga-PSMA, ^{18}F-PSMA-1007 and ^{18}F-DCFPyL PET/CT, respectively. Further diagnostic analysis with ultrasound was performed in less than half of the PTI cases (41%). Most of these cases (88%) underwent FNAC. In only few cases (7%) thyroid surgery was performed. Two patients had a histologically proven thyroid cancer, one patient a benign thyroid lesion and one patient a metastasis of a renal cell carcinoma. The majority of cases (20/25) who received additional PTI diagnostics had a less advanced stage of their primary malignancy. Six patients (10%) died due to their primary PCa.

The incidence of thyroid incidentalomas (TIs) has been described before. ^{18}FDG PET/CT TIs have been widely studied (32-35). FDG TIs are generally regarded as focally elevated thyroid uptake and up to one-third of the FDG TIs are malignant. The most frequent malignant histological subtype is PTC (32-35). Diffusely increased uptake of FDG in the thyroid is thought to be associated with autoimmune thyroiditis or hypothyroidism which may also explain the low rate of diagnostic follow-up for diffuse PTIs (36).

Because the PSMA PET/CT scan is a relatively new diagnostic tool, there is limited clinical experience with incidental detection of synchronous PSMA-avid malignancies. We have noticed a difference in the various PSMA tracers. The ^{68}Ga-PSMA tracer was the most used tracer and therefore the most reliable incidence.

The incidental expression of PSMA was also shown in other cancers such as renal cell carcinoma, neuroendocrine tumors, melanoma, colon carcinoma, lung cancer or breast cancer (37-40). Recently, PSMA uptake in thyroid cancer has been reported in case-reports and prospective studies (19, 25-27). Bychkov et al. found that PSMA expression was observed in a wide spectrum of thyroid tumors and that thyroid cancers had significantly higher PSMA expression than benign tumors. However, the detection of PSMA uptake in the thyroid gland did not guarantee thyroid origin of these lesions (15). The incidence of PTIs was studied by Kirchner et al. who found incidental uptake of ^{68}Ga-PSMA by the thyroid gland in 22% of 55 patients with urological cancers (41). This incidence is higher compared to our study population which can be related to a different study design. The current literature reveals one systematic review concerning ^{68}Ga-PSMA PTIs (26). Most of the included studies were retrospective in nature and consisted of case-reports. This review concluded that the risk of a PTI being malignant is not negligible. Among 23 PTIs with focal uptake, 6 were malignant (5 primary thyroid carcinomas and one renal cell carcinoma metastasis), one was a follicular lesion of undetermined significance and the other lesions were benign (26). Gossili et al. studied 341 patients with a ^{68}Ga-PSMA PET/CT scan of which 7 patients (2%) had increased focal PSMA uptake in the thyroid gland of which two were confirmed malignant (2/7) (27). In our cohort, 43 PTIs (70%) with focal uptake were included of which 3 had a proven malignant pathology (2 thyroid carcinomas and one metastasis from renal cell carcinoma). The incidence of confirmed malignancy (7.0%) in the current cohort is lower compared to the above-mentioned study. In general, the follow-up in our study was more comprehensive in cases with focal than diffuse PTIs which is similar to the findings of Gossili et al (27). Most patients with PSMA expression in a known thyroid nodule who were excluded from our analysis, had a multinodular goiter. PSMA expression in multinodular neoplasm has been reported in a case-reports only (42).

The ATA guidelines for thyroid nodules suggest further work-up in all thyroid nodules of 1 cm and larger, also when incidentally depicted on imaging, because they have a greater potential to be clinically significant malignancies (30) According to the 2015 Dutch guideline, the advice is to analyze thyroid incidentalomas by ultrasound and FNAC in cases without relevant comorbidities (43). The indication for PSMA PET/CT scan in this study was staging of the primary detected malignancy, predominantly PCa. This specific population therefore has relevant comorbidity. The strategy to actively pursue all PTIs of one cm and above in this cohort may lead to overtreatment of thyroid nodules that might never become clinically relevant. Besides, a large majority of PTIs is benign. The ultrasonography therefore remains an important imaging tool to stratify the risk of malignancy of thyroid nodules by TIRADS scores to avoid as many FNACs as possible and eventually thyroid surgeries (44). The ACR-TIRADS has a higher performance in selecting thyroid nodules for FNA compared to ATA or the Korean-TIRADS classification (45). FNAC is recommended for suspicious lesions (TIRADS 3-5) if the size criteria from the thyroid nodule are present (46). A recent study of 100 cases reported the correlation between TIRADS and Bethesda classification (47). The probability of a benign FNAC for TIRADS 2, 3, 4 and 5 was 100, 66.6, 33.3 and 40% respectively. This is similar to our findings of a probability rate of benign FNAC's of 100, 66.7, 33.3 and 57.1% for TIRADS 2, 3, 4 and 5, respectively. The reported risks of malignancy for the different TIRADS categories were higher in another study compared to our data: 0, 14.1, 45.0 and 89.6% for TIRADS 2, 3, 4 and 5 vs. 0, 0, 16.7, 0% for TIRADS 2, 3, 4 and 5 in our study (48). However, this can be due to chance because only 19 patients were included in our analysis compared to 1959 patients by Horvath et al. (48).

In our hospitals, different types of management strategies were applied. A minority of 4 patients underwent thyroid surgery, of which 3 were histologically proven malignant. The patient's comorbidity and life expectancy based on the primary non-thyroid cancer should be taken into account while deciding the further evaluation of a PTI. This study indicates that most physicians have indeed considered this, since patients with a less favorable expected outcome, for example with local- or distant metastasis, received PTI work-up significantly less often compared to patients with a more favorable prognosis. If more PTI workup was performed, more thyroid cancers may have been detected. However, analysis of the follow-up data indicates that these possible missed thyroid malignancies did not become clinically relevant for the patients in our study cohort. However, our follow-up period was relatively short.

Strengths and limitations

A strength of this study includes the large study population for a rarely described finding. Study limitations include the retrospective nature of this study. Another limitation is that the PSMA PET/CT scans were predominantly performed in male patients with prostate cancer. Therefore the conclusions cannot be extrapolated to general clinical practice. The physician dependent choices for PTI workup might also be a potential study bias. The nuclear medicine reports were generated by different nuclear medicine physicians in different hospitals, which might have led to heterogenous reporting. Also, only a minority of patients underwent thyroid surgery. Therefore, a final histological diagnosis was only available in few patients.

CONCLUSION

PTIs were found in 0.9%, 8% and 0.8% of patients who underwent ^{68}Ga-PSMA, ^{18}F-PSMA-1007 and ^{18}F-DCFPyL PET/CT, respectively. Less than half of PTI cases were analyzed and the risk of malignancy, despite being low, was not negligible. Of the remaining PTI cases without additional diagnostics, the PTI did not become clinically relevant during follow-up. The threshold for additional PTI diagnostics was logically higher in this population with significant comorbidities. No patients died from thyroid cancer and the strategy to withhold from thyroid diagnostics in PTI seems valid for a large group of patients with an unfavorable prognosis of their primary cancer based on this study. Though, in our opinion, in case of a well treatable underlying malignancy, diagnostic workup and treatment according to the ATA guidelines should be considered. These considerations should be part of the shared decision making in cancer patients with a PTI.

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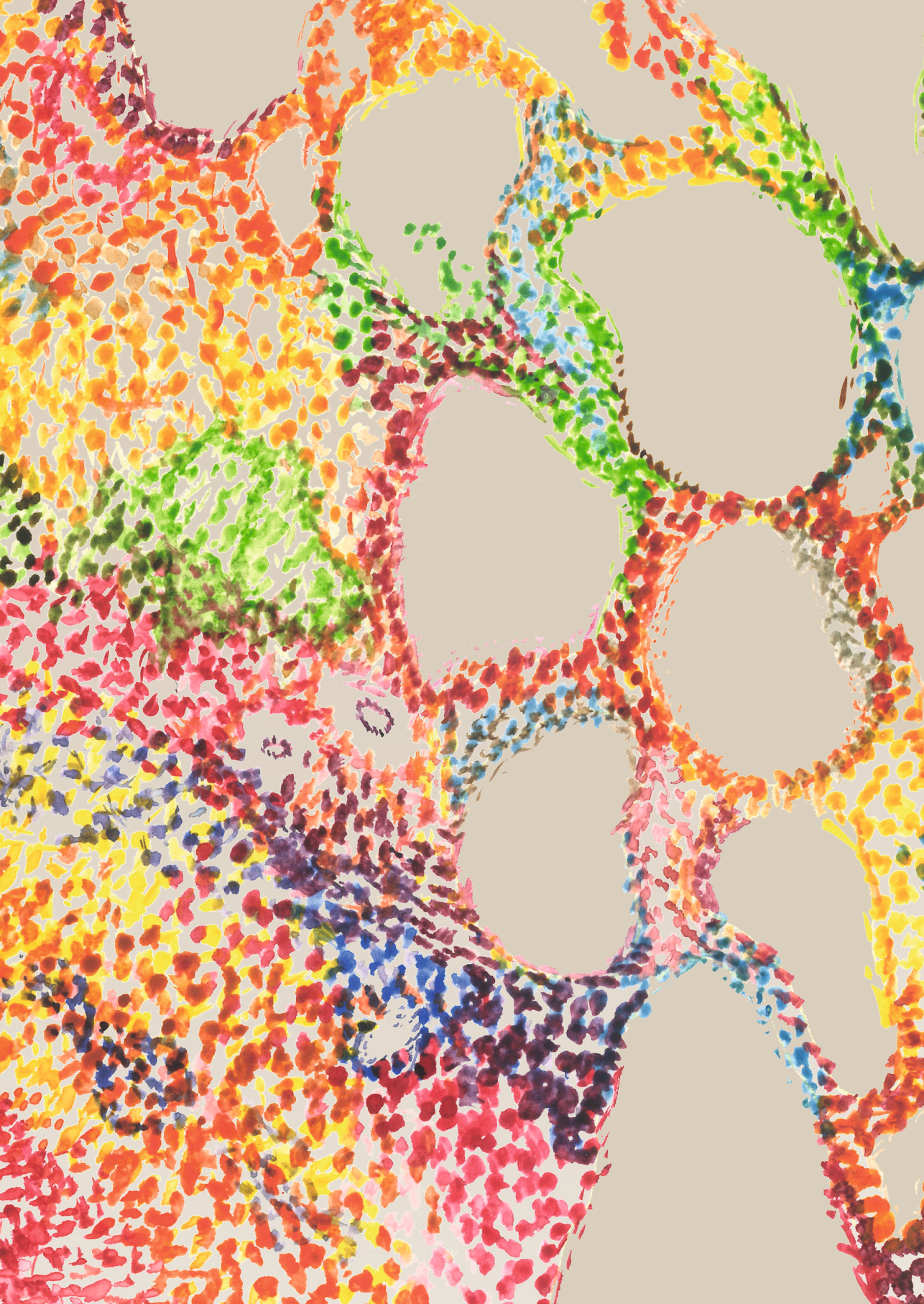

5 CHAPTER

Incidence of PSMA PET thyroid incidentaloma depends on analysis method and tracer

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ABSTRACT

To investigate the incidences of prostate-specific membrane antigen (PSMA) thyroid incidentaloma (PTI) using different methods to define PTI, to compare the incidence of PTI among different PSMA PET tracers and to evaluate the clinical consequences of PTI. PSMA PET/CT scans in consecutive patients with primary prostate cancer were analyzed for the presence of PTI using a structured visual (SV) analysis reporting any elevated thyroidal uptake; a semi-quantitative (SQ) analysis using a SUVmax thyroid/bloodpool (t/b) ratio ≥ 2.0 as cutoff; and an analysis of PTI incidence in the clinical reports (RV analysis). A total of 502 patients were included. The incidence of PTIs was 22% in the SV analysis, 7% in the SQ analysis and 2% in the RV analysis. PTI incidences differed significantly from 29 to 64% (SQ, resp. SV analysis) for [18F] PSMA- 1007, 7 to 23% for [68Ga]PSMA-11, 2 to 8% for [18F] DCFPyL and to 0% for [18F]PSMA-JK-7. The majority of PTI in the SV and SQ analyses consisted of diffuse (72–83%) and/or only slightly elevated thyroidal uptake (70%). Inter-observer agreement in the SV analysis was substantial (kappa = 0.76–0.78). During follow-up (median 16.8 months), there were no thyroid-related adverse events except in three patients. The incidence of PTI varies greatly among different PSMA PET tracers and is strongly dependent on the analysis method applied. PTI may safely be restricted to focal thyroidal uptake with a SUVmax t/b ratio ≥ 2.0. The clinical pursuit of a PTI must be weighed up to the expected outcome of the underlying disease.

INTRODUCTION

Prostate carcinoma (PCa) is the most common malignant tumor in men worldwide with an incidence rate of 13,665 patients in 2021 in the Netherlands (1, 2). The PCa incidence steadily rises with an age-standardized incidence of prostate cancer over 60 per 100,000 men in the early 1990s and over 110 per 100,000 men in 2011 (2). Positron emission tomography/computed tomography (PET/CT) imaging targeting the prostate-specific membrane antigen (PSMA) plays an important role in the staging of primary and recurrent PCa and has proven to be superior to conventional imaging methods (3, 4). The clinical adoption of PSMA PET/ CT has led to the detection of PSMA-ligand uptake in non- prostatic tissues as well, such as the thyroid gland (5). These PSMA PET thyroid incidentalomas (PTIs) include benign and malignant thyroid lesions with retrospective analyzed incidences ranging from 1 to 2% (6–8).

It is of additional value to provide practical tools to clinicians who treat prostate cancer patients on how to handle a PTI. Most available literature concerns FDG PET/CT thyroid incidentaloma (TI), which by convention includes only focal lesions, whereas diffuse FDG uptake is interpreted as a form of thyroiditis (9). Focal TIs appear to be malignant in up to one-third of the patients (10–13). Our earlier study showed an FDG-PET/CT TI incidence rate of 1.9% in oncological patients and demonstrated that the patient's survival was predominantly determined by the primary cancer, not by the possible malignant TI (14). In another retrospective study concerning PSMA PET thyroid incidentalomas, the patient's prognosis was also determined by the primary malignancy and not by the PTI (7).

The definition of the recently recognized PTI is still under debate: whereas some would only include focal lesions on PSMA PET, others have regarded PTI to include diffusely elevated thyroid uptake as well (6–8). Recently, the E-PSMA guidelines were developed to aid standardized interpretation and reporting of PSMA PET, which includes a system of grading the PSMA expression of PCa lesions in relation to reference tissues such as the bloodpool, liver and parotid glands (15). The thyroid gland is generally not taken into account in describing the physiological distribution of PSMA PET tracers, and thus, elevated thyroid uptake may not always be reported. This might be due to its presumed clinical irrelevance in the setting of PCa staging. These factors may have led to varying reporting rates of PTI in literature and possibly an underestimation of the incidence of PTI. Furthermore, the PTI incidence may be related to the applied PSMA tracer with higher reported incidences in the [18F]PSMA-1007 tracer (7). In this study, we aimed to investigate the incidence of PTI by reassessing a cohort of patients that underwent PSMA PET/CT using different methods to define PTI. A structured visual (SV) assessment

of thyroidal uptake and a semi-quantitative (SQ) analysis were deployed and compared with the PTI incidence rates in the clinical reports of the scans, i.e., the retrospective visual (RV) analysis. Furthermore, the PTI incidence was assessed for four commonly applied PSMA tracers: [18F]DCFPyL, [18F]PSMA-1007, [18F]PSMA-JK-7, and [68Ga]PSMA-11. Lastly, the clinical consequences of these PTIs were evaluated.

MATERIALS AND METHODS

Patients

This study was approved by the Institutional Review Board of the Antoni van Leeuwenhoek hospital (AVL) (IRBd21- 019). A cohort of consecutive patients who underwent PSMA PET/CT between August 2016 and May 2021 was selected from a prospectively maintained database at the AVL, a tertiary oncological referral hospital in the Netherlands. Patients underwent a PSMA PET/CT before prostatectomy because of intermediate/high-risk primary PCa (≥ cT3, International Society of Urologic Pathologists grade 2/Gleason score ≥ 4 + 3 or PSA ≥ 20 ng/mL) as per protocol. Patient characteristics and follow-up data were retrieved from the medical records.

PSMA PET imaging

PSMA PET imaging was performed in AVL or in one of the referring external centers using multiple tracers, according to local protocols. The applied PSMA tracers included the 18F bound tracers: [18F]DCFPyL, [18F]PSMA-1007, [18F] PSMA-JK-7, and the 68Ga bound tracer [68Ga]PSMA-11. The 18F bound tracers were synthesized via direct radiofluoration at an on-site cyclotron facility and [68Ga]PSMA-11 was produced on-site using a fully automated system (Scintom- ics GmbH), compliant to the Good Manufacturing Practices guidelines. PET images were acquired from mid-thigh to skull-base, median 118 min (interquartile range (IQR) 60–120) post-injection after a median dose of 288 MBq (IQR 204–312) for [18F]DCFPyL, 50 min (IQR 45–60) post-injection after a median dose of 105 MBq (IQR 96–148) for [68Ga]PSMA-11, a median of 90 (IQR 90–120) min post- injection after a median dose of 284 MBq (IQR 251–313) for [18F]PSMA-1007 and a median of 77 min (IQR 60–90) after a median dose of 201 MBq (IQR 194–265) for [18F] PSMA-JK7. PSMA PET/CT imaging was performed on Siemens Truepoint, Philips Ingenuity/Gemini TF or Philips Vereos integrated PET/CT systems. PET images were combined with either a low-dose CT scan (120–140 kV, 40–80 mAs with dose modulation) or a full-dose CT scan (130 kV, 110mAs) with or without intravenous contrast enhancement. All PET images were corrected for scatter, decay and random coincidences. All PSMA PET/CTs, whether performed in AVL or in one of the referring centers, were (re)-assessed and reported by a nuclear medicine physician in the AVL.

Data collection and image analysis

All PSMA PET/CT images were viewed using the Osirix Dicom Viewer (Pixmeo). For the SV analysis, three nuclear medicine physicians (M.D., M.W., Z.C.) with ample experience in reading PSMA PET/CT scans were instructed to visually analyze the PET/CT images and to indicate whether a PTI was present. Observers were blinded from clinical information including the clinical reports of the scans. The visual definition of PTI was defined as any focal uptake in the thyroid gland above the average thyroid tracer uptake, or diffuse uptake exceeding the normal background activity in the soft tissues in the head-neck area, as adapted from Gossili et al. (6). In any case, the PTI had to be discernable from noise and soft- tissue background activity in the head-neck area on a PET whole-body maximum intensity projection (MIP) (**Figure 1**). Furthermore, observers were asked to describe the pattern (focal, irregular, or diffuse) and intensity (slightly, moderately, or intensely elevated) of uptake. A random selection of 75 cases from each observer M.W. or Z.C. (in total 150 cases) was re-analyzed by observer M.D., blinded from information and the results of the first analysis to determine inter-observer reliability.

For the SQ analysis, a volume of interest (VOI) was placed over the thyroid gland and the maximum standardized uptake value (SUVmax) thyroid corrected for body weight was determined. Subsequently, a VOI was placed over the ascending thoracic aorta and the SUV_{max} value of the bloodpool was measured. The SUV_{max} thyroid/bloodpool (t/b) ratio was determined in every patient. Based on previous studies reporting on a SUV_{max} lesion-to-background ratio discriminating borderline/malignant thyroid lesions on FDG PET/CT [16] and malignant lesions on PSMA PET/CT [17, 18], a SUV_{max} t/b ratio of ≥ 2.0 was determined as positive for PTI. In the case of a PTI, the pattern was visually determined and categorized as focal, diffuse, or irregular.

Lastly, for the RV analysis, all clinical reports of the PSMA PET/CTs were reviewed. Used tracer and the presence of PTI were noted. Any remark of elevated thyroid uptake on PSMA PET/CT in the clinical report was regarded as positive for PTI. Furthermore, the description of the PTI was categorized according to the pattern: focal or diffuse and to intensity: slightly, moderately, or intensely elevated.

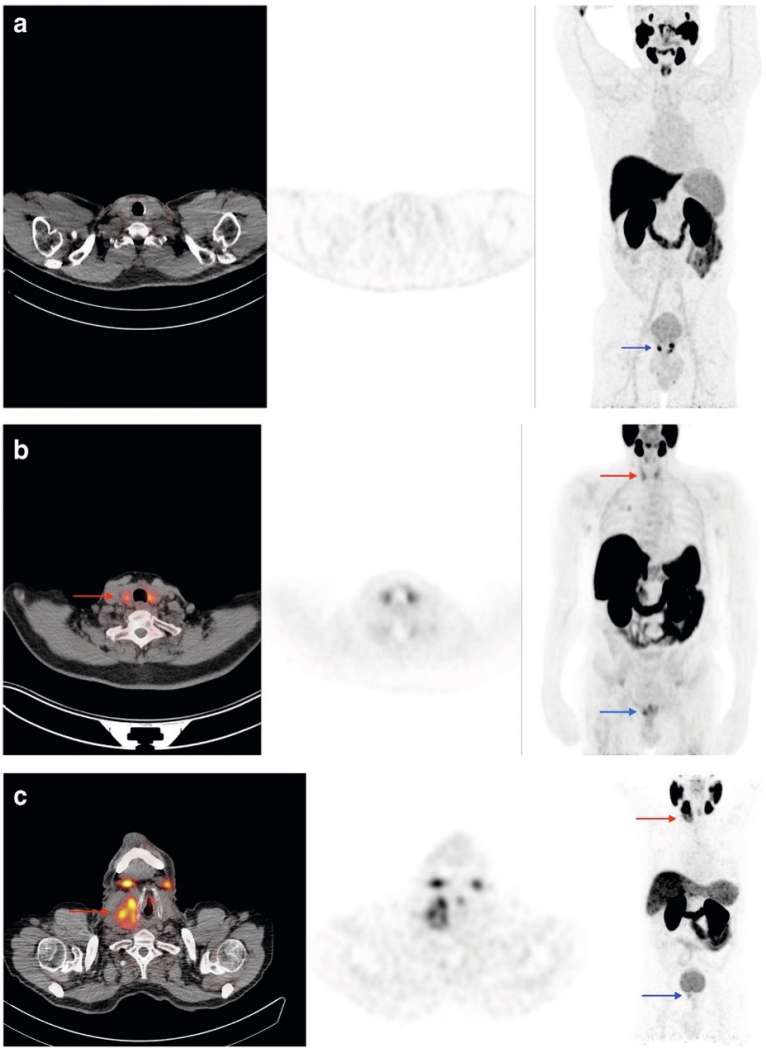

Figure 1 Example images of prostate-specific membrane antigen (PSMA) thyroid incidentaloma (PTI) with focal, irregular, and diffuse patterns and varying level of intensity. Transverse, transverse fused to low-dose CT, and maximum intensity projection (MIP) images of PSMA PET scans are shown. Applied window with SUV_{max} 0–7.

a. [18F]PSMA-JK-7 PET/CT showing no elevated tracer uptake in the thyroid. The primary prostate cancer is visible as multiple intense spots in the prostate (blue arrow, MIP).

b. [18F]PSMA-1007PET/CT showing moderately, diffusely elevated tracer uptake in the thyroid (red arrows).The primary prostate cancer is visible as multiple moderately intense spots in the prostate (blue arrow, MIP).

c. [68Ga] PSMA-11 PET/CT showing intensely, irregularly elevated tracer uptake in the thyroid (red arrows). The primary prostate cancer is visible as a relatively faint spot in the prostate (blue arrow, MIP)

Statistical analysis

Incidences in PTI were calculated for the different analyses (SV, SQ, RV). To test for an overall difference in the incidence of PTI, Cochran's Q test was used, followed by pairwise comparisons of the methods using McNemar's test with Bonferroni adjustment. For every analysis, differences in PTI incidence rates were compared between the various PSMA tracers using Fisher's exact test followed by post hoc pairwise Z-tests with Bonferroni adjustment. For the SV analysis, any difference in PTI incidence rates between the observers was tested using Fisher's exact test. Kappa coefficient was used to estimate agreement between the observers. The agreement between two observers was evaluated by Cohen's kappa with standard error and percent agreement. To determine kappa (κ) values, response categories were dichotomized as 0, no PTI present, and 1, PTI present (focal, diffuse, or irregular). As conventionally classified, kappa values of 0–0.20 indicate a poor, 0.21–0.40 a fair, 0.41–0.60 a moderate, 0.61–0.80 a substantial and 0.81–1.0 a nearly perfect agreement (19). All statistical tests were two-tailed and a value of $p \leq 0.05$ was considered statistically significant. Statistical analyses were conducted using R software, version 4.0.3, and Statistical Package for Social Sciences (SPSS, IBM; v27).

RESULTS

A total of 502 male patients with a mean age of 67 (± 6.5) years and PSMA PET/CT scans for intermediate/high- risk primary PCa were included in this analysis. The used PSMA tracers were [68Ga]PSMA-11 (n = 266), [18F]DCF- PyL (n = 154), [18F]PSMA-1007 (*n* = 56), and [18F]PSMA-JK-7 (n = 26). The median (IQR) follow-up time from the first date of the PSMA PET/CT scan was 16.8 (8.4–32.4) months.

PTI incidence per PSMA tracer

The incidence of PTI ranged from 0% for [18F]PSMA- JK-7 to 64% for [18F]PSMA-1007 and differed significantly among tracers in the SV method and SQ analysis (Fisher's exact test $p < 0.001$), whereas the incidence of PTI did not differ significantly among tracers in the RV analysis ($p = 0.520$; **Table 1**). Post hoc pairwise comparisons using Z-tests with Bonferroni correction for the SV analysis showed significantly lower PTI incidences in [18F]DCFPyL (8%; $p < 0.001$) and [18F]PSMA-JK-7 (0%; $p = 0.022$), and higher PTI incidence in [18F]PSMA-1007 (64%; $p < 0.001$; **Table 2**). Post hoc pairwise comparisons for the SQ method showed significantly lower PTI incidences in [18F] DCFPyL (2%; $p = 0.008$), and higher PTI incidence in [18F]PSMA-1007 (29%; $p < 0.001$)

Table 1 Overall comparison of PTI incidence between the different tracers 68Ga-PSMA-11, ^{18}F-DCFPyL, ^{18}F-PSMA-1007 and 18F-PSMA-JK-7, per method, using Fisher's exact test.

	Method	**Uptake pattern**	**Tracer**					***p*-value**
			^{68}Ga-PSMA-11	^{18}F-DCFPyL	^{18}F-PSMA-1007	^{18}F-PSMA-JK-7	*Total*	
PTI incidence (%)	SV	Diffuse	39 (15%)	8 (5%)	32 (57%)	0	79 (16%)	
		Focal	13 (5%)	2 (1%)	3 (5%)	0	18 (4%)	
		Irregular	10 (4%)	2 (1%)	1 (2%)	0	13 (3%)	
		Total	62/266 (23%)	12/154 (8%)	36/56 (64%)	0/26	110/502 (22%)	<0.001*
PTI incidence (%)	SQ	Diffuse	14 (5%)	3 (2%)	14 (25%)	0	31 (6%)	
		Focal	4 (2%)	0	2 (4%)	0	6 (1%)	
		Total	18/266 (7%)	3/154 (2%)	16/56 (29%)	0/26	37/502 (7%)	<0.001*
PTI incidence (%)	RV	Diffuse	4 (2%)	1 (1%)	0	0	5 (1%)	
		Focal	3 (1%)	1 (1%)	2 (4%)	0	6 (1%)	
		Total	7/266 (3%)	2/154 (1%)	2/56 (4%)	0/26	11/502 (2%)	0.520

Table 2 Post-hoc comparison of PTI incidence between the different tracers for the SV- and SQ analysis: results of pairwise Z-tests corrected for multiple testing are shown as *p*-values per tracer.

SV analysis		Tracer				
		^{68}Ga-PSMA-11	^{18}F-DCFPyL	^{18}F-PSMA-1007	^{18}F-PSMA-JK-7	Totals
PTI present	yes	62	12	36	0	110
	no	204	142	20	26	392
***p*-value**		1.000	<0.001*	<0.001*	0.022*	

SQ analysis		Tracer				
		^{68}Ga-PSMA-11	^{18}F-DCFPyL	^{18}F-PSMA-1007	^{18}F-PSMA-JK-7	Totals
PTI present	yes	18	3	16	0	37
	no	248	151	40	26	465
***p*-value**		1.000	0.008*	<0.001*	0.558	

PTI prostate-specific membrane antigen, PET thyroid incidentaloma, SV structured visual, SQ semiquantitative, RV retrospective visual
*Statistical significance ($p \leq 0.05$)

PTI incidence per analysis

The incidence of PTI varied considerably between the different analyses (**Table 3**). The incidence of PTI was 22% (n = 110) according to the SV analysis, 7% (n = 37) according to the SQ analysis, and 2% (n = 11) according to the RV analysis. Comparing the various analyses, Cochran's Q test indicated a significant overall difference in the incidence of PTI ($p < 0.001$). Post hoc pairwise comparisons of the several analyses using McNemar's test with Bonferroni adjustment showed significant differences in PTI incidence for all comparisons ($p < 0.001$), meaning that the three different analyses differed from each other in PTI incidence (**Table 4**).

Table 3 Overall comparison of PTI incidence between the SV, SQ and RV analyses using Cochran's Q test.

	Observer			
	RV	RSQ	*RT*	***p*-value**
PTI incidence (%)	110/502 (22%)	37/502 (7%)	10/502 (2%)	<0.001

PTI prostate-specific membrane antigen PET thyroid incidentaloma, SV structured visual, SQ semiquantitative, RV retrospective visual
*Statistical significance ($p \leq 0.05$)

Table 4 Results of McNemar's post hoc pairwise comparisons with Bonferroni adjustment showing the p-value per method comparison.

	RV	RSQ	RT
RV	-		
RSQ	<0.001*	-	
RS	<0.001*	<0.001*	

PTI prostate-specific membrane antigen PET thyroid incidentaloma, SV structured visual, SQ semiquantitative, RV retrospective visual
*Statistical significance ($p \leq 0.05$)

PTI patterns and intensity

The majority of PTIs showed a diffuse uptake pattern, both in the SV analysis (n = 79/110; 72%) and in the SQ analysis (n = 31/37; 83%). According to the SV analysis, most of the PTIs consisted of only slightly elevated thyroidal uptake (n = 77, 70% of all PTI) (**Table 5**). Non-diffuse, moderately- intensely elevated thyroid uptake consisted of 10/110 PTIs (9%) and 10/502 of all patients (2%).

Table 5 Numbers of PTI (total n = 110) subdivided according to uptake pattern and intensity.

		PTI intensity			
		Slight	Moderate	Intense	*Total*
PTI uptake pattern	Diffuse	56	20	3	79
	Focal	15	2	1	18
	Irregular	6	5	2	13
	Total	77	27	6	110

PTI prostate-specific membrane antigen PET thyroid incidentaloma

PTI inter-observer agreement

The incidence of PTI did not differ significantly between observers in the SV analysis (range 19–25%; Fisher's exact test $p = 0.459$; **Table 6**). There was a substantial agreement between the observers with Cohen's kappa values ranging from 0.76 to 0.78 and an overall level of agreement ranging from 91 to 93% (**Table 7**).

Table 6 Overall comparison of the PTI incidence between the observers in the structured visual (SV) method using Fisher's exact test.

	Observer				
	1	2	3	total	***p*-value**
PTI incidence (%)	30/155 (19%)	50/203 (25%)	30/144 (21%)	110/502 (22%)	0.46

Table 7 PTI inter-observer agreement for the SV method shown as % agreement and Cohen's kappa value per observer pairwise comparison.

Observer comparison	Kappa (standard error)	% Agreement	Number of shared PTIs
Observer 1 vs observer 3	0.78 (0.1)	93	12
Observer 2 vs observer 3	0.76 (0.09)	91	16
Observer 1 + 2 vs observer 3	0.77 (0.06)	92	28

Clinical consequences

Thirty-one patients with PTIs who were identified with the SV method had follow-up PSMA PET/CT performed within a median (IQR) of 12 (8.4–24) months of the initial study. In nineteen patients (61%), the thyroidal PSMA uptake resolved on follow-up PSMA PET/CT, in twelve patients (39%) the PTI persisted (**Figure 2**). Twelve patients, of which seven (58%) were identified in the SV or SQ analysis, underwent thyroid function screening to sudden hemorrhage of a cystic thyroid nodule which needed surgical intervention. Two patients received fine needle aspiration cytology (FNAC) (**Figure 2**). One patient had a focal PTI in the right thyroid lobe and a Bethesda IV score at FNAC. The patient underwent a hemithyroidectomy and the final pathology result showed pT1 papillary thyroid cancer. The other patient had a focal PTI in the left lobe and a Bethesda IV score as FNAC result with a difficult distinction between thyroid and parathyroid tissue. This patient had the final diagnosis of primary hyperparathyroidism based on elevated plasma levels of parathyroid hormone and received no thyroid surgery. In none of the patients in whom any form of further thyroid workup was withheld, the PTI became clinically relevant during a median (IQR) follow-up of 16.8 (8.4–39.6) months.

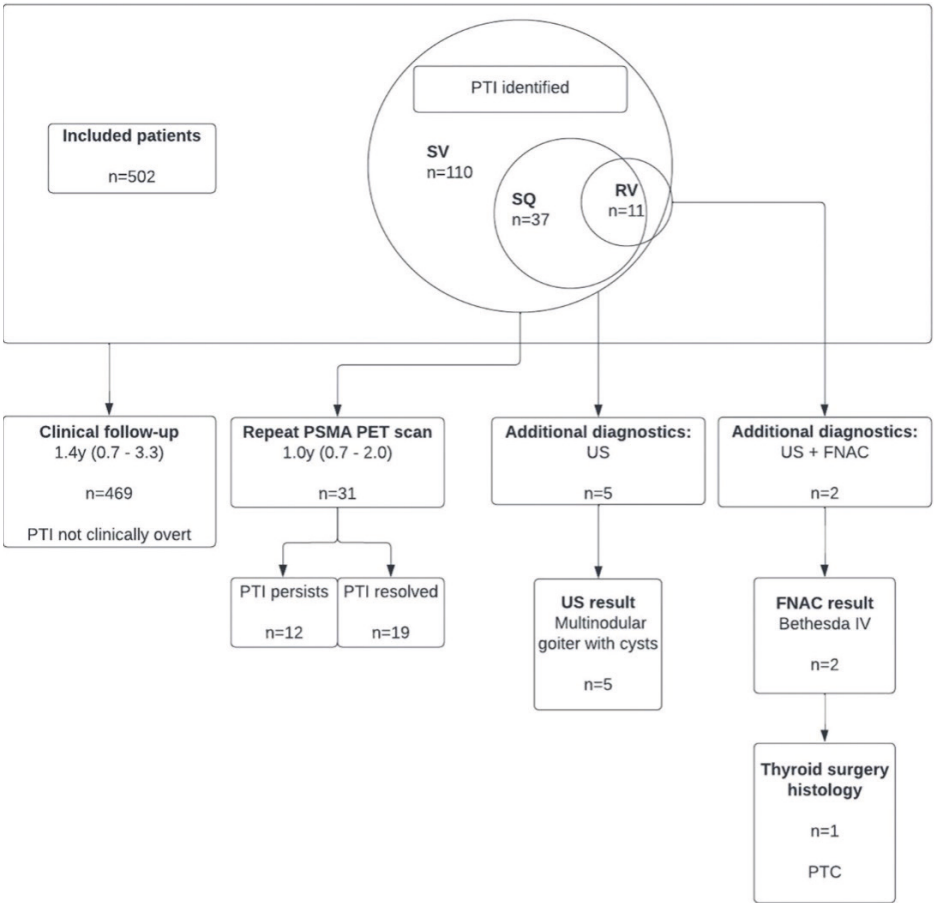

Figure 2 Graphical representation of PTI detected per method and number of shared PTIs; flow-chart of follow-up data. Follow-up duration displayed in years (y): median (interquartile range).

FNAC= Fine-needle aspiration cytology; PSMA PET= prostate-specific membrane antigen positron emission tomography; PTC = papillary thyroid carcinoma; PTI = PSMA thyroid incidentaloma; RV = Reassessment Visual, RSQ = Reassessment Semiquantitative; RT = Retrospective; US = ultrasound

DISCUSSION

The increasing clinical adoption of PSMA PET/CT for the staging of PCa has led to a rising detection of PSMA PET PTIs. This study aimed to investigate the incidences of PTI comparing several analysis methods and different PSMA PET tracers to assess the inter-observer agreement and to investigate the clinical consequences of PTI in PCa patients. The PTI incidence differed substantially between tracers with the highest incidence in the [18F]PSMA-1007 tracer in both the SQ and SV analyses (29%, resp.

64%), whereas lower incidences were found for [18F]DCFPyL (2%, resp. 8%) and no PTI at all for [18F]PSMA-JK-7. This is in line with our earlier two-center retrospective study in which we found a relatively high PTI incidence in [18F]PSMA-1007 (8%) compared to [18F]DCFPyL and [68Ga]PSMA-11 (0.8, resp. 0.9%) (7). The structured visual (SV) analysis yielded a significantly higher PTI incidence than the semi-quantitative (SQ) analysis (22% vs 7%). The PTI incidence rates in the clinical reports (RV analysis; 2%) were the lowest of the three analyses. Virtually, all PTIs described in the clinical reports (RV analysis) and detected using the SQ method were detected in the SV method as well, whereas the SQ and RV methods also had considerable overlap. The PTI incidence did not differ significantly between observers and the inter-observer agreement was substantial (kappa coefficient 0.76–0.78), indicating the robustness of PTI findings in the SV method.

A considerable majority of PTIs concerned PTIs with a diffusely elevated thyroidal uptake (72–83%) and contributed substantially to the higher incidence of PTI in the SV and SQ analyses. High incidences of diffuse thyroidal uptake were seen especially in [18F]PSMA-1007, and to a lesser extent in [68Ga]PSMA-11 (15%), which is in line with an earlier study reassessing PSMA PET/CTs for physiological tracer distribution patterns and incidental uptake (20). However, diffuse uptake patterns may be regarded as benign and may be ignored by observers because of their presumed clinically irrelevance in the setting of staging PCa (21). Furthermore, in the SV analysis, slightly elevated thyroidal uptake was regarded as positive for PTI, while in clinical practice of staging PCa this may easily be overlooked. These factors may attribute to the considerable differences in PTI incidence between the SV, SQ, and RV analyses. When excluding PTIs with a diffuse uptake pattern and/or only slight intensity from the SV analysis, the incidence of PTI was substantially lower (2%) and comparable to the incidence in the RV analysis and our earlier retrospective studies concerning PTI and FDG PET TI (7, 14). An argument to restrict the definition of PTI to focal thyroidal uptake with substantial intensity (moderately or intensely elevated uptake) may be the analogy with FDG PET in which only focal uptake has been associated with the risk of malignancy (22, 23). Furthermore, the intensity of TI uptake (SUV_{max}) in FDG PET may be associated with an increased risk of malignancy and high PSMA expression has been shown in cases of differentiated thyroid carcinoma as well (22–26). On the other hand, diffuse thyroidal uptake without any structural abnormalities on CT may reflect a physiologic phenomenon that is typical for tracers such as [18F]PSMA-1007 and [68Ga]PSMA-11. Kirchner et al. reported unremarkable thyroid function tests or imaging follow-up in 11/12 patients with diffusely elevated thyroid uptake on [68Ga]PSMA-11 PET/CT (20). Still, the clinical relevance of diffuse thyroidal PSMA-ligand uptake needs to be elucidated. During the clinical follow-up, there were no thyroid- related adverse events except for a small minority of patients with clinically reported PTI who received additional diagnostics. In our earlier

retrospective study, the patient's prognosis during a median follow-up of 1.8 years was also determined by the primary malignancy and not by the PTI (7). However, clear criteria for PTI and long-term follow-up data are lacking. Applying a SUVmax thyroid/SUV_{max} bloodpool ratio of 2.0 or more may serve as a threshold to qualify a focal PTI as clinically relevant. Prospective studies are needed to refine this SUV_{max} ratio criterion for clinically relevant PTIs. The possible benefits of (early) detection of thyroid cancer must be weighed against increased costs, risks and patients' anxiety about additional diagnostics and treatment in the setting of the underlying PCa, especially given the increasing recognition of low-risk thyroid cancer (27–31).

Strengths and limitations

The main strength of this study is the large consecutive cohort of patients that could be formed from a prospective institutional database. Furthermore, a comparison could be made between multiple clinically used PSMA tracers as well as an inter-observer comparison of PTI incidence reported by three different experienced nuclear medicine physicians, which has not been described before. Lastly, this study gives unprecedented insight into the uptake patterns and intensity levels of PTI. A limitation is the retrospective design of the study and a relatively short clinical follow-up period. Furthermore, there is no clear consensus on what a clinically relevant PTI is; therefore, the results of this study may be less reproducible in other centers.

CONCLUSION

The incidence of PTI varies greatly among different PSMA PET tracers with the highest incidence in the [18F]PSMA-1007 tracer and is strongly dependent on the analysis method applied. The structured visual assessment of thyroidal uptake showed a substantial inter-observer agreement and a considerably higher incidence of PTI, which may be attributed to a large proportion of PTIs with diffuse and/or slightly elevated uptake. Although the definition of clinically relevant PTI needs to be further refined, the current and former study results suggest that a PTI may safely be restricted to focal thyroidal uptake with a SUVmax t/b ratio ≥ 2.0. The clinical pursuit of a PTI must be weighed up to the expected outcome of the underlying disease by implementing a shared decision strategy..

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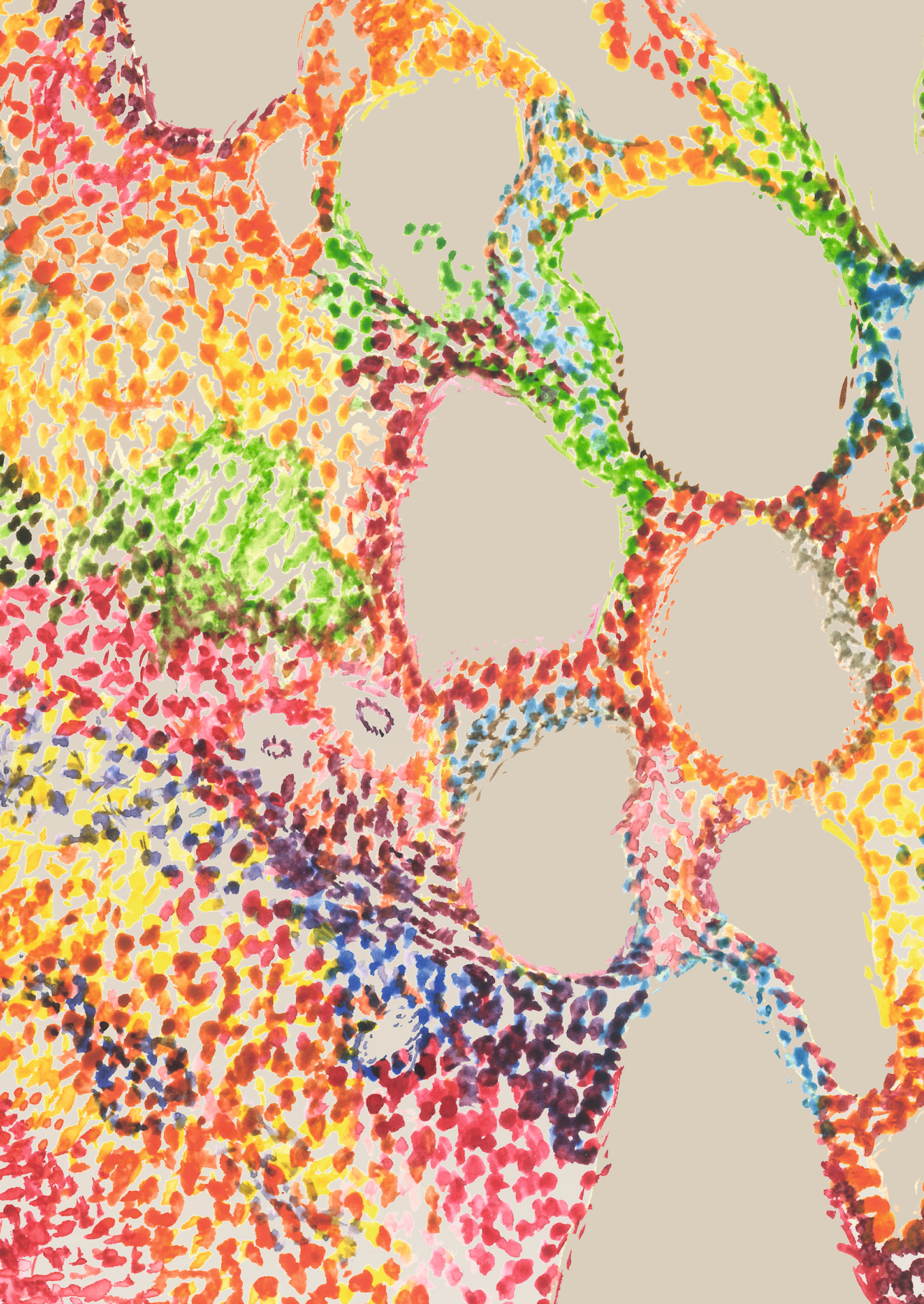
PART II

The optimization of care in the treatment of thyroid cancer



6 CHAPTER

The co-occurrence of both breast and thyroid cancer: incidence, association and clinical implications for daily practice

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ABSTRACT

Breast cancer (BC) and differentiated thyroid cancer (TC) are two common cancer types with the highest incidence in women. BC and TC can develop synchronous or metachronous and the occurrence of both is higher than expected by chance. This study aimed to examine the association between BC and TC in the Netherlands. This is a retrospective cohort study during the period of 1989-2020 retrieved from the Netherlands Cancer Registry (NCR). Patients diagnosed with BC-TC and BC alone as control group and TC-BC and TC alone as control group were included. The primary outcome was the standardized incidence ratio (SIR) of BC-TC and TC-BC. Secondary outcomes included data on the demographics, type of malignancy, treatment and overall survival (OS). The incidence of TC among 318.002 women with BC (BC-TC) was 0.1% (423 patients) (SIR = 1.86 (95% CI: 1.40-2.32) and the incidence of BC among 12370 patients with TC (TC-BC) was 2.9% (355 patients) (SIR=1.46 (95% CI: 1.09-1.83)). BC-TC patients were younger compared to the BC alone group at BC diagnosis (55 vs 60 years, $p < 0.001$). The age-adjusted odds ratio to develop TC was not significantly increased for patients who received chemotherapy and radiotherapy. Most TC cases were synchronous tumors after BC diagnosis (19%) with a TNM stage 1. Only 6% of the BC tumors after TC occurred synchronous with a TNM stage 1 in most cases. The overall survival (OS) of all groups was the most favorable in patients with both BC and TC compared to BC- and TC alone. The SIR of TC after BC diagnosis and BC after TC diagnosis was higher than predicted based on the rates of the general population. TC and BC as second primary tumors were diagnosed in an early stage and did not affect OS. Therefore, women who have been treated for BC or TC require no special surveillance for their thyroid- and breast gland.

INTRODUCTION

Breast cancer (BC) is the most diagnosed cancer in women worldwide and the leading cause of cancer-related death in women (1). Improvements in breast cancer screening, earlier detection and treatment options have resulted in increased long-term survival rates (2,3). Most women are diagnosed with early stage BC with a 5-year survival rate of > 95% (4). The relatively large group of breast cancer survivors may experience long-term treatment effects during follow-up. A considerable number of these long-term survivors may be at an increased risk of developing a second primary malignancy including thyroid cancer (2,5). Thyroid cancer (TC) is the most prevalent endocrine malignancy among women (6). According to data from the Dutch national cancer registry, the incidence of TC has increased in the Netherlands during the last decade with 906 new cases in 2021 (7,8). Well-differentiated papillary and follicular thyroid cancers account for approximately 90% of cases and have an excellent 20-year disease specific survival rate of > 95% (9). Given these favorable prognoses for both cancers, the risk of second primary malignancies is of particular concern (10).

Several articles have suggested that BC and TC can develop synchronous or metachronous in patients and that the rate of occurrence is higher than expected by chance (2,7,11,12,13). A large meta-analysis including patients from both Western- and non-Western countries demonstrated an increased risk of TC as a secondary malignancy following BC [odds ratio (OR) = 1.55; 95% confidence interval (CI), 1.44-1.67] and an increased risk of BC as a secondary malignancy following TC (OR = 1.18; 95% CI, 1.09-1.26) (2). In the Netherlands, the incidence of the occurrence of both diseases in the same patient and their possible correlation has not been extensively studied.

The hypotheses that may explain the higher incidence of one of these neoplasms following the other (BC-TC or TC-BC) is not clear (7,11). Common etiological factors, a genetic predisposition or a causal relation due to treatment-related factors, e.g chemotherapy, radiotherapy and radioactive iodine therapy, might play a role in the association (2,7,11).

The aim of this study is to estimate the incidence of TC as a second primary cancer after BC and BC as a second primary cancer after TC in a large national population of the Netherlands. The second aim is to identify the clinicopathological characteristics, overall survival and possible associations between TC and BC. A greater understanding of the clinical relationship between breast and thyroid cancer might help the post-treatment management of these patients.

METHODS

Patient selection

The study population of this retrospective cohort study consists of patients with a first primary breast cancer who subsequently developed thyroid cancer as a second primary malignancy and vice versa during the period of 1989-2020 in the Netherlands. The control groups consisted of patients with breast cancer or thyroid cancer without a second primary malignancy. The data was obtained from the Netherlands Cancer Registry (NCR) which collects data on all cancer patients diagnosed in the Netherlands, based on notification of newly diagnosed malignancies by the national automated pathological archive and of hospital discharge diagnoses. Information in the medical records on demographics, diagnosis, staging and treatment is extracted routinely by specially trained NCR personnel. The survival status is updated annually using a computerized link with the national civil registry. For the present analysis, information on survival and second primary cancers was analyzed up to the end of 2020. The study population included patients ≥ 18 years with the diagnoses of TC or BC and the second primary malignancies for these patients. Only patients with differentiated thyroid cancer (DTC) and/or invasive mammary carcinoma (BC) and/or ductal carcinoma in situ (DCIS) as a first primary- or second primary malignancy were selected for this study. Two cohorts were formed for further analyses: patients with BC followed by TC (BC-TC) versus BC alone as control group (first cohort) and patients with TC followed by BC (TC-BC) versus TC alone as control group (second cohort).

BC and TC clinicopathological features

Variables of the included patients were reviewed and data on the type, features, treatment and follow-up including the overall survival of BC and TC were collected and analyzed. Synchronous tumors refers to cases in which the second primary cancer was diagnosed within 6 months of the primary cancer. Metachronous tumors refers to tumors that were diagnosed more than 6 months after the diagnosis of the first primary cancer. The BC group was categorized in morphologically distinct groups based on immunohistochemistry. Estrogen (ER) and progesterone (PR) positivity were defined as tumor cell positivity of > 10%. Human epidermal growth factor receptor 2 (HER2) positivity was defined by immunohistochemistry (with FISH/SIHS when indicated). Clinical- and pathological Tumor-Node-Metastasis (TNM) staging was reported according to the 8th edition TNM classification by the American Joint Committee on Cancer (AJCC) for both BC and TC (14, 15). Additionally, specific information about genetic counseling was collected for patients who were diagnosed and/or treated in the Antoni van Leeuwenhoek hospital (n=31).

Statistical analysis

For the synchronous- and metachronous malignancies, standardized incidence ratios (SIR) were calculated as the ratio of the observed and expected number of cancer cases. In case of multiple metachronous cancers, only BC or TC as a second primary cancer was included in the analysis. The expected numbers were calculated by matching them with the incidence rates for the general population that were specified by age, gender, tumor type and year of diagnosis. Confidence intervals (95%) were calculated by assuming a Poisson distribution for the observed number of cases. A SIR of 1 means a similar incidence compared to the general population while a SIR of 10 indicates a 10-fold higher incidence in the studied population. The analysis was performed in Stata version 17.0 and *p*-values were at 0.05 significance alpha levels.

Baseline variables including normally distributed numeric data were reported with the mean and standard deviation. Differences between both groups were analyzed using the two-tailed, independent sample t-test. Non-normally distributed numeric data were described with the median and interquartile range and group differences were analyzed using the Wilcoxon rank-sum test. For categorical data frequency and percentages were reported, and differences between groups were analyzed with the Fisher's exact test or the Chi-squared test. Univariate logistic regression was performed to identify risk factors for the presence of TC and BC as second primary malignancies. The Kaplan–Meier method and a Cox proportional hazards model were used for the survival analysis. The OS was measured from the date of primary diagnosis (BC or TC) to the date of death from any cause, censoring patients who were still alive at the date of last contact. The OS was compared across the groups by using the log-rank test. A two-tailed $p < 0.05$ was considered statistically significant. These statistical analyses were conducted using R version 4.0.3.

RESULTS

Patient selection

In total, 890 patients with medullary thyroid cancer and 911 patients with anaplastic thyroid cancer were excluded. Patients with a second primary malignancy other than BC or TC were also excluded. **Figure 1** shows the patient-selection for this study. A total of 423 cases were identified in the BC-TC cohort with a control group of 317579 patients with BC alone. The TC-BC cohort consisted of 355 patients with a control group of 12015 patients with TC alone.

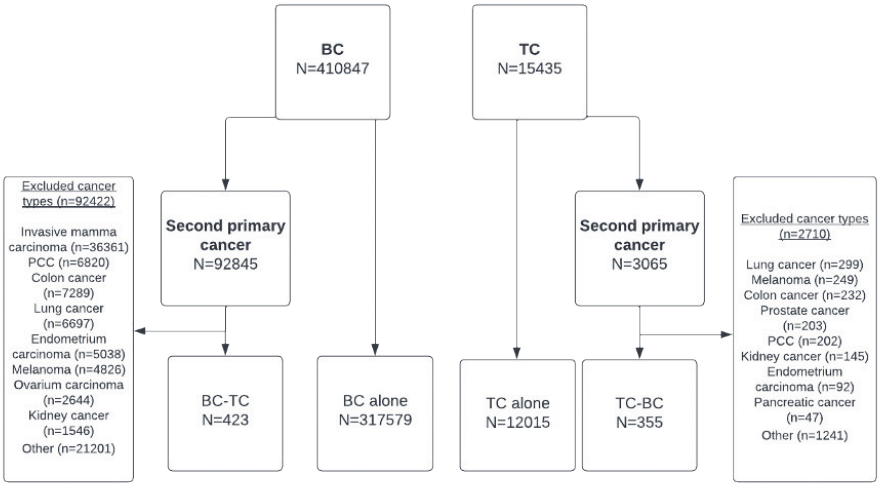

Figure 1 Flowchart of patient-selection.

Incidence of the BC-TC cohort and the TC-BC cohort

The incidence of TC among 318.002 women with BC was 0.1% (423 patients) (SIR = 1.86 (95% CI: 1.40-2.32)) and the incidence of BC among 12.370 patients with TC was 2.9% (355 patients) (SIR=1.46 (95% CI: 1.09-1.83)). The median (IQR) interval between BC and TC was 4.2 (1.0-10.4) years and between TC and BC 8.2 (3.6-14.9) years. The highest incidence of TC as a second primary tumor following BC was observed during the first year of follow-up (26%) and in 80 patients (19%) the tumors were synchronous. Thirty-five patients (10%) with BC were detected during the first year of TC follow-up and in 21 patients (6%) the tumors were synchronous. In **Figure 2** the distribution of new patients with BC-TC and TC-BC is shown for the complete follow-up period.

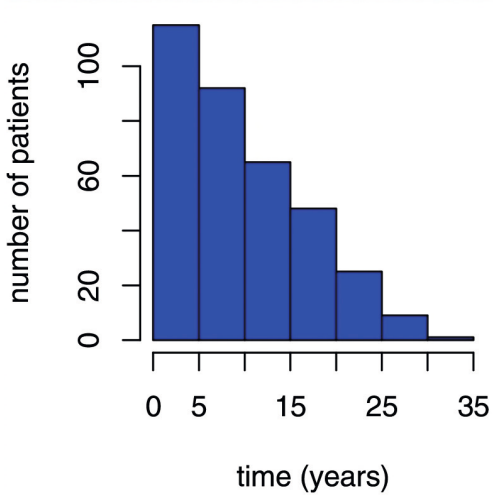

Figure 2a Histogram of the distribution of new TC-BC patients.

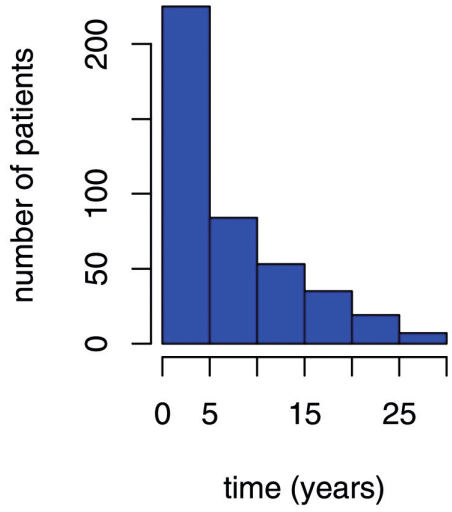

Figure 2b Histogram of the distribution of new BC-TC patients

Features of BC patients followed by TC (BC-TC) and BC alone patients (1st cohort)

The clinicopathological features and treatment of the BC-TC group and BC alone group are presented in **Table 1**. Patients with BC followed by TC had a significantly younger age at the time of BC diagnosis (55 vs 60 years, $p < 0.001$) and consisted of only women. The majority of patients had a TNM stage I TC (51.1%) at the time of diagnosis. The median (IQR) tumor size of TC was 1.5 (0.8-2.5) cm and papillary thyroid carcinoma (PTC) was the most common subtype (78.3% of cases). Relatively more patients underwent chemotherapy (CT) in the BC-TC group compared to the BC alone group (37.4% vs 30.8% respectively, $p <0.001$). Also, more patients underwent radiotherapy (RT) in the BC-TC group compared to the BC alone group (63.8% vs 58.8% respectively). The age-adjusted odds ratio to develop TC was 0.91 (95% CI: 0.73-1.13, $p = 0.4$) for patients who received CT and 1.06 (95% CI: 0.87-1.30, $p = 0.6$) for patients who received RT. These non-sigificant associations suggest that age affects the indication for both CT, RT and the outcome TC.

In subgroup analysis, two subsequent groups were formed consisting of Adolescents and Young Adults aged 18-39 years and patients > 39 years. The risk ratio to develop TC was not significantly increased for both subgroups of patients who received CT: 18-39 years: OR = 0.9, 95% CI: 0.7-1.3, $p = 0.9$ and > 39 years: OR = 0.9, 95% CI: 0.9-1.1, $p = 0.8$. The risk ratio to develop TC was not significantly increased for patients aged 18-39 years who received RT (OR = 0.9, 95% CI: 0.7-1.3, $p = 0.6$) but slightly increased for patients who received RT > 39 years (OR = 1.12, 95% CI: 1.0-1.2, $p = 0.02$).

Table 1 Clinicopathological features and treatment of breast cancer patients followed by thyroid cancer and breast cancer only patients (1st cohort).

Variables	BC-TC (median (IQR)/%)	BC alone (median (IQR)/%)	*p*-value
No. of patients	423	317579	
BC clinical characteristics			
Age at BC diagnosis	55 (46-65)	60 (50-71)	< 0.001
Female	423 (100)	315808 (99.4)	0.2
Tumor size in mm	15 (10-25)	17 (11-25)	0.1
Tumor side			1
Left	223 (52.7)	164071 (51.7)	
Right	199 (47.0)	152907 (48.1)	
Unknown	1 (0.2)	601 (0.2)	
TNM stage			0.3
0	38 (9.0)	29125 (9.2)	
I	154 (36.4)	112063 (35.3)	
II	176 (41.6)	122649 (38.6)	
III	43 (10.2)	33816 (10.6)	
IV	9 (2.1)	16746 (5.3)	
M	0 (0.0)	1562 (0.5)	
Unknown	3 (0.7)	1618 (0.5)	
ER-positivity	201 (87.41)	151727 (82.61)	0.1
PR-positivity	154 (67.81)	120837 (67.01)	0.8
HER2-positivity	35 (17.5[1])	23810 (14.8[1])	0.5
BC surgery2	406 (96.0)	286592 (90.2)	<0.001
Breast-conserving	226 (53.3)	163501 (51.5)	
Ablative	168 (39.7)	13995 (35.9)	
Surgery NNO	12 (2.8)	8867 (2.8)	
BC radiation therapy	270 (63.8)	186779 (58.8)	0.04
BC chemotherapy	158 (37.4)	97895 (30.8)	<0.001
BC hormone therapy	191 (45.2)	140908 (44.4)	0.7

Table 1 Continued

Variables	BC-TC (median (IQR)/%)	BC alone (median (IQR)/%)	*p*-value
TC clinical characteristics			
Age at TC diagnosis	62 (52-72)		
Tumor size in mm	15 (8-25)		
Papillary thyroid cancer	331 (78.3)		
Follicular thyroid cancer	81 (19.1)		
Unknown histology	11 (2.6)		
Lymph node metastasis	98 (23.2)		
Distant metastasis	11 (2.6)		

1 Missings substracted
2 Missing patients

Features of TC patients followed by BC (TC-BC) and TC only patients (2nd cohort)

The clinicopathological features and treatments of the TC-BC group and TC alone group are presented in **Table 2.** The median age at TC diagnosis in the TC-BC group was not significantly higher compared to the TC alone group (51 vs. 50 years). More patients with a TNM stage II and -III for TC were present in the TC-BC group compared to the TC alone group (25.0%, 15.5% vs 14.7% and 14.3%). Less patients in the TC-BC group underwent thyroid surgery compared to the TC alone group. Most BC patients had a TNM stage 0, I or II at the time of BC diagnosis and invasive ductal carcinoma (81.1%) was the most common pathology result. The ER-, PR- and HER-2 positive rate was comparable in this TC-BC group and the BC alone group (84.7%, 68.4% and 14.6% vs. 82.6%, 67.0%, 14.8% respectively). The percentage of radioactive iodine (RAI) treatment was not significantly different between the TC-BC- and TC alone group.

Table 2 Clinicopathological features and treatment of thyroid cancer patients followed by breast cancer and thyroid cancer only patients (2nd cohort).

Variables	TC-BC (median (IQR)/%)	TC alone (median (IQR)/%)	*p*-value
No. of patients	355	12015	
TC clinical characteristics			
Age at TC diagnosis	51 (42-61)	50 (38-64)	0.3
Female	353 (99.4)	8593 (71.5)	<0.001
Tumor size in mm	28 (18-39)	19 (9-34)	0.2
Tumor site			< 0.001
Left	4 (1.1)	737 (6.1)	
Right	5 (1.4)	1018 (8.5)	
Isthmus	2 (0.6)	103 (0.9)	
Ectopic	0	15 (0.1)	
Both sites	3 (0.8)	451 (3.7)	
Unknown	341 (96.1)	9623 (80.1)	
TNM stage			< 0.001
I	186 (52.4)	7017 (58.4)	
II	89 (25.0)	1769 (14.7)	
III	55 (15.5)	1715 (14.3)	
IV	6 (1.7)	221 (1.8)	
IVa	10 (2.8)	667 (5.6)	
IVb	3 (0.8)	107 (0.9)	
IVc	2 (0.6)	312 (2.6)	
M	1 (0.3)	40 (0.3)	
Unknown	3 (0.8)	168 (1.4)	
TC surgery	352 (99.2)	11351 (94.5)	< 0.001
Thyroidectomy	287 (80.8)	8954 (74.5)	
Hemithyroidectomy	65 (18.3)	2379 (19.8)	
Isthmusectomy	0	18 (0.1)	
TC radioactive iodine	252 (71.4)	8068 (67.1)	0.1
TC radiation therapy	6 (1.7)	280 (2.3)	0.7

Table 2 Continued

Variables	TC-BC (median (IQR)/%)	TC alone (median (IQR)/%)	*p*-value
BC clinical characteristics			
Age at BC diagnosis	61 (52-70)		
Tumor size	15 (11-25)		
TNM stage	331 (78.3)		
0	53 (15.0)		
I	149 (42.0)		
II	99 (27.9)		
III	32 (9.0)		
IV	13 (3.7)		
M	1 (0.3)		
Unknown	8 (2.3)		
ER-positvity	211 (84.7[1])		
PR-positivity	169 (68.4[1])		
HER2-positivity	34 (14.6[1])		

1 Missings substracted

Overall survival of BC-TC and TC-BC group

The median (IQR) follow-up time in the BC-TC group was 25.2 (22.6-28.0) years and in the BC alone group 16.9 (16.8-17.0) years. The median follow-up time in the TC-BC group was 25.4 (24.3-26.5) years and in the TC alone group 23.1 (22.8-23.4) years. Of 124.653 death events in de BC- and TC cohort, 124 occurred in the BC-TC group (29.3%) and 124.529 in the BC alone group (39.2%); 193.349 patients in total were censored without event. Of 2903 deaths in the TC- and BC cohort, 93 occurred in the TC-BC group (26.2%) and 2810 in the TC alone group (23.4%); 9467 patients in total were censored without an event.

The age-adjusted hazard ratio (HR) for OS was significantly higher in the BC-TC group compared to the BC alone group (HR=1.4, 95% CI: 1.2-1.7, $p < 0.001$). The age-adjusted HR for OS in the TC-BC group compared to the TC alone group was also significantly increased (HR=1.4, 95% CI: 1.1-1.7, $p = 0.001$). The survival curves are depicted in **Figure 3** and **Figure 4**.

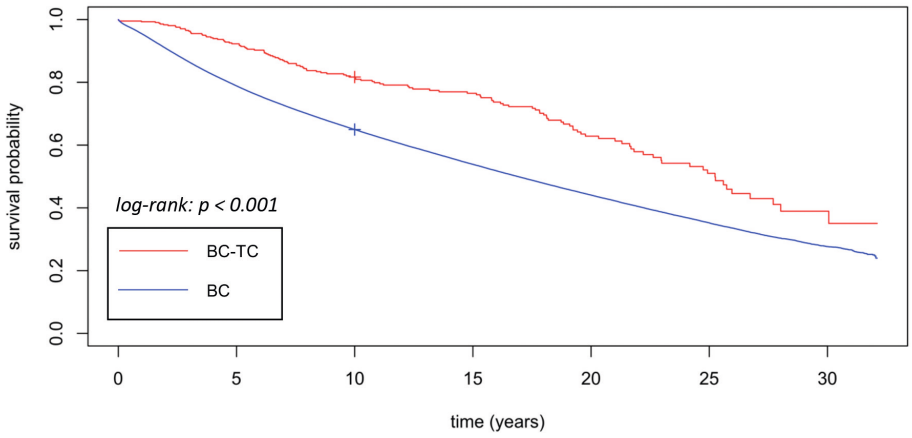

Figure 3 Kaplan Meier plot of overall survival of BC-TC patients and BC alone patients

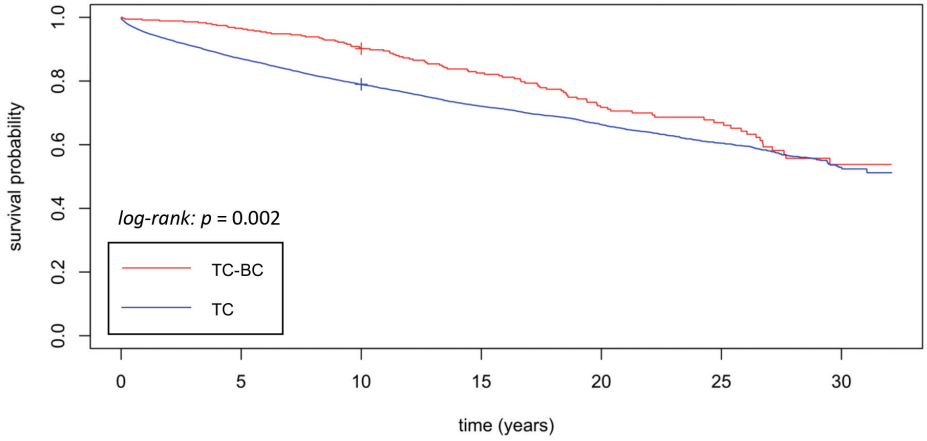

Figure 4 Kaplan Meier plot of overall survival (OS) of TC-BC (red) group and TC alone group

DISCUSSION

The SIR of TC after BC diagnosis (1.86) and the SIR of BC after TC diagnosis (1.46) was higher than predicted based on the rates of the general population. BC-TC patients were younger compared to the BC alone group (55 vs 60 years) at BC diagnosis and consisted of women only. Papillary thyroid carcinoma (PTC) and invasive ductal carcinoma respectively were the most common pathology results for second primary malignancies in the BC-TC and TC-BC group. Most TC diagnoses were depicted in the first year after BC treatment and were mostly TNM stage I. When comparing the studied cohorts, OS was less favorable in the BC alone group compared to the BC-TC group and in the TC alone group compared to the TC-BC group.

Association between BC and TC

The possible association between TC and BC has been suggested before. The higher incidence of TC in BC patients was confirmed by previous studies (2,12,13). Joseph et al. performed a meta-analysis of 18 studies and demonstrated a significantly increased risk of TC after a primary diagnosis of BC (BC-TC) ((SIR) = 1.59, 95% CI: 1.28–1.99, $p < 0.01$) (12). This SIR is slightly lower compared to our study (SIR = 1.86; 95% CI: 1.40-2.32, $p < 0.01$). Another large meta-analysis showed an odds ratio of developing TC as a secondary malignancy following BC of 1.55 (95% CI: 1.44, 1.67) (2). A previous study that was performed in the Netherlands included 9919 BC patients and observed a lower incidence of TC among BC patients compared to our study (0.02% vs. 0.1%) (13). This might be explained by the higher prevalence of TC in the general population of the Netherlands in the last decade (340 new TC patients in 1990 compared to 800 new TC patients in 2020) (8).

The incidence of TC among 13978 patients with BC in a Chinese cohort was 1.8% and the associated SIR was 4.48 compared to the general population (11). This higher SIR might be driven by overdiagnosis of thyroid cancer in China (16). Similarly, two meta-analyses showed a marginally increased risk of developing breast cancer as a second primary malignancy of thyroid cancer (SIR = 1.24, [95% CI:1.16-1.33], SIR = 1.25 [95% CI: 1.17-1.32]) compared to the general risk of developing a primary malignancy following thyroid cancer (12, 17). This number is also slightly lower compared to our study results.

Factors influencing BC and TC

The clinicopathological features of BC-TC and TC-BC patients were studied before. Studies show that the increased risk of BC among TC patients was higher in younger women under the age of 50 at the time of diagnosis (18-21). However, the age of TC-BC patients in our cohort was comparable to the TC alone group. Li et al. also showed a

significantly younger median age at the time of BC diagnosis in BC then TC patients (54 vs 59, $p < 0.001$) (22). In our cohort, BC-TC patients were also significantly younger compared to the BC alone group (55 vs 60, $p < 0.001$). This finding might also explain the relatively better survival in the BC-TC group during the first ± 18 years compared to the BC alone group (Fig. 3).

Despite several studies demonstrating an association between breast- and thyroid cancer, the mechanisms in which they are related remains elusive. Hypotheses focus on common etiologies such as hormonal, genetic, environmental and therapeutic factors (2). Another non-disease related factor includes the stringent cancer screening of these patients at a younger age which can result in more incidental findings (23). This can cause a lower stage of BC or TC at the time of diagnosis and probably a higher incidence. This study showed a relatively higher number of patients with DCIS in the TC-BC group compared to the BC alone group (15.0% vs. 9.2%). This finding is consistent with the study of Canchola et al. in which an increased incidence of DCIS following TC was found compared to invasive breast cancer (24). The tumor size of TC in the BC-TC group was smaller (Table 1) compared to the TC tumor size in the TC alone group (Table 2) (1.5 cm vs. 1.9 cm, $p = 0.03$) which is consistent with previous results (25). It has also been demonstrated that the risk for TC was significantly higher during the first 3 years of follow-up in BC patients compared to the general population (SIR 1.22, 95% CI [1.14, 1.31]) (22). The study of An et al. confirmed this with a higher incidence of second primary TC the first 5 years after BC diagnosis (26). These findings are consistent with our results and may reflect an increase in imaging surveillance in patients when diagnosed with BC. Follow-up of breast cancer treatment in the Netherlands aims for an early detection of locoregional breast cancer recurrences and metastastic disease (27). Positron emission tomography also called a PET/CT scan was found to be useful in the follow-up of patients with breast cancer and is used for BC patients with BRCA1/2 mutations during the first 5 years of follow-up (28). In 2% of PET/CT examinations, FDG-thyroid incidentaloma are detected with a thyroid cancer prevalence of 35-40% (29). These incidental findings may explain the increased TC incidence during the first 5 years of BC follow-up.

Other theories focus on hormonal factors because the breast and thyroid are glands regulated by the hypothalamic-pituitary axis. BC and TC are both predominantly hormone-related cancers with a specific carcinogenic mechanism (30). Both breast- and thyroid cancer demonstrate a gender disparity favoring women in this study. Both estrogen and progesterone have potential effects on thyroid cell- and breast cell proliferation (31, 32). Estrogen (ER) is a potent growth factor for malignant thyroid cells and it was demonstrated that the levels of ER were significantly higher in thyroid cancer compared

to normal thyroid tissue (32, 33). Both ER and PR are thought to have functional roles in MCF-7 breast cell proliferation (31). Previous studies have shown that the expression of estrogen receptors (ER) and progesterone receptors (PR) were significantly higher in BC patients with co-existing TC, compared to those without (34-36). However, the results of this study show a similar ER- and PR receptor rate in the TC-BC cohort compared to the BC alone group. The role of thyroid hormone in the development of breast cancer remains uncertain (37).

Other potential etiological factors are related to the treatment for the primary malignancy. The use of radioactive iodine (RAI) treatment has been studied in relation to the higher risk for BC in differentiated thyroid cancer (DTC) patients. RAI treatment did not seem to increase the risk of BC in previous studies and our study observations are consistent with these previous results (38-41).

Marcheselli et al. showed that chemotherapy and radiotherapy in BC patients were related to increased risk of developing any second cancer, whereas hormonal therapy (HT) had a protective effect (42). A recent prospective study showed that hormone replacement therapy (HRT) with estrogen alone was associated with an increased risk of DTC (HR 1.67, 95% CI 1.08–2.59) (43). However, HT had no protective effect for the development of DTC in our study. Radiotherapy is the most extensively researched treatment-related factor in the association between BC and the risk for TC. Some studies have shown that radiation can cause thyroid disorders such as hypothyroidism, Graves' disease and thyroid cancer (44-48). Another study could not confirm this finding (49).The study of Sun et al. showed that younger patients with BC exhibited a significantly higher risk of TC than those in the comparison control cohort, regardless of whether they received RT (50). The current study shows that patients > 39 years who received RT for BC had an increased risk for developing TC. In the study of Lin et al., chemotherapy for BC did not significantly increase HRs for the risk of thyroid cancer (adjusted HR = 1.02, 95% CI 0.62–1.66) (51). Our age-adjusted odds ratio also showed no significant association between chemotherapy and an increased risk for TC. The associations remained insignificant after stratification by age groups.

Genetic factors have also been suggested as a possible explanation for the association between BC and TC. The Cowden syndrome is currently the only tumor syndrome known that increases the risk of developing both breast and thyroid cancer in the same individual (2). Mutation in the tumor suppressor PTEN gene is the most common cause of Cowden syndrome (2,52). In our study, a small number of patients (N=31) underwent genetic counseling in the Antoni van Leeuwenhoek hospital and therefore had the results available. One of these patients had Cowden syndrome (CS) and the associated

mutation in the tumor suppressor gene PTEN. In a previous study, the propensity for breast and thyroid cancer as a second primary malignancy was higher in individuals with PTEN mutations (SIR = 8.92 for breast cancer and SIR = 5.83 for thyroid cancer) (2, 52). The study of Bakos et al. could not identify mutations in the PTEN gene in patients with synchronous breast and thyroid cancer (53). They did report an increased burden of single nucleotide polymorphisms (SNPs) in patients with TC and BC compared to patients with BC alone. If more genetic sequencing is brought into clinical practice, more variants and mutations might be identified.

Strengths and limitations

The main strength of this study is that it represents a comprehensive examination of the incidence and association of BC-TC and TC-BC for a large population in the Netherlands during a long follow-up period. Limitations of this study are related to the data source. For example, detailed information about genetic counseling was lacking for most patients outside of the Antoni van Leeuwenhoek hospital. Due to the retrospective nature of this study, missing information could not be verified. The cancer-specific survival was also not available through the NCR.

CONCLUSION

The SIR of TC after BC diagnosis (SIR 1.86) and BC after TC diagnosis (SIR 1.46) was higher than predicted based on the rates of the general population in the Netherlands. Treatment related factors such as chemotherapy and radiotherapy were not associated with developing BC followed by TC after adjusting for age. TC as second primary tumor was diagnosed in an early stage and did not compromise survival. Therefore, special surveillance of the thyroid gland in BC survivors is not advisable. All women aged 50-75 years in the Netherlands are enrolled in the national BC screening program. Earlier or more frequent surveillance of the breast gland in TC survivors is not recommended.

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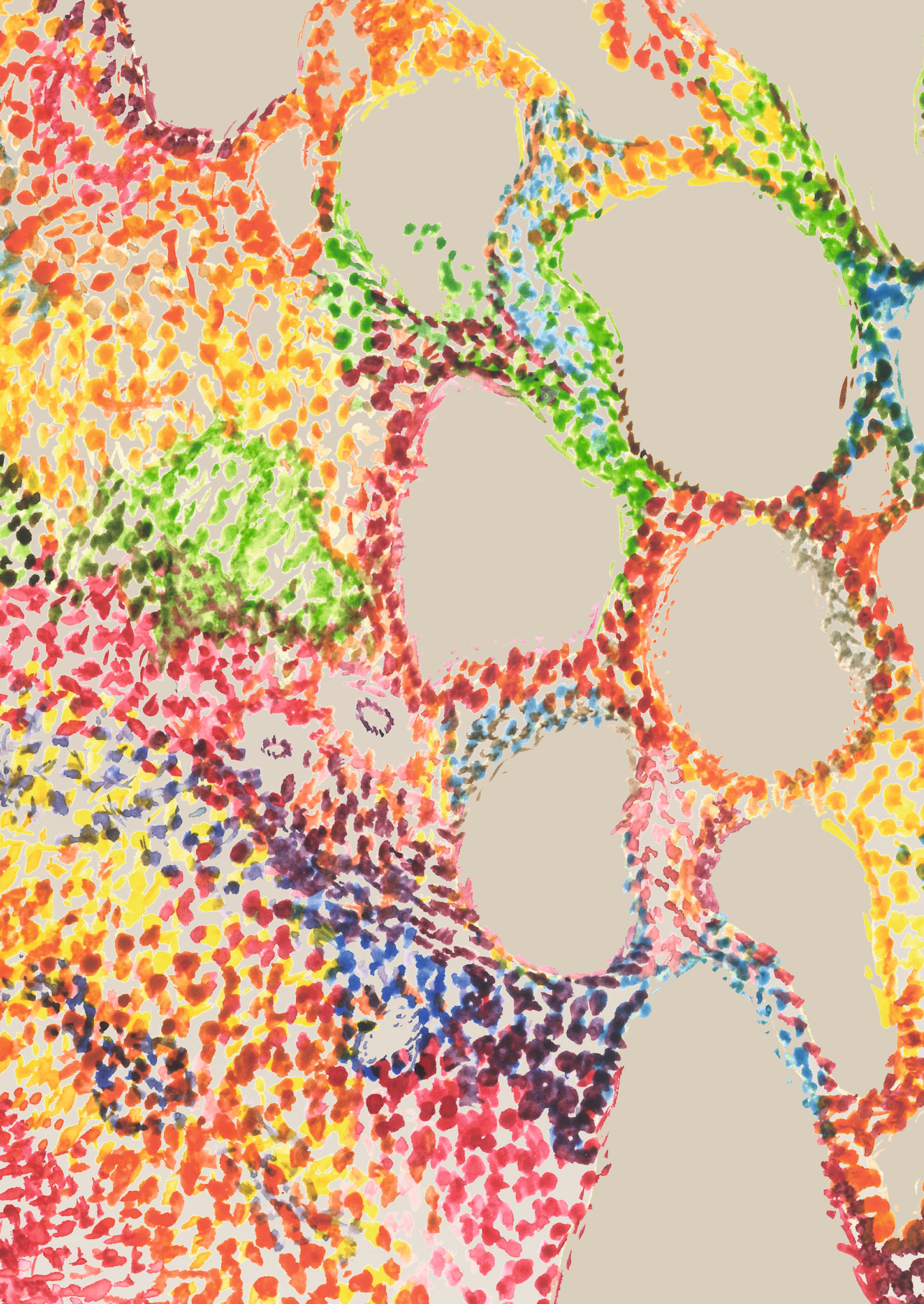

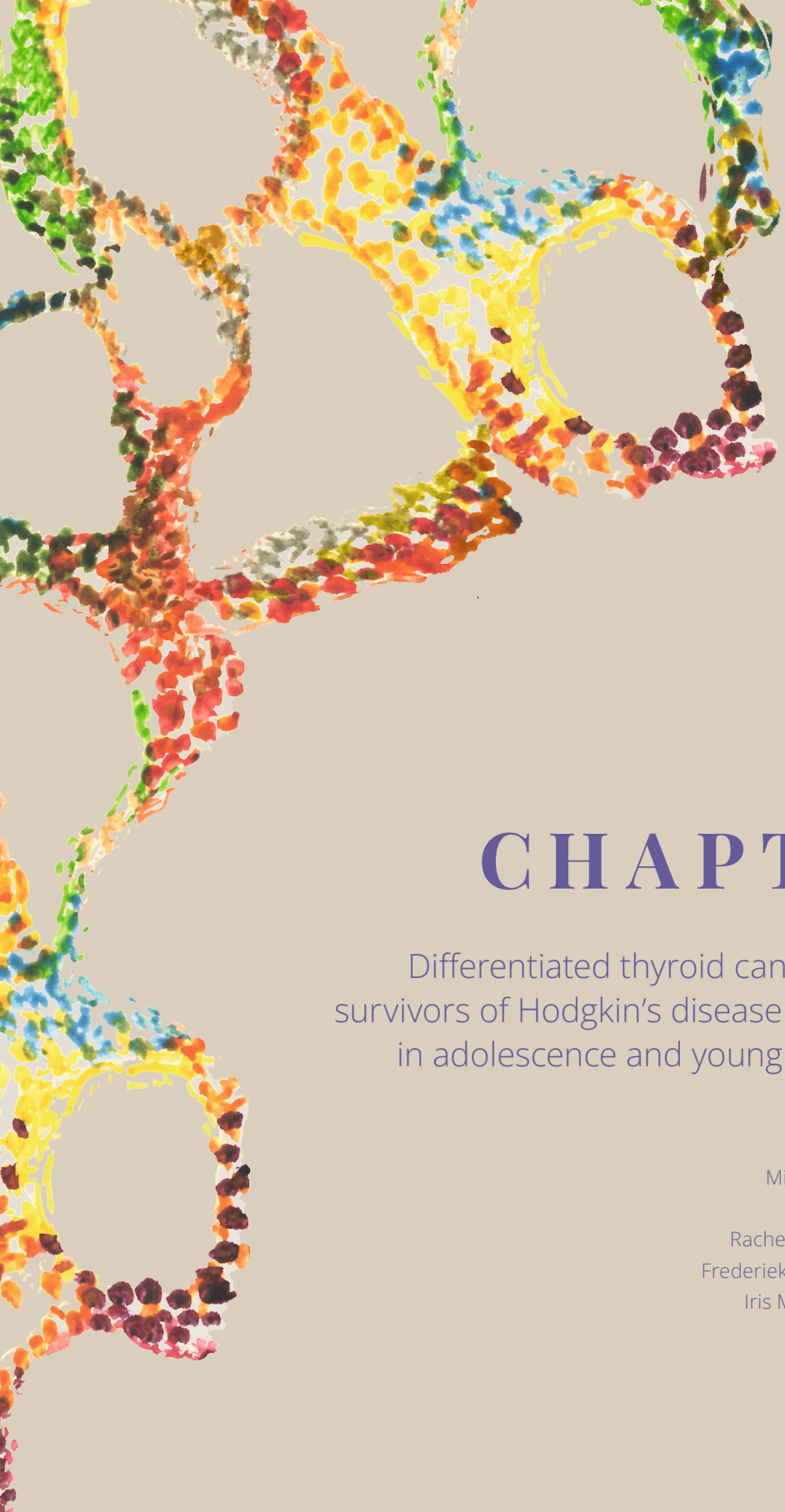

7 CHAPTER

Differentiated thyroid cancer among survivors of Hodgkin's disease diagnosed in adolescence and young adulthood

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ABSTRACT

To assess risk of differentiated thyroid cancer (fTC) after Hodgkin's disease (HD) treatment in adolescents and young adults compared to the general population and to compare histopathological subtypes, clinical and survival features of TC in HD survivors to that in frequency matched patients with primary TC. The Standardized Incidence Ratio (SIR) for TC was calculated among 9079 5-year HD survivors who were diagnosed from 1989 to 2016 in the Netherlands. Subsequently, the features of 35 TC patients who were diagnosed with TC between 1989 and 2021 and had a history of HD was compared with a frequency matched (matching ratio 1:5) control group of patients with primary TC, matched on age, sex and date of diagnosis (±5 years). Twenty-six HD patients developed a subsequent TC, resulting in a SIR of 6.8 (95% confidence interval (CI): 4.4-9.9) compared to TC incidence in the general population. The 35 patients with TC after a previous HD more often had pathological stage T3 thyroid cancer (23% vs 13%) and more often had metastases to regional cervical lymph nodes (32% vs 20%) compared to control group patients. All-cause mortality was not significantly different between patients who developed TC after HD and patients with primary TC (HR = 0.7, 95% CI: 0.3-1.9). This study demonstrated a significant increased TC risk for adolescents and young adults who were treated for HD compared to the general population. Although the pathologic subtypes of TC among HD survivors were more aggressive, the overall prognosis did not differ.

INTRODUCTION

Each year, approximately 480 patients are diagnosed with Hodgkin's disease (HD) in the Netherlands (1). Over the past decades, the use of combined/multi modality treatment combining different treatments such as radiotherapy, immunotherapy and systematic chemotherapy with curative intent has improved the disease-specific survival of HD (2). The current 5- and 10-year relative survival rates for HD patients treated before the age of 55 years are approximately 91% and 84%, respectively (1). HD survivors may be at risk for treatment-related effects such as secondary neoplasms that may manifest many years after treatment (3-5). A previous study on HD survivors reported a ten-fold increased risk for thyroid cancer (6). This risk of thyroid cancer was higher for children and adolescents treated for Hodgkin's disease than it was among adults (7-9).

Mantle field irradiation was the most common supradiaphragmatic radiation field applied from the early 1970s to the late 1980s (10,11). Since then, an increasing number of patients received more limited radiation fields referred to as involved field and more recently involved node irradiation (11,12). HD patients treated with radiotherapy alone usually receive 40 Gray (Gy) in fractions of 1.5-2.0 Gy, whereas patients treated with additional chemotherapy receive 30-36 Gy in similar fractions (13). A study of the German Hodgkin Study Group showed that treatment with chemotherapy followed by 20 Gy was as effective as 30 Gy in patients with early-stage HD (14). Hodgkin's disease often involves the mediastinal and head- and neck lymph node regions and radiation therapy to the neck or chest is known to be a risk factor for developing thyroid cancer (15,16).

Current literature on long term follow-up and development of secondary cancers is mainly focused on patients treated for HD in childhood; data including patients treated for HD during adolescence and young adult life is more limited (17,18). This retrospective cohort study aimed to assess the Standardized Incidence Ratio (SIR) of differentiated thyroid cancer (TC) in patients treated for HD during adolescence and young adulthood compared to TC rates in the general population. The histopathological subtypes, clinical features and survival of HD-TC patients compared to patients with primary TC was also assessed.

METHODS

Study population

A cohort of 9079 5-year survivors of HD treated between 1989 and 2016 at an age of 10-39 years were identified from the the population-based Netherlands Cancer Registry (NCR). Patients with TC before lymphoma diagnosis, patients who underwent radiotherapy to the trunk, head, or neck before lymphoma diagnosis and patients who developed a second malignancy that was treated with radiotherapy to the chest or neck within the first 5 years following treatment for lymphoma were excluded. The pathological reports for the cohort were retrieved from the Pathological Anatomical National Automated Archive (PALGA).

Subsequently, all patienst who developed TC between 1989-2021 and had a history of HD prior to TC diagnosis were selected from the file of the NCR. Of these 9 patients were diagnosed with HD before 1989. These 35 patients with TC after HD were frequency matched with patients (matching ratio 1:5) with primary TC diagnosed between 1989 and 2021, selected from 1576 patients with primary TC retrieved from the NCR. Matching variables included age, gender and the date of diagnosis with a range of 5 years. Data provided included information on diagnosis, histological findings, stage, received treatment, TC diagnosis dates and date of last-follow-up or death.

Statistical analysis

The standardized incidence ratio (SIR) was calculated as the ratio of the observed number of TC cases in HD survivors and the expected number of patienst with TC based on age-, gender- and calendar-year specific TC incidence rates for the general population. Confidence intervals (95%) were calculated by assuming a Poisson distribution for the observed number of cases. Differences between HD survivors who developed TC and sporadic TC controls in dichotomous or categorical data was assessed by chi-squared tests or Fisher's exact tests. Differences in continuous variables between groups was assessed by the two-tailed, independent sample t-test. The Kaplan–Meier method was used to estimate overall survival (OS), measured from the date of TC diagnosis to the date of death from any cause, censoring patients who were still alive at the date of the last contact. The OS was compared using the log-rank test. Statistical analyses were performed using R software (version 4.0.3.) and Stata (version 17.0). All P-values were two-sided, and an association with a p-value <0.05 was considered statistically significant. Only pseudonymized data was analyzed.

RESULTS

Standardized Incidence Ratio (SIR) for TC

In the first analysis, a total of 9079 5-year survivors of HD treated between 1989 and 2016 at an age of 10-39 years were included. In total, 26 out of 9097 HD survivors (0.3%) developed differentiated thyroid cancer (TC). Compared with an age- and sex-matched population, a 6.8-fold increased TC risk was observed (95% confidence interval (CI): 4.4-9.9).

Patient and tumor characteristics

In the second analysis, thirty-five HD survivors who developed TC between 1989 and 2021 were included. Thyroid malignancies were diagnosed at a median of 18.0 (IQR 13-22) years after initial HD treatment.The median age at HD diagnosis of patients who developed TC was 20 years (IQR 16-25 years) with the majority of patients being diagnosed < 35 years (97%). The most common histological subtype was nodular sclerosing Hodgkin's lymphoma (91%) followed by mixed cellularity Hodgkin's Lymphoma (9%). They mostly were treated with doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD) combination chemotherapy (74%) and received radiation to the neck (74%). Three of these patients underwent mantle field irradiation. In 9 patients (26%), the treatment information was missing.

In **Table 1**, the patient and clinicopathological TC characteristics for both the HD-TC and TC-1 cohorts are shown. Most HD survivors had unilobar thyroid disease (91%), two had involvement of the isthmus (6%) and one involvement of both lobes (3%). Six of the 35 patients (17%) had multifocal disease, 6 had capsular invasion (17%) and 14 had blood vessel invasion (40%). The HD survivors more often had pathological T stage III TC (23% in the HD-TC group vs 13% in TC-1 group). The rate of lymph node metastases was also higher in the HD-TC patients compared to TC-1 patients (32% vs 20%). The higher rate of lymph node metastases in HD-TC patients resulted in more extensive regional lymph node surgery compared to TC-1 patients (29% vs. 14%, p = 0.03). The proportion of patienst who received radioactive iodine treatment was significantly higher in the HD-TC group. None of the HD-TC patients developed a recurrence during follow-up.

Table 1 Histopathological features of thyroid cancer in Hodgkin's lymphoma survivors compared to controls.

Variables	TC after HD N = 35 (n (%))	First primary TC N = 175 (n (%))	*p*-value
Sex			NA
Female	20 (57)	100 (57)	
Male	15 (43)	75 (43)	
Age			NA
19-39 years	18 (51)	90 (51)	
> 39 years	17 (49)	85 (49)	
Morphology			0.01
Papillary histology	26 (74)	158 (90)	
Follicular histology	9 (26)	15 (9)	
Hurtle cell carcinoma		2 (1)	
Differentiation grade			0.09
I		5 (3)	
II	1 (3)		
III		2 (1)	
IV			
Tumor size in cm (mean (±SD)	2.0 (±1.2)	1.4 (±1.5)	0.11
Pathological T stage			0.3
I	16 (46)	84 (48)	
II	8 (23)	32 (18)	
III	8 (23)	23 (13)	
IV	2 (6)	10 (6)	
X	1 (3)	26 (15)	
Pathological N stage			0.13
0	3 (9)	30 (17)	
I	11 (32)	35 (20)	
X	21 (60)	87 (50)	

Table 1 Continued

Variables	TC after HD N = 35 (n (%))	First primary TC N = 175 (n (%))	*p*-value
Pathological M stage			0.38
0	9 (26)	48 (27)	
I	0	3 (2)	
X	26 (74)	25 (14)	
Surgery TC	35 (100)	152 (87)	0.02
Thyroidectomy	24 (69)	77 (44)	
Hemithyroidectomy	8 (23)	70 (40)	
Thyroid isthmusectomy	0	5 (3)	
Unknown	3 (9)	0	
Chemotherapy TC	0	0	
Radioactive iodine TC	25 (71)	84 (48)	0.01
Surgery cervical metastases*	10 (29)	24 (14)	0.03
Radiotherapy metastases	1 (3)	3 (2)	0.65
Radioactive iodine metastases	1 (3)	3 (2)	0.65

NA = not applicable

* Some patients underwent multiple neck dissections

The mean (± SD) follow-up time in the HD-TC group was 9.3 (± 6.2) years and 9.6 (± 5.4) years in the TC-1 group. During follow-up, 6 deaths (17%) occurred in the HD-TC group compared to 20 in the TC-1 group (11%). The rate of all-cause death was not sigficantly different between HD-TC patients and TC-1 patients (log-rank 0.54, p = 0.54). (**Figure 1**)

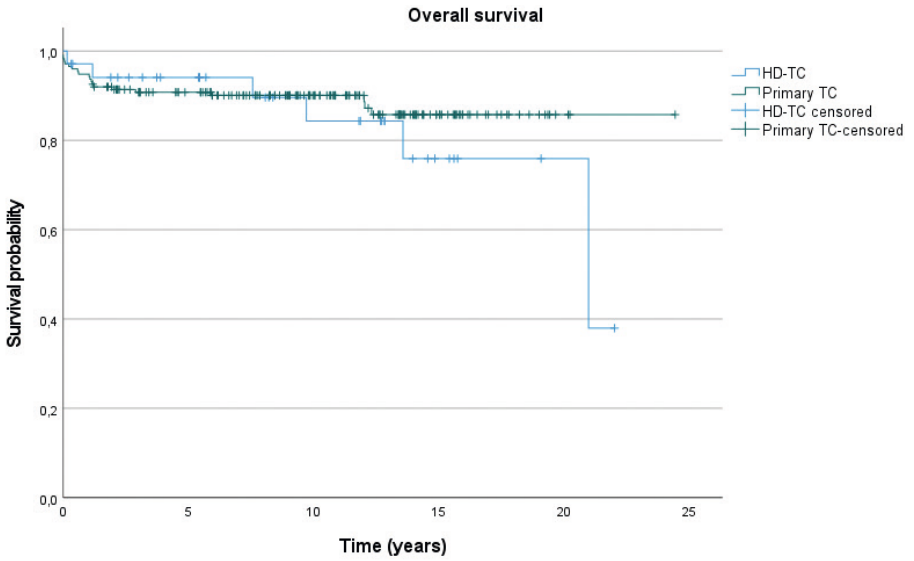

Figure 1 Survival analysis.

DISCUSSION

Increased risk of second primary TC after HD

In the Netherlands 26 HD patients treated between 10-39 years and diagnosed between 1989 and 2016, developed a subsequent TC, resulting in a SIR of 6.8 (95% confidence interval (CI): 4.4-9.9) compared to TC incidence in the general population.

The risk of second primary malignancies in HD survivors was studied previously, with the majority of previous studies on TC after HD focussing on pediatric HD survivors. The risk ratio of thyroid cancer in pediatric HD survivors was 18.3 compared to that in the general population (19). In our study the majority of HD-TC patients were adolescents and young adults who were < 35 years at the time of HD diagnosis (97%). Schaapveld et al. showed a ten-fold increased incidence of TC in patients treated for HD between 15 and 51 years (6). Michaelson et al. observed a 9.2-fold increased thyroid cancer risk (95% confidence interval, 6.1-33) compared with a normal, age- and sex- matched population in patients treated for HD between 13 and 28 years (17). Schonfeld et al. calculated a

standardized incidence ratio (SIR) for papillary thyroid cancer of 2.1 for patients < 50 years and 1.4 for patients > 50 years at diagnosis of HD (20). The lower estimated thyroid cancer risk in the current study compared to pediatric cancer survivors may be related to the mostly young adult HD cohort. Radiation therapy (RT) to the thyroid gland has been associatied with an increased risk of thyroid cancer (17,16,21). Head and neck radiation treatments in childhood are a known risk factor for thyroid cancer as thyroid glands of children are more sensitive to radiation (22,23). The adult thyroid gland is less sensitive to radiation compared to children, but can also be affected during radiation therapy in the head- and neck region (23). Among adult cancer survivors who received radiation treatment, patients with Hodgkin lymphoma had a strongly increased risk of thyroid cancer (SIR = 6.73) based on the Surveillance, Epidemiology and End-Results cancer registries (24). Our study found that almost all patients with TC as a second primary tumor after HD had received radiation therapy for HD in the neck area before the age of 35 years (for 26% of the patienst treatment data for HD was missing). The study of Michaelson et al. also observed no thyroid cancer cases in patients irradiated after the age of 35 years (17).

In the Netherlands, there is no national screening program for HD survivors. Nevertheless, some HD survivors are screened by their physicians for thyroid abnormalities after radiation in the neck region by annual laboratory assessment and palpation of the thyroid gland every 1-3 years (25). The use of ultrasound during follow-up remains controversial since although it enables the detection of nonpalpable thyroid cancer, it also detects more nonmalignant nodules that are not clinically relevant (26-28). Enhanced surveillance can contribute to the increased detection of thyroid cancer in HD survivors (29).The study of Michaelson et al. shows that half of the detected thyroid malignancies were discovered through screening or incidentally (17). In the current study, it was not clear if the thyroid cancers were found incidentally but the number of (incidental) microcarcinomas < 1 cm was low in HD-TC patients.

Subtype of malignancy

The majority of adult HD survivors with thyroid cancer developed papillary- and follicular thyroid carcinomas (30,19,17). A minority of HD patients (16% of patients) developed thyroid cancers with a poor prognosis such as anaplastic, medullary, sarcoma, and squamous cell carcinoma (31). This rate of more aggressive variants of thyroid cancrinoma is comparable to the rate in the general population (10%-15%) (32). As our experience has hinted at a worse prognosis for undifferentiated thyroid cancers, we thought it of interest to study the most common well-differerentiated thyroid cancers (32). Robinson et al. found that thyroid malignancies after radiotherapy for HD are more advanced than those not associated with RT (33). Radiation-exposed patients in

childhood and adulthood were more likely to develop thyroid cancer in both lobes and demonstrated extrathyroidal spread (34,35). In the current study, HD survivors with TC were more likely to develop regional disease compared to patients with primary TC (32 vs 20%). This is in contrast to the study of Chowdry et al., who did not observe more metastatic- or regional disease at TC diagnosis in HD survivors (31). These contradicting results might be related to the lower percentage of patients treated with radiation in the latter study compared to our study (53% vs 75%). The increased extent of second primary thyroid carcinoma also resulted in a more aggressive therapeutic approach with a higher rate of total thyroidectomies and neck dissections (35).

Overall survival for TC patients is not worse after history of HD

The long-term overall survival of TC in HD survivors was similar compared to first primary TC patients. Studies assessing outcomes of other second cancers such as head- and neck cancer, breast cancer and gastrointestinal cancer show a worse prognosis for HD survivors (36-38). For patients with non-small cell lung cancer (NSCLC), a history of mixed cellularity Hodgkin Lymphoma subtype without radiotherapy was a favorable prognostic factor (39). The patient's prognosis is most likely determined by the type of cancer with the lowest survival rate and the stage at the time of HD diagnosis. The predominant subtype in this study was differentiated thyroid cancer which has an excellent prognosis with a 5-year relative survival rate of 98.3% (40).

Strengths and limitations

This study provides information about the clinicopathological characteristics of differentiated thyroid cancer in adolescents and young adults treated for HD in the Netherlands during a long interval, which was not yet assessed in previous publications. A strength of this study is the complete data of the pathological results for all the HD-TC patients. This study is limited by the data source and missing variables. The NCR collects data from 1989, so patients with a diagnosis of HD before 1989 could not be included in the SIR analysis. The NCR also had no data available about the anatomic site of HD, radiation dose, and fields during 1989-2014. This study design did enable us to include a five-year interval between HD and TC which was the minimum for the possible treatment-induced side-effect of HD. Another limitation includes the inclusion of the overall survival instead of the cancer-specific survival due to data unavailability.

CONCLUSION

Although TC was more common in HD patients during adolescence and young adulthood compared to the general population, the relative numbers were low suggesting that the majority of HD survivors do not develop TC. A history of HD < 35 years may be considered a risk factor for TC with a relatively higher frequency and tumor load of regional lymph node metastases at TC diagnosis resulting in more surgical neck dissections. Prior HD was not associated with a worse overall survival. Based upon these results, we recommend diagnostic work-up of HD survivors with palpable and/or symptomatic thyroid nodules according to the Dutch guidelines. There is insufficient evidence that routine screening of the neck in all HD survivors is beneficial.

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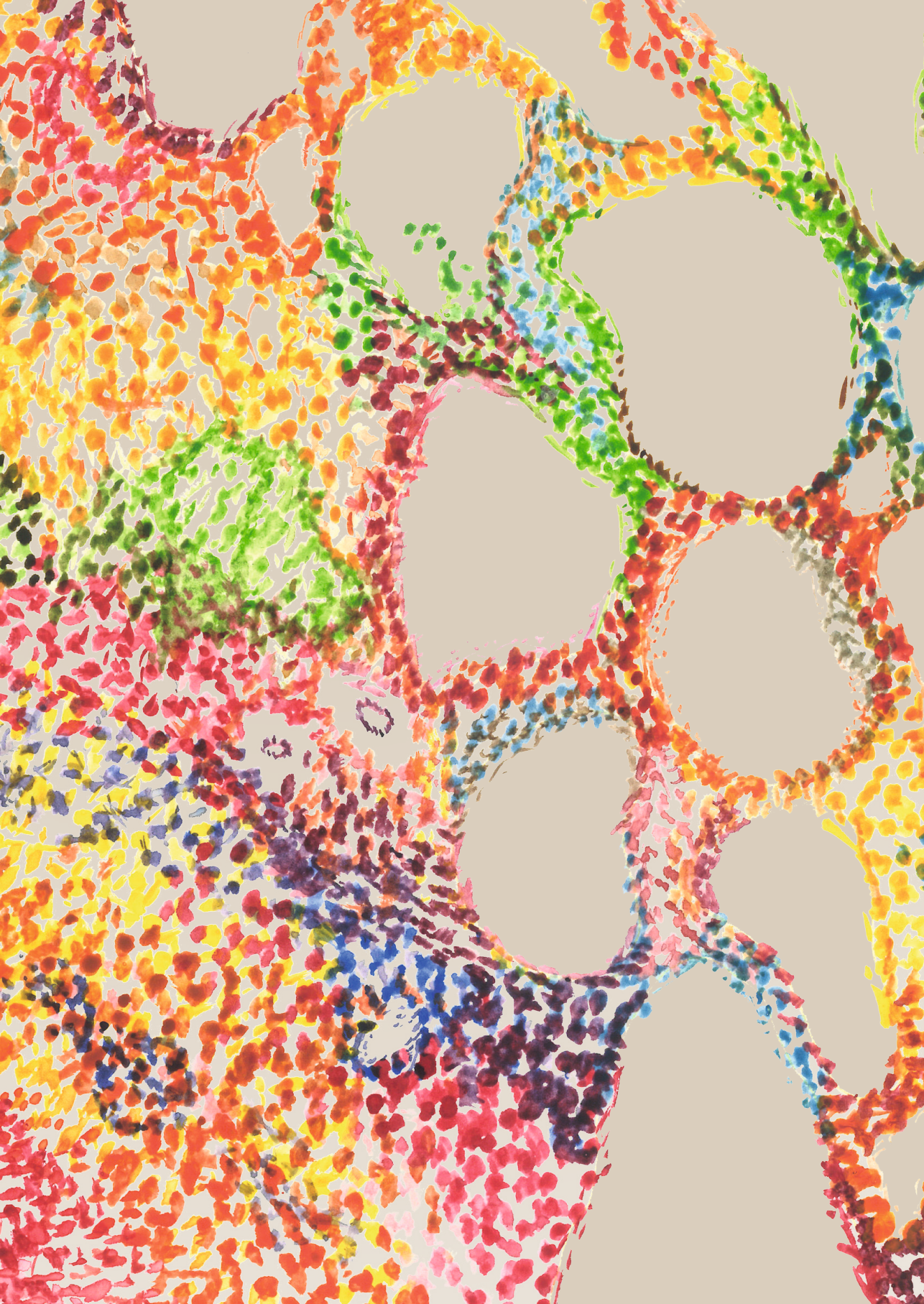

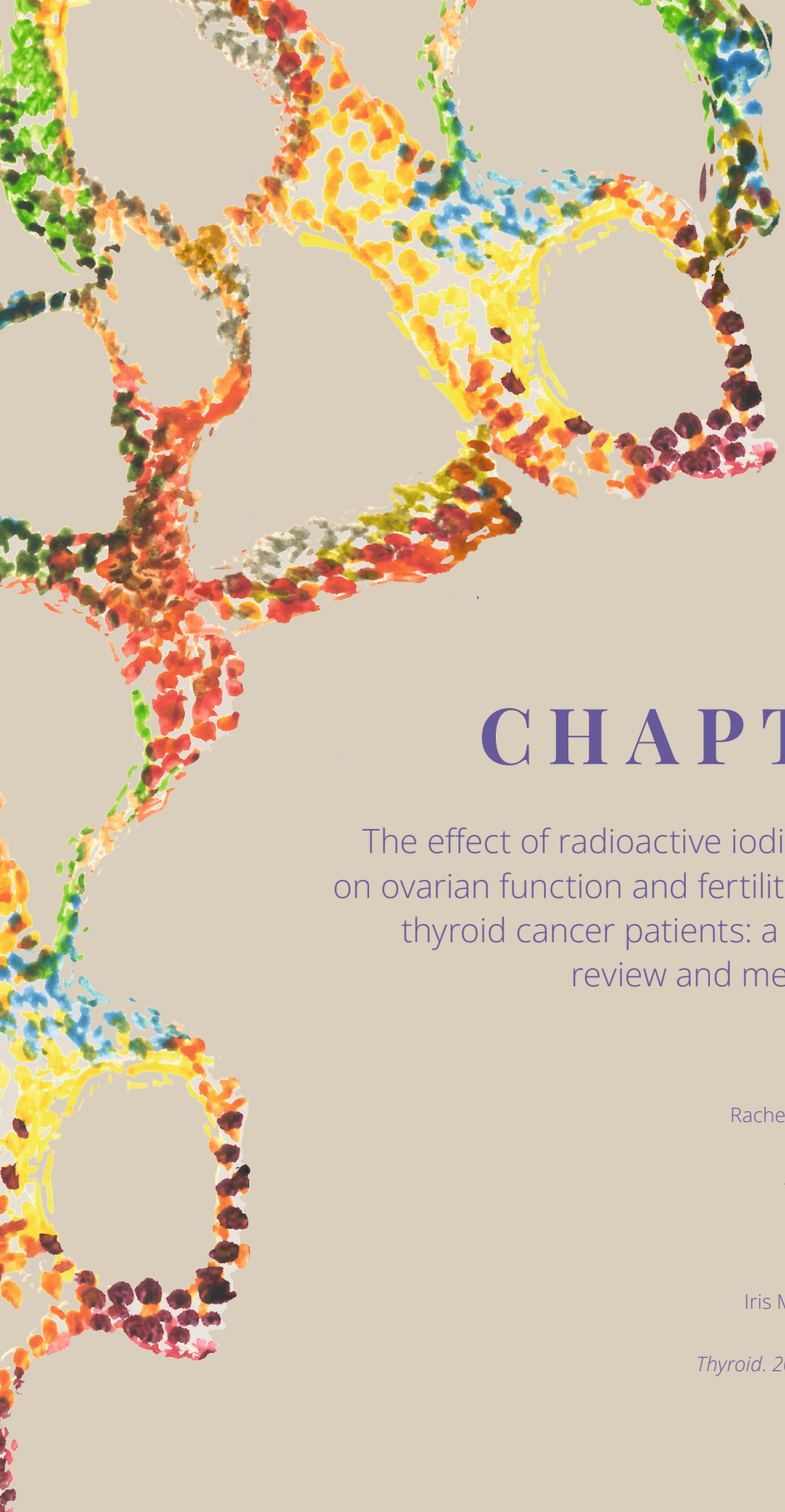

8 CHAPTER

The effect of radioactive iodine therapy on ovarian function and fertility in female thyroid cancer patients: a systematic review and meta-analysis

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ABSTRACT

Thyroid cancer is one of the most common carcinomas diagnosed in adolescents and young adults (AYA), with a rapidly rising incidence over the past three decades. Surgery is the standard treatment for patients with differentiated thyroid carcinoma (DTC), and when indicated, followed by radioactive iodine (RAI) treatment. The aim of this study was to evaluate the possible effects of RAI therapy on ovarian function and fertility in women. The PubMed, Embase and Web of Science databases were systematically searched up to Jan 2020. Additionally, meta-analyses were performed for anti-Mullerian hormone (AMH) levels after RAI, comparison of AMH levels prior and one year after RAI, and pregnancy rates in patient with thyroid cancer receiving RAI compared to patients with thyroid cancer who did not receive RAI. A total of 36 studies were eligible for full-text screening and 22 studies were included. The majority of the studies had a retrospective design. Menstrual irregularities were present in the first year after RAI in 12% and up to 31% of the patients. Approximately 8% - 16% of the patients experienced amenorrhea in the first year after RAI. Women who received RAI treatment (median dose 3700 MBq (range 1,110-40,700 MBq)); had menopause at a slightly younger age compared to women who did not receive RAI treatment, 49.5 years and 51 years, respectively ($p < 0.001$). Pooled AMH of the seven studies reporting AMH concentrations after RAI was 1.79 ng/ml. Of these, four studies reported AMH concentrations prior and 1 year after RAI. The mean difference was 1.50 ng/ml, which was significant. Finally, a meta-analysis showed that patients undergoing RAI were not at a decreased risk of becoming pregnant. Most of the studies indicate that RAI therapy for DTC is not associated with a long-term decrease in pregnancy rates although meta-analyses show a significant decrease in AMH levels after RAI therapy. Prospective studies are needed to confirm these results. We recommend counseling patients about the possible effects of I131 and incorporate today's knowledge in multidisciplinary counseling.

INTRODUCTION

Thyroid carcinoma is the most common endocrine malignancy and its incidence is rapidly rising. In the Netherlands, the incidence has doubled from 340 new patients in 1990 to around 700 in 2018 (1). This increase was more extensive than what would be expected based on population growth and aging. Among adolescents and young adults (AYA's) between 15 and 39 years, thyroid carcinoma is the fifth most frequent type of cancer (2). It occurs more frequently in women than in men and it is most often diagnosed in females at the age of 30 and 39 years old (3). Papillary and follicular thyroid carcinomas are referred to as differentiated thyroid carcinomas (DTC) and they comprise about 80-85% of all thyroid tumors. The prognosis of DTC is excellent with a 5-year survival rate near 100% for localized stage and 96% for locoregional disease with lymph node metastasis (4). Surgery is the standard treatment for patients with DTC, and when indicated this is followed by radioactive iodine (RAI) treatment. Despite international movements towards less aggressive treatment, many guidelines still recommend a total thyroidectomy followed by radioactive iodine in all patients with a DTC >1 cm (5). This treatment strategy is associated with significant morbidity rates due to hypothyroidism, hypoparathyroidism, recurrent laryngeal nerve damage, dysgeusia and xerostomia, resulting in long-term poor quality of life (QoL) (6). The excellent prognosis of DTC suggests overtreatment of a large group of patients with DTC. Many studies are now focusing on de-escalation and selecting patients in whom aggressive management is not warranted.

One of the concerns of the current protocols is the widespread use of RAI for the post-surgical treatment of DTC and its possible effect on reproductive function and fertility in the AYA population. There is growing awareness that temporary or permanent impaired fertility due to cancer treatment may have an important impact on the quality of life in young adults. Many cancer survivors desire to have children in the future and prefer their physician to raise fertility issues proactively (7). In the past, two systematic reviews concerning the effect of RAI therapy on fertility in young women have been performed. These two reviews (performed in 2008 and 2011) concluded that there is limited observational evidence suggesting persistent (> 12 months) adverse effects of RAI treatment on gonadal function, fertility, or pregnancy. However, a slightly younger age at menopause was seen in patients treated with RAI.

All the studies included in both these reviews were retrospective and the majority involved a small number of patients (8, 9). New studies have been published over the last decade focusing on the effects of RAI on ovarian function by evaluating the antiMullerian hormone (AMH) levels in women (10, 11, 12, 13, 14). AMH is strongly correlated

with antral follicle count and this may be a tool to measure fertility status (15). By incorporating studies performed after 2011, our aim was to summarize the current best evidence regarding fertility risks in young female thyroid cancer survivors treated with RAI. This will enable clinicians to counsel these women about their risks and potential indication for fertility preservation.

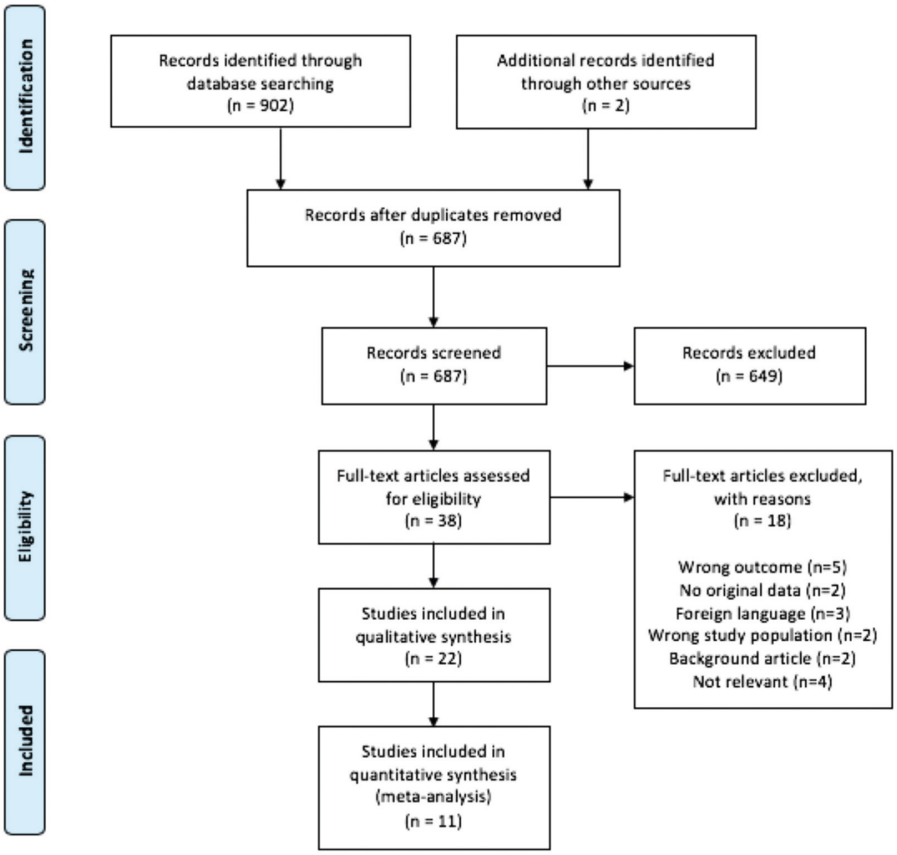
METHODS

This systematic review was performed according to the guidelines of the requirements of the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) checklist (Supplemental data 1*) (16). A systematic literature search was performed through Pubmed, Embase and Web of Science on the 5th of January 2020. Search terms were formulated using the *PICO* structure and were reviewed by an experienced librarian. Patients (P) included young adult women who underwent treatment for DTC in their fertile years. Intervention (I) included a total thyroidectomy followed by RAI therapy. Comparisons (C) consisted of either women who only had a total thyroidectomy or healthy women. Outcomes (O) included ovarian- reserve or function, AMH levels, fertility, menstrual cycle disorders, menopause and pregnancy outcomes. Database subject terms, such as Mesh terms (Medline) and Emtree terms (Embase), were used when appropriate. Keywords included thyroid carcinoma, thyroid tumor, thyroid papillary carcinoma, thyroid neoplasms, thyroid cancer and radioactive iodine, iodine, radioisotope, iodine radioisotopies, I-131 and fertility, Mullerian inhibiting factor, follicle stimulating hormone, gonadotropins, follitropin, infertility, pregnancy, spontaneous abortion, menstrual cycle, menstruation disorder. Detailed search queries are reported in Supplemental data 2***.**

Selection of studies

The identified titles were entered in Rayyan QRCI (17) and screened by two independent reviewers based on title and abstract. Subsequently, full text review of potentially relevant studies was performed, and studies were selected if eligibility criteria were fulfilled (MP and EP). Original studies assessing the effects of RAI therapy for DTC on female gonads, AMH levels, menstrual cycles and pregnancy outcomes were included. Case reports and reviews were excluded. Selection of articles was restricted to English, Dutch, German, and French. Studies published after 1970 were included in this review. Disagreements were resolved by consensus and when unsuccessful, with the help of a third reviewer (I.P.). The reason for exclusion of articles were recorded. All included studies were cross referenced for additional relevant articles. (**Supplemental Figure S1**).

*suppemental data available upon request



Supplemental Figure S1 Flowchart (Abbreviations: n = number)

Risk of bias

The ROBINS-I Tool was used to evaluate the quality of each eligible study (18). The entire scale constituted seven domains for the risk of bias: confounding, selection of participants, classification of interventions, deviations from intended interventions, missing data, measurement of outcomes and selection of the reported result. Each domain was judged for three levels of bias: low risk, moderate or high risk of bias. Full assessment criteria can be found in the supplementary data (Supplemental data 3).

Statistical analysis

Meta-analysis was performed to determine differences in pregnancy rates with 95% confidence intervals (CI). Pooled postoperative pregnancy rates were determined using random effects model and odds ratio (OR) with 95% CI was used to assess whether patients undergoing RAI were at a decreased risk of becoming pregnant. Additionally, meta-analysis was performed to determine AMH levels after RAI. The meta-regression

analysis of the different AMH levels were corrected for the follow-up period. Subgroup analysis in studies was performed to compare AMH levels before and one year after RAI using mean differences and random effects model. Missing standard deviations (SD) from studies were imputed and all meta-analyses were performed using random effects model. *P*-values under 0.05 were considered statistically significant. All calculations were performed using RStudio 1.2.5001 (with R version: x64 3.6.3). Additionally, statistical packages *meta* and *metaphor* were used for all computations of the meta-analyses. Visualization of plots was done using the *ggplot2* package.

RESULTS

After excluding duplicates, 689 references were retrieved for review of title or abstract. Thirty-eight papers were selected for review of the full text and 22 were selected for this review (**Supplemental Figure S1**) including 36,215 patients. Study characteristics of the included studies are reported in **Table 1**. Most studies were based on single center patient populations and performed retrospectively. Four studies focused on the effects of RAI therapy on female gonadal function (i.e. amenorrhea, menstrual cycle irregularities, estrogen/progesterone levels and the age of menopause) (**Table 2**). Seven studies reported AMH levels in patients with DTC after receiving RAI therapy (**Table 3**). Fourteen studies evaluated pregnancy outcomes after RAI therapy (**Table 4**). Some studies focused on multiple outcome measures such as AMH levels and gonadal effects of RAI therapy.

Table 1 Study characteristics of included studies.

Author	Study design	Patient population	Study period	Age[1] median (range)	Dosage RAI[2]	Level of clinical evidence[3]
Acibucu[11]	Prospective cohort	N=45 TT[4] + RAI[5] N=40 control (healthy females)	2015-2016	35.27 (28-42)	3700-5,550 MBq (100-150 mCi)	2b
Anderson[33]	Retrospective cohort	N=1251 TT + RAI N=1109 control TT	2000-2014	32 (15-39)	Not documented	2b
Azem[13]	Prospective cohort	N=30 RAI	2015-2016	33.3 (20-45)	3700-5,550 MBq (100-150 mCi)	2b
Balenovic[28]	Retrospective cohort	N = 76 TT + RAI	1971-2005	25.9 (12-35)	1,850- 28,786 MBq (50-778 mCi)	2b
Bal[24]	Retrospective cohort	N= 692 TT + RAI	1967-2002	23 (18-45)	925-15,910 MBq (25-208 mCi)	2b
Brandao[25]	Case control	N= 48 TT + RAI N = 60 control (healthy females)	2000-2002	26.5 (13-42)	1,850-11,100 MBq (50-300 mCi)	2b
Cecarelli[20]	Retrospective cohort	N=130 TT + RAI + LT4 N=127 control group (LT4[6])	1974-1993	39.2 (23-45)	1,110-40,700 MBq (30-100 mCi)	2b

Table 1 Continued

Author	Study design	Patient population	Study period	Age[1] median (range)	Dosage RAI[2]	Level of clinical evidence[3]
Chow[26]	Retrospective cohort	N= 153 TT + RAI-treatment N=110 control (no RAI)	1960-2002	26.3 (20-35)	185-5,550 MBq (5-150 mCi)	2b
Dottorini[30]	Case control	N = 627 TT + RAI N = 187 TT	1960-1993	<43[7]	2183 – 22,200 MBq (59-600 mCi)	2b
Evranos[12]	Prospective cohort	N=33 TT + RAI	2015-2017	31.15 (21-38)	2775-5550 MBq (75-150 mCi)	2a
Fard-Esfahani[29]	Retrospective cohort	N = 653 TT + RAI	1999-2004	30.1 (15-45)	3700 – 22,200 MBq (100-600 mCi)	2b
Giusti[14]	Prospective cohort	N=34 TT+ RAI N=23 TT	2011-2018	40.7 (27-50)	3700-17,020 MBq (100-460 mCi)	2b
Ko[32]	Retrospective cohort	N= 6.824 TT + RAI N = 4.884 TT	1998-2010	37.1 (15-50)	Mean cumulative dosage: 4440 MBq (120.1 mCi)	2b

Table 1 Continued

Author	Study design	Patient population	Study period	Age[1] median (range)	Dosage RAI[2]	Level of clinical evidence[3]
Metallo[35]	Retrospective cohort	N = 18 RAI dosage > 3848 MBq (104 mCi) N = 27: RAI dosage < 3848 MBq (104 mCi)	2004-2013	19.9 (16-23)	3848 MBq (104 mCi)	2b
Mittica[23]	Prospective + cross sectional	N=59 TT+ RAI N=30 TT N=141 control (healthy females)	2017-2019	41.2 (20-56)	Median 3700 MBq (100.1 mCi)	2b
Sioka[21]	Retrospective cohort	N=45 TT+ RAI N=83 control (healthy females)	1996-2003	20-40[g]	3700 MBq (100 mCi)	2b
Sarkar[31]	Retrospective cohort	N= 33 TT + RAI	1947-1960	14.6 (6-20)	Mean total dosage: 7252 MBq (range 2960-25,567) (196 mCi (range 80-691 mCi))	2b
Smith[26]	Retrospective cohort	N = 35 TT + RAI	1951-1991	18.3 (14.1-20.8)	2849 - 9250 MBq (77.2-250 mCi)	2b

Table 1 Continued

Author	Study design	Patient population	Study period	Age[1] median (range)	Dosage RAI[2]	Level of clinical evidence[3]
Vini[19]	Retrospective cohort	N= 409 TT/HT+ RAI	1949-1977	31 (8-40)	1.1-59 GBq (30-1595 mCi))	2b
Wu[34]	Retrospective cohort	N = 9883 TT + RAI N = 8967 TT	1999-2008	46.3 (15-40+)	not documented	2b
Yaisch[10]	Prospective cohort	N = 30 TT + RAI	2017-2018	34 (20-45)	1110-5550 MBq (30-150 mCi)	2b
Van Velsen[22]	Prospective cohort	N=85 TT + RAI	2013-2017	32 (23.6-40.4)	1850-10,767 MBq (50-290 mCi)	2b

[1] Mean age at diagnosis
[2] Dosages in mCi were converted to MBq
[3] Oxford Level of Evidence: -centre-evidencebased-medicine-levels-evidence-march-2009/
[4] TT = total thyroidectomy
[5] RAI = radioactive iodine
[6] LT4 = Levothyroxine (thyroid hormone)
[7] Mean age not mentioned [8] HT = hemi thyroidectomy

Table 2 RAI treatment and ovarian function.

Author	RAI[1]	Amenorrhea (4-10 months)	Menstrual irregularities	Median age at menopause: years	*p-value*
Acibucu 2016	Yes N[2]=45 No N=40	RAI: 15.6% Control: n.a.[3]			n.a.
Sioka 2006	Yes N=45 No N=83		RAI: 31% Control: 15%		$p = 0.02^*$
Vini 2002	Yes N=409	8%	12%		n.a.
Ceccarelli 2001	Yes N=130 No N=127	-	-	RAI: 49.5 Control: 51	$p < 0.001^*$

[1] RAI = radioactive iodine

[2] N = number

[3] n.a. = evaluation not done

* Significant difference between the RAI- and the control group

Table 3 Effect on AMH levels.

Author	RAI[1]	CV[2] AMH assay	AMH at baseline	AMH after 3 months	AMH levels after 1 year	AMH levels after long follow-up (time since primary treatment (years))	*p*-value
Van Velsen 2020	Yes N=85	10.8%	3.34 ± 1.2 ng/ml[3]	-	1.37 ± 1. 19 ng/ml	n.a.[4]	p <0.05*
Mittica2020	Yes N=59 (group 1) No N=141: N=30 TT[5] (group 2) N=141 healthy women (group 3)	0.5%- 2.9%	n.a.	n.a.	n.a.	Group 1: 1.37 ± 1.60 ng/ml (7.2 ± 6.8) Group 2: 1.22 ± 1.48 (4.6 ± 4.1) Group 3: 2.98± 3.33 ng/ml (n.a.c)	Group 3 vs group 1: p=.0002** Group 3 vs group 2: p=.001**
Yaisch 2018	Yes N=30	10.8%	3.25 ± 2.75 ng/ml	1.9 ± 1.74 ng/ml	2.36 ± 1.88 ng/ml	n.a.	3 months: p=.001* 1 year: p<.005*
Giusti 2018	Yes N=34 (group 1) No N=23 (group 2)	0.5%-2.9%	n.a.	n.a.	n.a.	Group 1: 1.498 ± 0.24 ng/ml (7.1 ±0.9) Group 2: 2.45 ± 0.66 ng/ml (5.3 ±1.4)	p = .075
Evranos2018	Yes N=33	Intraassay: 7.1 % Interassay: 9.8%	3.25 ng/ml	1 ng/ml	1.37 ng/ml	n.a.	p =.001*

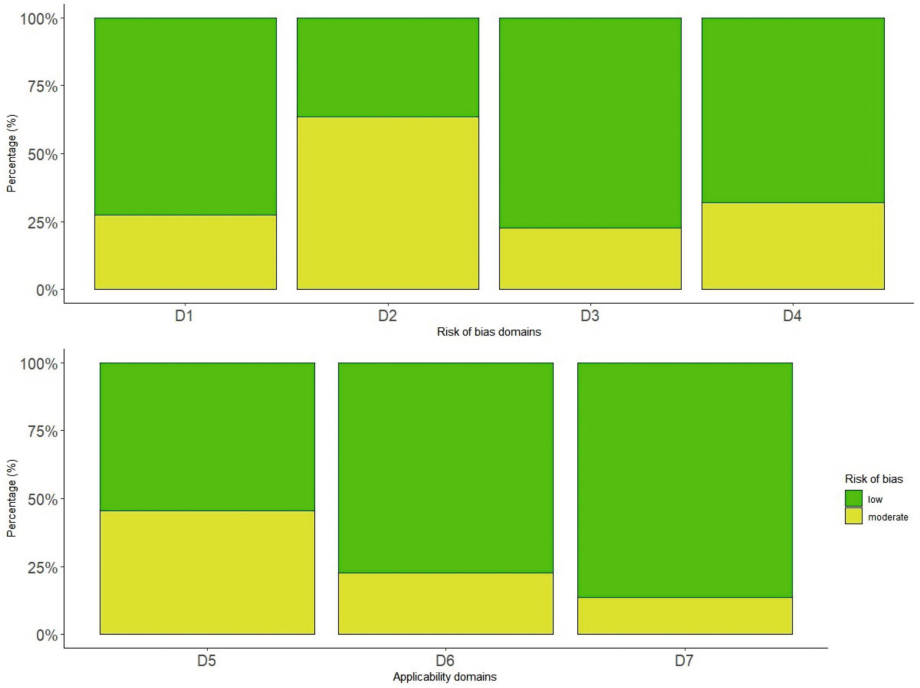
Table 3 Continued

Author	RAI[1]	CV[2] AMH assay	AMH at baseline	AMH after 3 months	AMH levels after 1 year	AMH levels after long follow-up (time since primary treatment (years))	*p*-value
Acibucu2016	Yes N=45 (group 1) No N=40 (group 2)	Intra-assay: < 10% Interassay: < 12%	n.a	n.a.	n.a.	Group 1: 2.82±1.8 8 µg/l[7] (3.71 ± 3.30) Group 2: 3.35±1.8 4 µg/l (3.71 ± 3.30)	$p < 0.05^{**}$
Azem 2016	Yes N=30	n.a.	3.43 ng/ml	1.9 ng/ml	2.8 ng/ml	n.a.[k]	3 months: $p = 0.001^{*}$

[1]RAI = radioactive iodine
[2]CV = coefficient of variation
[3]ng/ml = nanogram/milliliter
[4]n.a. = evaluation not done
[5]TT= total thyroidectomy
[6]AMH levels were significantly higher before than after RAI therapy
[7] µg = microgram/liter *Significance for paired comparisons relative to baseline **Significant difference among groups

Risk of bias assessment

The result of the ROBINS tool revealed that all the included studies were of sufficient quality based on risk-of-bias domains and applicability domains (**Supplemental Figure S2**). Specific assessment for each of the studies included in this systematic review and metaanalysis can be found in Supplemental data 4*.



Supplemental Figure S2: Summary of Risks of Bias and Applicability Domains.

Abbreviations: D1=bias due to confounding D2=bias in selection of participants into the study D3=Bias due to deviations from intended interventions D4=bias due to missing data D5=bias in measurement of outcomes D7=bias in selection of the reported results

RAI treatment and ovarian function

Four studies focused on the gonadal effects of RAI therapy (**Table 2**). All studies were observational and in only one study prospective data were collected. The age at first RAI treatment varied from 8 to 45 years and the cumulative dosages of RAI varied from 2997 MBq to 59 GBq (81 to 1595 mCi). In the study by Vini et al., 496 women under the age of 40 were included (19). A full obstetric history was taken and details of the menstrual cycle were noted in the first two years after treatment (surgery followed by radioiodine).

Menstrual cycle irregularities comprising either lighter menses or changed duration of cycle were documented in 12% of the patients in the first year after RAI. Amenorrhea

was depicted in 8% of the patients lasting between four and ten months. Ceccarelli et al. retrospectively compared the menopausal age of DTC patients treated with RAI and suppressive levothyroxine (LT)4 (n=130) with the menopausal age of patients with a goiter (n=127) treated with suppressive LT4. The first group of women experienced menopause at a slightly younger age than women who did not receive RAI treatment (49.5 years vs 51 years, $P < 0.001$) (20). Sioka and colleagues compared 45 females <40 years old who had received RAI therapy for DTC to age-matched control females (n=83). Significantly more menstrual cycle alterations were seen during the first year after RAI therapy in the group of patients compared to the control group (31.1% vs 14.5%, $P = 0.02$) (21).

Acibucu, et al. prospectively compared 45 women who received RAI ablation treatment for well-differentiated thyroid cancer in their premenopausal period to 49 healthy females as controls. Transient oligo/anovulation was detected in 7 patients (15.6% of the patient group) after RAI treatment (11).

Seven studies examined the effect of RAI treatment on the ovarian reserve by assessing AMH levels after RAI treatment (**Table 3**) (9, 10, 11, 12, 13, 22, 23). Yaisch et al. studied 30 women with DTC whom received RAI doses ranging from 1110 to 5550 MBq (30 to 150 mCi) after recombinant human thyrotropin stimulation. RAI treatment resulted in a significant decrease in AMH concentrations at three months. Eighty-two percent of the women had final values below baseline levels at one year (3.25 ng/ml at baseline and 2.36 ± 1.88 ng/mL after one year; $p < 0.005$). The studies of Azem et al. and Evranos et al. confirm these results. In the study of Azem and colleagues, 30 premenopausal women were included who underwent RAI treatment for DTC (dose range 1110-5550 MBq (30 – 150 mCi)). In the study of Evranos et al., 33 premenopausal women were enrolled who received a high dose of RAI (range 2775 – 5550 MBq (75 – 150 mCi). Both studies state that large doses of RAI as adjunct therapy to women with DTC appear to impair ovarian reserve as assessed by AMH levels (see Table 3). The lowest point in AMH levels is seen at 3 months after treatment and there is no complete recovery at one year. In contrast, lower dosages up to 1110 MBq (30 mCi), such as given for ablation of thyroid remnants, appear to be innocuous.

In the study of Acibucu et al., AMH levels of 45 patients after (mean follow up of 44 months) receiving RAI therapy for DTC were compared to the AMH levels of 40 healthy females. The difference in AMH levels between the patient- and control group was found to be significantly different (2.28 vs. 3.35 ng/mL, $p = 0.038$). An important drawback of this study is that the AMH levels before RAI treatment were not reported.

Recently, van Velsen and colleagues conducted a prospective study evaluating AMH levels after RAI for thyroid cancer in female patients (22). AMH concentrations decreased by 50% compared to baseline levels until 12 months after a single RAI treatment and then stabilized. Patients younger than 35 years had a gentler decrease in AMH levels. The authors suggested a less aggressive RAI treatment in low-risk patients, in particular women over 35 years old with an active child wish.

Giusti, et al. found no statistically significant relationship between RAI exposure and AMH levels. They found that AMH levels were only negatively correlated with age in the treatment group (rS −0.58; $p = 0.0003$) and in the control group (rS −0.81 $p < 0.0001$). Mittica et al. performed a cross-sectional study comparing 59 women who underwent surgery and RAI for DTC, 30 women only receiving surgery and 141 healthy women (23). In this study, the main factor for lower AMH levels was also age and not the type of treatment.

Despite the reduction in AMH levels, the correlation between AMH levels and fertility was not evident. The study of Evranos et al reports that AMH levels did not differ among patients with a pregnancy wish, patients without an active child wish and pregnant patients ($p > 0.05$) (12).

This section indicates that in the first year after RAI therapy women experienced more menstrual cycle irregularities compared to control groups. In four studies, the AMH levels were significantly lower 1 year after RAI treatment compared to baseline levels (mean difference 1.50 ng/ml [95% CI: 0.82; 2.17] see **Figure 1a**)**.** Pooled AMH levels of patients undergoing RAI was 1.79 ng/ml (**Figure 1b**). The time of AMH measurement after RAI was not a predictor for the level of AMH (OR 0.93, 95% CI 0.80 – 1.08; $p = 0.355$).

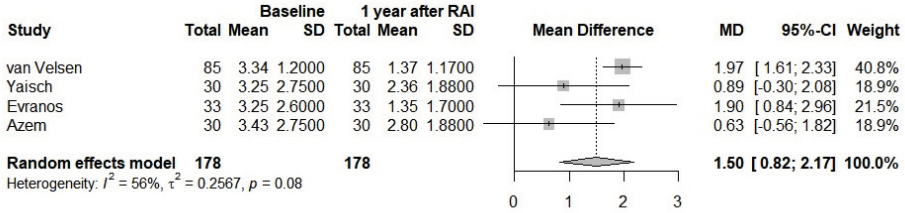


Figure 1a Mean difference in AMH between before and 1 year after RAI in patients with differentiated thyroid carcinoma.

Abbreviations: AMH = anti mullerian hormone, RAI = Radioactive Iodine, CI = confidence interval

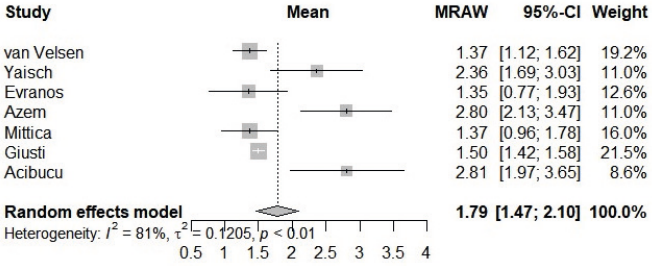


Figure 1b Pooled AMH levels after RAI in patients with differentiated thyroid carcinoma.

Abbreviations: AMH = anti mullerian hormone, RAI = Radioactive Iodine, MRAW = mean raw, CI = confidence interval

RAI treatment and pregnancy outcomes

Several studies reported on the effects of RAI therapy in women on subsequent pregnancy rates (**Table 4**) (21, 24, 25, 26). Two studies report increased rates of spontaneous and induced abortions in the first year after RAI therapy in 17% -18% of the pregnancies (27, 28). Fard-Esfahani et al. report an increased incidence of abortions early after the administration of RAI therapy from 16.83% before RAI to 26.19% after RAI (29). However, this increase was related to induced abortions while the risk for spontaneous abortions was reduced from 16.8% to 10.3%. There is little observational evidence that RAI treatment was associated with significantly increased risk of spontaneous abortions. Long-term infertility or neonatal mortality were comparable to various control groups (30, 31). Most authors do recommend to avoid pregnancy for at least one year after RAI therapy to reduce the possible adverse effects of radiation on gonads and subsequently on the neonates (29, 30).

Table 4 RAI treatment and pregnancy outcomes.

Article	RAI[1]	Pregnancy	Abnormalities	Infertility	*p*-value
Anderson 2017	Yes N[2]= 1251 No N= 1109	RAI group: 30% pregnant patients Control group: 29% pregnant patients Adjusted HR[3]: 1.00 (95% CI:0.82, 1.23)			NS[4]
Ko 2016	Yes N= 6.824 No N = 4.884	Group 1: 11% pregnant patients Group 2: 14% pregnant patients Adjusted HR: 0.77 (95% CI: 0.82, 1.23)	Group 1: 11% Group 2: 10% HR = 0.79 (95% CI: 0.71–0.88)		$p < 0.001$[5] (*log-rank*)
Metallo 2016	Yes N=45: N = 18: RAI dosage > 3848 MBq[6] (104 mCi) (group 1) N = 27: RAI dosage < 3848 MBq (104 mCi) (group 2)	Group 1: 33% pregnant patients Group 2: 56% pregnant patients	Group 1: 17% miscarriage Group 2: 10% miscarriage		NS

Table 4 Continued

Article	RAI[1]	Pregnancy	Abnormalities	Infertility	*p*-value
Wu 2015	Yes N=9883 (group 1) No N=8967 (group 2)	All ages: Group 1: 7% Group 2: 6% Subgroup analysis (35-39 yrs): RAI group: 11.5 births/1000 women years Non-RAI group: 16.3 births/1000 women years			All ages: NS Subgroup analysis: $p<0.001$
Fard-Esfahani 2009	Yes N=653	15% pregnant patients (126 pregnancies)	26% after RAI treatment		-
Brandao 2007	Yes N= 48 (pregnant women) No N = 60 (pregnant women)	66 pregnancies (RAI group)	6%		NS
Sioka 2006	Yes N = 45 (group 1)	Group 1: 13% pregnant patients	Group 1: 2% abortion		-
Bal 2005	Yes N= 692	6% pregnant patients (50 pregnancies)	No miscarriages after RAI		-
Balenovic 2006	Yes N = 76 (pregnant women)	49 pregnancies	5 miscarriages (7%)		

Table 4 Continued

Article	RAI[1]	Pregnancy	Abnormalities	Infertility	*p*-value
Chow 2004	Yes N= 153 (pregnant women): n=85 scanning dose[7] n=68 ablative dose No N=110 (pregnant women)	37 pregnancies (scanning group) 116 pregnancies (ablative group) 110 pregnancies (no RAI group)	Miscarriage: 13.5% (scanning group) 11.2% (ablative group) 6.4% (no RAI group) Premature birth: 16% (scanning group) 9% (ablation group) 1.4% (no RAI group)		*Premature birth:* $p = 0.005$ (scanning group) $p = 0.04$ (ablation group)
Vini 2002	Yes N= 409 (N=322 ablation dosage[8], N=87 therapeutic dosage)	62% pregnant patients (427 pregnancies)	3.4% miscarriages		-
Dottorini 1995	Yes N = 627 (group 1) No N = 187 (group 2)	Group 1: 7% pregnant women (fertility rate 23) Group 2: 8% pregnant patients (fertility rate 19)	Miscarriages: Group 1: 0.5% Group 2: 0.5%		NS
Smith 1994	Yes N = 35 (pregnant women)	69 pregnancies	5 abortions (14,3%)	8.6%	

Table 4 Continued

Article	RAI[1]	Pregnancy	Abnormalities	Infertility	*p*-value
Sarkar 1967	Yes N= 33 (pregnant women)	71 pregnancies	3% miscarriages 18% premature births	12%	-

[1]RAI = radioactive iodine
[2]N = number
[3]HR = hazard ratio
[4]NS = no significant differences between the two groups
[5]Significant difference between the RAI- and the no RAI group
[6]Dosages in mCi were converted to MBq
[7]Scanning RAI = low-dose RAI (≤5 mCi) and ablative RAI = high-dose RAI (>5 mCi)
[8]The ablation dosage was 1.1 or 3 GBq (30 or 80 mCi) and the therapeutic dosage was 8.5–59 GBq (229-1595 mCi)

Three large clinical studies were performed to evaluate the effect of RAI therapy on pregnancy rates (32, 33, 34). The study of Ko et al. involved 11,708 women with a mean age of 37.1 years with DTC. The mean follow-up period was 6.4 years. The overall incidence of pregnancy was significantly lower in the RAI cohort (adjusted HR = 0.77, 95% CI = 0.70-0.86, $p < 0.001$) also after stratification for age (HR = 0.73, 95% CI = 0.64-0.83, $P < 0.05$ in 25-34 years; HR = 0.63, 95% CI = 0.49-0.82, $P < 0.05$ in 35-44 years). In 2015, Wu and coworkers reported on a large cohort of patients (18,850 women) with DTC using the California Cancer registry with a median follow-up of 4.1 years (31). In a subgroup analysis, the birth rate in women aged 35-39 who received RAI was significantly lower than in patients who did not receive RAI (11.5 versus 16.3 births per 1000 woman-years, $p<0.001$). They also observed a delay to first live births in women aged 20-39 years (34.5 versus 26.1 months; $p<0.0001$).

This is in contrast to the study of Anderson et al. that described 2,360 women, in whom 53% of the patients received RAI treatment. The cumulative incidence of birth at the end of follow-up (maximum 14.5 years) was 30.0% in the RAI cohort compared to 29.3% in the non-RAI group. In this observational cohort, treatment with RAI was thus not associated with a reduced birth rate. The study of Metallo et al. confirms these findings in 54 women and states that the pregnancy rates and the frequency of miscarriages in the RAI cohort are consistent with the French general population (35). **Figure 2** showed that patients undergoing RAI were not at a decreased risk of becoming pregnant compared to control group (OR 0.98 [95% CI: 0.72, 1.33]; $p = 0.909$). This section indicates that RAI therapy was not associated with long-term infertility and neonatal mortality.

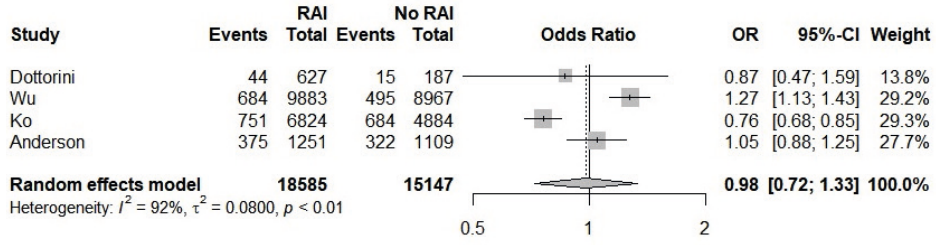


Figure 2 Differences in pregnancy rates between patients undergoing RAI and patients not undergoing.

RAI = Radioactive Iodine, CI = confidence interval

Dosage RAI therapy and fertility

In total, three studies found a negative relationship between the dosage of RAI therapy and fertility. Vini et al. states that higher dosages of RAI (8473 MBq-59 GBq (229-1595 mCi)) are associated with more menstrual cycle irregularities compared to the group who received lower dosages of RAI. Azem et al. found that high dosages of RAI given as a therapeutic dosage in patients with DTC, impair ovarian reserve as assessed by AMH levels. Van Velsen et al. found that after multiple RAI procedures, a further reduction of AMH levels was seen up to 85% of baseline levels in 4 years' time (baseline AMH 3.34 ± 1.20; after 48 months AMH 0.95 ± 1.23 (p<0.05)) (22). However, four other studies did not detect an association between the RAI dosage and the extent of AMH reduction. Ceccarelli et al. found no relationship between menopausal age and the cumulative RAI dosage received. The studies of Chow et al. and Balenovic et al. show that a higher ablative dosage (>2960 MBq (80 mCi) and > 3700 MBq (100 mCi) did not significantly alter the pregnancy outcome. Metallo et al. found the frequency of miscarriages was 17% in females from the group receiving > 3848 MBq (104 mCi) and 10% in patients with a cumulative RAI dosage < 3848 MBq (104 mCi). No birth defects or first year mortality was observed. This section indicates that the association between RAI dosages and fertility is still controversial.

DISCUSSION

In this systematic review including 22 studies, we evaluated the effect of RAI therapy on ovarian function and fertility in women with DTC who received RAI treatment in their reproductive years. An overview of the currently available literature is provided, enabling clinicians to counsel these women about their risks and potential indication for fertility preservation. Most of the selected studies indicate that RAI therapy for DTC is not associated with a long-term decrease in pregnancy rates. However, in the first year directly after RAI treatment many women experienced irregularities in their menstrual cycle and some studies found significant lower AMH levels, both possibly leading to a diminished fertility shortly after I131 treatment for DTC. Thus, it might be most prudent for women with an active child wish in their latter reproductive years to have counseling of treatment potential effects. This review also shows that women treated with RAI therapy were exposed to menopause at a slightly younger age than women without RAI treatment.

In recent years, AMH has become an outcome of interest as a possible predictor of ovarian reserve (14). In normo-ovulatory women, the serum AMH level is positively correlated with the number of oocytes retrieved (R=0.6, p < 0.0001) (34). This correlation is of current value in women who undergo in vitro fertilization (IVF) or hyperstimulation

in order to harvest a fair amount of ovarian eggs. The studies included in this review evaluating AMH as a representative of ovarian reserve were prospective with a small number of patients, the majority of included patients did not receive a high dosage or multiple I131 treatments and the follow-up time was relatively short. Nonetheless, these studies suggest a direct relationship to AMH levels and fertility. There are other insights in the literature on this topic. Liebenthron et al. studied the relation between AMH serum levels and follicle densities (FD) and concluded that this hypothesis should be looked at with suspicion (36). In this retrospective study, 830 women treated for several types of malignant (*n* =806) and benign (*n* =24) diseases were observed who cryopreserved tissue in a single center and in whom AMH levels were tested before and after gonadotoxic therapies. AMH and FD were not correlated in women ≤20 years and weakly to moderately correlated in women 21–40 years (*r* =0.24–0.39). It was stated that AMH should be carefully used to estimate ovarian reserve of female cancer patients, especially when used as a single factor.

It must be considered that the outcomes of the studies mentioned in this review regarding pregnancy rates, menstrual irregularities and AMH levels might all be more or less influenced by differences in study design and study population. For example, a 45-year-old woman in Taiwan, a country known for low birth rates due to low socioeconomic circumstances, is expected to have lower AMH levels, an irregular menstrual cycle and thus a lower chance of pregnancy (32). However, one study has taken these normal biologicals features into account and still found remarkable differences in favor of women who did not receive I131 treatment (34).

Recently van Velsen et al. investigated the influence of the diagnosis and treatment of thyroid cancer on the desire to have a child (22). In total, 40% of the patients in the single RAI group and 33% of the patients in the multiple RAI group stated that their desire to have a child was influenced by the diagnosis or treatment. Most of the patients did not want a child anymore. These findings might also be an explanation for the lower birth rates in women who received RAI compared to patients without RAI treatment. Hypothyroidism after cancer treatment is another important reason for worse reproductive outcomes (37). Previous studies show that TSH and thyroid hormones act directly on the ovary through binding to their specific receptors and have a specific function during folliculogenesis and ovulation in the healthy state (38). Chin, et al. reported that women with hypothyroidism after cancer treatment were twice as likely to fail to achieve their desired family size (adjusted OR [aOR] 1.91; 95% CI 1.09-3.33) and be childless (aOR 2.13, 95% CI 1.25-3.65).39 Total thyroidectomy causes hypothyroidism by definition and a (sub)total thyroidectomy is associated with postoperative hypothyroidism in 62 to 87% of cases (40). Therefore, hypothyroidism is another important factor

to consider when counseling patients on the risks for impaired fertility. However, over the last years recombinant TSH (RhTSH) has been used to provide elevated TSH levels without making patients hypothyroid during the post-surgical follow-up. The use of RhTSH avoids the side effects of hypothyroidism and promotes iodine uptake (41). Of the included studies in this review, only one (Yaish et al) mentioned the use of RhTSH. It has been shown that TSH levels are negatively correlated with AMH levels in infertile patients. This association suggests a direct beneficial effect of normal TSH levels on follicular recruitment in infertile women (42). Also, it has been observed that TSH levels were significantly higher among women undergoing IVF who produced oocytes that failed to be fertilized (43). As the number of women treated with RhTSH is increasing it will be important to assess the effect of RhTSH on ovarian function and fertility in future studies.

Polycystic ovary syndrome (PCOS) is another heterogenous disorder affecting 6-15% of women in their reproductive years (44). The clinical features of PCOS include reproductive abnormalities such as irregular menses and infertility. It is important to consider that women with PCOS may have higher TSH levels compared to healthy control women (2.29 ± 1.24 vs. 1.86 ± 0.90 mu/L, $p < 0.001$) (45). There is increasing evidence that higher TSH concentrations in patients also increase the risk for thyroid cancer (44). The percentage of women with PCOS in the studies assessed for this review is not specified. However, this common endocrine disorder in young women might have been present in a percentage of patients with thyroid carcinoma in these studies, possibly leading to a higher percentage of reproductive abnormalities.

Also, it should be taken into account when interpreting the data that patients treated with total thyroidectomy may have low calcium levels. Some observational studies show that vitamin D deficiency is a risk factor for reduced fertility (47, 48, 49). Since vitamin D and calcium status are correlated, this is another factor that should be considered but such patients are all under close counseling and would be treated for low calcium levels when necessary. Cancer related issues in female cancer survivors in their reproductive years such as potential loss of fertility are distressing and over the past few years the awareness of fertility issues in these patients has grown significantly. The incidence of DTC is increasing and more young adults are confronted with such fertility issues. The age of the patients included in this review ranges from 8-50 years. This makes that not all the results can be directly extrapolated to the AYA population or specifically women in their reproductive years. Future clinical studies in patients with DTC should aim to collect long term patient reported data on fertility in these patient groups, providing clinicians reliable data to counsel these patients optimally.

Strengths and limitations

The strengths of the review include the comprehensive search strategy, independent screening and the risk of bias assessment. One of the limitations of this study is that not many studies have described the association of DTC treatments and fertility. However, the current study does pool the studies that have described fertility into various meta-analyses showing that pregnancy rates do not change in patients undergoing RAI but AMH concentrations significantly decreases after RAI. Another limitation is that most studies describing AMH concentrations do not describe pregnancy rates and vice versa. Finally, AMH concentrations were measured in the different studies were performed using different types of assays, which could make absolute values difficult to compare. However, within the studies there still is a decrease in AMH concentrations, which means while it is possible that that the concentrations might be different because of the different assays used, there still is a steady mean difference in AMH concentration after RAI. More prospective studies are needed to determine whether AMH is a clinically relevant proxy to determine fertility in patients with DTC undergoing RAI.

CONCLUSION

There is no clear evidence that young adults (AYA´s), or otherwise stated all women in their reproductive years, have a long-term diminished fertility after receiving RAI for DTC. It is also not associated with a long-term decrease in pregnancy rates. There is a strong suggestion that RAI negatively influences the menstrual cycle in the first year after treatment. AMH concentrations are frequently reduced in this same period of time potentially effecting ovarian reserve and thus short-term fertility. Further prospective studies are needed. In this current time of awareness of cancer treatment side-effects, we believe there is a role for physicians to inform their patients of these literature finding, and especially to counsel women over 35 years with an active short-term child wish who are scheduled for RAI treatment.

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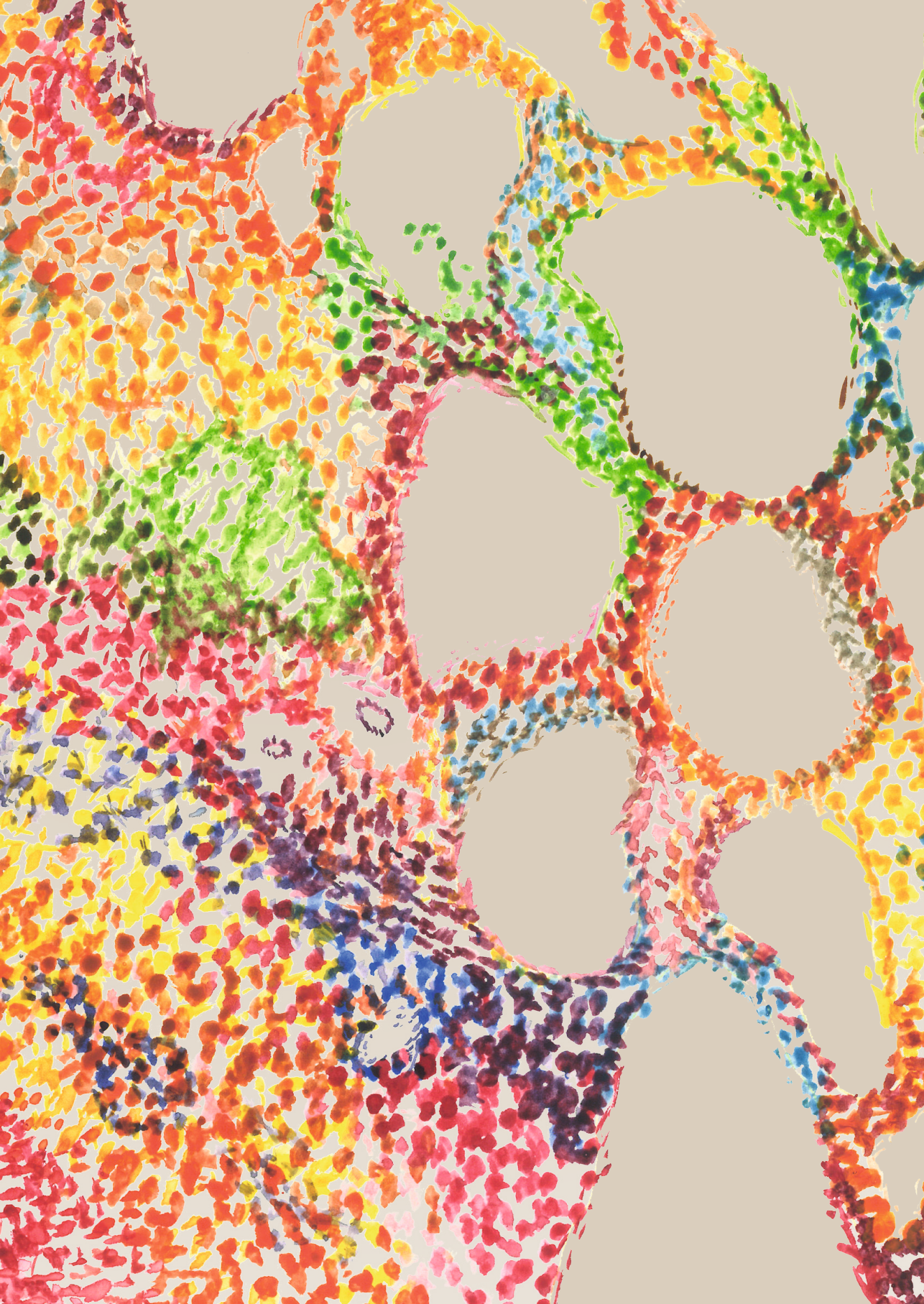
PART III

Summary and future perspectives



SUMMARY

Samenvatting

SUMMARY

Differentiated thyroid carcinoma is a rare clinical condition that has experienced an increased incidence in recent years. The diagnosis, treatment and follow-up of this condition is complex and hold significant importance for the patient's overall outcome and quality of life. This thesis aims to enhance the personalized management of differentiated thyroid carcinoma. **Chapter 1** offers a comprehensive introduction, discussing the current diagnostic methods and management approaches for patients with differentiated thyroid cancer. The first part of this thesis focuses on studies concerning incidental findings in the thyroid gland detected through imaging studies in patients with an underlying malignancy. In the second part, we examine the co-occurrence of differentiated thyroid cancer with other malignancies. Lastly, we evaluate the impact of thyroid cancer treatment with radioactive iodine on fertility in adolescents and young adults.

Part I

The detection of incidental thyroid nodules is increasing due to advancements in imaging techniques used in oncological practice. The first part of this thesis focuses on the occurrence of unintended uptake of radioactive agents, specifically ^{18}F-FDG and PSMA, in the thyroid during ^{18}F-FDG-PET/CT scans in oncological patients.

Imaging techniques are increasingly used in oncological practice and play a central role in cancer diagnosis and treatment. However, a challenge faced by physicians and patients is that comprehensive scans can often reveal unexpected findings. Incidental uptake of radioactive agents in the thyroid, known as thyroid incidentaloma, is one such occurrence. The ^{18}F-FDG-PET/CT scan is widely used in oncology for disease staging and recurrence assessment, and thyroid incidentalomas are detected in approximately 2% of these examinations. The American Thyroid Association recommends additional diagnostic evaluations for thyroid incidentalomas in patients without relevant comorbidities. However, it remains unclear when additional diagnostic procedures should be performed for thyroid incidentalomas in oncological patients with relevant comorbidities. In **Chapter 2**, we specifically investigate ^{18}F-FDG-PET/CT thyroid incidentalomas in patients with an underlying malignancy. To conduct this study, we examined a cohort of 1003 patients with documented thyroid incidentalomas from the Netherlands Cancer Institute database.

The clinical outcomes of thyroid incidentalomas in these patients were found to be favorable, despite only 32% of patients undergoing additional diagnostic procedures such as ultrasound and Fine Needle Aspiration Cytology (FNAC). Active treatment of

thyroid incidentalomas may provide benefits to a subset of patients with either cured or stable underlying cancer. A wait-and-see approach using ultrasound could serve as an alternative strategy.

Medical images play a crucial role in extrapolating data and analyzing quantitative features to enhance clinical decision-making. This approach, known as "radiomics," can be implemented to predict the risk of malignancy for thyroid incidentalomas. In **Chapter 3**, we investigate the diagnostic value of radiomics in predicting the malignancy risk of thyroid incidentalomas on ^{18}F-FDG-PET/CT scans compared to the validated TIRADS classification. One combined radiomics feature, the Run Length Non-Uniformity, derived from the ^{18}F-FDG PET/CT scan demonstrates a comparable diagnostic value to the validated TIRADS classification.

Thyroid incidentalomas can also be detected on PSMA-PET/CT scans, primarily used for detecting and staging prostate cancer. However, PSMA thyroid incidentalomas are rare and have not been extensively studied literature. In **Chapter 4**, we conducted a retrospective study involving 61 patients with PSMA thyroid incidentalomas, detected between 2016 and 2021 at the Netherlands Cancer Institute and the University Medical Center Utrecht. The incidence of PSMA thyroid incidentalomas was low, representing only 1.1% of patients with prostate cancer in this study. Favorable clinical outcomes were observed, with a minority of patients (36%) undergoing additional diagnostic procedures such as ultrasound and FNAC. Decisions regarding the management of PSMA thyroid incidentalomas should be based on the stage and prognosis of the underlying cancer, with shared clinical decision-making playing a crucial role.

In **Chapter 5**, we prospectively determined the incidence of PSMA thyroid incidentalomas at the Netherlands Cancer Institute between 2016 and 2021. We analyzed two different methods for defining PSMA thyroid incidentalomas, namely a structured visual analysis and a semi-quantitative analysis, and compared them with the reports in patient files. The incidence of PSMA thyroid incidentalomas varied among the different methods, with rates of 22% in the structured visual analysis, 7% in the semi-quantitative analysis, and 2% in the patient files. This variation was primarily due to diffuse and/or slightly increased PSMA uptake. The definition of a PSMA thyroid incidentaloma can be reliably limited to focal uptake with an SUVmax thyroid/bloodpool ratio of ≥ 2.0.

Part II

Part II of this thesis focuses on evaluating the association of differentiated thyroid cancer with other types of cancer. The emergence of second primary malignancies following oncological treatment is not uncommon and has become a significant concern for cancer survivors. The development of an additional malignancy either before- or after differentiated thyroid cancer may arise by chance or be associated with risk factors such as genetic predisposition or harmful therapies.

In **Chapter 6**, we examined whether the risk of breast cancer was elevated in patients with differentiated thyroid cancer compared to the general population. Conversely, we also investigated if the risk of differentiated thyroid cancer was increased in patients with breast cancer compared to the general population. We included patients with both breast- and differentiated thyroid cancer in the Netherlands from 1989 to 2020. A total of 423 patients with breast cancer followed by differentiated thyroid cancer and 355 patients with differentiated thyroid cancer followed by breast cancer were analyzed and compared to control groups of patients with breast cancer or differentiated thyroid cancer alone. Data was obtained from the Netherlands Cancer Registry.

We found that patients with breast cancer had a higher risk of developing differentiated thyroid cancer as a second primary malignancy compared to the general population (standardized incidence ratio = 1.86). Similarly, patients with differentiated thyroid cancer had a higher risk of developing breast cancer compared to the general population (standardized incidence ratio = 1.46). The combination of breast cancer followed by differentiated thyroid cancer was more prevalent among young female patients, potentially attributable to comprehensive diagnostic procedures during follow-up, which increase the likelihood of incidental findings in the thyroid gland. Importantly, patients with the combination of breast- and differentiated thyroid cancer did not have a worse overall survival compared to those with breast- or differentiated thyroid cancer as the primary malignancy. Therefore, additional screening beyond the Dutch national population screening programs is not warranted for these patient groups based on these studies.

In **Chapter 7**, we investigated whether adolescent and young adult patients treated for Hodgkin's disease had an increased risk of developing differentiated thyroid cancer. Radiotherapy in the neck region during childhood for Hodgkin's disease is a known risk factor for developing thyroid cancer later in life. The study revealed an elevated risk of differentiated thyroid cancer in this group of patients compared to the general population. All patients included in the study had a history of radiation therapy in the neck region. Furthermore, cases with a history of Hodgkin's disease showed a higher

frequency of lymph node metastasis compared to matched control patients with primary differentiated thyroid cancer. Therefore, a history of Hodgkin's disease during adolescence and young adulthood can be considered a risk factor for metastatic differentiated thyroid cancer based on our study results.

The incidence of thyroid cancer has witnessed a significant rise, particularly among adolescents and young adults. This part of the thesis focuses on the clinical management of thyroid cancer in this specific age group. Providing care for young adults diagnosed with cancer, aged 18 to 39 years, presents complex challenges due to crucial factors such as fertility, which hold substantial importance in their lives. Radioactive iodine treatment is commonly administered to many young adults with thyroid cancer, and its impact on female fertility remains controversial. In **Chapter 8**, we performed a systematic review and meta-analysis of the available literature to explore the effects of radioactive iodine therapy on fertility in women. The review included 22 retrospective studies conducted until January 2020. The findings reveal that women experienced menstrual irregularities and a decline in Anti-Müllerian Hormone levels during the first year following radioactive iodine treatment. However, there was no significant decrease observed in long-term pregnancy rates. It is recommended that women consult with a fertility specialist for personalized guidance and support, enabling them to make informed decisions regarding their fertility options.

Chapter 9 presents a comprehensive discussion of the results obtained from the studies presented in this thesis. Additionally, the chapter explores future perspectives, highlighting the limitations encountered during our analyses and suggesting potential directions for future research to address these limitations.

NEDERLANDSE SAMENVATTING

Gedifferentieerd schildkliercarcinoom is een zeldzame aandoening waarvan de incidentie in de afgelopen jaren is gestegen. Adequate diagnostiek, behandeling en follow-up zijn complex en van belang voor het resultaat van de behandeling en de kwaliteit van leven van de patiënt. Dit proefschrift richt zich op het verbeteren van de behandeling van patiënten met gedifferentieerd schildkliercarcinoom. In de introductie van dit proefschrift wordt beschreven waar de behandeling van gedifferentieerd schildkliercarcinoom momenteel uit bestaat en wat de nieuwe ontwikkelingen zijn op dit gebied. Het eerste deel van dit proefschrift gaat over het voorkomen van toevalsbevindingen in de schildklier op beeldvorming bij patiënten die onder behandeling zijn voor een andere vorm van kanker. In het tweede deel wordt het voorkomen van gedifferentieerd schildkliercarcinoom in combinatie met andere vormen van kanker besproken. Het derde deel gaat over de effecten van de behandeling van schildklierkanker met radioactief jodium op de vruchtbaarheid bij adolescenten en jongvolwassenen.

Deel I

Schildklierknobbels worden in toenemende mate ontdekt door de verbeteringen van beeldvormende technieken in de oncologie. In het eerste deel wordt de opname van de radioactieve stoffen ^{18}FDG en PSMA in de schildklier op PET/CT scans besproken bij oncologische patiënten. Beeldvormingstechnieken spelen een centrale rol bij de diagnose en behandeling van kanker. Een uitdaging voor artsen en patiënten is dat een nauwkeurige scan van het hele lichaam kan leiden tot onverwachte bevindingen. Er is sprake van een schildklierincidentaloom bij incidentele opname van radioactieve stoffen in de schildklier. De ^{18}FDG-PET/CT-scan wordt veel gebruikt in de oncologie voor het monitoren van kanker en schildklierincidentalomen komen in circa 2% van deze onderzoeken voor. De Amerikaanse Schildklier Associatie adviseert om schildklierincidentalomen alleen te vervolgen bij patiënten zonder relevante comorbiditeit, maar er wordt geen duidelijke definitie hiervan gegeven. Dit is een grijs gebied in de oncologie omdat het niet duidelijk is bij welke onderliggende tumorsoort een schildklierincidentaloom moet worden vervolgd. In **hoofdstuk 2** richten wij ons op schildklierincidentalomen op ^{18}FDG-PET/CT-scans bij patiënten met een onderliggende kankersoort. Voor deze studie werden 1003 oncologische patiënten uit de database van het Nederlands Kanker Instituut met schildklierincidentalomen bestudeerd. De klinische follow-up van deze patiënten was gunstig, terwijl slechts 32% van de patiënten aanvullende diagnostische procedures zoals echografie en fijne naald aspiratie cytologie onderging. Actieve behandeling van schildklierincidentalomen komt ten goede aan een groep patiënten bij wie de onderliggende kankersoort genezen is of naar alle waarschijnlijkheid stabiel

blijft. Een afwachtend beleid met follow-up door middel van echografie zou een alternatieve strategie kunnen zijn.

Beeldvormend medisch onderzoek kan worden gebruikt om gegevens te extrapoleren en kwantitatieve kenmerken te analyseren, wat kan leiden tot verbetering van de klinische besluitvorming. Deze methode staat bekend als "radiomics" en kan worden toegepast om het risico op maligniteit van schildklierincidentalomen te voorspellen. In **hoofdstuk 3** onderzoeken we de diagnostische waarde van radiomics bij het onderscheiden van goedaardige- en kwaadaardige schildklierincidentalomen op ^{18}FDG-PET/CT-scans, in vergelijking met de gevalideerde TIRADS-classificatie. Eén gecombineerd radiomics-kenmerk van de ^{18}FDG-PET/CT-scan vertoonde een vergelijkbare diagnostische waarde als de gevalideerde TIRADS-classificatie.

Schildklierincidentalomen komen ook voor op PSMA-PET/CT-scans, die voornamelijk worden gebruikt voor de opsporing en stadiëring van prostaatkanker. PSMA-schildklierincidentalomen komen weinig voor en zijn in de literatuur niet uitgebreid bestudeerd. In **hoofdstuk 4** hebben we een retrospectieve studie uitgevoerd bij 61 patiënten met PSMA-schildklierincidentalomen, die tussen 2016 en 2021 zijn gedetecteerd in het Nederlands Kanker Instituut en het Universitair Medisch Centrum Utrecht. De incidentie van PSMA-schildklierincidentalomen was laag (1,1% van de patiënten met prostaatkanker) in deze studie. De klinische uitkomsten waren gunstig, terwijl slechts een minderheid van de patiënten (36%) aanvullende diagnostiek met echografie en fijne naald aspiratie cytologie onderging. De overweging om PSMA-schildklierincidentalomen te onderzoeken is afhankelijk van het stadium en de prognose van de onderliggende kankersoort en moet onderdeel zijn van gedeelde besluitvorming tussen arts en patiënt. In **hoofdstuk 5** bepalen we prospectief de incidentie van PSMA-schildklierincidentalomen in het Nederlands Kanker Instituut tussen 2016 en 2021. Twee verschillende methoden om PSMA-schildklierincidentalomen te definiëren werden geanalyseerd (een gestructureerde visuele en een semi-kwantitatieve methode) en vervolgens vergeleken met de verslagen in de patiëntendossiers. De incidentie van PSMA-schildklierincidentalomen verschilde per methode (22% in de gestructureerde visuele methode, 7% in de semi-kwantitatieve methode en 2% in de patiëntendossiers). Dit werd voornamelijk veroorzaakt door diffuse en/of licht verhoogde PSMA opname. De definitie van een PSMA-schildklierincidentaloom kan veilig worden beperkt tot focale opname met een SUV_{max} schildklier/bloedvat ratio van ≥ 2.0.

Deel II

In deel II van dit proefschrift wordt onderzocht hoe vaak gedifferentieerde schildklierkanker samen voorkomt met andere vormen van kanker. Het aantal tweede primaire maligniteiten neemt toe en vormt een zorg voor overlevenden van kanker. Het ontstaan van een andere maligniteit vóór- of na gedifferentieerde schildklierkanker kan toeval zijn of geassocieerd worden met risicofactoren zoals een genetische aanleg of schadelijke behandeling.

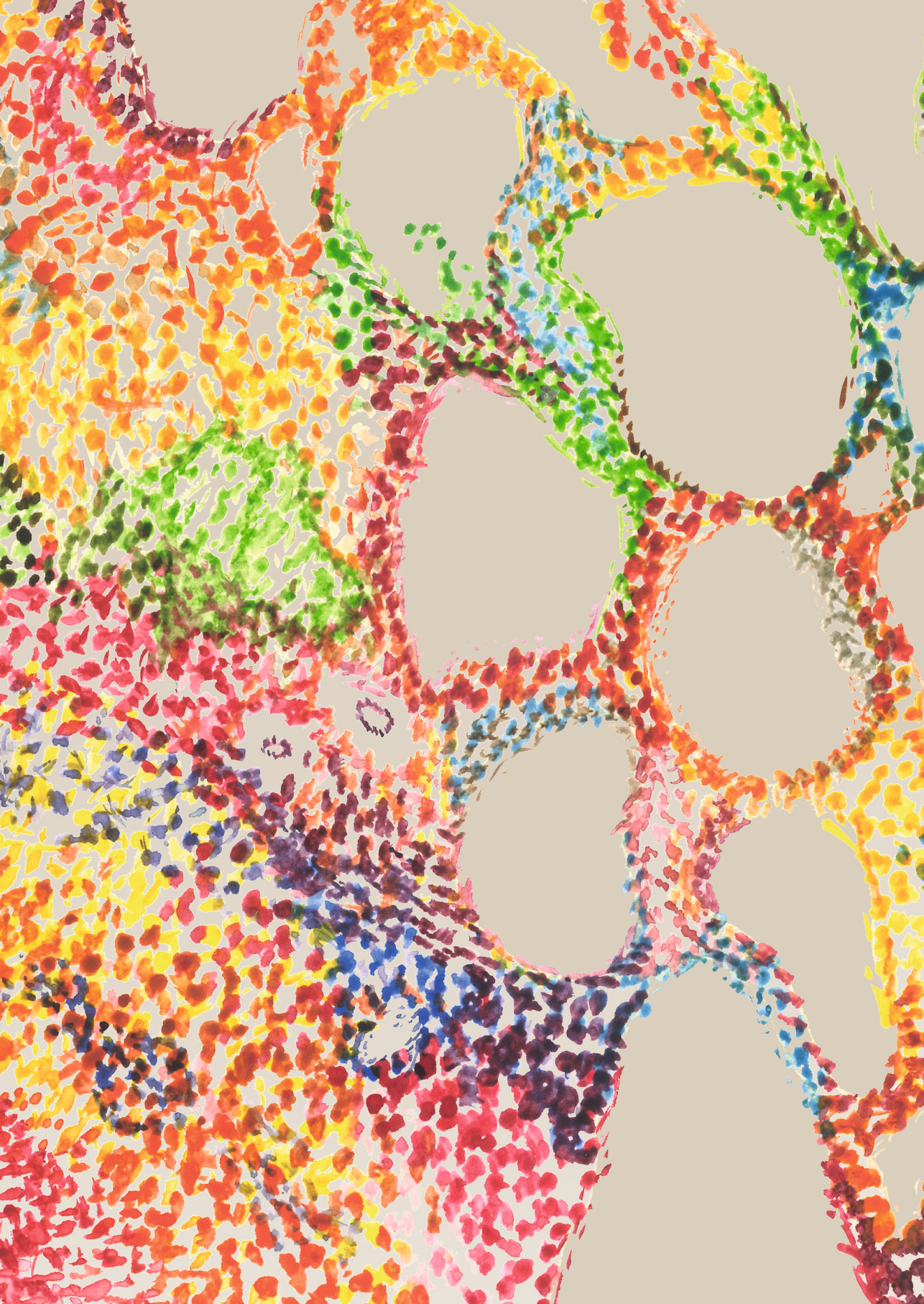
In **hoofdstuk 6** is onderzocht of het risico op gedifferentieerde schildklierkanker na borstkanker en vice versa verhoogd is in vergelijking met de algemene bevolking. We hebben gegevens bestudeerd van patiënten in Nederland bij wie tussen 1989 en 2020 zowel borstkanker als gedifferentieerde schildklierkanker is vastgesteld. We hebben 423 patiënten geanalyseerd die eerst borstkanker hadden en daarna gedifferentieerde schildklierkanker, en 355 patiënten die eerst gedifferentieerde schildklierkanker hadden en daarna borstkanker. Deze groepen werden vergeleken met controlegroepen van patiënten die alleen borstkanker of alleen schildklierkanker hadden. Patiënten met borstkanker hadden een hoger risico op het ontwikkelen van gedifferentieerde schildklierkanker als tweede primaire maligniteit in vergelijking met het risico in de algemene bevolking (gestandaardiseerde incidentieratio = 1.86). Ook hadden patiënten met gedifferentieerde schildklierkanker een hoger risico op het ontwikkelen van borstkanker in vergelijking met het risico in de algemene bevolking (gestandaardiseerde incidentieratio = 1.46). De combinatie van borstkanker gevolgd door gedifferentieerde schildklierkanker kwam vaker voor bij jonge vrouwelijke patiënten. Dit kan worden veroorzaakt door uitgebreidere diagnostiek met meer toevallige bevindingen in de schildklier bij deze groep patiënten. De combinatie van borstkanker en gedifferentieerde schildklierkanker leidde echter niet tot een slechtere overleving in vergelijking met patiënten die alleen borstkanker of schildklierkanker hadden. Er is geen noodzaak voor aanvullende diagnostiek bij deze groepen patiënten naast de bestaande bevolkingsonderzoeken in Nederland.

Radiotherapie in het halsgebied op kinderleeftijd voor de behandeling van de ziekte van Hodgkin is een bekende risicofactor voor het ontwikkelen van schildklierkanker op latere leeftijd. In **hoofdstuk 7** is onderzocht of adolescenten en jongvolwassenen die behandeld zijn voor de ziekte van Hodgkin een verhoogd risico hebben op gedifferentieerde schildklierkanker. De studie toont aan dat het risico op gedifferentieerde schildklierkanker in deze groep patiënten verhoogd was in vergelijking met het risico in de algemene bevolking (gestandaardiseerde incidentieratio = 6.8). Alle patiënten met beschikbare gegevens waren bestraald in het halsgebied. Bovendien bleken de schildkliertumoren vaker uitgezaaid naar de lymfeklieren in vergelijking met een ge-

matchte controlegroep van patiënten met primaire gedifferentieerde schildklierkanker. Een voorgeschiedenis van de ziekte van Hodgkin bij adolescenten en jongvolwassenen kan dus een risicofactor zijn voor uitgezaaide schildklierkanker.

Een andere focus van dit proefschrift is de zorg voor schildklierkanker bij jongvolwassenen, aangezien de verhoogde incidentie van schildklierkanker met name zichtbaar is in deze leeftijdsgroep. De zorg voor jongvolwassenen die gediagnosticeerd zijn met kanker in de leeftijd van 18 tot 39 jaar is complex vanwege belangrijke aspecten, zoals vruchtbaarheid, die een rol spelen in het leven van jonge mensen. Veel jongvolwassenen met schildklierkanker ondergaan behandeling met radioactief jodium, maar het effect hiervan op de vruchtbaarheid bij vrouwen is nog onduidelijk. In **hoofdstuk 8** hebben we een systematische review en meta-analyse uitgevoerd van de bestaande literatuur over de effecten van radioactieve jodiumtherapie op de vruchtbaarheid bij vrouwen. Deze review omvatte 22 retrospectieve studies tot januari 2020. De resultaten laten zien dat vrouwen in het eerste jaar na radioactieve jodiumtherapie menstruatiestoornissen ervaren en dat de AMH-spiegels verlaagd zijn. Desondanks bleken de zwangerschapspercentages op latere leeftijd niet te zijn gedaald. Voor vrouwen met een actieve kinderwens wordt een consult bij een fertiliteitsarts dan ook aanbevolen voordat ze worden behandeld met radioactief jodium.

Hoofdstuk 9 van dit proefschrift bespreekt de gepresenteerde resultaten van de studies, inclusief de beperkingen ervan, die als basis kunnen dienen voor toekomstig onderzoek.



GENERAL DISCUSSION AND FUTURE PERSPECTIVES

Toekomstperspectieven

GENERAL DISCUSSION

Following advancements in diagnostic imaging and its widespread use, there has been an increase in the detection of differentiated thyroid cancers (DTC), contributing to the rising incidence of this disease. The increasing incidence of early-stage thyroid tumors with a favorable prognosis raises questions about the necessity of traditional oncological treatment approaches for all cases of DTC. Scientific research in various types of cancer with positive oncological outcomes has shifted towards exploring treatment omission without compromising safety and preserving quality of life. These trends towards a refined treatment de-escalation reflect better risk stratification in cancer care indicating that some cancers can be treated conservatively.

Considering the excellent survival rates of DTC, it is worth exploring de-escalation strategies. International guidelines have been evolving to incorporate higher thresholds for thyroid cancer therapy. However, variations in clinical practice patterns exist due to discrepancies among guidelines and a lack of literature on the role of active surveillance in low-risk thyroid cancer. In this thesis we evaluate the current clinical challenges in the management of thyroid cancer patients, focusing on incidental thyroid nodules, second primary thyroid malignancies, and thyroid cancer in adolescents and young adults.

Optimization of the care for thyroid nodules incidentally discovered through imaging techniques in oncological patients

High-resolution computed tomography, ultrasonography and nuclear imaging have all contributed to improving the accuracy of diagnosis and treatment in oncology. The increasing use of highly sensitive imaging techniques has led to the detection of many non-palpable nodules, referred to as "incidentalomas," in the thyroid. The identification of these unexpected lesions present diagnostic and treatment dilemmas during initial work-up and follow-up. The optimal management strategy for thyroid incidentalomas in oncological practice has not been clearly established. While some thyroid cancers are detected at an early stage, most of these subclinical cancers do not progress to a clinically overt state. Overdiagnosis and overtreatment pose potential harms, particularly in patients with an underlying primary malignancy. In Chapter 2 and Chapter 4, the retrospective studies on ^{18}F-FDG-PET/CT thyroid incidentaloma and PSMA thyroid incidentaloma reveal that only a minority of oncological patients receive additional diagnostics and treatment for (P)TI. In the context of the underlying primary malignancy, most incidental thyroidal uptake is harmless. Thus, additional diagnostics and treatment for a thyroid incidentaloma do not improve life expectancy, as demonstrated in this thesis. The identification of a thyroid incidentaloma may cause anxiety and gener-

ate healthcare costs. However, some patients and clinicians prefer overtreatment over accepting uncertainty. The issue of pursuing all thyroid incidentalomas without clinical relevance could be resolved if we were able to distinguish significant from non-significant thyroid lesions on imaging studies. In Chapter 3, we investigated the role of PET-derived radiomics features in distinguishing benign- from malignant TI and found that Run Length Non-Uniformity, extracted from PET/CT scans, performed best as a radiomics feature. In Chapter 5, we recommended excluding a large proportion of PTI by implementing a restricted definition of focal thyroidal uptake with a Standardized Uptake Value thyroid/blood pool ratio of ≥ 2.0.

The management of thyroid incidentalomas in oncological patients should focus on ensuring patient and physician comfort with a watchful waiting approach, if it is deemed safe. Our studies indicate that this strategy is already implemented in daily oncological practice due to physicians' preference for prioritizing the management of the underlying oncological disease that is most relevant to the patient's survival. Future studies should concentrate on exploring the de-escalation of invasive procedures for thyroid incidentaloma in a prospective setting. Radiomics using ^{18}F-FDG-PET/CT appears to be a promising approach for evaluating thyroid incidentaloma without the need for additional diagnostics such as biopsies. However, larger prospective studies are needed to confirm the clinical application of radiomics in the diagnostic evaluation of thyroid incidentalomas.

The optimization of care in the treatment of thyroid cancer

Evaluation of the occurrence of differentiated thyroid cancer (DTC) as a second primary tumor is another focus of this thesis. The current American Thyroid Association (ATA) guidelines describe an increased risk of thyroid cancer (TC), particularly in women with breast cancer (BC). However, this association may be influenced by screening bias. The prevalence of BC after TC is also higher which may be associated with radioactive iodine therapy (RAI) and other factors (Recommendation C2) (1). Additionally, historical risk factors predicting thyroid malignancy include neck radiation therapy, commonly used to treat patients with Hodgkin's disease (HD) (1). In Chapter 6 and Chapter 7, the associations between DTC and BC and between DTC and HD were analyzed for the Netherlands. In Chapter 6, we demonstrated a marginal increase in the risk of BC after treatment for DTC and DTC after BC compared to the general population in the Netherlands. In Chapter 7, we observed a higher risk of DTC after treatment for HD compared to the general population in the Netherlands. It is important to note that these results may be influenced by surveillance bias since patients with a primary tumor are closely monitored, increasing the chances of detecting a second primary tumor that may remain concealed in the general population. Many thyroid cancers are clinically

"silent" and will only be detected if appropriate diagnostic tests are performed. The ^{18}F-FDG-PET/CT scan is an accurate and sensitive modality for screening and detecting BC recurrence and relapsed lymphoma (2, 3). The frequency of diagnostic techniques employed will also impact the rate of "silent" thyroid cancers, also known as thyroid incidentalomas (4). In both the BC and HD studies, the majority of second primary thyroid cancers were detected during the initial years of follow-up. It was observed that patients with BC followed by DTC were younger and received more intensive treatment regimens for BC, possibly leading to more active surveillance as part of the treatment. For both the BC and HD studies, we obtained data from the Netherlands Cancer Registry, which included diverse diagnostic and surveillance methods. Consequently, we were unable to correct for any inequalities, such as lack of imaging, in the control groups. Potential variations in surveillance in the BC and HD groups, as compared to the control groups, could have influenced the number of detected asymptomatic cancers. We have also focused on etiological and treatment-related risk factors as potential causes for the occurrence of second primary malignancies (5, 6). Almost all patients with BC and DTC were females in their menopausal or postmenopausal phase. The precise mechanisms by which hormones affect the risk of breast- and thyroid cancer require further detailed investigation (7, 8). The majority of Hodgkin's survivors who developed subsequent DTC had a history of neck radiation and presented with more extensive disease at the time of diagnosis. Neck irradiation can be considered a risk factor for more advanced thyroid cancer in accordance with the ATA guidelines (1). Further studies investigating associations between thyroid cancer and other cancer types should adjust for various screening methods, including the evaluation of associated risk factors. We found no evidence that active screening for thyroid cancer in asymptomatic Hodgkin- and breast cancer patients improves overall survival. Screening for thyroid cancer in asymptomatic patients may be more harmful than beneficial.

The optimization of care for adolescents and young adults (AYAs) with thyroid cancer is another important aspect of our research. Thyroid cancer is the most common cancer among AYAs aged 18-39 years (9). The reasons behind the rapid increase in thyroid cancer diagnosis among AYAs are currently unknown. The incidence of TC is more than five times higher in females than in males among AYAs (10). Despite the high rates of survival, these patients are at risk of local recurrences and local- or distant metastases (12). RAI treatment is often used to prevent disease recurrence and to treat persistent or metastatic thyroid cancer (1). Adjuvant RAI treatment in low-risk patients is a topic of debate since these patients have an excellent prognosis and RAI treatment's impact on reducing loco-regional recurrence is questionable (13, 14). RAI treatment may have harmful effects as it can lead to uptake in other tissues, potentially impairing fertility (15,16). In Chapter 8, we conducted a systematic review and meta-analysis of the avail-

able literature on this topic. The results demonstrate that female AYA patients experience menstrual irregularities and decreased anti-Mullerian hormone (AMH) levels in the first year after RAI treatment. However, RAI treatment was not associated with a long-term decrease in pregnancy rates. Considering these results, it is crucial to carefully select AYA patients who should receive RAI treatment, particularly in low-risk tumors. When patients are at higher risk according to the ATA guidelines, they should be well informed about the potential impact of RAI treatment on fertility. In women with severely diminished ovarian reserve, such as due to age, fertility preservation should be considered. Future studies are needed to prospectively evaluate the effects of RAI treatment on fertility. The overall quality of life of the patient, their life expectancy, and their preferences should be important factors in the decision-making process regarding RAI treatment, and individual considerations should be taken into account.

Future directions

Differentiated thyroid cancer (DTC) is a disease that is rapidly increasing in incidence and prevalence, posing a challenge for its clinical management. The studies conducted in this thesis reveal that thyroid incidentalomas are frequently detected during the diagnostic work-up of oncological patients. The current guidelines from the American Thyroid Association (ATA) lack a consistent diagnostic strategy once thyroid incidentalomas are detected in patients with relevant comorbidities. We found that these incidentalomas have a relatively benign prognosis in the presence of another primary tumor. However, it is important to note that these studies were based on retrospective data, which limits their findings. Despite these limitations, the studies suggest that thyroid incidentalomas generally have a favorable prognosis. Therefore, our data needs to be validated in prospective studies that compare active treatment with a conservative approach, the latter being justified by the benign nature of most thyroid incidentalomas, as demonstrated in this thesis. Additionally, the control groups used for incidence analyses in the second primary malignancies studies were constructed from a national database. To accurately calculate the incidence rate of second primary malignancies, a well-defined control group is necessary, ideally consisting of asymptomatic patients undergoing the same screening methods as the cases.

The use of artificial intelligence (AI) is rapidly expanding in the medical field, particularly in diagnostics- and treatment management. AI can be an important tool for integrating clinical characteristics with medical imaging data in the management of DTC. Computer models designed to assist in risk stratification for complex clinical scenarios have shown good performance in clinical practice. In the future, AI applications may be applied in the diagnostic phase and follow-up of DTC patients, effectively aiding in the early detection of aggressive tumor features. Based on the studies, including

those presented in this thesis, the incidence of aggressive thyroid cancers in oncological patients is likely to be relatively low, suggesting that the majority of patients can be managed conservatively. A prospective study that incorporates AI technology can be designed to optimize the diagnosis of thyroid incidentalomas and minimize unnecessary interventions. Moreover, personalized decision-making can be valuable in minimizing risks and maximizing benefits for individual patients. Patient decision aids are already being used to inform patients about healthcare choices, such as in the decision-making process for adjuvant radioactive iodine treatment in early-stage papillary thyroid cancer (17). Computerized decision aid models have improved decision-making in patients with early papillary thyroid cancer. The future of personalized DTC management involves enhancing patients' medical knowledge, including prognosis, potential short- and long-term treatment effects and addressing uncertainties in medical evidence. AI strategies should be combined with patient-directed decision aids to support personalized management for DTC patients. Physicians should actively involve patients in the decision-making process, while encouraging the use of new technologies for risk stratification and overcoming emotional reflexes that may lead to excluding any risks. Innovative research and appropriate professional training are necessary to find solutions that further support doctors and patients in this process.

TOEKOMSTPERSPECTIEVEN

Gedifferentieerde schildklierkanker (DTC) is een ziekte die snel toeneemt qua incidentie en prevalentie en vormt daarom een uitdaging vormt voor de klinische behandeling. De studies die in dit proefschrift zijn uitgevoerd, laten zien dat schildklierincidentalomen vaak worden ontdekt tijdens het standaard diagnostisch onderzoek van oncologische patiënten. In de huidige richtlijnen van de American Thyroid Association (ATA) ontbreekt een diagnostische strategie en behandeladvies voor schildklierincidentalomen bij patiënten met relevante comorbiditeiten. In dit proefschrift laten wij zien dat deze incidentalomen in het algemeen een relatief goedaardig beloop hebben in aanwezigheid van een andere primaire tumor. Het is echter belangrijk op te merken dat deze studies veelal gebaseerd zijn op retrospectieve gegevens. Ondanks deze beperkingen suggereren deze studies dat schildklierincidentalomen over het algemeen een gunstige prognose hebben. Deze veronderstelling moet nog wel worden gevalideerd in prospectieve studies, waarin een actieve behandeling (chirurgie) vergeleken wordt met een conservatieve aanpak. Dit laatste lijkt gerechtvaardigd omdat de meeste schildklierincidentalomen vermoedelijk goedaardig zijn, zoals in dit proefschrift beschreven. In onze analyse werden de controlegroepen, die voor de incidentieanalyses van de studies naar tweede primaire maligniteiten werden gebruikt, samengesteld uit een nationale database. Om de incidentie van tweede primaire maligniteiten nauwkeurig te berekenen is een goed gedefinieerde controlegroep nodig, idealiter bestaande uit asymptomatische patiënten die dezelfde screeningsmethoden ondergaan als de patiënten met vastgestelde schildklierkanker.

Het gebruik van kunstmatige intelligentie (AI) neemt snel toe in de medische wereld, met name op het gebied van diagnostiek en behandelmanagement. AI kan een belangrijk hulpmiddel zijn voor het integreren van klinische kenmerken met medische beeldvormingsgegevens in de behandeling van DTC. Computermodellen die zijn ontworpen om te helpen bij de risicostratificatie voor complexe scenario's hebben goede resultaten laten zien in de klinische praktijk. In de toekomst kunnen AI-toepassingen wellicht worden gebruikt in de diagnostische fase en follow-up van DTC-patiënten, waarbij ze effectief kunnen helpen bij vroege detectie van agressieve tumorkenmerken. Op basis van de onderzoeken, die onder meer in dit proefschrift zijn beschreven, is de incidentie van agressieve schildklierkanker bij oncologische patiënten waarschijnlijk relatief laag. Dit suggereert dat de meerderheid van de patiënten vermoedelijk conservatief kan worden behandeld. Prospectieve studies die gebruik maken van AI-technologie kunnen zo worden ontworpen om de diagnose van schildklierincidentalomen te optimaliseren en daardoor onnodige interventies te voorkomen. Bovendien kan gepersonaliseerde besluitvorming waardevol zijn bij het minimaliseren van risico's en het maximaliseren

van voordelen voor individuele patiënten. Hulpmiddelen voor besluitvorming bij patiënten worden nu al gebruikt om patiënten beter te informeren over keuzes in de gezondheidszorg. Een voorbeeld is het besluitvormingsproces voor aanvullende behandeling met radioactief jodium bij papillaire schildklierkanker, die in een vroeg stadium is vastgesteld (17). Gecomputeriseerde hulpmiddelen hebben de besluitvorming verbeterd bij patiënten met een vroege vorm van papillaire schildklierkanker. De toekomst van gepersonaliseerd DTC-management omvat het verbeteren van de medische kennis van patiënten omtrent de korte- en langetermijneffecten van de voorgestelde behandeling. AI-strategieën moeten worden gecombineerd met patiëntgerichte hulpmiddelen om de gepersonaliseerde behandeling van DTC-patiënten te ondersteunen. Artsen moeten patiënten actief betrekken bij dit besluitvormingsproces, terwijl ze het gebruik van nieuwe technologieën voor risicostratificatie toepassen. Innovatief onderzoek en professionele training zijn nodig om oplossingen te vinden die artsen en patiënten verder ondersteunen in dit proces.

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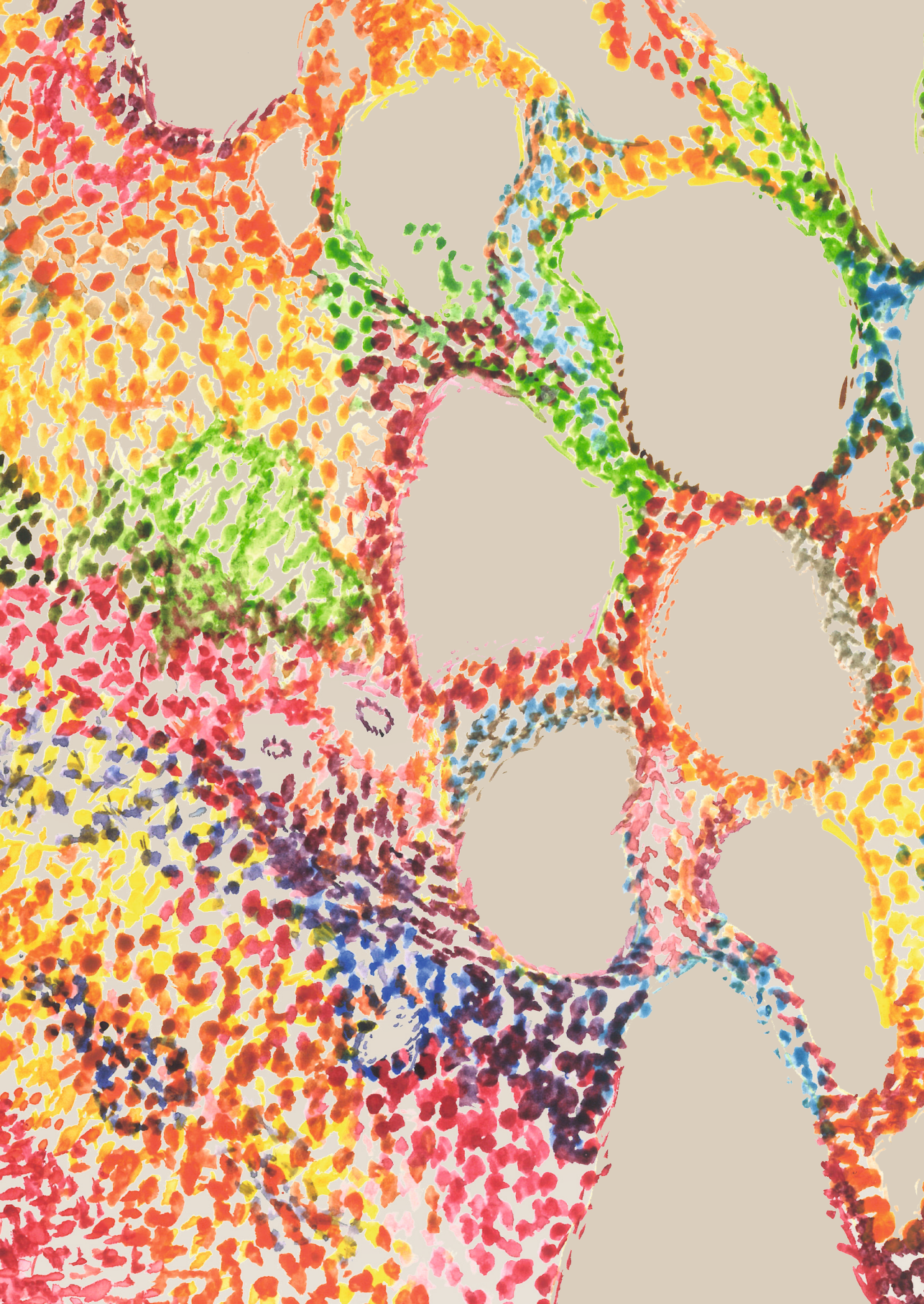

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Differentiated thyroid cancer in young adult survivors of Hodgkin lymphoma; histopathological, clinical and prognostic features
Piek MW, de Boer JP, Schaapveld M, van Leeuwen F, van Leeuwaarde RS, van Duijnhoven F, van der Ploeg IMC
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PRESENTATIONS

Radiomics Analysis for Thyroid Incidentalomas Malignancy Classification using PET/CT Scans; preliminary results
ESSO-European Society of Surgical Oncology Congress 2022, Bordeaux

The co-occurrence of both breast- and differentiated thyroid cancer: incidence, association and clinical implications for daily practice.
ESSO- European Society of Surgical Oncology Congress 2022, Bordeaux
Endo-research meeting 2022, Amsterdam

A Comparison of PSMA-targeted PET/CT assessments for Thyroid Incidentaloma Detection
ECR Congress 2022, Vienna

Retrospective Analyses of ^{18}FDG-PET/CT Thyroid Incidentaloma in Adults: Incidence, Treatment, and Outcome in a Tertiary Cancer Referral Center
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CURRICULUM VITAE

Marceline Piek was born on April 23rd, 1994, in Amsterdam, the Netherlands. She graduated from the St. Ignatius Gymnasium in Amsterdam, the Netherlands, in 2012. After graduation, she went to Roanoke College in Salem, Virginia USA, with the Fulbright Scholarship program to study Liberal Arts & Sciences with a major in Economics. After this year, she started her medical training at Utrecht University in 2013. After she received her medical degree at Utrecht University in 2020, she started as a PhD candidate at the Netherlands Cancer Institute and University Medical Center Utrecht at the Department of Surgery and Internal Medicine under the supervision of Dr. van der Ploeg, Dr. de Boer and Prof. dr. Vriens. She focused on the personalized management of differentiated thyroid cancer. In April 2023 she started as internal medicine resident not in training at the Department of Internal Medicine at the BovenIJ hospital, Amsterdam, the Netherlands.

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