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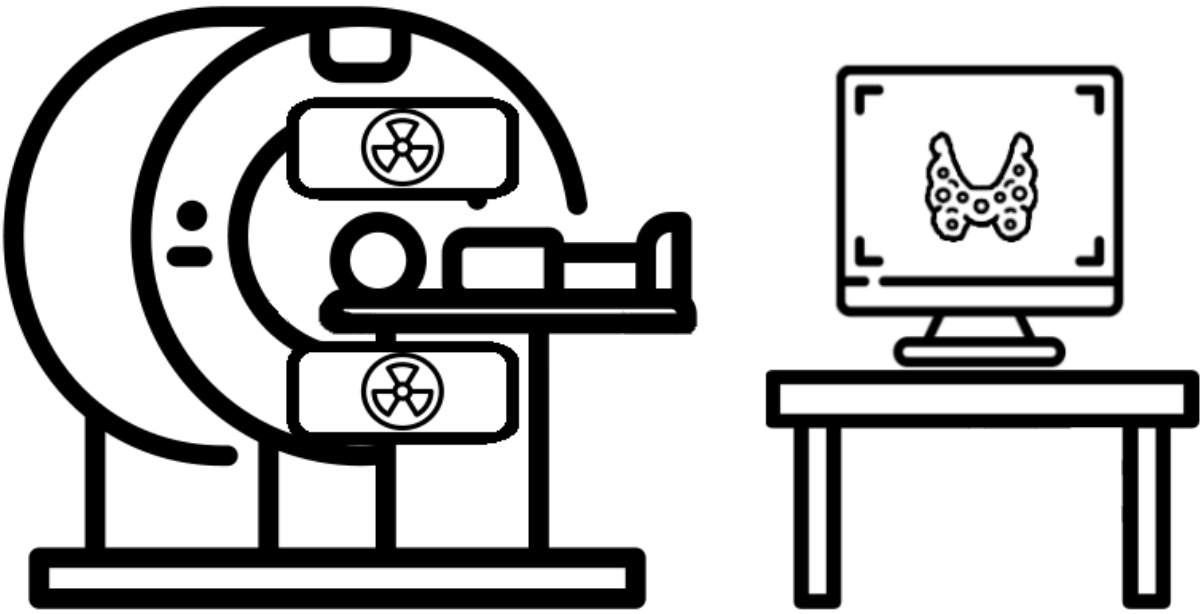

Quantitative single-photon emission computed tomography for dose calculation of radioiodine therapy in benign thyroid diseases

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Preface

Van april 2023 tot en met maart 2024 heb ik stage gelopen op de afdeling Radiologie en Nucleaire Geneeskunde in het Rijnstate ziekenhuis in Arnhem. Ik had hier al eerder een korte stage gelopen en vond het zo'n fijne en interessante afdeling dat ik hier graag nog veel meer wilde leren. Om deze reden ben ik met Laura en Femke gaan zoeken naar afstudeermogelijkheden op de nucleaire geneeskunde, en vonden we al snel een onderwerp wat me erg leuk leek om te onderzoeken. Ik heb het afgelopen jaar ontzettend veel geleerd op professioneel, medisch, en technisch vlak en kijk terug op een hele fijne tijd op de afdeling met diverse borrels, uitjes en natuurlijk de 'Heel Nucleaire Bakt' wedstrijd! Ik wil graag bij deze alle mensen bedanken die mij hebben geholpen bij het volbrengen van mijn afstudeeronderzoek en van wie ik heb mogen leren gedurende mijn tijd op de afdeling.

Femke, bedankt dat jij altijd tijd voor mij hebt vrijgemaakt om mee te kijken of te sparren en het vertrouwen dat je had in mij en mijn onderzoek. Je was erg enthousiast als ik weer wat nieuws had gevonden en je wilde graag meedenken over de volgende stap. Hierdoor wist je me altijd weer te motiveren, ook als ik soms vastliep op een bepaald stuk en het zelf even niet meer wist. Ik heb ontzettend veel van je geleerd op medisch en professioneel vlak, waardoor ik mij heb kunnen ontwikkelen tot de Technisch Geneeskundige die ik nu ben.

Laura, bedankt voor je kritische blik en dat je me altijd overal mee naartoe wilde nemen. Je bood altijd aan om stukken te lezen en mee te denken over de invulling van mijn verslag of presentaties, wat ik enorm heb gewaardeerd. Jij daagde me altijd uit om verder na te denken over de bevindingen die ik had, waardoor ik het gevoel heb een extra verdieping te hebben gegeven aan mijn onderzoek. Daarnaast heb ik me door jou meer kunnen oriënteren op de periode na mijn afstuderen, doordat je me vaak mee hebt genomen naar plekken om te netwerken met promovendi, klinisch fysici en andere Technisch Geneeskundigen.

Willem, bedankt voor je inzichten en de technische verdieping die ik samen met jou heb kunnen geven aan mijn onderzoek. Ondanks je drukke schema stond je er altijd voor open om te sparren over technische vraagstukken in mijn onderzoek. Ik mocht in de zomer met je meelopen bij de acceptatietesten van de nieuwe PET scanner, waarbij ik ook de technische en organisatorische kant van de afdeling heb kunnen zien. Daarnaast wil ik je ook bedanken voor de autoritjes richting huis, als er weer eens een storing was bij de NS en ik gestrand stond op Arnhem Centraal.

Ik wil verder alle collega's op de radiologie en nucleaire geneeskunde bedanken die mij hebben geholpen het afgelopen jaar. Het leren uitvoeren en uitwerken van de schildklierscintigrafieën en het uitvoeren van mijn fantoommetingen had ik allemaal niet kunnen doen zonder de medisch nucleair werkers op de afdeling. Daarnaast stonden zij er altijd voor open om met me mee te denken en heb ik een erg fijne samenwerking met hen ervaren. Door alle specialisten op de radiologie en nucleaire geneeskunde heb ik geleerd om zelf echo's van de hals te maken en verschillende soorten scans te leren verslaan, waardoor ik zowel mijn medische als technische kennis op het gebied van patiëntenzorg heb kunnen verbreden. Iedereen stond er altijd voor open om uitleg te geven en me mee te laten kijken, wat ik als erg prettig heb ervaren. Op de interne geneeskunde heb ik meerdere keren mee mogen lopen op de schildklierpoli, waardoor ik zelf kon oefenen met patiëntcontact, meer heb geleerd over schildklierfysiologie, en heb ik me verder kunnen ontwikkelen in het klinisch redeneren.

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Jessie Rijntjes, 19 maart 2024

Abstract

Introduction: Treatment of hyperthyroidism caused by Graves' disease (GD) or toxic multinodular goiter (tMNG) is commonly performed with radioiodine (I-131) therapy, aiming to achieve permanent euthyroidism. Currently, the patient-specific required I-131 dose is calculated based on the iodine uptake and thyroid volume measured in I-123 planar scintigraphy. It is hypothesized that these measurements lack accuracy, because patients often develop life-impacting complications after I-131 therapy, such as persistent hyperthyroidism or iatrogenic hypothyroidism. Improvement of I-131 dose calculation with quantitative SPECT/CT may be a solution to reduce the incidences of these complications. This study is divided into three sections: 1) assessment of the accuracy and workflow of planar scintigraphy, 2) establishment of a detailed quantification workflow for quantitative SPECT/CT data, and 3) comparison of planar scintigraphy and quantitative SPECT/CT and evaluation of administered I-131 activity concentration in relation to thyroid function one year after I-131 therapy.

Methods: For the first aim, a phantom study was performed to investigate the calibration factor, region-of-interest delineation for measuring iodine uptake, and to compare images obtained with the low -and medium energy collimator in planar scintigraphy. Furthermore, a patient study was performed to investigate the interobserver variability in estimating the thyroid volume in planar scintigraphy. For the second aim, a phantom study was performed to set up a workflow for measuring the iodine uptake and thyroid volume in quantitative SPECT/CT. For the third aim, the iodine uptake, thyroid volume and calculated I-131 dose obtained with planar scintigraphy and quantitative SPECT/CT were compared in a patient study. Additionally, the administered I-131 activity concentration was estimated based on SPECT data and evaluated in relation to the thyroid function one year after I-131 therapy.

Results: Assessment of planar scintigraphy accuracy and workflow showed a stable calibration factor over time and that an incorrect threshold was used for iodine uptake measurements. Thyroid volume estimation showed clinically relevant differences in volume between operators, impacting the calculated I-131 dose. Planar scintigraphy with the medium energy collimator showed less scattering and background noise in the image. A workflow for iodine uptake and thyroid volume measurements in quantitative SPECT/CT was successfully set up. Comparison of planar scintigraphy and quantitative SPECT/CT showed a reduction in calculated I-131 dose using quantitative SPECT/CT, as a result of higher measured iodine uptakes and more accurate volume estimations. In patients who developed hypothyroidism after I-131 therapy the administered I-131 activity concentration was the highest compared to patients who developed euthyroidism or had persistent hyperthyroidism.

Conclusion: Lowered I-131 doses calculated with quantitative SPECT/CT may be a first step towards reducing the incidence of the development of hypothyroidism after radioiodine therapy.

Keywords: Thyroid, radioiodine therapy, quantitative SPECT/CT, iodine uptake, planar scintigraphy

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List of Abbreviations

24h	24 hours
ATD	Antithyroid drugs
CF	Calibration factor
CT	Computed tomography
EANM	European association of Nuclear Medicine
FDG	Fluorodeoxyglucose
fT3	Free triiodothyronine
fT4	Free tetrathyroxine
GD	Graves' disease
IQR	Interquartile range
LEHRS	Low energy high resolution sensitivity
MEGP	Medium energy general purpose
NEMA	National electrical manufacturers association
NIS	Sodium iodide (NaI) symporter
PET	Positron emission tomography
PMT	Photomultiplier tubes
PVE	Partial volume effect
ROI	Region-of-interest
SPECT	Single-photon emission computed tomography
SUV	Standardized uptake value
tMNG	Toxic multinodular goiter
TSH	Thyroid stimulating hormone
TSI	Thyroid stimulating immunoglobulins
VOI	Volume-of-interest

1. General Introduction

1.1 Background information

Hyperthyroidism is a disorder of the thyroid, characterized by an overproduction of thyroid hormones [1–3]. The prevalence of hyperthyroidism is 0.8% in the European adult population, and the disorder is more common in women [4]. Symptoms of hyperthyroidism include anxiety, (extreme) fatigue, weight loss, rapid and irregular heartbeat, tremors, diarrhea, increased sweating, trouble sleeping, and ophthalmopathy [1,5]. Long term complications that may occur include osteoporosis, cardiovascular disease, thyrotoxic periodic paralysis and decreased fertility [1,3]. Hyperthyroidism is diagnosed based on general anamnesis, physical examination, and serum levels of thyroid stimulating hormone (TSH), free tetrathyroxine (fT4), and free triiodothyronine (fT3) (TSH between 0.3 – 4.8 mU/L, fT4 between 12 – 23 pmol/L, fT3 between 3.5 – 6.5 pmol/L) [1,2,6,7]. Additional clinical background information about thyroid physiology and hyperthyroidism is presented in the supplementary material, *Appendix A*.

Graves' disease (GD) and toxic multinodular goiter (tMNG) are the most common causes of hyperthyroidism [1,7–9]. In iodine-sufficient areas such as Europe, GD accounts for 70% to 80% of hyperthyroidism cases, while tMNG accounts for 20% to 30% of hyperthyroidism cases [1]. Graves' disease is an autoimmune disorder and occurs typically between the age of 20 to 60 years [10]. It is characterized by the production of thyroid stimulating immunoglobulins (TSI), which overstimulates the thyroid stimulating hormone receptors resulting in overproduction of thyroid hormones [3,8,11]. Toxic multinodular goiter typically occurs above the age of 50 years, and is associated with an enlarged thyroid gland and multiple toxic nodules autonomously producing thyroid hormones [6,8,12]. Prolonged overproduction of thyroid hormones inhibits TSH secretion in the pituitary gland, typically resulting in suppression of the normal thyroid tissue.

Treatment of hyperthyroidism

Disease management and treatment in GD is important to prevent long term complications of hyperthyroidism [1,3,13]. Graves' disease is typically treated with antithyroid medication (ATD) (i.e. Strumazol) to block thyroid function and Levothyroxine to replace thyroid hormones, also referred to as block and replace therapy [3,7,13]. However, the use of ATD for a prolonged period of time is not desired because of its severe side effects, such as agranulocytosis and hepatotoxicity [1,13]. Therefore, ATD is most commonly given during a period of 1 to 1.5 years, achieving permanent normalized thyroid function (euthyroidism) in 30 to 50% of patients [3,13]. When block and replace therapy is insufficient, the (over)production of thyroid hormones is diminished by radioiodine therapy or a (sub)total thyroidectomy [3,13]. Subtotal or total thyroidectomy is considered in GD only

when radioiodine therapy is contraindicated, which is the case in pregnancy, breastfeeding or Graves' ophthalmopathy [13].

Achieving euthyroidism is the main goal in treating tMNG, followed by a secondary goal of reducing goiter size [13–15]. The preferred primary treatment of tMNG is radioiodine therapy, as this type of treatment is relatively cheap, generally well-tolerated and attractive especially in elder patients with comorbidities [7,13,16]. Alternatively, surgery can be considered in large goiters, but this treatment is not preferred in elderly and is associated with the risk of damage to the laryngeal nerves, hypoparathyroidism, and a 15% to 40% recurrence of goiter. Medication has a limited effect and is not a definitive treatment for hyperthyroidism in tMNG [1,12,13].

Radioiodine therapy

Radioiodine therapy is commonly the treatment of choice in GD and tMNG, and has been widely used since the 1940s to treat benign thyroid diseases [9,17,18]. It is based on the ability of the thyroid tissue to take up iodine from the blood circulation via the sodium iodide symporter (NIS) [13,17,19,20]. After administration of radioiodine (I-131), the thyroid takes up a portion of the administered iodine from the blood, while the remaining portion of radioiodine leaves the body through the urinary tract. In patients with GD, overstimulation of the thyroid-stimulating hormone receptor leads to an increased iodine uptake within the entire thyroid [21]. The iodine uptake in patients with tMNG is only increased within the autonomously functioning toxic nodules, which often results in suppression of the normal thyroid tissue due to the lack of TSH in the blood [22].

The radionuclide I-131 is used for radioiodine therapy, which emits both beta (β^-) and gamma (γ) radiation during radioactive decay and has a relatively short half-life of 8.1 days (192 hours) [9,13,19,20]. The energy of the gamma ray is 364 keV, and the β^--particle has a maximum energy of 610 keV and an average energy of 192 keV [17,19,20]. The beta radiation component ensures the therapeutic effect of radioiodine therapy. Beta radiation causes ionization of cellular water, forming free radicals [18,19]. This induces oxidative degradation of plasma membrane lipids, resulting in multiple double-strand breaks of the DNA. These levels of DNA damage cannot be repaired by DNA repair mechanisms and induces apoptosis of the cell. The range of the β^--particles of I-131 in tissue is maximum 0.8 mm, therefore the radiation damage is restricted to (diseased) thyroid tissue with an iodine uptake [13,19,20].

Planar scintigraphy

Diagnostic and quantitative imaging of the thyroid is typically performed with planar scintigraphy, a single two-dimensional anterior view of the thyroid generated with a gamma camera [17,23–25]. Thyroid planar scintigraphy is usually performed with pertechnetate (Tc-99m sodium) or

radioiodine (I-123 sodium iodide or I-131 sodium iodide). Pertechnetate for planar scintigraphy of the thyroid is possible, because the thyroid is able to take up pertechnetate as the pertechnetate ion (TcO_4^-) has the same ion charge and dimensions as iodine (I^-) [23,24]. Pertechnetate is widely available, has lower cost, and has a shorter half-life than I-123 and I-131 (6 hours, 13.3 hours, and 192 hours, respectively), making it an accessible method for thyroid scintigraphy [24,26]. However, quantification of the iodine uptake with pertechnetate is complicated, because unlike radioiodine, pertechnetate is not organified by the thyroid [17,23]. Furthermore, planar scintigraphy at 24 hours (24h) after radioiodine administration usually provides the most accurate iodine uptake measurement, as it corresponds to the peak of iodine uptake [27]. Scintigraphy with pertechnetate after 24h is not possible, due to its short half-life [17]. The use of radioiodine is therefore superior to pertechnetate for quantitative imaging of the thyroid. The radionuclide I-123 is more suitable for quantitative planar scintigraphy compared to I-131, as I-123 results in better image quality, has a higher gamma yield, has a shorter half-life, and does not emit β^--particles [18]. Thyroid scintigraphy with I-123 is therefore often the recommended method for I-131 dose calculation in radioiodine therapy [25].

Dose calculation for radioiodine therapy

Quantitative data derived from thyroid planar scintigraphy is used to calculate the required radioiodine activity for radioiodine therapy [13]. Dose calculation is based on the iodine uptake of the thyroid, the thyroid volume, and the type of benign thyroid disease (GD or tMNG). Photons emitted by radioiodine within the thyroid are quantified and translated into radioactivity using a calibration factor (CF) [9,23–25]. The iodine uptake is determined by the ratio of the measured thyroid radioactivity to the total administered radioactivity. The thyroid volume is usually determined in planar scintigraphy or using ultrasound [9,24]. For treatment of GD, the desired activity concentration of radioiodine is 3.7 MBq/mL, while this is 7.4 MBq/mL for patients with tMNG, a thyroid volume larger than 50 mL, or rapid iodine turnover with iodine uptakes > 80%.

Long term complications

Long term complications associated with radioiodine therapy are radiation induced thyroiditis, thyrotoxic crise (rare), permanent hypothyroidism, or induced GD in the case of tMNG [13,18]. In our institute (Rijnstate, Arnhem, The Netherlands), it is hypothesized that the method of radioiodine dose calculation based on thyroid planar scintigraphy lacks accuracy, resulting in over- or underestimation of the required I-131 dose for radioiodine therapy. This may cause a high incidence of iatrogenic permanent hypothyroidism (overtreatment) or persistent hyperthyroidism (undertreatment). In literature, the reported incidence of iatrogenic hypothyroidism in tMNG patients ranges from 20% to 75% eight years after therapy, while 32% has persistent

hyperthyroidism 25 years after therapy [18,28–30]. In GD, incidence of iatrogenic hypothyroidism after radioiodine therapy is even larger: up to 80% develops hypothyroidism within 25 years after therapy. Approximately 18% of GD patients has persistent hypothyroidism one year after therapy [13,31]. In Rijnstate, the incidence of iatrogenic hypothyroidism is 23% in patients with tMNG and 47% in patients with GD, one year after treatment. Persistent hyperthyroidism after I-131 therapy occurred in 11% of patients with tMNG and 37% of patients with GD. Improving the dose calculation may be an important solution to reduce the incidences of iatrogenic hypothyroidism and persistent hyperthyroidism after radioiodine therapy.

Quantitative single-photon emission computed tomography

Recently, quantitative single-photon emission computed tomography combined with low-dose computed tomography (SPECT/CT) is emerging as a promising tool for absolute quantification in nuclear medicine [32–35]. The principle of SPECT is similar to that of planar scintigraphy: a gamma radiation-emitting radionuclide is administered to the patient and a gamma camera measures the radionuclide uptake during acquisition [36–38]. While in planar scintigraphy a single two-dimensional field-of-view is used for imaging, SPECT/CT is able to obtain a three-dimensional view as the gamma camera rotates around the patient [37]. In quantitative SPECT/CT, the number of photons emitted is counted within a specific volume-of-interest (VOI) [38,39]. These counts are converted to an activity concentration (MBq/mL) using a gamma camera specific reference, also known as the calibration factor (CF) [33,40,41]. The addition of low dose CT enables attenuation and scatter correction of the quantitative data for more precise uptake measurements, and provides anatomical information of the patient for thyroid volume estimation [33,34,39,42]. Some studies investigated the use of quantitative SPECT/CT with Tc-99m in benign thyroid diseases, but the topic remains relatively unexplored [39,42,43].

1.2 Purpose of this study

The overall objective of this study is to improve I-131 dose calculation for radioiodine therapy in patients with Graves' disease and toxic multinodular goiter with quantitative SPECT/CT. This study is divided into three sections to investigate our hypothesis. Firstly, the accuracy and workflow of I-123 planar scintigraphy of the thyroid is assessed. Secondly, a detailed quantification workflow for the preparation and image processing of quantitative SPECT/CT data is established. Lastly, the quantitative data derived from the planar scintigraphy and SPECT/CT are compared and evaluated in relation to the thyroid function after radioiodine therapy in a patient study. These topics are discussed in separate chapters; *Chapter 2 Planar Scintigraphy, Chapter 3 Quantitative SPECT/CT,* and *Chapter 4 Comparison of planar scintigraphy and quantitative SPECT/CT for dose calculation in I-131 therapy.*

2. Planar Scintigraphy

2.1 Introduction

Diagnostic and quantitative imaging of benign thyroid disorders such as Graves' disease (GD) and toxic multinodular goiter (tMNG) is currently performed using planar scintigraphy [7,23–25]. Planar scintigraphy is typically performed with pertechnetate (Tc-99m) or radioiodine (I-123), but radioiodine is the most suitable radionuclide for quantification of the iodine uptake [23,25]. It visualizes the iodine uptake of the thyroid, which enables identification of the benign thyroid disorder causing hyperthyroidism [9,24]. Furthermore, quantification of the iodine uptake and thyroid volume with planar scintigraphy is used for I-131 dose calculation in radioiodine therapy [9,20,24].

Gamma camera

Planar scintigraphy of the thyroid is performed with a gamma camera. The gamma camera consists of several elements, the most important being the collimator, detector, and photomultiplier tubes (PMT) [44]. The collimator is usually a sheet of lead with many small holes that allow controlled passage of the gamma photons [44–47]. The purpose of the collimator is to improve the signal to noise ratio of the image by attenuation of the background noise and scattered photons. The collimator thickness, septum width, hole direction, and -shape can be modified to enable optimal imaging of radionuclides emitting low, medium, or high gamma photon energies.

After passage of the gamma photons through the collimator, the photons reach the detector [44,46]. The detector usually contains sodium iodide (NaI) scintillation crystal, which absorbs the incoming gamma photons and converts the photon energy into visible light photons [44]. Higher gamma photon energies result in creation of more visible light photons [47].

Visible light photons created by the scintillation crystal strike on one of the PMTs [44,46,47]. The incoming visible light photons interact with a photocathode, which converts their energy to electrons. The dynodes multiply and accelerate the electrons, amplifying the signal. The anode captures all the electrons and converts it into an electric pulse.

The electric pulses resulting from the PMTs are used to generate the planar scintigraphy image [47,48]. Each PMT corresponds to a specific region of the scintillation crystal, enabling projection of individual electric pulses at the location (x,y) corresponding to the location of the interaction between the gamma photon and detector. The pulse-height analyzer analyzes the amplitude of each electric signal, and only selects the pulses within the desired photopeak window. The selected electric pulses are represented as individual counts on the planar scintigraphy image.

Scatter and background correction are applied to improve visualization and quantification of the planar scintigraphy image [38,48]. A scatter window just below the photopeak window is used to subtract counts produced by scattered photons from the counts within the photopeak window. A region-of-interest (ROI) is typically drawn at the edge of the image to subtract the counts originating from background noise from the counts in the photopeak window.

Planar scintigraphy of the thyroid

Planar scintigraphy enables identification of the benign thyroid disorder, based on thyroid volume, morphology and radioiodine distribution throughout the thyroid [9,24]. In GD, the iodine uptake of the thyroid is diffusely increased, with a normal to slightly enlarged thyroid volume. The manifestation of tMNG on planar scintigraphy is different from GD, as patients with tMNG have multiple hyperfunctioning thyroid nodules resulting in focal hotspots with an increased iodine uptake. Furthermore, in tMNG the thyroid is more enlarged, and the planar scintigraphy image may contain cold spots as a result of suppressed thyroid tissue or non-functioning thyroid nodules.

The iodine uptake is quantified in planar scintigraphy for I-131 dose calculation in radioiodine therapy, and is defined as the ratio between total administered radioiodine activity and measured radioactivity [23–25]. Planar scintigraphy is typically performed 24 hours (24h) after administration of I-123, to measure the maximum iodine uptake of the thyroid [24,27]. In the case of rapid iodine turnover, the iodine uptake reaches its peak at 4 to 6 hours after radioiodine administration. In such cases, planar scintigraphy at 4 to 6 hours after I-123 administration is recommend [9,24,25]. The iodine uptake is quantified by measuring the total number of counts originating from the thyroid. To only incorporate the counts directly originating from the thyroid, a ROI is delineated around the thyroid on the image. Delineation of the ROI is typically performed with a threshold based on a percentage of the maximum pixel value (Figure 1) [49]. The number of counts within the ROI are converted to total radioactivity using a calibration factor (CF) [25,41].

The CF is a measure for the sensitivity of the gamma camera in thyroid planar scintigraphy, but also corrects for the influence of scatter, attenuation and specific reconstruction method [24,41,50]. The current guidelines suggest to measure the CF regularly, using in a standardized neck phantom containing the identical radionuclide and amount of radioactivity used in patient examinations [24].

The thyroid volume is usually estimated using ultrasound or planar scintigraphy [9,23,51]. The volume of each thyroid lobe is often assumed as the shape of a cylinder or ellipsoid [52]. Volume estimation on ultrasound is performed by manual estimation of three dimensions per thyroid lobe (height, width, depth) [51]. In planar scintigraphy, two dimensions are manually estimated per thyroid lobe (length, width), and it is assumed the depth is equal to the width (Figure 1).

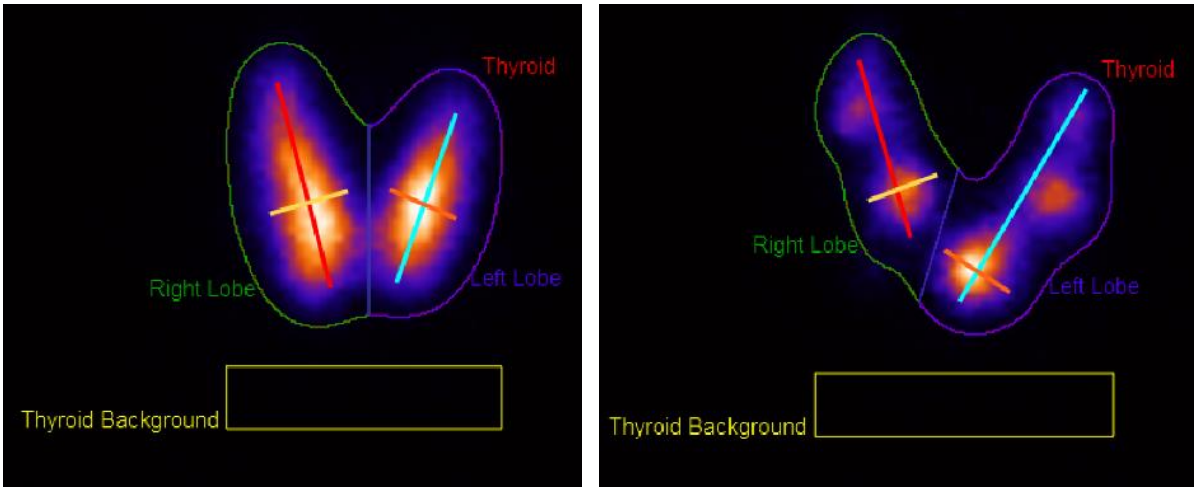

Figure 1: *The method for estimation of the thyroid iodine uptake and thyroid volume, for Graves' disease (left) and toxic multinodular goiter (right). Delineation of the ROI for measuring the iodine uptake is performed with a threshold of the maximum voxel value, indicated with the purple line (left thyroid lobe) and green line (right thyroid lobe). The thyroid volume is calculated based on the volume of a cylinder for each thyroid lobe. In each thyroid lobe, a short axis (yellow and orange) and a long axis (red and cyan) is manually drawn to estimate the thyroid volume.*

Dose calculation in radioiodine therapy

The quantified iodine uptake and thyroid volume obtained with planar scintigraphy are used to calculate the patient-specific I-131 dose for radioiodine therapy (Equation 1) [9,13,20,23–25]. The goal of radioiodine therapy is to decrease the (over)production of thyroid hormones, and to ultimately achieve permanent euthyroidism.

$$A = \frac{k \bullet V}{U/100} \tag{1}$$

where A is defined as the calculated radioiodine dose to be administered in MBq, U is the iodine uptake in the thyroid after 24h in %, V is the thyroid volume in mL, and k is the conversion factor (correcting for the thyroid disease) in MBq/mL. For treatment of GD k is 3.7 MBq/mL, while for treatment of tMNG, thyroid volumes larger than 50 mL, high iodine uptake (> 80%) and organification disturbances (4h/24h>0.8), k is 7.4 MBq/mL.

There are several factors in planar scintigraphy that affect the dose calculation for radioiodine therapy, such as the ROI delineation for iodine uptake, the calibration factor, volume calculation method, and the collimator choice [23,50,51,53,54]. Incorrect delineation of an ROI results in measuring more or less counts, over- or underestimating the iodine uptake [41,55]. The calibration factor has to be determined precisely, otherwise it results in incorrect conversion of measured counts to radioactivity [50]. The thyroid volume is determined by manual estimation of the thyroid length and width on planar scintigraphy and is presumably affected by interobserver variability. The choice of collimator impacts the visualization and quantification of iodine uptake in the thyroid [45,53,54]. In our institute, a low energy collimator is used for planar scintigraphy with I-123 according to the

Dutch guidelines [23,25]. Recent studies show that a medium energy collimator might be more suitable for scintigraphy with I-123, as the gamma photon energy of I-123 (159 keV) lies within the medium energy window (150 and 400 keV). Medium energy collimators reduce septal penetration, which mostly occurs with a small percentage of high energy photons emitted by I-123 [54].

Aim of this study

It is hypothesized that quantification for radioiodine therapy based on planar scintigraphy in our institute may be influenced by incorrect ROI delineation for iodine uptake, inaccurate calibration factor, interobserver variability and the collimator used. In this chapter, the accuracy of these factors are evaluated. First, the calibration factors measured in the past three years are evaluated, in order to investigate the accuracy and precision of these measurements. Secondly, the accuracy of the threshold used for ROI delineation for measuring the iodine uptake is tested in a phantom study. Thirdly, the interobserver variability of the volume estimation is assessed in a patient study, performed by two experienced operators. Lastly, the effect of the collimator for planar scintigraphy with I-123 is visually investigated in a phantom study.

2.2 Methods

In this study, we investigated four topics influencing the dose calculation for radioiodine therapy with planar scintigraphy: the precision of the calibration factor measurements, the threshold for ROI delineation of the iodine uptake, the influence of interobserver variability in manual thyroid volume estimation, and the effect of collimator on the visualization of the thyroid on the image.

2.2.1 Phantom measurements

Two phantoms were used in this study: the standard neck phantom and the Picker phantom. The neck phantom has a height of 15 cm and diameter of 15 cm, with a cylindrical space of 9.5 cm height and 2.6 cm diameter (50 mL capacity) for activity placement (Figure 2). Phantom placement is shown in Figure 2. The Picker phantom contains three cold spots and a hot spot, with a total capacity of 32 mL (Figure 3). The Picker phantom was placed on top of a pillow to achieve the same position as the neck phantom (Figure 3). Both phantoms were filled with a dilution of I-123 dissolved in heated NaCl 0.9% solution to mimic the radioiodine distribution in the thyroid.

Several phantom set ups were used to mimic the usual patient characteristics. The neck phantom was used to simulate variation in thyroid volume and iodine uptake. Variation in volume was achieved by using I-123 diluted in 10 to 50 mL NaCl 0.9% solution, all containing the same radioactivity (4.3 MBq, equivalent to ~85% iodine uptake). Radioactivity was varied from 0.6 to 5.5 MBq I-123 (equivalent to 13% - 100% iodine uptake), all diluted in 50 mL NaCl 0.9% solution. One experiment was performed with the Picker phantom to mimic inhomogeneous iodine distribution within the thyroid (4.2 MBq I-123 diluted in 32 mL NaCl 0.9% solution).

2.2.2 Acquisition and image processing

Planar scintigraphy images were obtained with the gamma camera system GE Healthcare NM/CT 870 DR (GE Healthcare Technologies Inc., Chicago, Illinois, United States of America), using a NaI scintillation crystal detector with a parallel-hole Low Energy High Resolution Sensitivity (LEHRS) collimator. Quantification was performed with an energy peak of 159 keV with a ±10% window (143-175 keV), field of view of 22 cm, zoom of 2.57, matrix size of 128x128 and patient- and phantom-detector distance of 10 cm or as close as possible. The acquisition time was 300s. The uptake and volume calculations are performed using HybridViewer Thyroid Analysis Hermes V5.1 software© (Hermes Medical Solutions, Stockholm, Sweden). The thyroid volume is based on the volume of two cylinders (left and right thyroid lobe). The detailed dose calculation method incorporated in Hermes software is presented in the supplementary material in *Appendix B*.

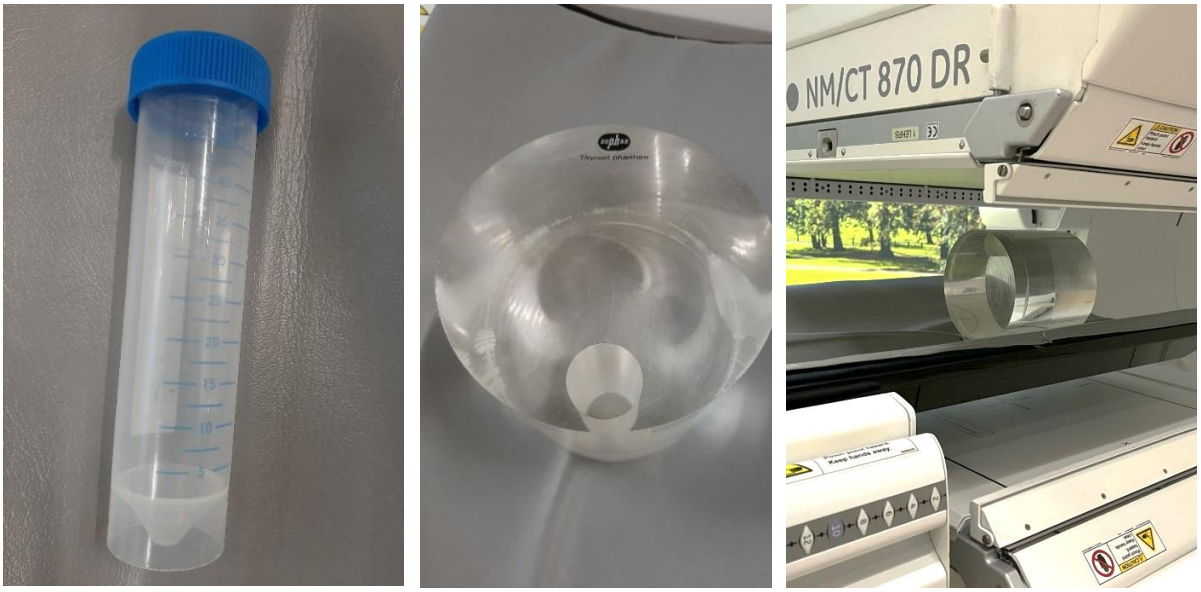

Figure 2: *The 50 mL cup containing I-123 (left), the perspex thyroid phantom (middle), and the experimental set up in the gamma camera (right).*

Figure 3: *The Picker phantom (left), and the Picker phantom in the experimental set up (right).*

2.2.3 Calibration factor

The calibration factor was measured weekly and according to the protocol of the software manufacturer Hermes Medical Solutions (Stockholm, Sweden) with the neck phantom. The I-123 capsule of 18.5 MBq was diluted in 50 mL NaCl 0.9% solution and measured after 24h, for 60s at a 10 cm distance from the collimator, and was calculated in cts/s/MBq. The accuracy and precision of the measurements from February 2021 to September 2023 was assessed with the median and interquartile range (IQR).

2.2.4 Region-of-interest delineation for iodine uptake

Three thresholds were assessed to determine the most accurate threshold for ROI delineation of the iodine uptake: 6% (current method), 10%, and 11% of the maximum pixel value in the planar scintigraphy image. All thresholds were assessed with the phantom measurements described in *2.2.1 Phantom measurements*. The median and IQR of the iodine uptake for each threshold was determined. Conversion from counts to radioactivity was performed with the median calibration factor determined in *2.2.3 Calibration factor*, to calculate the iodine uptake.

2.2.5 Interobserver variability in thyroid volume estimation

To investigate the influence of interobserver variability between operators in manually estimating the thyroid volume, 65 patients with GD or tMNG who underwent planar scintigraphy in our institute between February 2021 and December 2022 were included. Patients were all administered an I-123 capsule approximately 18.5 MBq at 24h before the planar scintigraphy. All planar scintigraphy images were processed by two experienced operators, and the difference in thyroid volume between operators was determined for each patient. The difference in estimated thyroid volume were separately analyzed for patients with GD and tMNG. The differences in estimated thyroid volume were compared with the median and IQR and shown in a boxplot. The effect of differences in thyroid volume in I-131 therapy dose calculation was determined per thyroid disorder. The average administered I-131 dose for radioiodine therapy was collected for these patients, to correlate the difference in I-131 dose calculation to the administered doses. A difference of 10% in calculated I-131 dose was assumed a clinically relevant difference.

2.2.6 Comparison of the low- and medium energy collimator

The phantom measurements with varying activities and homogeneity described in *2.2.1 Phantom measurements* were repeated with the Medium Energy General Purpose (MEGP) collimator. Delineation of the ROI was performed with the found threshold in *2.2.4 Region-of-interest delineation for iodine uptake*. All measurements were visually compared based on presence of scatter and measured counts. Additionally, a line diagram was developed for one measurement performed with both collimators, by generating a mean intensity line based on 23 horizontal lines across the planar scintigraphy image. The intensity was scaled between 0 and 1.

2.3 Results

2.3.1 Calibration factor

All weekly measured calibration factors from February 2021 until September 2023 are plotted over time in Figure 4. Since January 2022, almost all regularly acquired calibration factors are consistent around 80 cts/s/MBq. The median calibration factor since January 2022 is 80.1 counts/s/MBq (IQR 78.3 – 81.5). Between 1 September 2021 and 1 December 2021, the calibration factors were higher compared to other periods within the three year assessment period, with a median value of 109.5 cts/s/MBq (IQR 108.6 – 110.3).

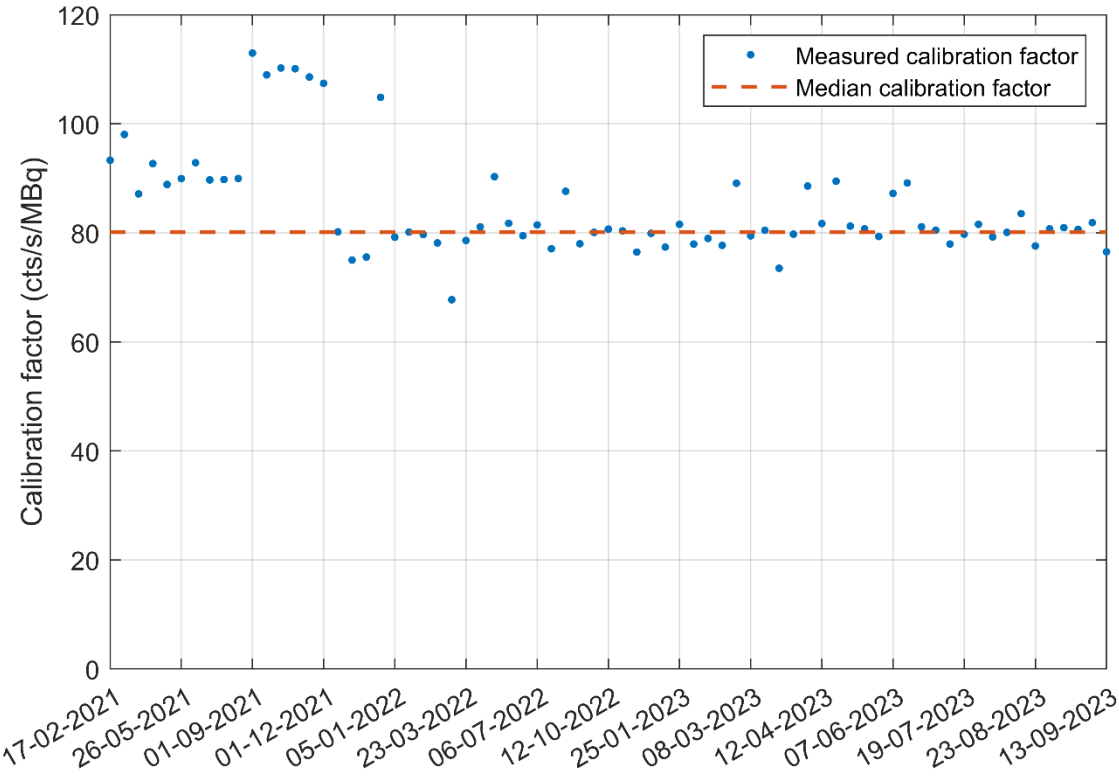

Figure 4: *The calibration factors calculated for I-123 planar scintigraphy from February 2021 until September 2023. The blue dots are all individual measurements of calibration factors. The orange dashed line is the median calibration factor based on the calibration factors measured since January 2022.*

2.3.2 Region-of-interest delineation for iodine uptake

The median iodine uptake was 107.3% (IQR 105.5 – 110.3) for a threshold of 6%, 99% (IQR 97.9 – 100.3) for a threshold of 10%, and 98.1% (IQR 97.3 – 99.1) for a threshold of 11% (Figure 5). The iodine uptake was similar in different thyroid volumes and most activities, but decreased in very low activities (< 1.1 MBq, equivalent to 22% uptake). A higher threshold results in a smaller ROI, subsequently leading to a decrease in measured uptake. The iodine uptake measured within the Picker phantom is above 100% using all three thresholds (threshold 6%: 120.3%, threshold 10%: 107.9%, threshold 11%: 107.2%). All measurements are shown in Table C.1 in *Appendix C*.

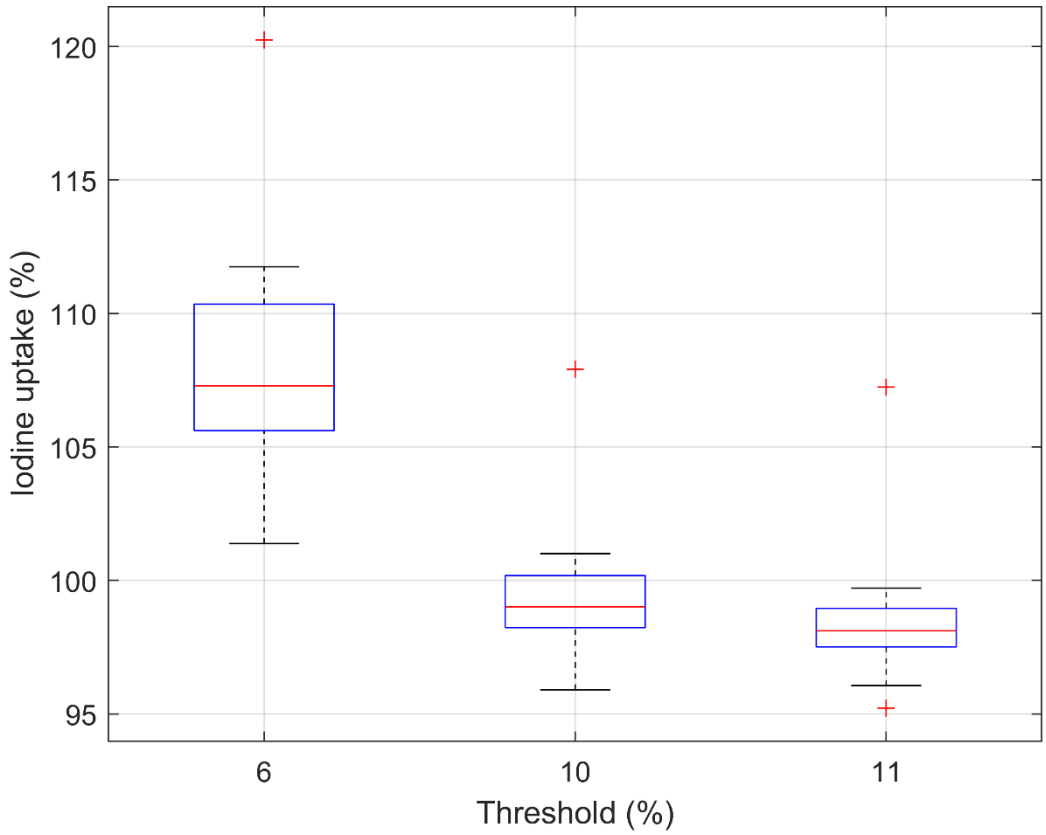

Figure 5: *The measured iodine uptake when using a 6% threshold (left), a 10% threshold (middle), and a 11% threshold (right).*

2.3.3 Interobserver variability in thyroid volume estimation

In total, 31 patients diagnosed with GD (21 females, mean age 48 years, range 20 – 80 years), and 34 patients with tMNG (32 females, mean age 67 years, range 41 – 85 years) were included. For GD, the median difference in measured thyroid volume was +5.4 mL (IQR +2.3 – +8.9) between the operators. In tMNG, the median difference was -0.2 mL (IQR -8.2 – +7.0). The range of differences in estimating the thyroid volume are shown in Figure 6. The variations in volume measurements influence the calculated dose of I-131 for radioiodine therapy. In GD, this results in a median variation of +44.2 MBq (IQR +25.5 – +84.4), which is 15% of the average administered I-131 dose of 300 MBq ± 173.6. In tMNG, this results in -8.6 MBq (IQR -200.4 – +125.1) (Figure 7), which is a particularly small percentage (0.6%) compared to the average administered I-131 dose for patients with tMNG (1184 MBq ± 665.1). However, the IQR suggests that variation in measured thyroid volume results in a 10% difference in calculated I-131 dose in tMNG (IQR -200.4 – +125.1) when compared to the average I-131 dose of 1184 MBq in tMNG patients. In Table C.2 and Table C.3 in *Appendix C*, the thyroid volumes are shown for each patient and operator.

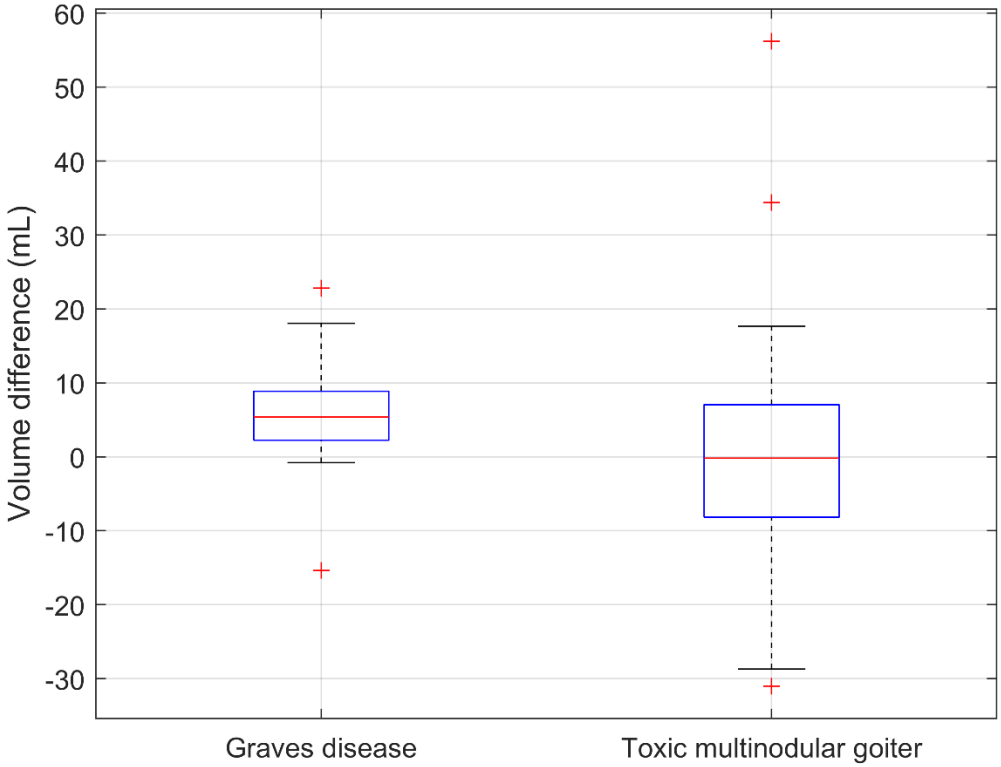

Figure 6: *The difference in manually estimated thyroid volume between two experienced operators for GD and tMNG.*

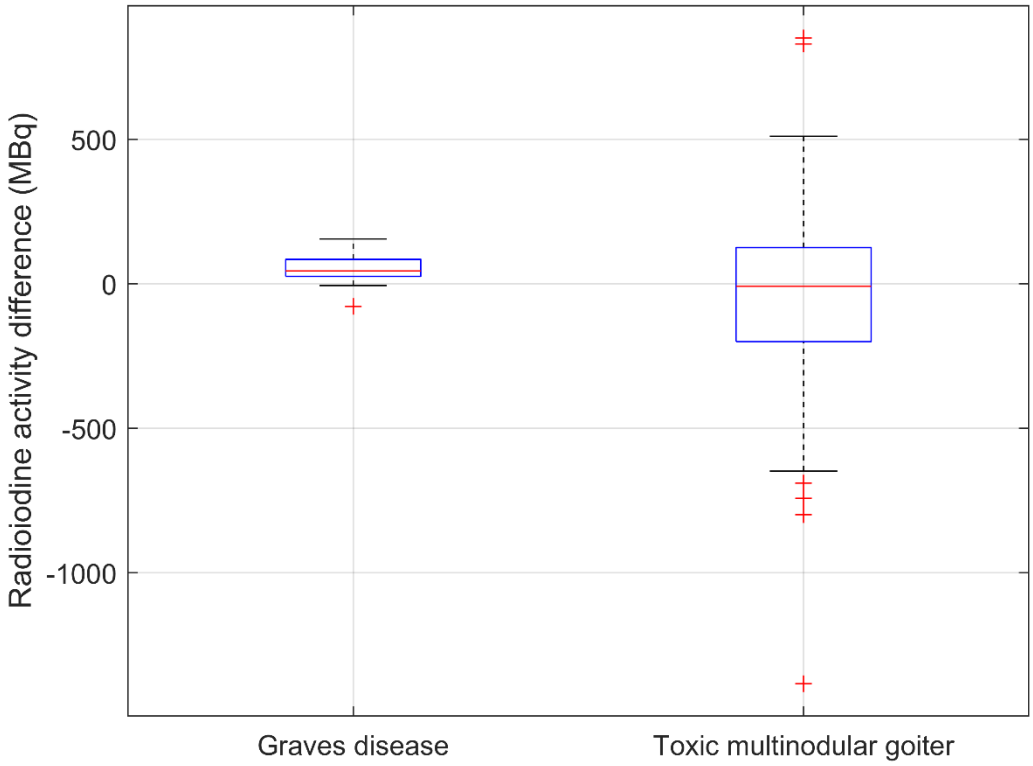

Figure 7: *The difference in calculated I-131 dose for radioiodine therapy as a result of variation in thyroid volume between two operators, for GD and tMNG.*

2.3.4 Comparison of the low and medium energy collimator

The planar scintigraphy images obtained with the MEGP collimator are less affected by background noise and scattered photons compared to the images obtained with the LEHRS collimator. Region-of-interest delineation with a threshold of 10% of the maximum voxel value results in a smaller ROI for the MEGP images compared to the LEHRS images (Figure 8).

The line diagram is the example of one measurement (2.5 MBq I-123), which shows the relative difference in measured counts, scatter and noise between both collimators (Figure 9). It shows that planar scintigraphy images obtained with the MEGP collimator contain less measured counts in general as maximum peak is lower compared to LEHRS. Furthermore, the use of the MEGP collimator diminishes the presence of scatter and background noise even closely around the radioactivity in the phantom (Figure 9). Planar scintigraphy images obtained with the LEHRS collimator incorporate more scatter and background noise around the radioactivity of the phantom, which slightly decreases towards the edges of the image. In all other measurements, the difference between MEGP and LEHRS collimator is similar.

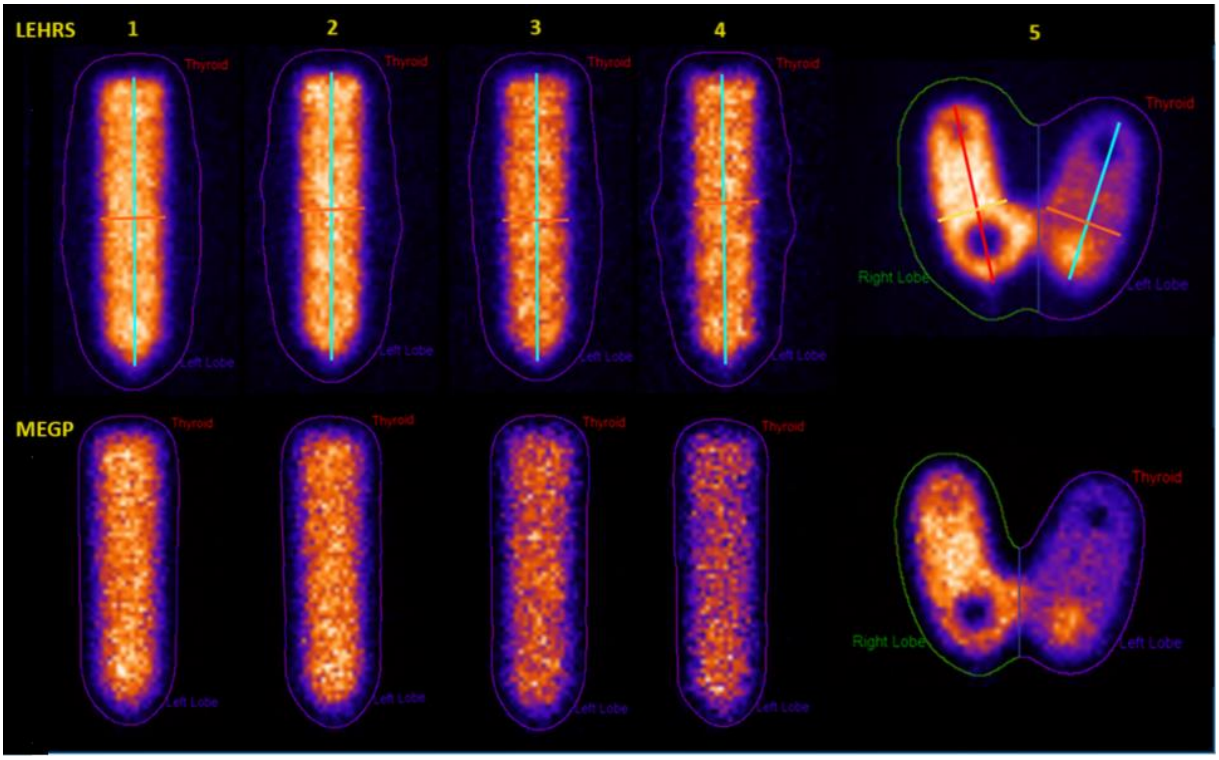

Figure 8: *Phantom measurements performed with the LEHRS and MEGP collimator. The upper row represents measurements with the LEHRS collimator, the lower row represents the measurements performed with the MEGP collimator.* ***1****: LEHRS 3.2 MBq, MEGP 3.7 MBq,* ***2:*** *LEHRS 2.5 MBq, MEGP 2.8 MBq,* ***3:*** *LEHRS 1.6 MBq, MEGP 1.7 MBq,* ***4:*** *LEHRS 0.7 MBq, MEGP 0.9 MBq,* ***5****: LEHRS 4.2 MBq, MEGP 4.1 MBq (Picker phantom).*

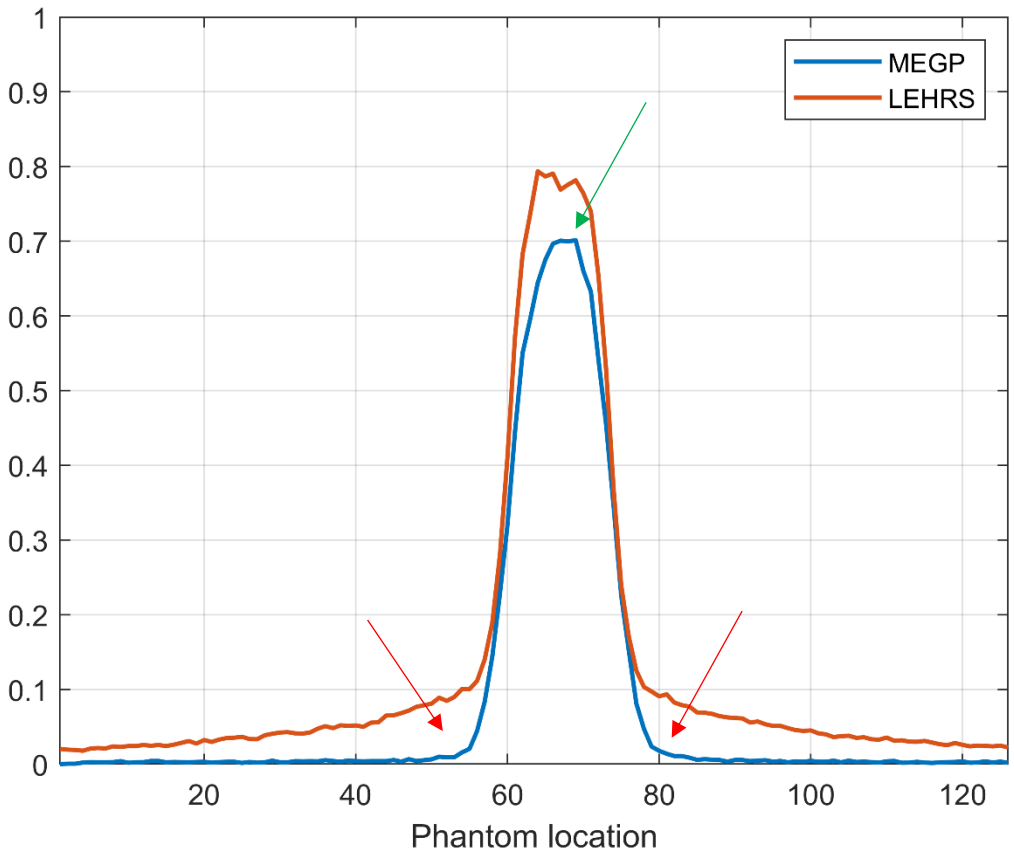

Figure 9: *The measured counts scaled within 0 to 1 for the MEGP collimator (blue), and the LEHRS collimator (orange) for one measurement (approximately 2.5 MBq in both measurements). The red arrows point to the absence of scatter and noise around the source in scintigraphy with the MEGP collimator. The green arrow points to the maximum peak of the MEGP collimator, which is lower than the maximum peak of the LEHRS collimator.*

2.4 Discussion

In this study, several factors influencing the dose calculation for I-131 therapy were evaluated. Calibration factors measured in the past three years showed high consistency with only small variation over time. Iodine uptake quantification is most accurately performed when using a threshold set at 10% of the maximum pixel value, rather than the currently used 6% threshold. The manually estimated thyroid volume is influenced by the interobserver variability and impacts the calculated I-131 dose, which may result in over- or underdosing in radioiodine therapy. Moreover, the MEGP collimator resulted in less scattered photons and background noise on the planar scintigraphy image compared to the LEHRS collimator.

2.4.1 Calibration factor

Assessment of the CF showed that from January 2022 until September 2023 the obtained measurements are stable with some small variations (median 80.1 cts/s/MBq (IQR 78.3 – 81.5)). Research indicates that gamma camera sensitivity is stable over time, which is in line with our findings since January 2022 [41,50]. Therefore, the frequency of the I-123 CF measurements in our institute is decreased from once a week to three times a year after maintenance of the gamma camera as recommended by the European Association of Nuclear Medicine (EANM) [33].

From 1 September 2021 to 1 December 2021, a higher CF was measured (median 109.5 cts/s/MBq (IQR 108.6 – 110.3)), as a result of maintaining a phantom-detector distance of 1 cm instead of the advised 10 cm [55]. The higher the CF, the lower the measured iodine uptake, resulting in a higher calculated dose for radioiodine therapy. Utilizing a CF of 108.6 cts/s/MBq instead of 80.1 cts/s/MBq, results in a percental decrease in iodine uptake of approximately 26%. Subsequently, the calculated I-131 dose for radioiodine therapy increases with 26%. Maintaining a distance during the calibration factor measurement which represents the patient-detector distance is therefore crucial in quantification for dose calculation in radioiodine therapy.

It is recommended to standardize the protocol for the CF measurement not only in our institute, but nationally, to overcome differences between staff and hospitals. Mourik *et al.* recently studied the gamma camera-specific reference standards for radioiodine uptake measurements among several hospital in The Netherlands [41]. They discovered that the protocol for the CF measurement varies heavily between institutes in acquisition time, radioactivity (I-123 or I-131), source – detector distance, radioactivity volume, and the use of a neck phantom or no phantom. Anizan *et al.* state that while the CF is stable over time, existing background noise, incorrect measurements of the dose calibrator, phantom placement on the table, and distance to the detector should be controlled to prevent incorrect measurements [50]. In our study, it was not investigated how each

operator individually performs the CF measurement. Differences in phantom placement, distance to the detector or incorrect measurement of the radioactivity may explain the variation in measured CF from January 2022 until September 2023.

2.4.2 Region-of-interest delineation for iodine uptake

The phantom study showed that the threshold currently used for ROI delineation in our institute (6%) overestimates the iodine uptake of the thyroid by 7%, due to an amount of background noise and septal penetration of high energy gamma photons that reach the detector. A threshold of 10% of the maximum pixel value appeared generally as the most optimal threshold with a median iodine uptake of 99.0%. Therefore, in all of our other experiments with planar scintigraphy in this study, a threshold of 10% for ROI delineation was used. Furthermore, we changed the threshold in our planar scintigraphy protocol to 10%.

Compared to literature, the threshold we found to be the most optimal is relatively low. Mourik *et al.* have estimated the most optimal threshold at 27%[41], while Li *et al.* found to be the most optimal threshold at 30%[54]. Differences in threshold between our found threshold and literature is likely caused by differences in acquisition protocol, measured CF, or software differences, but were not investigated in this study.

Although a threshold at 10% of the maximum pixel value results overall in the most accurate iodine uptakes, the iodine uptake in the Picker phantom measurement was still overestimated (threshold at 6%: 120.3%, threshold at 10%: 107.9%, threshold at 11%: 107.2%). This may be the result of a wrongful measurement in planar scintigraphy or wrongful measurement of the phantom iodine radioactivity by the dose calibrator, but may also be the result of the mix of hot- and cold spots within the phantom causing spill-in due to the partial volume effect. Future studies should further investigate the effect of an inhomogeneous radioiodine distribution within the thyroid on the measured iodine uptake.

2.4.3 Interobserver variability in thyroid volume estimation

Three outliers were observed in the patients with tMNG, with a difference in estimated thyroid volume of -32, 34 and 55 mL. Analysis of the processed data showed a variation in length of the manually drawn axes of maximally 4 mm, which is not considered a large difference in a manual estimation. The large difference in volume is mainly caused by variation in length of the short axis (thyroid width). The short axis of a cylinder has a quadratic relation to the volume of a cylinder, which directly causes a difference in thyroid volume of 32 mL when both short axes differ 4 mm between operators. Manual estimation is therefore very sensitive to errors, as a small variation in

axis length may result in large volume differences. A more operator-independent method, such as ultrasound or SPECT/CT, may prevent these errors [52,56–58].

The dose calculation for radioiodine therapy is influenced by the variation in estimated thyroid volume between operators in planar scintigraphy. For patients with GD, this is approximately 15% of the administered I-131 dose in GD patients in our institute which may impact the therapy outcome. For patients with tMNG the median difference in I-131 dose was very small (0.6%), but it does show a large variation in the IQR between -200.4 and + 125.1 MBq as a result of both over- and underestimation of the thyroid volume between operators.

2.4.4 Comparison of the low and medium energy collimator

The use of the MEGP collimator resulted in less detection of scatter and background noise compared to the LEHRS collimator. The LEHRS collimator allows low energy photons to reach the detector, leading to incorporation of scatter, background noise, and septal penetration on the planar scintigraphy image. The MEGP collimator is thicker and contains wider septa, which prevents the passage of low energy photons and septal penetration of high energy photons of I-123 to the detector [54]. It is expected that the filtering of low energy photons in the MEGP collimator results in better quantitative imaging, as stated in literature [53,54]. Therefore, future research should emphasize on quantitative thyroid imaging with the MEGP collimator.

2.5 Conclusion

In conclusion, several parameters influence the quantitative data acquired in planar scintigraphy, resulting in inaccuracies in calculated dose for radioiodine therapy. Evaluation of CF showed that the gamma camera sensitivity is stable over time, resulting in the decrease of the CF measurement to three times a year in our institute. The phantom study showed the importance of a correct threshold for ROI delineation of the iodine uptake, as the previously used threshold overestimated the radioiodine uptake. Manual thyroid volume estimation depends heavily on the operator and influences the calculated radioiodine activity up to 15%. The use of the MEGP collimator shows promising results based on visual comparison, by reducing scatter and background noise in the planar scintigraphy image.

3. Quantitative SPECT/CT

3.1 Introduction

Treatment of benign thyroid disorders causing hyperthyroidism, such as Graves' disease (GD) and toxic multinodular goiter (tMNG), has been performed with I-131 radioiodine therapy since the 1940s [9,17,20,24]. The hyperfunctioning parts of the thyroid take up the radioiodine, resulting in local radiation damage and elimination of the diseased thyroid tissue [18,19]. The goal of radioiodine therapy is to achieve normal thyroid function (euthyroidism), and secondly reduce goiter size in enlarged thyroid glands [9].

Diagnosis of the type of benign thyroid disorder and I-131 dose calculation for radioiodine therapy is currently performed with planar scintigraphy, in which the patient is administered a small portion of radioiodine (I-123) or pertechnetate (Tc-99m) [13,15,21,23,25]. The distribution of radiotracer is different for the types of thyroid disease (GD or tMNG), which allows differentiation of the type of thyroid disease [23]. Furthermore, measurement of the iodine uptake of the thyroid and the thyroid volume allows for patient-specific dose calculation in radioiodine therapy [9,13,15,25]. The use of the radionuclide I-123 is preferred for planar scintigraphy in our institute, as it visualizes both the iodine uptake and organification process.

The outcomes of radioiodine therapy in terms of thyroid function vary heavily according to literature. The estimated percentage of iatrogenic hypothyroidism after radioiodine therapy is 80%[59] at 25 years after therapy for patients with GD and 20% to 75%[18] at eight years after therapy in patients with tMNG. The estimated percentage of persistent hyperthyroidism is 18%[31] at one year after therapy for patients with GD and 32% [28,29] at 25 years after therapy for patients with tMNG. It is hypothesized the current method for dose calculation in radioiodine therapy with planar scintigraphy lacks accuracy, resulting in over- or underestimation of the calculated I-131 dose for radioiodine therapy. Over- or underestimation of the I-131 dose in radioiodine therapy may result in high incidence of iatrogenic hypothyroidism (overtreatment) and persistent hyperthyroidism (undertreatment).

Quantitative SPECT/CT

Three-dimensional imaging with a gamma camera, referred to as single-photon emission computed tomography (SPECT), is a widely used modality in nuclear medicine for visualization of radiotracer distribution [33,34,38,40,60,61]. A combination of SPECT and low dose computed tomography (SPECT/CT) allows for anatomical correlation of the radiotracer distribution in the human body, which is not achievable in two-dimensional planar scintigraphy [57,62].

In recent years, SPECT imaging and quantification has gained popularity as a result of equipment and software developments [33–35,40,63]. The addition of low dose computed tomography scan (CT) enables incorporation of CT-based corrections which reduce distortion of attenuation and scatter, improving quantification of radiotracers in SPECT significantly [33,35,64]. Other important corrections in SPECT quantification are partial volume effect correction, dead time correction, detector response, and decay correction [33,64].

Quantification for radionuclide dose calculation in SPECT is based on including a reference standard or by use of a calibration factor (CF), which converts measured counts to a total activity (in MBq) or activity concentration (in MBq/mL) [33,35,40,43,64]. The CF is different for each imaging system, detector, collimator and radionuclide, and should be determined according to the current guidelines [33]. The protocol for measurement of the CF is outlined by the National Electrical Manufacturers Association (NEMA): a phantom mimicking the patient source geometry is filled with the radionuclide of interest. Acquisition and reconstruction is performed according to the patient study protocol used in the institute. The CF is determined by dividing the total measured counts within the volume-of-interest (VOI) by the product of known acquisition time and radioactivity of the source [35,40,64].

Delineation of the volume-of-interest

Delineation of a VOI in quantitative SPECT/CT is usually performed with a standardized uptake value (SUV) or a percentage of the maximum voxel value [57]. Delineation of a VOI based on a percentage of the maximum voxel value seems the most appropriate method for quantification of the iodine uptake with I-123, as I-123 is only absorbed by thyroid tissue (and the salivary glands to a small extent). In literature, delineation based on the maximum voxel value has only been investigated for Tc-99m to measure the iodine uptake and thyroid volumes for dose calculation in radioiodine therapy [34,39,43,57,65,66].

Aim of this study

It is hypothesized that quantitative SPECT/CT with I-123 can be used for the quantification of iodine uptake and thyroid volume for I-131 dose calculation in radioiodine therapy. In this study, we aim to develop a quantification protocol for measuring the iodine uptake and thyroid volume with I-123 quantitative SPECT/CT. First, a threshold for VOI delineation to estimate the thyroid volume was determined in a phantom and in a patient study. Second, the calibration factor and threshold for VOI delineation to determine the iodine uptake were investigated by comparing two methods: the method described by Peters *et al.*[40] and a trial-and-error method, using a phantom study.

3.2 Methods

The calibration factor and thresholds for VOI delineation of the thyroid to measure the thyroid volume and iodine uptake were determined based on phantom and patient measurements. The found calibration factor and thresholds were used to develop a quantification protocol.

3.2.1 Phantom measurements

The phantoms (standard neck phantom and Picker phantom) and measurements described in *2.2.1 Phantom measurements* were used in the phantom study.

3.2.2 Patient population

Data of nine patients with Graves' disease who underwent quantitative SPECT/CT with I-123 between June 2023 and October 2023 was collected. Patients had received a capsule of I-123 with approximately 18.5 MBq at 24h before the quantitative SPECT/CT examination.

3.2.3 Acquisition and image processing

Quantitative SPECT/CT was performed using two opposite NaI scintillation crystal detectors and two parallel-hole Low Energy High Resolution Sensitivity (LEHRS) collimators. Acquisition was performed for 12 minutes (720 seconds) in a step-and-shoot configuration, measuring 10s per projection and also in between projections, with 60 projections, and a 3° projection angle. Patients were placed in supine position on the table. The gamma camera rotated using auto-contouring to achieve the smallest patient – detector and phantom – detector distance per projection. The energy peak used was 159 keV with a ±10% window (143-175 keV), scatter peak of 130 keV with a ±10% window (117-143 keV), and zoom factor of 1.5. The images were reconstructed using OS-EM (ordered-subset expectation-maximization) with 10 subsets and 2 iterations, CT attenuation correction, scatter correction, matrix of 128x128, and slice thickness of 2.5 mm. The CT was performed using a tube voltage of 120 kVp, tube current ranging between 20 mA to 250 mA based on automatic exposure control, beam collimation of 20 mm, slice thickness 2.5 mm, table speed 46 mm/s, table speed per rotation 27.5 mm/rot, tube rotation time 0.6s, pitch 1.375:1, and matrix size of 512x512.

Quantification of the iodine uptake and thyroid volume was performed using a custom-made thyroid application in Q.Volumetrix (GE Healthcare Technologies Inc., Chicago, Illinois, United States of America).

3.2.4 Measurement of the thyroid volume

The phantom study was performed to roughly determine the best threshold for measuring the thyroid volume. Delineation of the VOI was tested in all phantom measurements with a threshold of 20%, 22%, 25%, 27%, and 30% of the maximum voxel value. The patient study was performed to correlate the findings in the phantom study to patient data. Quantification of the thyroid volume was performed based on the SPECT data, and visually correlated to the VOI delineation registered on CT. Three experienced operators were asked to choose the best fitting threshold for nine patients with GD. Ultimately, the best threshold was chosen based on the most accurate volume estimation in both studies and incorporated in the quantification workflow. Additionally, the CT is visually inspected to identify factors influencing the thyroid volume estimation.

3.2.5 Determination of the calibration factor

Calculation of calibration factor

The first method for determining the CF was performed using the neck phantom, which was filled with 4.3 MBq of I-123, diluted in 50 mL NaCl 0.9% solution. Eight different VOIs were manually drawn on SPECT/CT to determine the mean count density (cts/mL) of the source. Each VOI consisted of a different region within the radioiodine source: the upper third (VOI1), middle third (VOI2), lower third (VOI3), upper half (VOI4), lower half (VOI5), upper two-third (VOI6), lower two-third (VOI7), and entire source volume (VOI8) (Figure 10). The count density was determined for each VOI, and the mean counts density was calculated based on the count densities of all eight VOIs. The CF is calculated in cts/s/MBq with Equation 2:

$$Calibration\ Factor = \frac{\mu}{t \cdot n \cdot v} \cdot \frac{1}{AC} \tag{2}$$

where μ is the mean voxel value in the source (cts), t is the time per projection (s), n is the number of projections, v is the voxel size (mL), AC is the true activity concentration in the phantom (MBq/mL).

Trial-and-error method

The second method was designed to test several calibration factors in relation to different sizes of VOI delineation around the source. The neck phantom was filled with 4.3 MBq of I-123, diluted in 50 mL NaCl 0.9% solution. Thresholds at 0%, 1%, 4%, and 20% of the maximum voxel value were tested. These thresholds were chosen based on trial-and-error, to investigate several sizes of VOI: the entire field of view (0%), a large margin around the source (1%), a small margin around the source (4%), and delineation with an exact circumference around the source (20%). For all four thresholds, the optimal CF was chosen based on a measured iodine uptake of 100%.

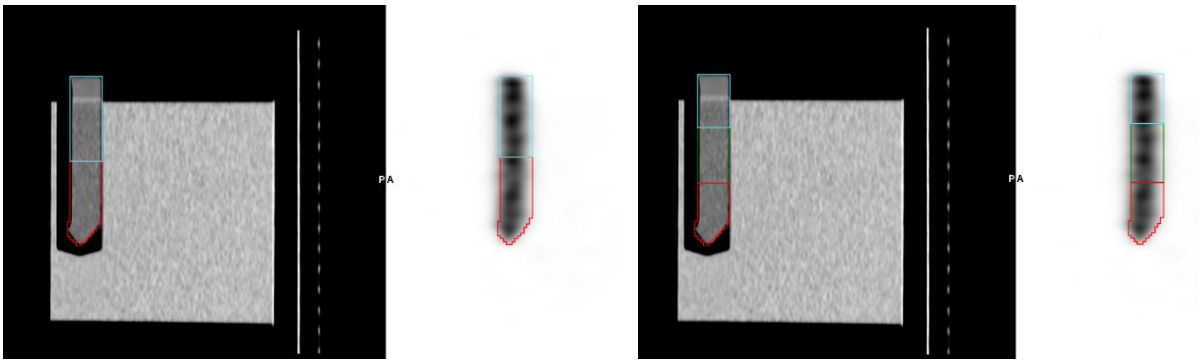

Figure 10: *Examples of manual delineation of VOIs on the SPECT/CT in calculating the calibration factor.* ***Left:*** *The VOI delineation of the upper half (VOI4) and lower half (VOI5) of the source.* ***Right:*** *The VOI delineation of the upper third (VOI1), middle third (VOI2), and lower third (VOI3) of the source.*

3.2.6 Measurement of the iodine uptake

Thresholds for VOI delineation to measure the iodine uptake were tested for the previously determined calibration factors in *3.2.5 Calibration factor measurements*.

Calculation method

Three thresholds were tested for VOI delineation of the iodine uptake using the calculated CF: 20%, 22%, and 25% of the maximum voxel value. These thresholds were chosen based on VOI delineation of the exact circumference of the source volume on SPECT. Assessment of the thresholds was performed with phantom measurements with varying volume, radioactivity and radiotracer distribution as described in *2.2.1 Phantom measurements*. The three thresholds are compared based on ability to measure an iodine uptake of 100%. The results are plotted in a boxplot and compared based on the median and interquartile range (IQR). The most accurate threshold is chosen based on highest accuracy (uptake at 100%), precision (smallest IQR) and least outliers to compare to the results of the trial-and-error method.

Trial-and-error method

The phantom measurements with varying radioactivity (0.7 MBq to 5.5 MBq of I-123, all diluted in 50 mL NaCl 0.9% solution) were used to evaluate the measured iodine uptake of the four calibration factors found in the trial-and-error method in *3.2.5 Calibration factor measurements*. Each calibration factor was based on VOI delineation of a specific volume (entire field-of-view (0%), large margin around the source (1%), small margin around the source (4%), and the exact circumference around the source (20%)). Boxplots were plotted to visualize the range in iodine uptake for each calibration factor and threshold combination. The calibration factor and threshold combination resulting in the most accurate and precise iodine uptake measurements with the least outliers (uptake at 100%, smallest IQR) was chosen and compared to the calculation method.

Comparison of calculation and trial-and-error method

The found CF and threshold of the calculation method and trial-and-error method are compared based on all phantom measurements described in *2.2.1 Phantom measurements* in which the phantom volume, radioactivity and radiotracer distribution is varied alternately. All measured uptakes are plotted in a boxplot for each method and compared based on the highest accuracy (uptake at 100%), precision (smallest IQR) and least outliers. Ultimately, the most optimal calibration factor and threshold are incorporated into the quantification workflow.

3.3 Results

3.3.1 Thyroid volume measurement

The phantom study showed that the threshold for the estimation of the thyroid volume varies between large volumes (40 – 50 mL) and small volumes (< 20 mL): large volumes are most accurately measured with a threshold of 22% of the maximum voxel value, while small volumes are most accurately measured with a threshold at 30% of the maximum voxel value (Figure 11). Variation of radioactivity in the phantom between 1.1 MBq and 5.4 MBq (21% to 100% iodine uptake in patients) did not have an impact on the VOI delineation: a threshold between 22% and 25% of the maximum voxel value was overall the most accurate for thyroid volume estimation (Figure 12). For the phantom experiment with a radioactivity reflecting an iodine uptake of 13%, a threshold of 15% of the maximum voxel value resulted in the best volume measurement. The experiment with the Picker phantom showed that for inhomogeneous radioiodine distribution, the volume is accurately estimated with a threshold of 25% of the maximum voxel value (Figure 13). In Table C.4 in *Appendix C*, all phantom volumes measured with all thresholds are shown.

Volume measurements on quantitative SPECT/CT of nine patients with GD (8 females, mean age 41 years, range 27 – 58 years, volume on planar scintigraphy 8 – 55 mL) confirmed the findings of the phantom study. The optimal threshold was between 20% and 30% (Table 1). Thresholds did not differ between small and large volumes as observed in the phantom study. In some patients, the identification of thyroid tissue on CT scans was hindered due to similarity with surrounding tissues (Figure 14) or due to the occurrence of beam hardening artifacts induced by the presence of shoulders and clavicles (Figure 15).

***Table 1**: Assessment of optimal threshold for thyroid volume estimation on quantitative SPECT/CT.*

Patient	Thyroid volume on planar scintigraphy (mL)	Operator 1 threshold (%)	Operator 2 threshold (%)	Operator 3 threshold (%)
1	8.0	24	25	20
2	13.7	22	20	23
3	16.2	25	20	20
4	23.7	21	22	23
5	30.1	24	22	24
6	36.0	24	25	24
7	39.0	20	25	24
8	48.0	31	25	25
9	54.7	28	25	23

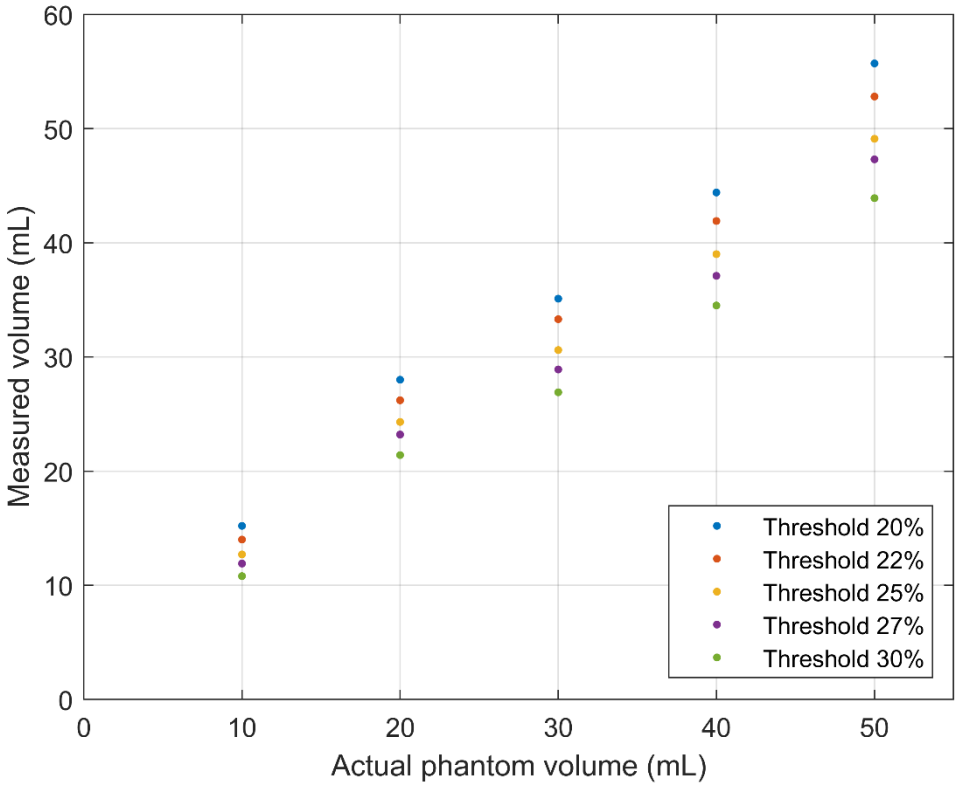

***Figure 11**: Different thresholds for the estimation of thyroid volume for phantom volumes of 10 mL, 20 mL, 30 mL, 40 mL, and 50 mL NaCl 0.9% solution, all containing 4.3 MBq of I-123.*

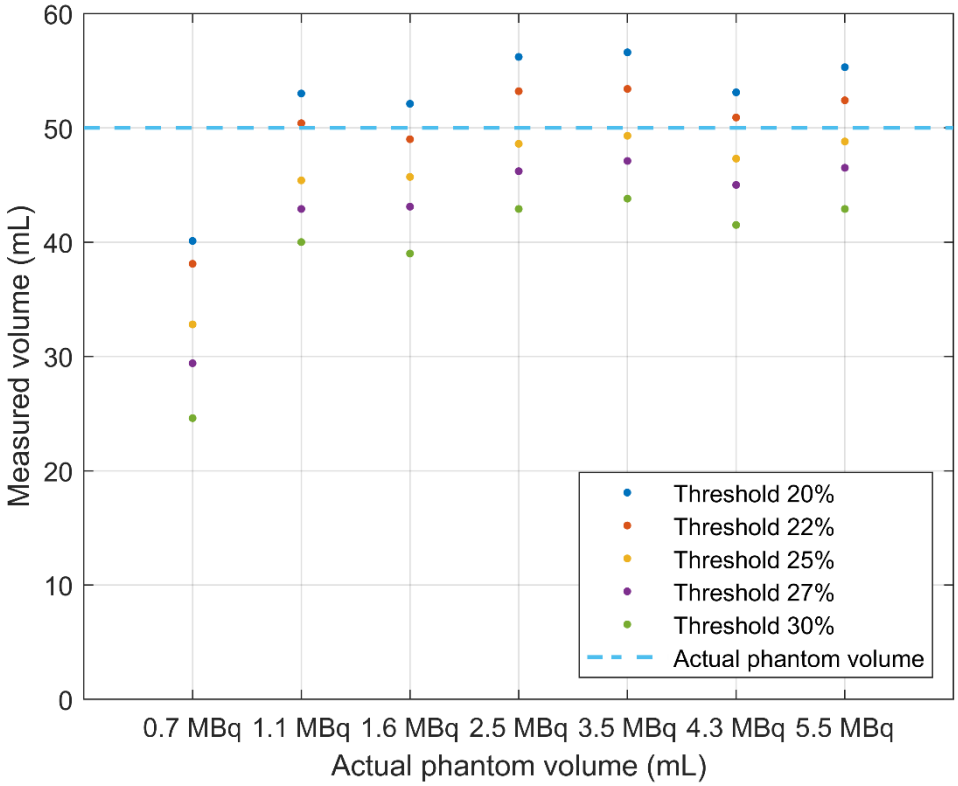

***Figure 12**: Different thresholds for the estimation of the thyroid volume for different I-123 phantom activities: 0.7 MBq, 1.1 MBq, 1.6 MBq, 2.5 MBq, 3.5 MBq, 4.3 MBq, and 5.2 MBq, all containing I-123 diluted in 50 mL NaCl 0.9% solution.*

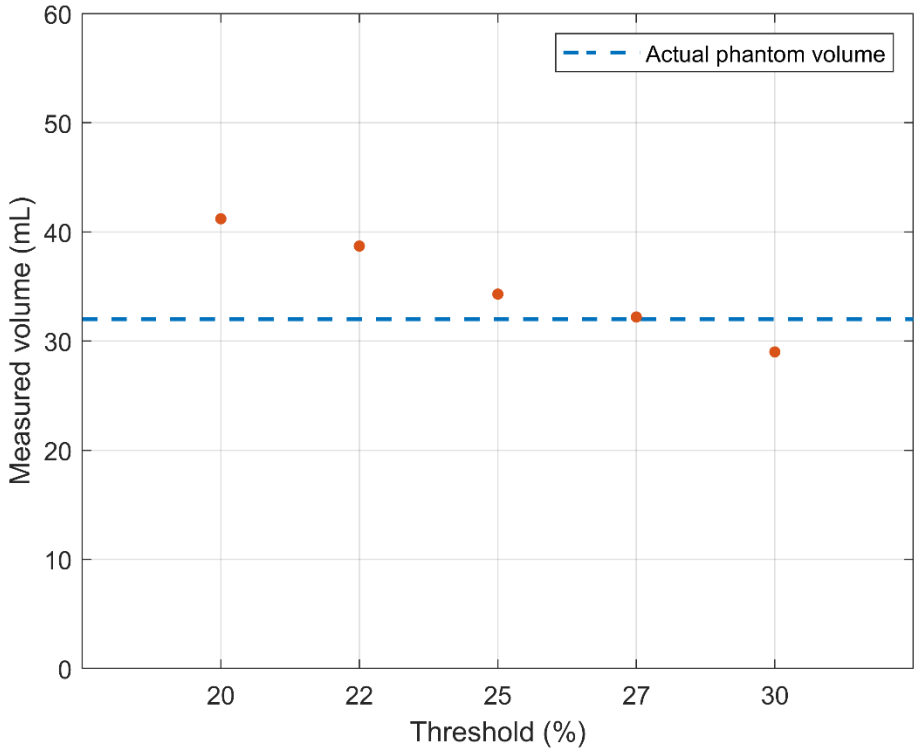

***Figure 13**: Different thresholds for the estimation of thyroid volume in a thyroid with an inhomogeneous iodine uptake (Picker phantom).*

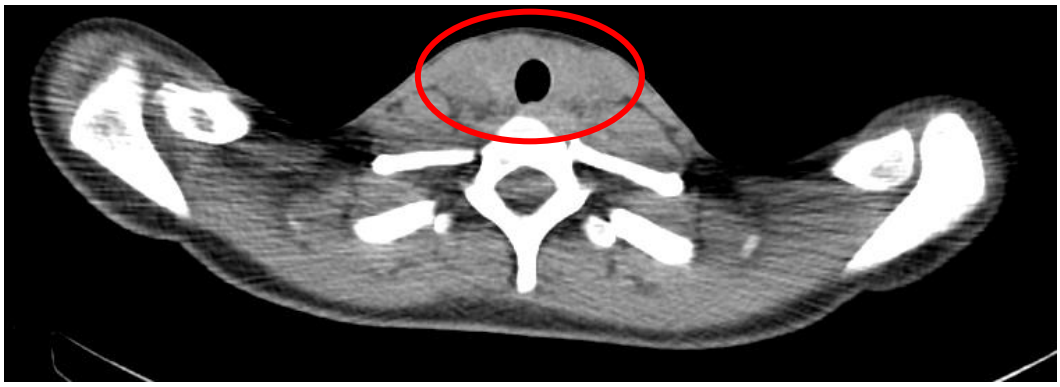

***Figure 14:** Identification of the thyroid tissue surrounded by similar-looking tissue.*

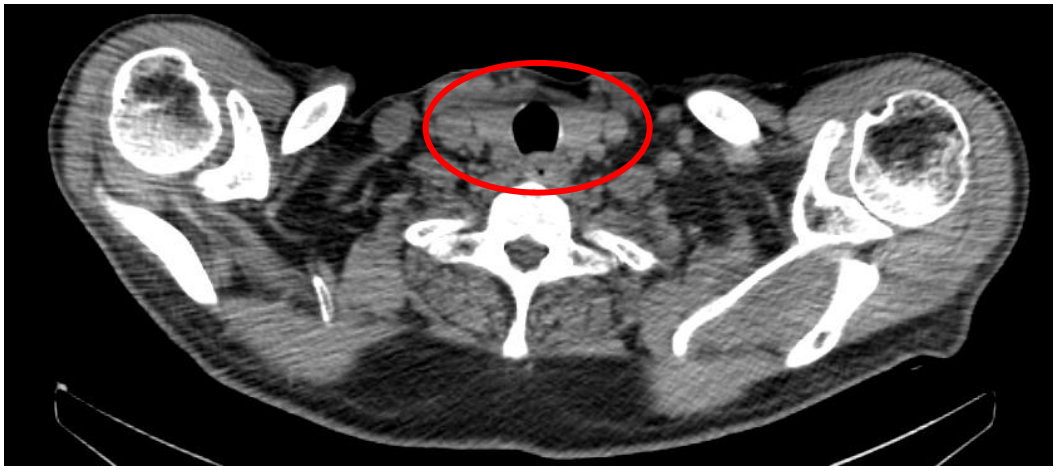

***Figure 15:** The effect of beam hardening caused by the shoulder bones and claviculae on the thyroid tissue on CT.*

3.3.2 Calibration factor measurements

Calculation method

The mean count density of the source was 7050 cts/mL. The count density for each VOI is shown in Table 2. Subsequently, the calibration factor resulted in 57.3 cts/s/MBq, with an acquisition time of 720s, 2 detectors, and activity concentration of 0.0854 MBq/mL.

Trial-and-error method

The VOIs delineated with a threshold of 0%, 1%, 4% and 20% of the maximum voxel value corresponded to a calibration factor of 110.3, 86.1, 69.8, and 59.2 cts/s/MBq, respectively. These four calibration factors are used to determine the most accurate method for thyroid iodine uptake measurements.

Table 2: *The count density for each VOI in the radioiodine phantom source.*

VOI	Region in source	VOI volume (mL)	Counts in VOI	Count concentration in VOI (counts/mL)
1	1	15.8	118245	7484
2	2	13.5	94793	7022
3	3	17.6	116551	6622
4	4	23.7	166093	7008
5	5	23.4	162137	6929
6	6	30.6	225380	7365
7	7	29.1	202332	6953
8	8	48.3	339020	7019

3.3.3 Iodine uptake measurement

Calculation method

The median iodine uptake for a threshold of 20%, 22%, and 25% of the maximum voxel value was 99.5% (IQR 97.6 – 101.0), 97.0% (IQR 94.8 – 98.8), and 93.9% (IQR 90.7 – 94.8), respectively (Figure 16). A threshold of 20% of the maximum voxel value was considered the best threshold in combination with the calibration factor of 57.3 cts/s/MBq, as it has the smallest IQR and the highest accuracy (closest to 100% uptake). However, each threshold contains two outliers: the measurement with a volume of 10 mL and the measurement with a radioactivity of 0.7 MBq.

Trial-and-error method

The calibration factor of 69.8 cts/s/MBq with a threshold of 4% of the maximum voxel value has the highest accuracy in measuring the iodine uptake based on the phantom measurements with varying radioactivity (0.7 MBq to 5.5 MBq, all diluted in 50 mL NaCl 0.9% solution) (Figure 17). Although the CF of 59.2 cts/s/MBq and threshold of 20% have a high accuracy and precision (median 99.6% IQR (98.7 – 100.6), the iodine uptake for the phantom measurement with the lowest

radioiodine activity (0.7 MBq) was measured at 85%. The CF of 69.8 cts/s/MBq and a threshold of 4% has high accuracy (median of 100.1% iodine uptake), small range (IQR 97.9 – 101.9), and does not contain any outliers. This calibration factor and threshold is therefore chosen as the most accurate method for measuring the iodine uptake within the trial-and-error experiments.

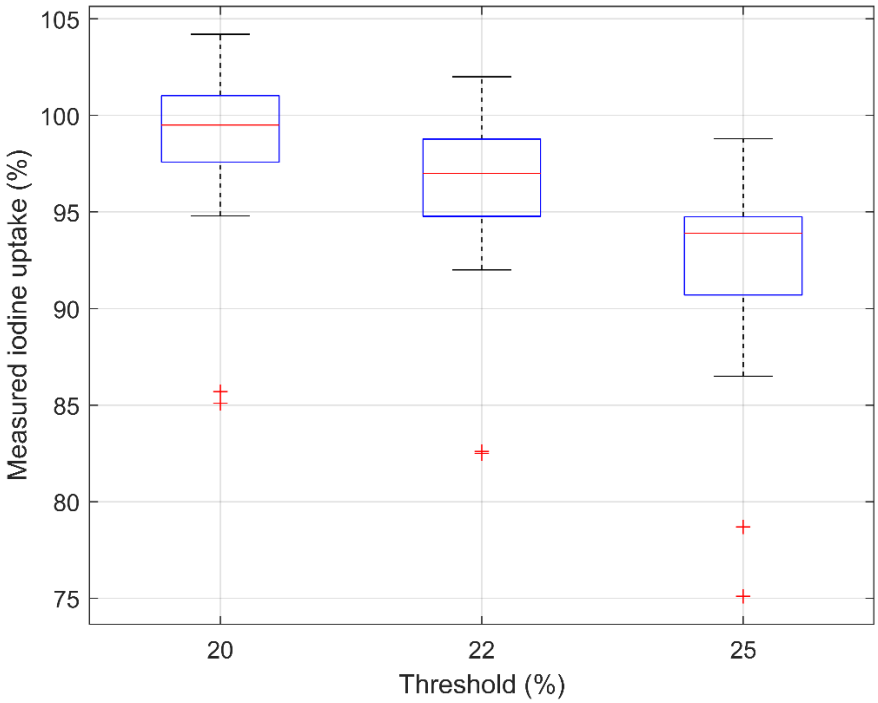

Figure 16: *Three different thresholds for VOI delineation to measure the iodine uptake based on a calibration factor of 57.3 cts/s/MBq.*

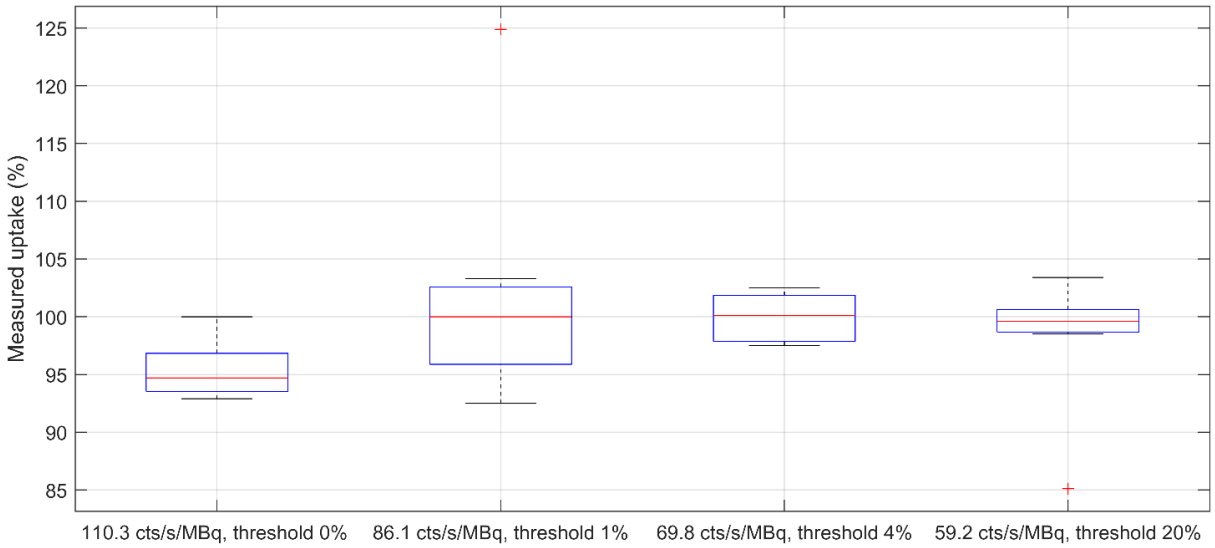

Figure 17: *Boxplots of four different thresholds and corresponding calibration factors for estimation of the thyroid volume.*

Table 3: *The median and IQR of each calibration factor and threshold for measuring the iodine uptake.*

Calibration factor (cts/s/MBq)	Threshold (%)	Median	IQR
110.3	0	94.7	93.5 – 96.8
86.1	1	100.0	95.9 – 102.5
69.8	4	100.1	97.9 – 101.9
59.2	20	99.6	98.7 – 100.6

Comparison of calculation method and trial-and-error method

The calculation method for the CF (57.3 cts/s/MBq) with a threshold of 20% of the maximum voxel value resulted in a median iodine uptake of 99.5% (IQR 97.6 – 101.0), while the CF obtained with the trial-and-error method (69.8 cts/s/MBq with a threshold of 4% of the maximum voxel value) resulted in a median iodine uptake with a slightly smaller IQR of 99.4% (IQR 98.2 – 101.3) (Figure 18). The calculation method resulted in two outliers in measured iodine uptake: the measurement with 10 mL volume (85.4%) and the measurement with 0.7 MBq of I-123 (85.1%). The trial-and-error method resulted in one outlier: the measurement with 10 mL volume (91.8%).

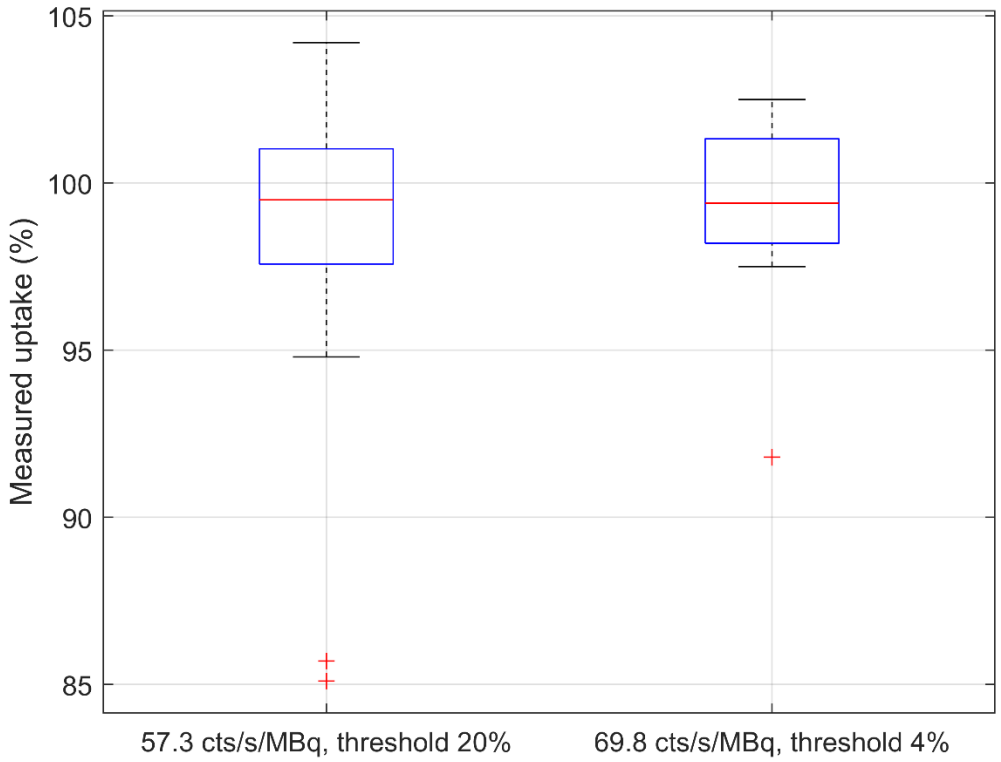

Figure 18: *The measured iodine uptake in all phantom measurements (varying volume, varying radioactivity, varying homogeneity), with the found CF and threshold for VOI delineation of the calculation method and trial-and-error method.*

3.3.4 Quantification workflow

A quantification workflow for measuring the iodine uptake and thyroid volume is set up, based on the findings in the phantom studies and patient study (Figure 19). The phantom and patient study showed correlation in the optimal threshold for thyroid volume measurement between 20% and 30% of the maximum voxel value. The phantom study showed a difference in optimal threshold for small volumes (< 20 mL) compared to volumes above 20 mL. Therefore, small volumes (< 20 mL) are delineated with a threshold between 25% and 30%, while volumes larger than 20 mL are delineated with a threshold between 20% and 25%. For the phantom measurement with low radioactivity (0.7 MBq, reflecting an iodine uptake of 13%), a threshold of 15% of the maximum voxel value results in the most accurate volume measurement. Visual inspection of the VOI delineation registered on CT is used to choose the best threshold. The calibration factor and threshold found in the trial-and-error method (69.8 cts/s/MBq with a threshold of 4% of the maximum voxel value) was determined as the most accurate method for iodine uptake measurements, based on high accuracy (median 99.4%), smallest IQR (98.2 – 101.3), and least outliers. For small volumes (< 10 mL), the accurate threshold for iodine uptake measurement was established at 1% of the maximum voxel value.

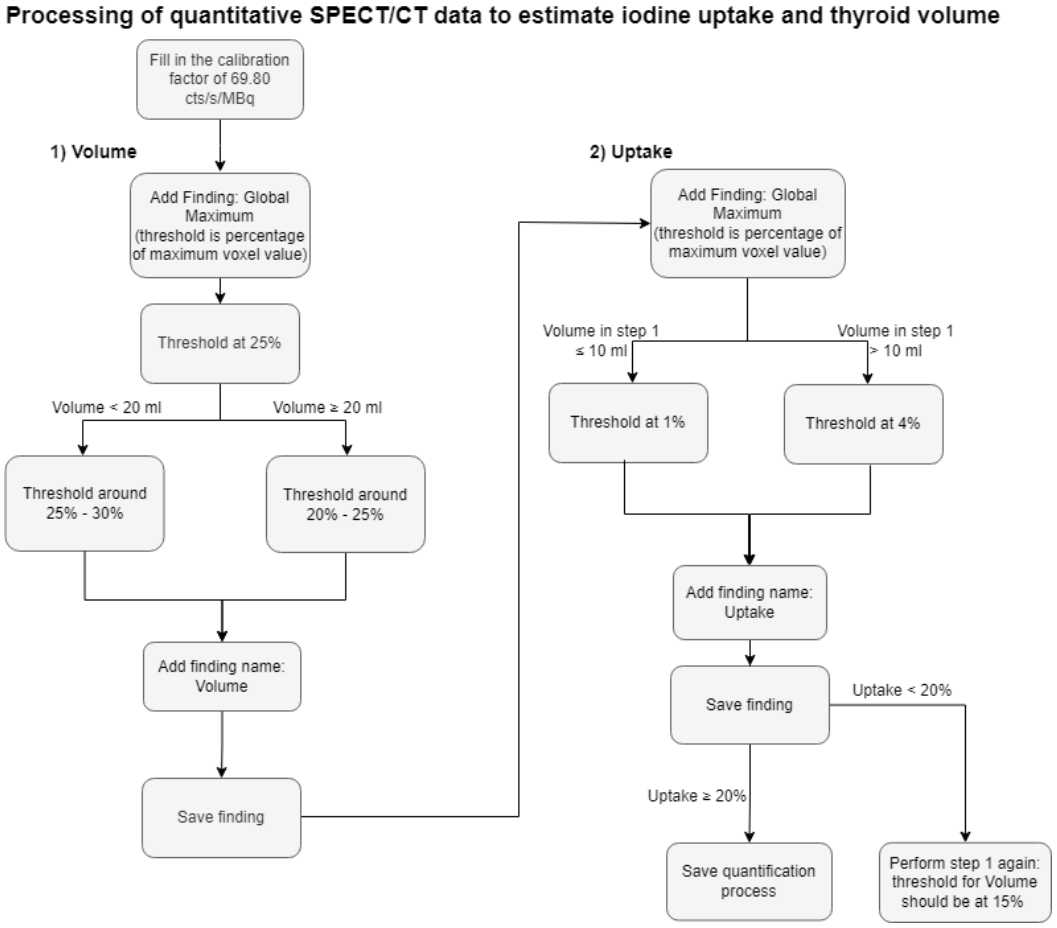

Figure 19: *The quantification workflow for estimation of the iodine uptake and thyroid volume with quantitative SPECT/CT.*

3.4 Discussion

In this study, we aimed to develop a quantification protocol for the measurement of the thyroid volume and the iodine uptake of the thyroid with quantitative SPECT/CT, to accurately calculate the radioiodine dose for I-131 therapy. The optimal threshold for measurement of the thyroid volume was determined around 25% of the maximum voxel value, with 25% to 30% specifically for small thyroid volumes (< 20 mL) and around 20% to 25% for volumes larger than 20 mL). A calibration factor of 69.8 cts/s/MBq with a threshold of 4% of the maximum voxel value resulted in the most accurate measured iodine uptake.

Several studies investigated quantification of iodine uptake and thyroid volume with quantitative SPECT/CT, using the SUV or the a percentage of the maximum voxel value with pertechnetate [34,39,57,63,65]. The use of SUV originates from fluorodeoxyglucose (FDG) in positron emission tomography (PET) imaging and quantification, which is a type of glucose absorbed by all cells in the body [32]. The SUV corrects the measured activity concentration for the body weight [32,66]. However, radioiodine is only taken up by the thyroid and therefore needs no correction for body weight in estimating the iodine uptake and thyroid volume [57,65]. Delineation based on the maximum voxel value was therefore chosen as the most appropriate method for measuring the iodine uptake and thyroid volume in quantitative SPECT.

Thyroid volume measurement

We found that a threshold of around 25% of the maximum voxel value enables accurate delineation of a VOI to estimate the thyroid volume on SPECT. In other studies it was found that accurate thyroid volume estimation on SPECT/CT with pertechnetate is accurately delineated with a threshold of 25% and 30%, for thyroid volumes between 5.0 mL and 110 mL in Graves' disease [52,57,67]. It is expected that for I-123, the best fitting threshold for thyroid volume estimation is the same, as both radionuclides are taken up by hyperfunctioning thyroid tissue, and have approximately the same photon energy (140 keV vs 159 keV, respectively).

The results of the phantom study indicate that small thyroid volumes (< 20 mL) require a larger threshold of 25 to 30%, an effect that is hypothesized to be caused by the partial volume effect. As a result of poor spatial resolution, the measured counts are reconstructed both in and around the source, also referred to as spill-out [35,64,66]. The smaller the source, the greater the influence of the partial volume effect on the reconstruction of the SPECT scan.

In low activities (0.7 MBq, reflecting an uptake value of 13%), a threshold of 20% to 25% of the maximum voxel value still resulted in underestimation of the phantom volume. A threshold of 15% of the maximum voxel value was found to estimate the thyroid volume correctly in low iodine

uptakes. It is hypothesized that the low signal to noise ratio in this particular measurement results in spill-in from background noise caused by the partial volume effect, increasing the radioactivity within the source. Subsequently, delineation based on the maximum voxel value excludes voxels at the edges of the source, resulting in an underestimation of the phantom volume. Another explanation for underestimation of the phantom volume in this measurement could be inaccuracies in the SPECT reconstruction, but this is not expected because the phantom volumes in all other measurements were accurately delineated with a threshold between 20% and 30%.

Calibration factor and threshold for VOI delineation to determine the iodine uptake

The calibration factor and threshold found in the trial-and-error method was found to be the most accurate method for iodine uptake measurements compared to the calculation method found in literature. The method described by Peters *et al.* resulted in a CF of 57.3 cts/s/MBq and a threshold 20% of the maximum voxel value, but lead to multiple outliers. This method is useful for accurate estimation of the radioactivity concentration, which is used to determine the received radiation dose in radionuclide therapy of several cancers including thyroid cancer [40,68,69]. As a result of poor spatial resolution in SPECT, the radioactivity is reconstructed both in and around the source (spill-out) which is also known as the partial volume effect [64,66]. The count density is therefore higher within the source, and gradually decreases towards the region around the source. To measure the iodine uptake correctly, the region containing spill-out of radioactivity needs to be incorporated in the VOI. However, to measure the mean activity concentration in the source, the region around the source should not be included as this reduces the mean activity concentration. Therefore, measurement of the iodine uptake in the thyroid requires a different approach.

Several calibration factors and threshold were tested in the trial-and-error method and a calibration factor of 69.8 cts/s/MBq with a threshold of 4% of the maximum voxel value corresponded with the most accurate iodine uptake measurements. The median uptake value in 110.3 cts/s/MBq with a threshold of 0% of the maximum voxel value is too low (94.7%), which would consistently underestimate the iodine uptake. Furthermore, incorporation of all counts measured in SPECT is not desired, as this incorporates scatter, background noise, and counts resulting from septal penetration of a small fraction of high energy gamma photons [41]. While the median uptake value with a CF of 86.1 cts/s/MBq with a threshold of 1% is exactly at 100%, the IQR is too large (95.8% – 102.6%) and contains an outlier with a measured iodine uptake of 125%. The outlier is the measurement with radioactivity of 0.7 MBq, which would result in an extreme overestimation of low activities (13% iodine uptake) when using this CF and threshold. With the

CF of 59.2 cts/s/MBq and threshold of 20% of the maximum voxel value, no spill-out region is incorporated, resulting in an underestimation of the iodine uptake in small volumes.

In the previous chapter (*Chapter 2 Planar Scintigraphy*), we concluded that the sensitivity of the gamma camera is stable, but that the calibration factor should be measured after maintenance or hardware changes [33]. For quantitative SPECT/CT, such measurement may also be performed to prevent incorrect measurements of the iodine uptake in the future. We recommend performing a quantitative SPECT/CT with a reference after maintenance or hardware changes.

Limitations

A disadvantage of the method we developed for VOI delineation of the thyroid volume based on the SPECT data is that it depends on the visual examination of correct VOI delineation registered on the low dose CT. In some patients, identification of thyroid tissue is complicated by surrounding similar-looking tissues (Figure 14) or beam hardening caused by the shoulders and clavicles (Figure 15). Therefore, the VOI delineation of the thyroid volume should be visually inspected by a nuclear medicine physician on the CT, to confirm correct VOI delineation.

One of the limitations in this study is that we only included patients with GD to find the optimal threshold for measuring thyroid volume in SPECT, as we expected that VOI delineation based on the maximum voxel value is the same in patients with tMNG. However, delineation of the thyroid volume in tMNG might require another threshold. Using a threshold around 25% of the maximum voxel value in a thyroid with an inhomogeneous radiotracer distribution (with multiple cold spots, mild hot spots, and extreme hot spots) results in exclusion of the mild hot spots in VOI delineation, as the voxel value within mild spots is too low. It is necessary to also include the mild hot spots to accurately determine the active thyroid volume for I-131 dose calculation. Future research should therefore focus on the appropriate threshold for the VOI delineation in patients with tMNG in quantitative SPECT/CT.

Another limitation is the lack of large volumes in our phantom studies. We investigated the threshold for VOI delineation of the iodine uptake in phantom volumes of 10 mL to 50 mL. However, thyroid volumes, especially in tMNG, can be much larger (up to 100 mL) [18]. The partial volume effect decreases when the source volume is increased, therefore resulting in less spill-out. Therefore, delineation of a VOI for estimation of the iodine uptake in larger volumes may be more accurately performed with a higher threshold [66]. Phantom measurements with volumes above 50 mL should be performed in the future to investigate the optimal threshold for measuring the iodine uptake in larger thyroid volumes.

Lastly, we only performed a few phantom experiments to assess different calibration factors and thresholds for iodine uptake measurements. We varied only one parameter per phantom measurement (volume, radioactivity, or homogeneity) and did not include measurements with combinations of varying variables. We found that a small activity (0.7 MBq) and small volume (10 mL) required other thresholds, but we did not perform measurements to investigate this effect in a combination of small volume and low radioactivity. Additional measurements with a combination of variations in volume, radioactivity and homogeneity should be included to determine if the chosen calibration factor and threshold for estimation of the iodine uptake are suitable in for all patients.

3.5 Conclusion

We developed a quantification workflow to measure the iodine uptake and thyroid volume in quantitative SPECT/CT to potentially improve I-131 dose calculation for radioiodine therapy. Estimation of the thyroid volume is accurately performed with a threshold of approximately 25% of the maximum voxel value, based on visual inspection of VOI delineation on CT. A calibration factor of 69.8 cts/s/MBq with a threshold of 4% of the maximum voxel value which incorporates spill-out of counts was found to be the most accurate for iodine uptake measurements. Future research should emphasize on phantom measurements with larger volumes and multiple parameter variations to improve the quantification workflow.

4. Comparison of planar scintigraphy and quantitative SPECT/CT for I-131 dose calculation in radioiodine therapy

4.1 Introduction

Diagnostic and functional imaging of the thyroid in patients with hyperthyroidism is commonly performed with planar scintigraphy [9,13,24]. Planar scintigraphy with the radionuclide I-123 allows both diagnosis of the benign thyroid disorder and quantification of thyroid iodine uptake and volume. Pertechnetate (Tc-99m) is another radionuclide used for imaging of the thyroid, but is less suitable for quantification of the iodine uptake due to its inability of organification by the thyroid [34]. To allow simultaneous diagnostic and quantitative imaging, I-123 is the preferred radionuclide for thyroid planar scintigraphy in our institute (Rijnstate, Arnhem, The Netherlands).

Radioiodine therapy

Radioiodine therapy with I-131 is a common treatment of hyperthyroidism caused by benign diseases of the thyroid gland, such as Graves' disease (GD) and toxic multinodular goiter (tMNG). The goal of treatment is to achieve euthyroidism and prevent life-impacting complications such as thyrotoxicosis and ophthalmopathy [13,15,17,18,20,68]. The overproducing parts of the thyroid gland take up most of the radioiodine, resulting in local ablation of the diseased thyroid tissue.

The required I-131 dose for radioiodine therapy is individually determined with planar scintigraphy with I-123 in our institute. The individual approach is used to administer a specific amount of radioiodine which only ablates the hyperfunctioning thyroid tissue. The calculated I-131 dose for radioiodine therapy is based on the iodine uptake, thyroid volume, and type of benign thyroid disorder (GD or tMNG). For treatment of GD, the desired activity concentration of radioiodine is 3.7 MBq/mL, while this is 7.4 MBq/mL for patients with tMNG, a thyroid volume larger than 50 mL, high iodine uptake (> 80%) or organification disturbances (4h/24h > 0.8) [9,13,20].

Therapy outcomes

Until now, therapy with I-131 has led to varying results in thyroid function in patients with GD and tMNG in our institute (Rijnstate, Arnhem, The Netherlands). Approximately 47% of patients with GD developed hypothyroidism one year after I-131 therapy, while 37% had persistent hyperthyroidism at one year after therapy. Therapy with I-131 in patients with tMNG resulted in hypothyroidism in 23% of patients at one year after therapy, while 11% had persistent hyperthyroidism one year after therapy. In literature, the reported incidence of hypothyroidism

after radioiodine therapy in GD is 80% within 25 years, of which 5% to 50% occurs within one year after therapy [18,30,59]. The reported percentage of persistent hyperthyroidism in GD after radioiodine therapy is 18% after one year [31]. It is widely known that the incidence of iatrogenic hypothyroidism after radioiodine therapy increases over time in patients with GD increases. In patients with tMNG, 20% to 75% have developed hypothyroidism within eight years after radioiodine therapy, while 32% had persistent hyperthyroidism 25 years after therapy [18,29,30,69].

It is hypothesized that the method for I-131 dose calculation for radioiodine therapy with planar scintigraphy is inaccurate, which may result in over- or underestimation of the required I-131 dose for therapy. Subsequently, this may result in iatrogenic hypothyroidism (overdosing) or persistent hyperthyroidism (underdosing). Thyroid volume measurements on planar scintigraphy have a reported inaccuracy of 30%, resulting in a 30% increase in calculated I-131 dose for radioiodine therapy when thyroid volume is overestimated and resulting in a 30% decrease in calculated I-131 dose for radioiodine therapy when thyroid volume is underestimated [13,52]. Furthermore, the lack of corrections for scatter and attenuation in planar scintigraphy can result in underestimation of the iodine uptake, which may result in higher calculated I-131 doses for radioiodine therapy [60].

A quantitative method with a higher accuracy in measuring the thyroid iodine uptake and thyroid volume may contribute to improved I-131 dose calculations and potentially less complications after radioiodine therapy. A possible method to improve quantification of the iodine uptake and thyroid volume is quantitative SPECT/CT [34,52,65,66,70]. Quantitative SPECT/CT enables three-dimensional functional imaging of the thyroid and has improved quantification due to incorporation of CT-based corrections. The use of quantitative SPECT/CT with Tc-99m for dose calculation in radioiodine therapy shows promising results [39,43,52,57,65,66]. However, the application of quantitative SPECT/CT with I-123 for I-131 dose calculation has not been studied yet.

Aim of this study

This study aims to compare planar scintigraphy and quantitative SPECT/CT with I-123 for dose calculation of I-131 therapy in a retrospective patient study, based on the measured iodine uptake, thyroid volume, and calculated I-131 dose for radioiodine therapy in both quantitative modalities. Furthermore, the administered I-131 activity concentration (MBq/mL) used in radioiodine therapy is evaluated in relation to the desired activity concentration (3.7 MBq/mL for GD and 7.4 MBq/mL for tMNG), and in relation thyroid function one year after radioiodine therapy.

4.2 Methods

The difference in thyroid volume, iodine uptake and I-131 calculated dose between planar scintigraphy and quantitative SPECT/CT was investigated. Furthermore, the relation between the administered I-131 activity concentration for radioiodine therapy and thyroid function after one year was investigated.

4.2.1 Patient population

Adult patients with GD and tMNG who received I-131 radioiodine therapy and underwent planar scintigraphy and quantitative SPECT with I-123 between February 2021 and December 2022 were retrospectively included in this study. The administered I-131 dose and time between iodine uptake measurement and radioiodine therapy was retrieved for each patient. Serum levels of TSH (reference 0.30 – 4.8 mU/L) and fT4 (reference 12 – 23 pmol/L) and prescribed thyroid medication (ATD) until one year after therapy were collected to establish the thyroid function after I-131 therapy (hypothyroidism, euthyroidism, or hyperthyroidism). It was assumed patients with euthyroid serum levels who are prescribed Levothyroxine or Tirosint had hypothyroidism, and patients with euthyroid serum levels and a prescription of Strumazol or Propylthiouracil had hyperthyroidism.

This study did not subject to the Medical Research Involving Human Subjects Act (WMO in The Netherlands), as it only concerns analysis of retrospective patient data. The study was approved by the local research committee of the Rijnstate hospital.

4.2.2 Image acquisition and processing

Planar scintigraphy

Acquisition of planar scintigraphy images was performed using the acquisition protocol in *2.2.2 Acquisition and image processing*. Processing of the quantitative data was performed in Hermes software© (Hermes Medical Solutions, Stockholm, Sweden). The findings in *Chapter 2 Planar scintigraphy* were applied: 1) a threshold of 10% of the maximum voxel value is used for region-of-interest (ROI) delineation to determine the iodine uptake of the thyroid, 2) a calibration factor (CF) of 80 cts/s/MBq is used to convert the measured counts within the ROI to radioactivity (MBq) and calculate the iodine uptake as the ratio between administered and measured radioactivity, 3) the thyroid volume is manually estimated based on the volume of a cylinder for each thyroid lobe. The required I-131 dose for radioiodine therapy is calculated with Equation 3.

$$A = \frac{k \bullet V}{U/100} \tag{3}$$

Where A is defined as the calculated radioiodine activity to be administered in MBq, U is the iodine uptake in the thyroid after 24h in %, V is the thyroid volume in mL, and k is the conversion factor (correcting for the thyroid disease) in MBq/mL. For treatment of GD k is 3.7 MBq/mL, while for treatment of tMNG k is 7.4 MBq/mL.

Quantitative SPECT/CT

Acquisition of quantitative SPECT/CT was performed with the gamma camera system GE Healthcare NM/CT 870 DR (GE Healthcare Technologies Inc., Chicago, Illinois, United States of America) and according to the acquisition protocol described in *3.2.3 Acquisition and image processing*. Processing of the quantitative data was performed in a custom-made application in Q.Volumetrix (GE Healthcare Technologies Inc., Chicago, Illinois, United States of America), and was performed using the quantification workflow developed in *3.3.4 Quantification workflow*. Thyroid volume was estimated based on the SPECT data. The threshold for volume estimation was categorized for homogeneous and inhomogeneous uptake (around 25% and 15% of the maximum voxel value, respectively), and checked by visual inspection of the VOI delineation registered on CT. Thyroid iodine uptake was determined using a threshold of 4% of the maximum voxel value for VOI delineation, and the measured counts were converted to radioactivity using a calibration factor of 69.8 cts/s/MBq. The required I-131 dose for radioiodine therapy is calculated with Equation 3.

The administered I-131 activity concentration (MBq/mL) for radioiodine therapy is compared to the desired activity concentration for patients with GD (3.7 MBq/mL) and patients with tMNG (7.4 MBq/mL). Furthermore, the thyroid function one year after radioiodine therapy is compared to the administered I-131 activity concentration for patients with GD and patients with tMNG separately. The administered dose concentration AC (MBq/mL) is calculated with Equation 4.

$$AC = \frac{A}{V} \cdot \frac{U}{100} \tag{4}$$

Where A is the administered I-131 dose in radioiodine therapy in MBq, V is the thyroid volume measured on quantitative SPECT in mL, U is the iodine uptake measured on quantitative SPECT after 24h in %.

4.2.3 Statistical analysis

Comparison of I-131 dose calculation obtained with both quantitative modalities

The iodine uptake, thyroid volume and calculated I-131 dose for radioiodine therapy obtained with planar scintigraphy and quantitative SPECT/CT were compared with the median and interquartile range (IQR) in a boxplot. The median and IQR were used due to absence of normal distributions in thyroid volume ($p < 0.05$ in Shapiro Wilk Test) and subsequently calculated I-131 dose, probably caused by a small patient population. The percental differences were calculated between quantitative modalities. A ±15% percental difference in calculated I-131 dose for therapy was considered a clinically relevant difference, based on the error margin in ordering I-131 for radioiodine therapy of ±10%. Therefore, a percental difference of ± 15% in iodine uptake and thyroid volume was also considered clinically relevant, as a 15% difference in iodine uptake or thyroid volume results in a percental difference in I-131 dose of 15%. All data was categorized for patients with GD and tMNG.

Administered I-131 activity concentration in relation to thyroid function after therapy

The administered I-131 activity concentration (MBq/mL) was compared to the desired I-131 activity concentration in our institute (GD: 3.7 MBq/mL, tMNG: 7.4 MBq/mL), using a Wilcoxon Signed Rank Test. In patients with tMNG, the administered I-131 activity concentration did not follow a normal distribution ($p < 0.05$ in Shapiro-Wilk Test), possibly due to the calculated I-131 doses exceeding the maximum dose for treatment of benign thyroid diseases in some patients (maximum 2000 MBq). The median and IQR in administered I-131 activity concentration are compared and shown in a boxplot.

Statistical correlation of the administered I-131 activity concentration to the thyroid function one year after I-131 therapy (hypothyroidism, euthyroidism, hyperthyroidism) is not performed, because the patient population within each group is too small (the smallest group being 4 patients). Therefore, the median and IQR of the administered activity concentration for each group is determined and compared in a boxplot, to observe possible correlations between administered I-131 activity concentration and thyroid function after radioiodine therapy.

4.3 Results

4.3.1 Patient population

A population of 65 patients was included in this study: 31 patients with GD and 34 patients with tMNG. All patient characteristics are shown in Table 4.

Table 4: *Characteristics of the patient population, categorized for Graves' disease and toxic multinodular goiter.*

Parameter	Graves' disease	Toxic multinodular goiter
Nr. of patients	31	34
Mean age (years)	48 ± 16	67 ± 10
Females	21	32
Median time between uptake measurement and therapy (days)	5 (5 – 11)	61 (27 – 82)
Median administered I-131 dose (MBq)	232 (176 – 373)	1132 (538 – 1946)
Median calculated I-131 dose for therapy (MBq)	232 (164 – 367)	1326 (747 – 2006)
ATD one year after I-131	21	9
Thyroid function one year after I-131:		
Hypothyroidism	13 (42%)	10 (29%)
Euthyroidism	9 (29%)	20 (59%)
Hyperthyroidism	9 (29%)	4 (12%)
2nd treatment with radioiodine within one year	5 (16%)	0 (0%)

4.3.2 Planar scintigraphy vs quantitative SPECT/CT in Graves' disease

Calculated I-131 dose

The I-131 doses calculated for radioiodine therapy in patients with GD differed between modalities, with a median calculated dose in planar scintigraphy of 222.9 MBq (IQR 156.1 – 314.6), and a median calculated dose in quantitative SPECT/CT of 138.6 MBq (IQR 111.8 – 182.4) (Figure 20). The calculated dose in planar scintigraphy was on average 38% higher than the dose calculated with quantitative SPECT/CT. In two patients (6.5%), the percental difference in calculated I-131 dose was within the ±15% range, meaning the difference in calculated I-131 dose between modalities is clinically irrelevant (Figure 21). In three patients (9.6%), the calculated I-131 dose was 200 MBq to 300 MBq higher based on planar scintigraphy than based on quantitative SPECT/CT (Figure 22). In Table C.5 in *Appendix C*, the calculated I-131 doses are shown for planar scintigraphy and quantitative SPECT/CT for each patient.

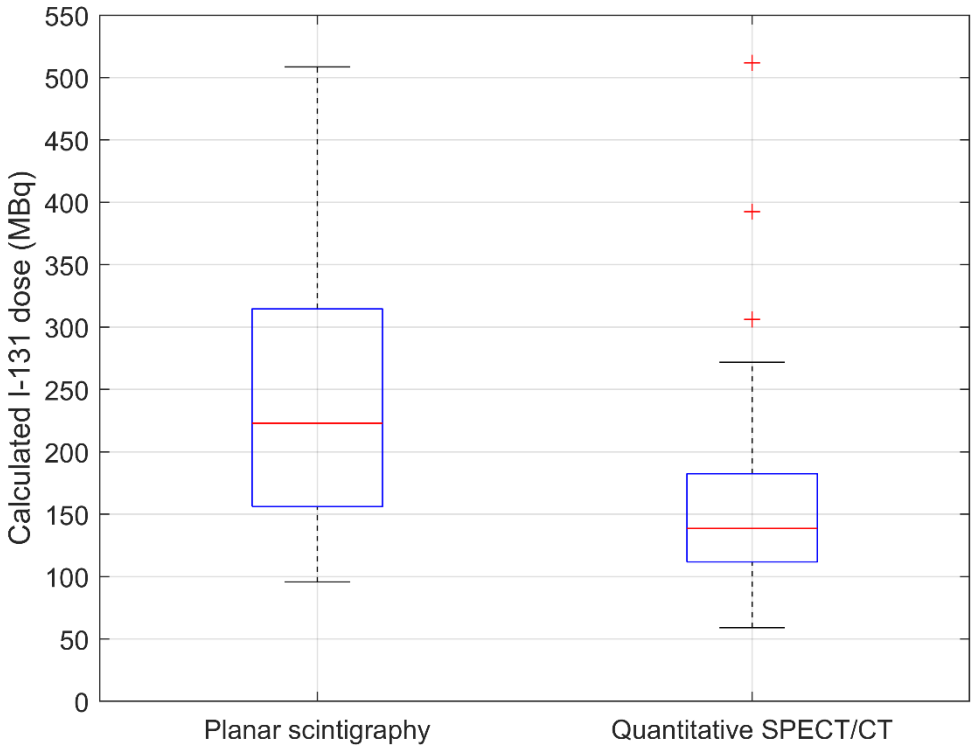

Figure 20: *The calculated I-131 dose for radioiodine therapy in GD in planar scintigraphy (left) and quantitative SPECT/CT (right).*

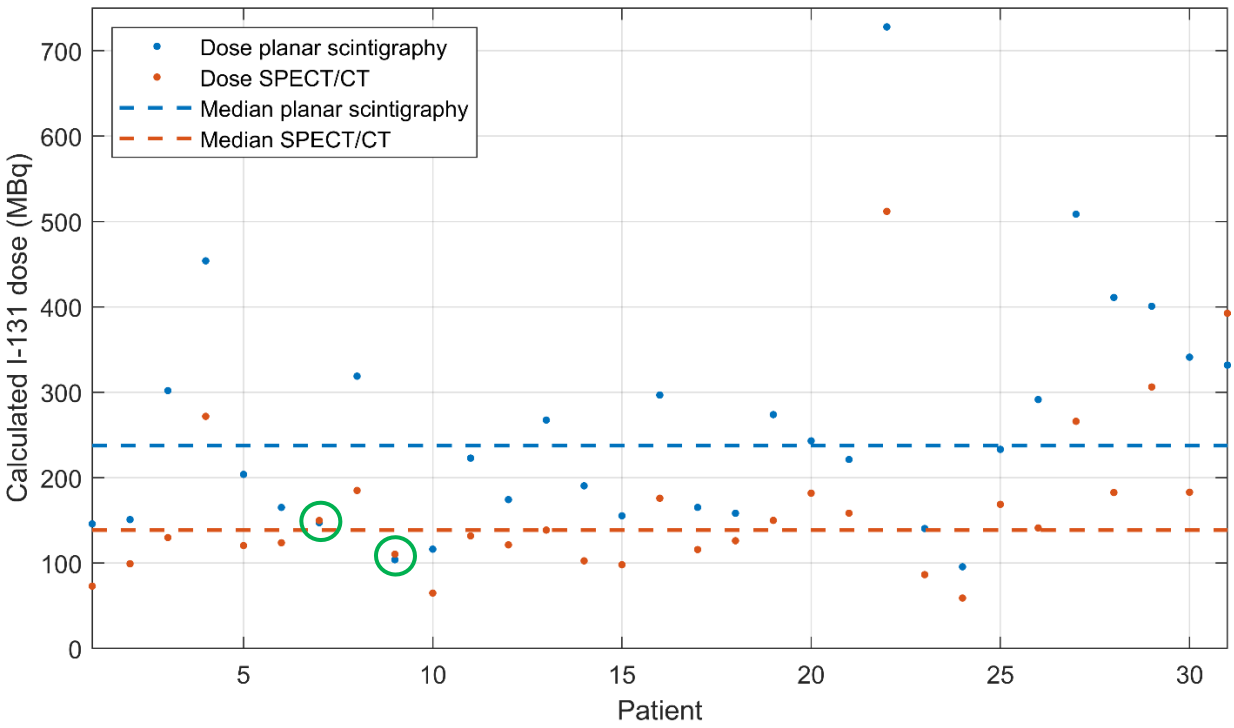

Figure 21: *Individual calculated I-131 doses based on planar scintigraphy (blue) and quantitative SPECT/CT (orange) for GD. The two green circles indicate the two patients with a clinically irrelevant difference in calculated I-131 dose.*

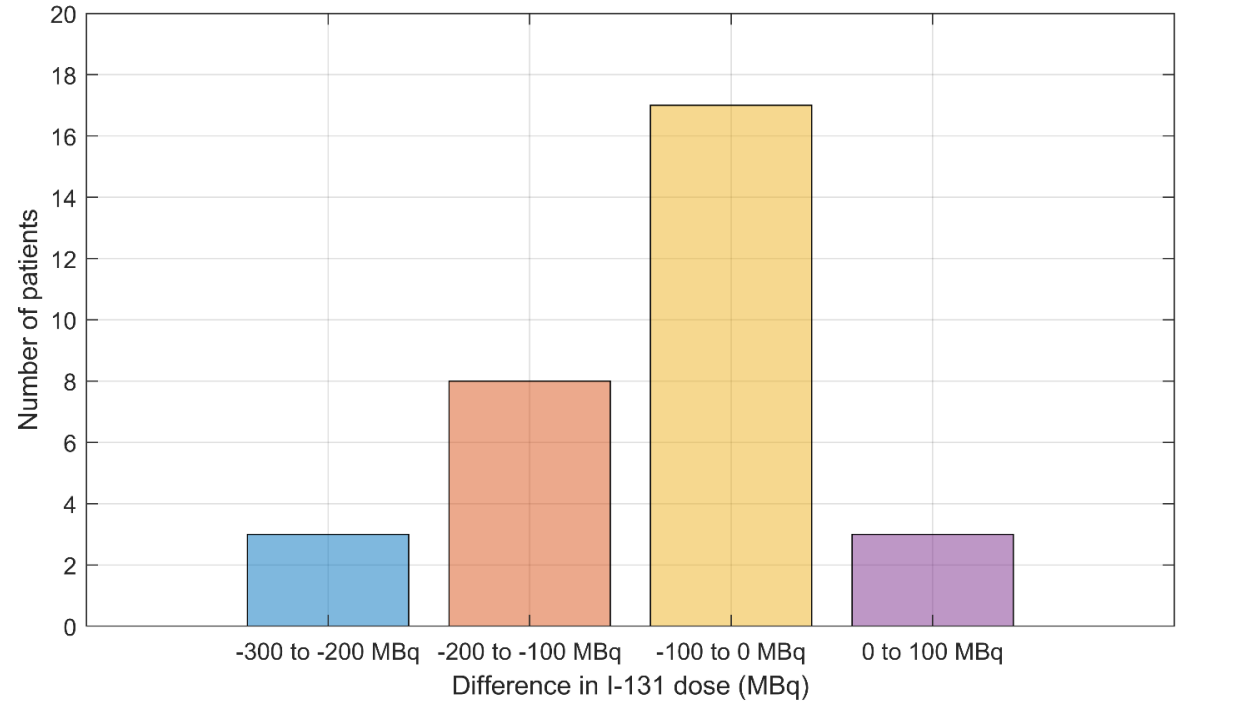

Figure 22: *The difference in calculated dose between quantitative SPECT/CT and planar scintigraphy in GD.*

Measured iodine uptake

The median iodine uptake in patients with GD in planar scintigraphy was 51.5% (IQR 43.8 – 59.6) and was in quantitative SPECT/CT 65.4% (IQR 53.3 – 77.7) (Figure 23). In 23 patients (74.2%), the measured iodine uptake was higher based in quantitative SPECT/CT than in planar scintigraphy with a clinically relevant percental difference above 15%. The average percental difference in iodine uptake between modalities was 24%. Table C.5 in *Appendix C*, the measured iodine uptakes are shown for planar scintigraphy and quantitative SPECT/CT for each patient.

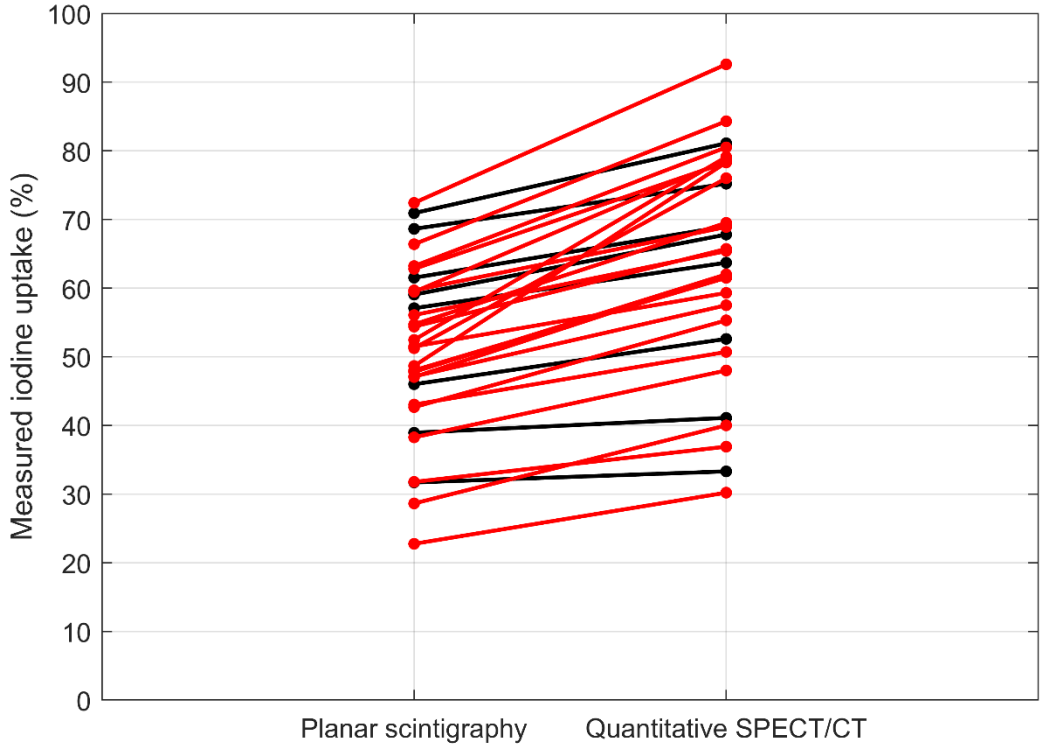

Figure 23: *The individual differences in measured iodine uptake between planar scintigraphy (left) and quantitative SPECT/CT (right) in GD. The red lines indicate volume differences above 15%. Black lines indicate volume differences below 15%.*

Measured thyroid volume

The median measured thyroid volume in patients with GD was in planar scintigraphy 25.6 mL (IQR 20.7 – 41.5) and in quantitative SPECT/CT 22.3 mL (IQR 16.6 – 30.8) (Figure 24). Planar scintigraphy measured overall larger thyroid volumes with a median difference of 5.8 mL (IQR 8.9 – 2.9) (Figure 25). In ten patients (32.2%), the measured thyroid volume was similar in both modalities (within ±15% range). In 21 patients (67.7%), the difference in measured thyroid volume was clinically relevant, of which in nineteen patients (61.2%) the thyroid volume was larger in planar scintigraphy and in two patients (6.5%) the measured thyroid volume was smaller in planar scintigraphy. The average percental difference in thyroid volume between modalities was 18%. In Table C.5 in *Appendix C*, the measured thyroid volumes are shown for planar scintigraphy and quantitative SPECT/CT for each patient.

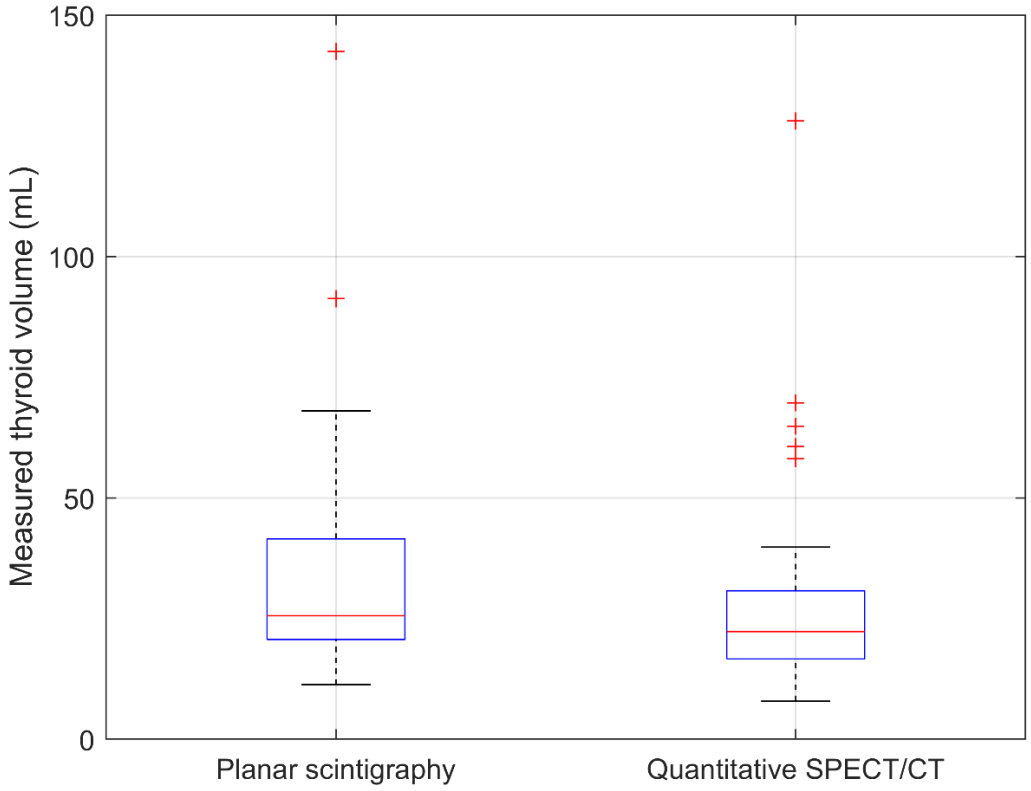

Figure 24: *The thyroid volumes measured with planar scintigraphy (left) and quantitative SPECT/CT (right) in GD.*

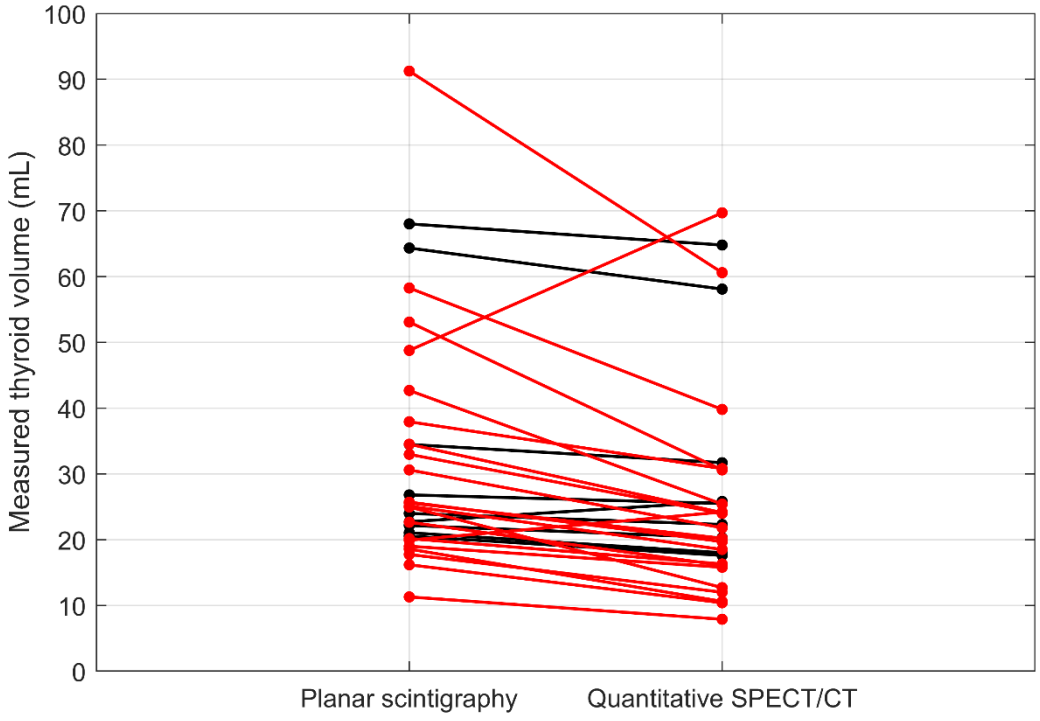

Figure 25: *The individual differences in thyroid volume between planar scintigraphy (left) and quantitative SPECT/CT (right) in GD. The red lines indicate volume differences above 15%. Black lines indicate volume differences below 15%.*

4.3.2 Planar scintigraphy vs quantitative SPECT/CT in toxic multinodular goiter

Calculated I-131 dose

Dose calculation for radioiodine therapy in patients with tMNG resulted in a median I-131 dose based on planar scintigraphy in 1244.5 MBq (IQR 647.0 – 2187.5) and based on quantitative SPECT/CT resulted in 880.6 MBq (IQR 525.0 – 1477.7) (Figure 26). On average, the I-131 dose was 23% higher based on planar scintigraphy. In four patients (11.7%), the percental difference in calculated I-131 dose was within the ±15% range, meaning the difference in calculated I-131 dose between modalities is clinically irrelevant (Figure 27). In nineteen patients (55.9%), the calculated I-131 dose was 300 to 1800 MBq higher based on planar scintigraphy (Figure 28). In Table C.6 in *Appendix C*, the calculated I-131 doses are shown for planar scintigraphy and quantitative SPECT/CT for each patient.

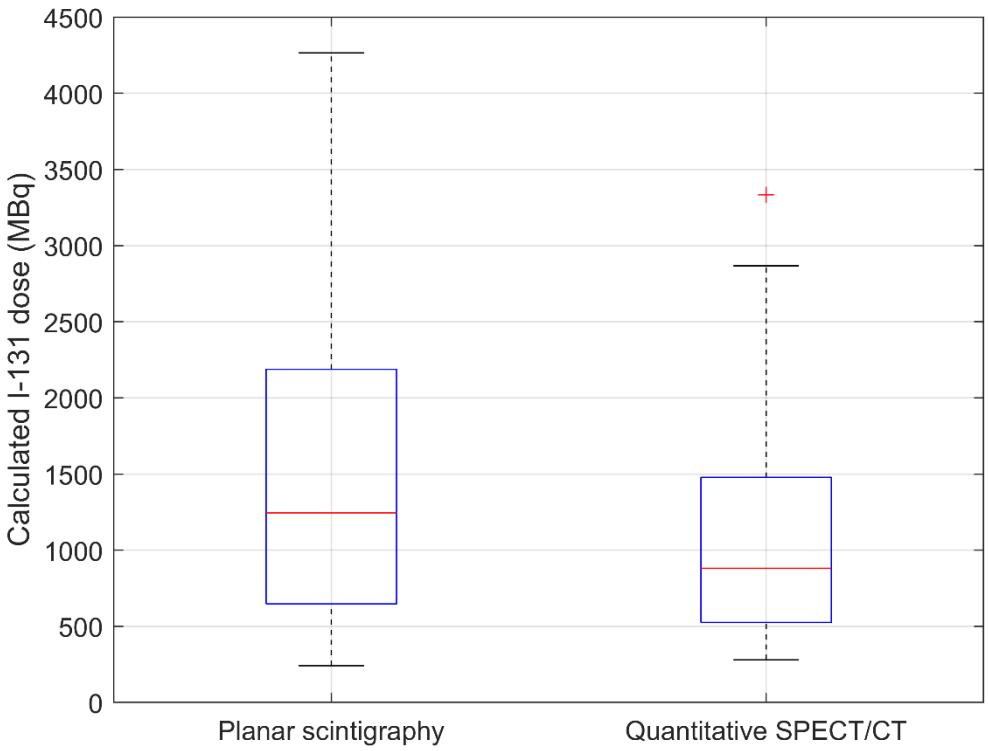

Figure 26: *The calculated I-131 dose for radioiodine therapy in tMNG in planar scintigraphy (left) and quantitative SPECT/CT (right).*

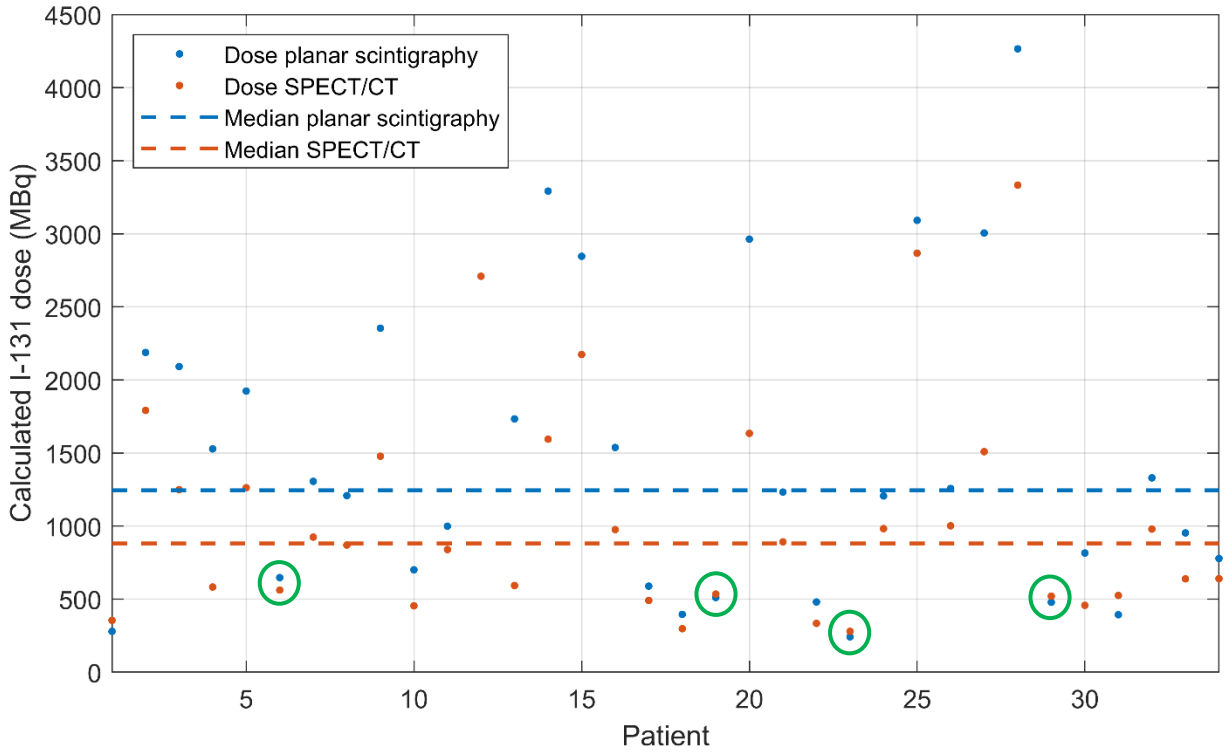

Figure 27: *Individual calculated I-131 doses based on planar scintigraphy (blue) and quantitative SPECT/CT (orange) in tMNG. The three green circles indicate the three patients with a clinically irrelevant difference in calculated I-131 dose.*

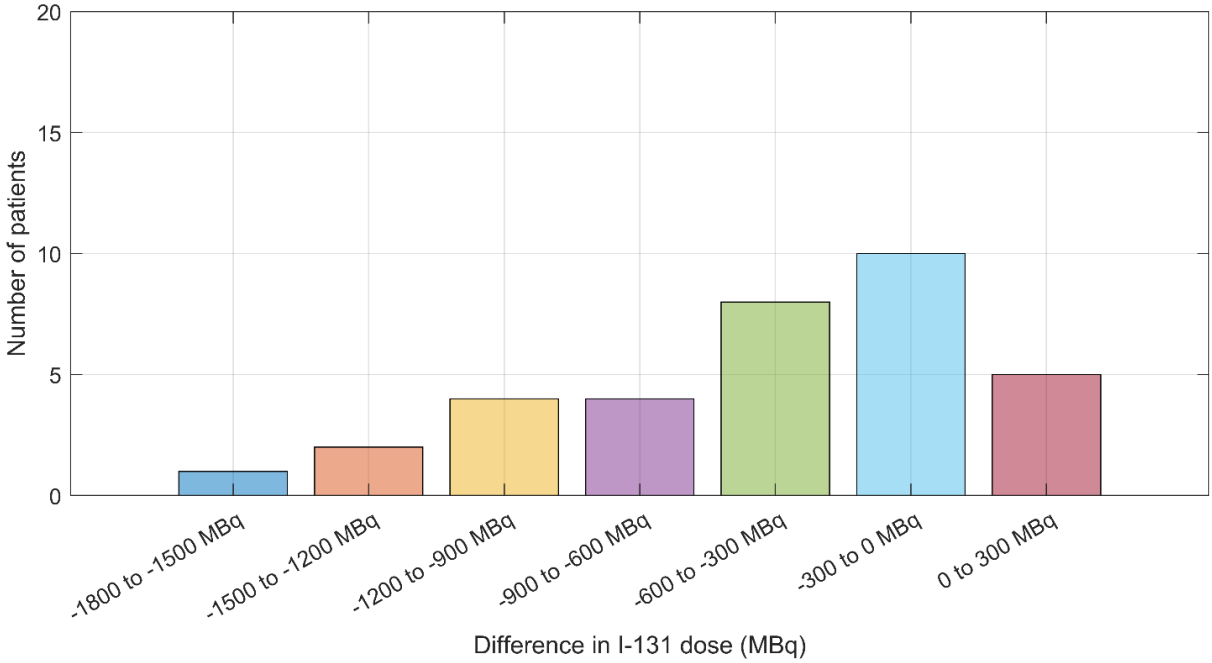

Figure 28: *The difference in calculated dose between quantitative SPECT/CT and planar scintigraphy in tMNG.*

Measured iodine uptake

The median iodine uptake in patients with tMNG was in planar scintigraphy 26.4% (IQR 19.9 – 37.0) and in quantitative SPECT/CT 37.3% (IQR 31.4 – 47.8) and shown for each individual patient in Figure 29. The average percental difference in iodine uptake between modalities was 46.0%. In 31 patients (91.2%), the measured iodine uptake was higher in quantitative SPECT/CT than in planar scintigraphy with a clinically relevant percental difference outside the ±15% range. In three patients (8.8%), the percental difference in iodine uptake was clinically irrelevant (< 15%). In Table C.6 in *Appendix C*, the measured iodine uptakes are shown for planar scintigraphy and quantitative SPECT/CT for each patient.

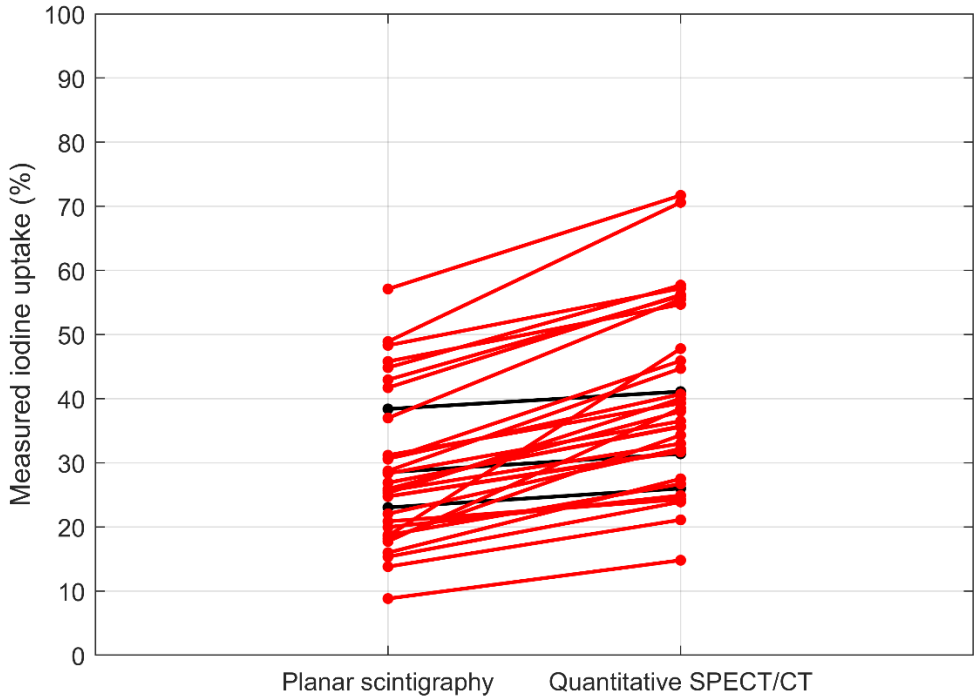

Figure 29: *The individual differences in measured iodine uptake between planar scintigraphy (left) and quantitative SPECT/CT (right) in tMNG. The red lines indicate volume differences above 15%. Black lines indicate volume differences below 15%.*

Measured thyroid volume

The median measured thyroid volume in patients with tMNG was in planar scintigraphy 42.0 mL (IQR 26.0 – 78.8) and in quantitative SPECT/CT 37.6 mL (26.2 – 73.8) (Figure 30). Individual measurements are shown in Figure 31 and Figure 32. The average percental difference in thyroid volume between modalities was 7.8%. In sixteen patients (47.1%), the measured thyroid volume was similar with both modalities (within ±15% range). In eighteen patients (52.9%) the difference in measured thyroid volume was clinically relevant, of which in eight patients (23.5%) the thyroid volume was lower in quantitative SPECT/CT, and in ten patients (29.4%) the measured thyroid volume was higher in quantitative SPECT/CT. In Table C.6 in *Appendix C*, the measured thyroid volumes are shown for planar scintigraphy and quantitative SPECT/CT for each patient.

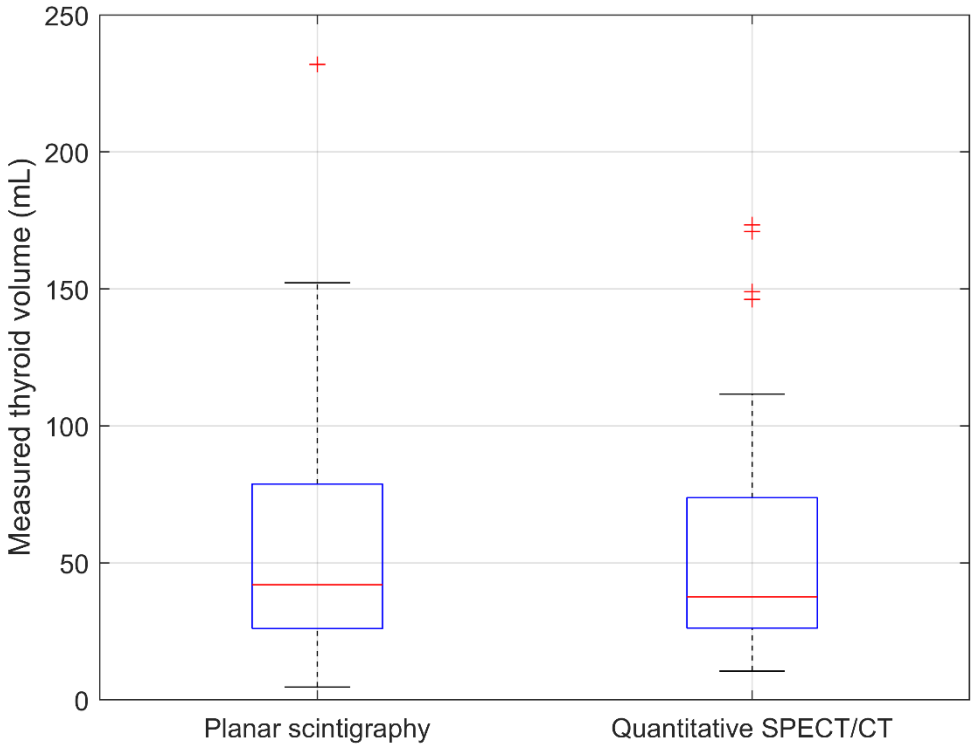

Figure 30: *The thyroid volumes measured with planar scintigraphy (left) and quantitative SPECT/CT (right) in tMNG.*

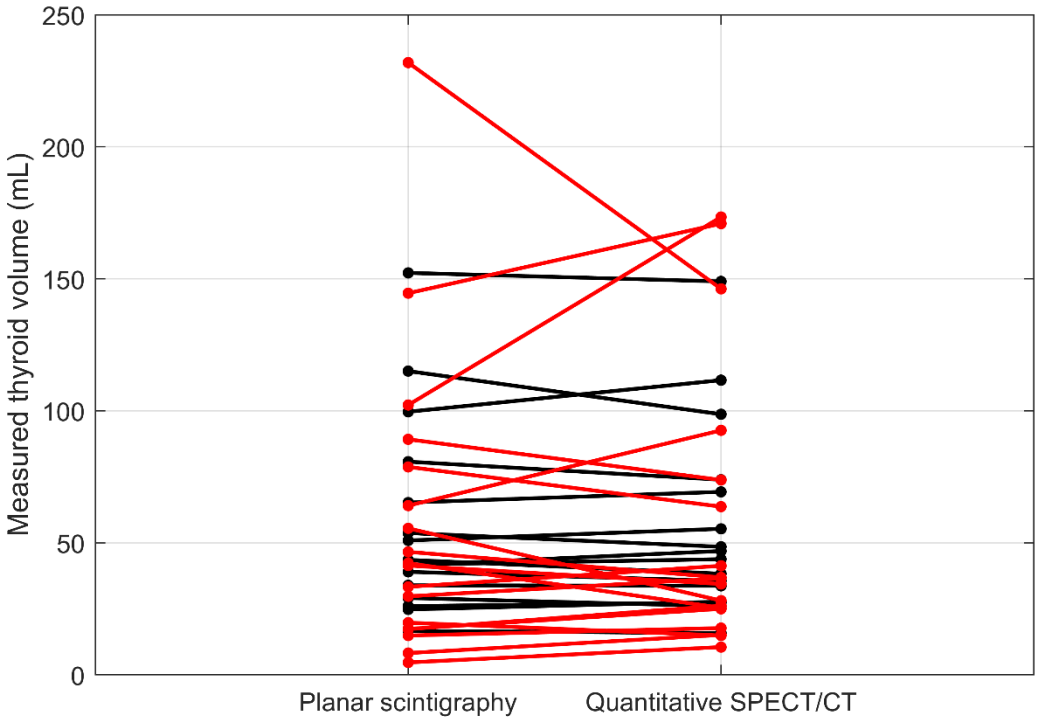

Figure 31: *The individual differences in measured thyroid volume between planar scintigraphy (left) and quantitative SPECT/CT (right) in tMNG. The red lines indicate volume differences above 15%. Black lines indicate volume differences below 15%.*

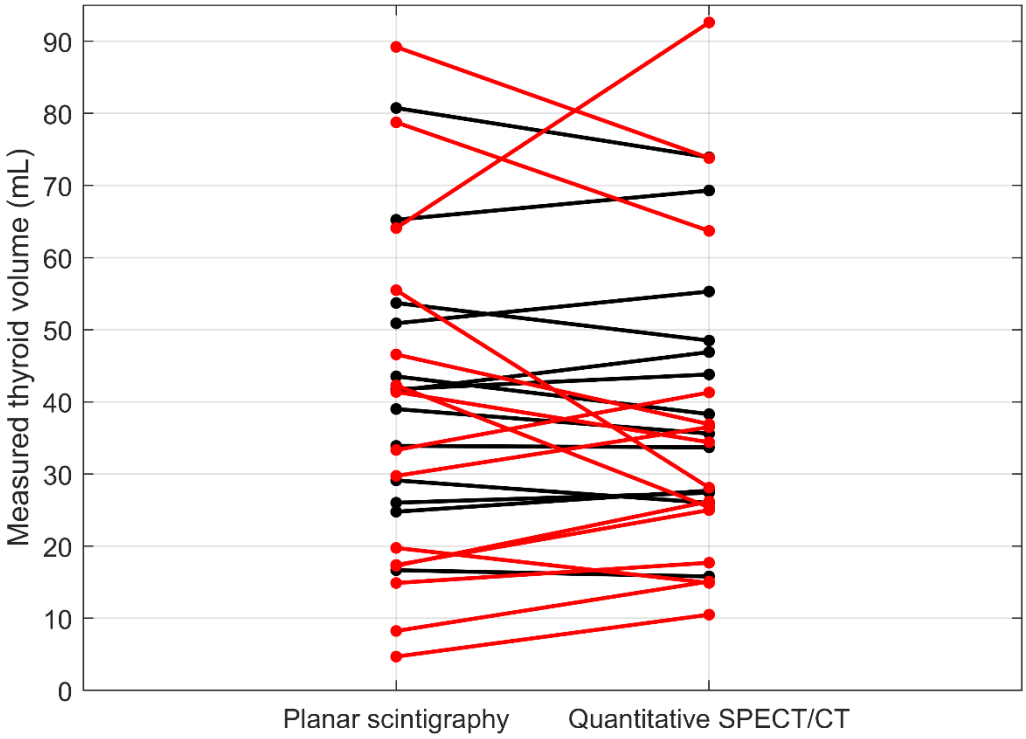

Figure 32: *The individual measurements for smaller thyroid volumes (< 100 mL) shown in more detail for tMNG. The red lines indicate volume differences above 15%. Black lines indicate volume differences below 15%.*

4.3.3 Administered activity concentration

Graves' disease

The median administered I-131 activity concentration was 6.8 MBq/mL (IQR 5.2 – 8.7) for patients with GD, which is statistically different from the desired activity concentration of 3.7 MBq/mL (Wilcoxon Signed Rank test, $p < 0.001$).

Patients with GD who achieved euthyroidism after I-131 therapy (n = 9, 29%) received a median I-131 activity concentration of 5.6 MBq/mL (IQR 4.4 – 8.2) (Figure 33). Patients who developed hypothyroidism (n = 13, 42%) received an activity concentration of 7.8 MBq/mL (IQR 6.1 – 9.1). Patients with persistent hyperthyroidism (n = 9, 29%) received an administered activity concentration similar to the population with euthyroidism after therapy, of 6.1 MBq/mL (IQR 4.4 – 8.1). Eight out of nine patients who had persistent hyperthyroidism after therapy (89%) had an iodine uptake above 60% (Figure 34). In Table C.5 in *Appendix C*, the thyroid function and administered I-131 activity concentration are shown for each patient.

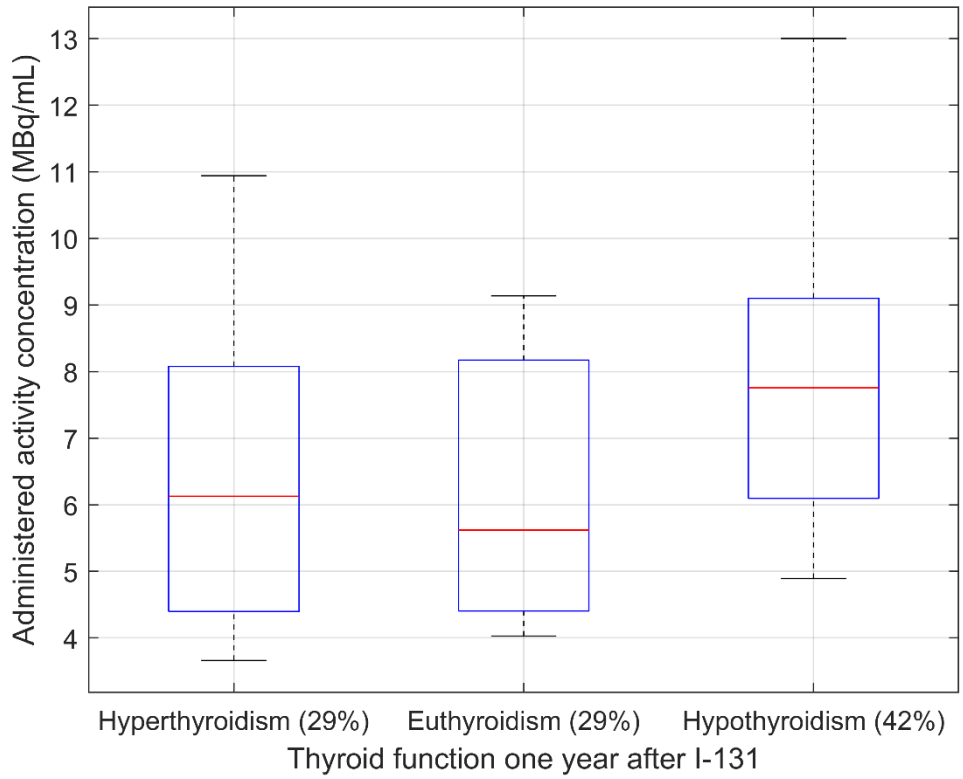

***Figure 33**: The administered I-131 activity concentration (MBq/mL) in relation to thyroid function one year after radioiodine therapy in GD.*

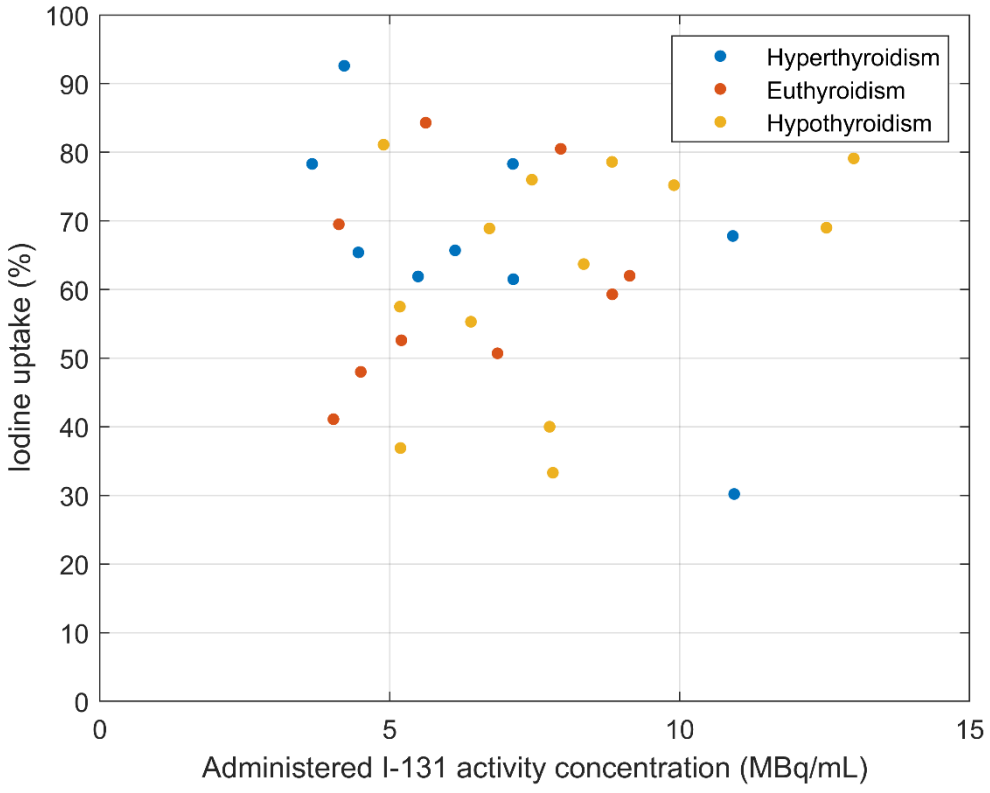

***Figure 34**: The iodine uptake in relation to the administered I-131 activity concentration (MBq/mL) in GD, categorized for patients with hyperthyroidism, euthyroidism or hypothyroidism one year after radioiodine therapy.*

Toxic multinodular goiter

In patients with tMNG, the median administered I-131 activity concentration was 8.7 MBq/mL (IQR 5.6 – 10.4) and did not statistically vary from the desired activity concentration of 7.4 MBq/mL (Wilcoxon Signed Rank test, Z = 1.889, p = 0.059).

Patients with tMNG who achieved euthyroidism after I-131 therapy (n = 20, 58.8%) received a median I-131 activity concentration of 8.3 MBq/mL (IQR 5.6 – 9.8) (Figure 35). Patients who developed hypothyroidism (n = 10, 29.4%) received 10.4 MBq/mL (IQR 10.17 – 11.7) and four patients with persistent hyperthyroidism after I-131 therapy (11.8%) received 6.7 MBq/mL (IQR 4.0 – 9.3). Seven out of ten patients who developed hypothyroidism after radioiodine therapy (70%) had a thyroid volume smaller than 50 mL (Figure 36). In Table C.6 in *Appendix C*, the thyroid function and administered I-131 activity concentration are shown for each patient.

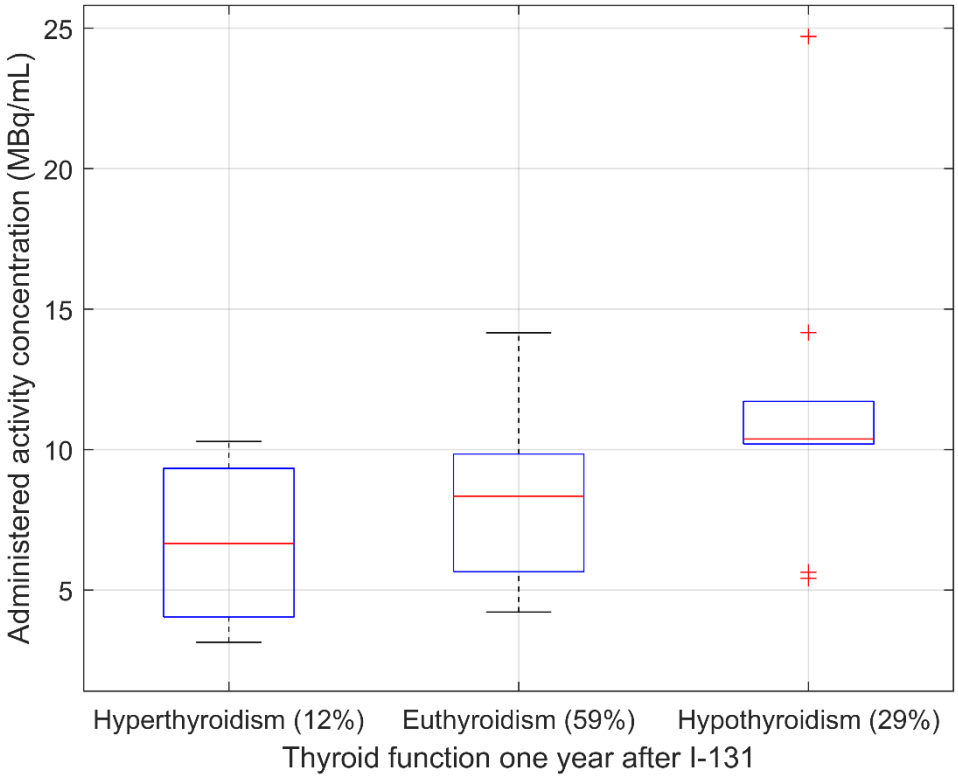

***Figure 35**: The administered I-131 activity concentration (MBq/mL) in relation to thyroid function one year after radioiodine therapy in tMNG.*

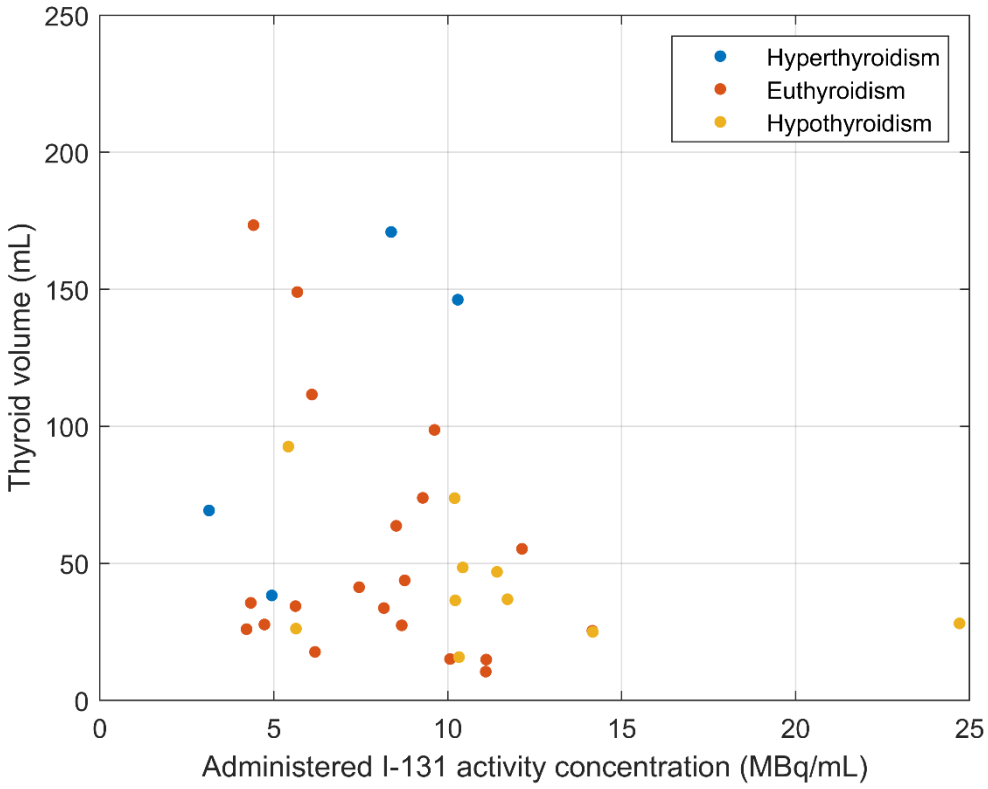

***Figure 36**: The thyroid volume in relation to the administered I-131 activity concentration (MBq/mL) in tMNG, categorized for patients with hyperthyroidism, euthyroidism or hypothyroidism one year after radioiodine therapy.*

4.4 Discussion

In this study, the I-131 dose calculation using quantitative SPECT/CT and planar scintigraphy with I-123 were compared, and the administered I-131 activity concentration and desired I-131 activity concentration were compared. Dose calculations based on quantitative SPECT/CT resulted in a clinically relevant decrease in dosage of more than 15% compared to planar scintigraphy. In both patients with GD and TMNG, the population who developed hypothyroidism after therapy received a higher I-131 activity concentration compared to the euthyroidism and hyperthyroidism population.

4.4.1 Graves' disease

The I-131 doses for treatment of GD calculated with planar scintigraphy were 38% higher compared to quantitative SPECT/CT, probably resulting in a large overestimation of the I-131 dose. In only two patients (6.5%), there was no clinical relevant difference in calculated I-131 dose (percental difference within 15%). This was not due to similar iodine uptakes and thyroid volumes measured in both quantitative modalities, but the percental increase in iodine uptake canceled out the percental decrease in thyroid volume measured in quantitative SPECT/CT. It is therefore important to analyze both the differences in iodine uptake and thyroid volume between quantitative modalities, to determine the cause of similarity or difference in calculated I-131 dose.

The large difference in calculated I-131 dose is caused by an overall higher iodine uptake and an overall smaller thyroid volume measured in quantitative SPECT. The iodine uptake measured in quantitative SPECT/CT was substantially higher than in planar scintigraphy, with a clinically relevant difference in twenty-three patients (74.2%). In other words, planar scintigraphy underestimates the iodine uptake in 74.2% of patients. Thyroid volumes measured in quantitative SPECT/CT were overall smaller compared to planar scintigraphy with a clinically relevant difference in twenty-one patients (67.7%), meaning that planar scintigraphy overestimates the thyroid volume. The use of quantitative SPECT/CT in I-131 dose calculation therefore results in a decrease in I-131 dose compared to the doses calculated with planar scintigraphy.

The mean administered I-131 activity concentration was higher than the desired activity concentration for patients with GD, which may be an explanation for the high incidence of hypothyroidism in patients treated for GD (42%, n = 13). Furthermore, we observed the highest median administrated I-131 activity concentration in the hypothyroidism group compared to the euthyroidism and hyperthyroidism group. No difference was observed between the euthyroidism and hyperthyroidism group. Unfortunately, the number of patients in the population was too small to determine the clinical significance of these differences.

The high incidence of developing hypothyroidism after radioiodine therapy and the high median administered I-131 activity concentration of 6.8 MBq/mL suggest that patients with GD were overtreated. Lower calculated I-131 dosages in quantitative SPECT/CT may reduce the incidence of hypothyroidism after radioiodine therapy. However, several studies have shown that administration of low I-131 doses for the treatment of GD does not reduce the incidence of hypothyroidism after radioiodine therapy. De Jong *et al.* investigated thyroid function after I-131 dose administration of 3.7 MBq/mL and 7.4 MBq/mL and reported an incidence of hypothyroidism of 41% and 54% one year after therapy, respectively [59]. A longer follow-up study performed by Sridama *et al.* found a cumulative incidence of hypothyroidism in patients treated for GD of 76.1% at eleven years after radioiodine therapy, even with very low administered I-131 doses (as low as 1.1 MBq/mL) [71]. It is known that in patients treated for GD, the incidence of iatrogenic hypothyroidism after radioiodine therapy increases over time. The mechanism behind the development of hypothyroidism several years after radioiodine therapy is still not understood, but improved I-131 dose calculation with quantitative SPECT/CT may be a first step towards lowering the incidence of hypothyroidism after radioiodine therapy.

In this study, we found that two patients with GD received 11 MBq/mL, and still had persistent hyperthyroidism (patient 3 and 13 in Table C.5 in *Appendix C*). In literature, possible causes of persistent hyperthyroidism are described as large thyroid volumes (> 50 mL), high iodine uptakes (> 80%), prolonged time between uptake measurements and administration of radioiodine therapy, or organification disturbances (4h/24h > 0.8). The patients had an iodine uptake of 30% and 68% and a thyroid volume of 10 mL and 25 mL based on quantitative SPECT/CT, which both do not explain the occurrence of persistent hyperthyroidism [59,72]. A prolonged time between the iodine uptake measurement and administration of radioiodine therapy may influence the therapy outcome, because thyroid function in GD can fluctuate over time [13]. However, this was not the case in these patients because they were treated 5 and 19 days after iodine uptake measurement. An organification disturbance could result in persistent hyperthyroidism in these patients, but unfortunately we did not perform iodine uptake measurements at 4h after I-123 administration to investigate this. Future research should incorporate iodine uptake measurements at 4h after administration of I-123, to investigate the possibility of an organification disturbance.

4.4.2 Toxic multinodular goiter

In patients with tMNG, the I-131 doses for radioiodine therapy calculated with planar scintigraphy were 23% higher compared to quantitative SPECT/CT, probably resulting in an overestimation of the I-131 dose. In only four patients (11.7%), there was no clinical relevant difference in calculated I-131 dose, which is caused by a similar percental increase in both the iodine uptake and the

thyroid volume measured in quantitative SPECT/CT. In three patients (8.8%), planar scintigraphy overestimated the I-131 dose with more than 1200 MBq. Two of these patients had a lower iodine uptake on planar scintigraphy with a percental difference in iodine uptake of 44% and 89%, resulting in a particularly high I-131 dose based on calculations with planar scintigraphy. The third patient had a percental difference in iodine uptake of 24%, but the thyroid volume was overestimated in planar scintigraphy by 85 mL with a percental difference of 37%. These three patients demonstrate the large impact of cumulative errors in iodine uptake and thyroid volume measured in planar scintigraphy on the calculated I-131 dose.

Differences in iodine uptake and thyroid volume between quantitative modalities result in a decrease in calculated I-131 dose in quantitative SPECT/CT for patients with tMNG. The iodine uptake is 46% higher using quantitative SPECT/CT, with a clinically relevant difference in iodine uptake above 15% in thirty-one patients (91%). In eighteen patients (53%), there was a clinical relevant difference in thyroid volume, of which in ten patients the volume was underestimated with planar scintigraphy and in eight patients the volume was overestimated with planar scintigraphy. In patients with tMNG, the measurement of thyroid volume is complicated by the presence of multiple hot nodules within the thyroid, resulting in equal over- and underestimations of thyroid volume in planar scintigraphy. Furthermore, the thyroid depth is not incorporated in volume estimations, resulting in over- or underestimations. Since the iodine uptake is low in tMNG patients in general, small differences in thyroid volume have a large impact on the calculated I-131 dose. Therefore, accurate thyroid volume estimation is important for calculation of I-131 dose in radioiodine therapy for tMNG patients, as well as accurate iodine uptake measurements.

In patients with tMNG, we found that the administered I-131 activity concentration is significantly similar to the desired activity concentration of 7.4 MBq/mL and 59% of patients (n = 20) developed euthyroidism one year after radioiodine therapy. However, we did observe differences in administered I-131 activity concentration, with the hyperthyroidism group receiving the lowest activity concentration and the hypothyroidism group receiving the highest. This suggests that a higher administered I-131 activity concentration is associated with the development of hypothyroidism, and a low activity concentration with persistent hyperthyroidism. However, the patient population was too limited to find a statistical significance in these differences.

Three patients received an I-131 activity concentration far above the desired activity concentration (two received 14 MBq/mL and one 25 MBq/mL), of which two patients developed hypothyroidism within one year after radioiodine therapy. These two patients were overtreated as a result of underestimation of the iodine uptake in planar scintigraphy. The third patient, who developed euthyroidism one year after receiving 14 MBq/mL had a similar iodine uptake in planar

scintigraphy and quantitative SPECT/CT, but the thyroid volume was overestimated by planar scintigraphy by 39% resulting in the high administered I-131 activity concentration. The normal thyroid tissue was completely suppressed in this patient, which explains the preservation of thyroid function. Although the thyroid function one year after therapy was normal, longer follow-up studies are needed to confirm the final thyroid function after radioiodine therapy.

Limitations

A limitation of this study is the relative small patient population per thyroid disease and treatment outcome. More patients should be included to investigate whether administered I-131 activity concentration differs between patients who developed hypothyroidism, euthyroidism, or hyperthyroidism.

Another limitation of this study is that we did not incorporate doubled dosages for patients with a thyroid volume larger than 50 mL, high iodine uptake (80%) or organification disturbances (4h/24h > 0.8). These patients would normally receive a doubled I-131 dose (7.4 MBq/mL instead of 3.7 MBq/mL) when treated with radioiodine therapy, because it is known that these circumstances require higher dosages to cure hyperthyroidism. Future studies should incorporate doubled dosages when indicated, to determine differences in calculated I-131 dose between planar scintigraphy and quantitative SPECT/CT more accurately.

Lastly, we only incorporated follow-up of thyroid function until one year after radioiodine therapy. Follow-up beyond one year was unfortunately not available, because we perform quantitative SPECT/CT only since 2021. In our study, 42% of patients with GD developed hypothyroidism one year after radioiodine therapy while 29% of patients with tMNG developed hypothyroidism after one year. However, according to literature almost 80% of patients with Graves' disease and 32% of patients with tMNG who had radioiodine therapy developed hypothyroidism within 25 years [30,59]. Thyroid function may still decline beyond the one year follow-up. Future research should include longer follow-ups of thyroid function after radioiodine therapy.

4.5 Conclusion

In conclusion, quantitative SPECT/CT enables more accurate measurements of thyroid volume compared to planar scintigraphy. The calculated I-131 doses based on quantitative SPECT/CT are lower than those based on planar scintigraphy, as a result of an increase in measured iodine uptake and more accurate volume measurements in quantitative SPECT/CT. The use of quantitative SPECT/CT for this purpose may be effective in preventing overdosage and hypothyroidism in both GD and tMNG in the future. However, it should be validated in a prospective study, whether this will not lead to undertreatment and persistent hyperthyroidism.

5. General Discussion

In this study, we focused on the accuracy and workflow of planar scintigraphy with I-123 for I-131 dose calculation and developed a quantification workflow for I-131 dose calculation with quantitative SPECT/CT in a phantom study. Furthermore, we performed a patient study in which we compared the quantitative accuracy of planar scintigraphy and quantitative SPECT/CT in I-131 dose calculation and compared the administered I-131 activity concentration to the thyroid function one year after therapy.

The measured iodine uptake was in both Graves' disease (GD) and toxic multinodular goiter (tMNG) higher in quantitative SPECT/CT compared to planar scintigraphy. One of the factors which may reduce the measured iodine uptake in planar scintigraphy is the patient-detector distance. A large patient-detector distance results in less measured counts, which is typically not corrected for. Unfortunately, we did not measure the patient-detector distance in the patient study. Another factor which may reduce the iodine uptake in planar scintigraphy is the lack of corrections. Unlike quantitative SPECT/CT, in planar scintigraphy there are no corrections applied for attenuation, scatter and the partial volume effect. The lack of corrections may contribute to a decrease in measured counts and thus a lower iodine uptake compared to quantitative SPECT/CT. Lastly, an oversized volume-of-interest (VOI) in quantitative SPECT/CT may have resulted in overestimation of the iodine uptake in thyroid volumes above 50 mL. The method for delineation of the VOI in quantitative SPECT/CT was designed to incorporate the spill-out region, but larger sources are less affected by the partial volume effect. We only performed phantom measurements with volumes of maximally 50 mL and did not test delineation in larger volumes. Therefore, the iodine uptake in larger volumes could be overestimated in quantitative SPECT/CT.

We performed visual comparison of planar scintigraphy images performed with the medium energy collimator and low energy collimator in a phantom study and concluded that the use of the medium energy collimator results in less scattering, septal penetration and background noise in the planar scintigraphy image. We did not investigate the quantitative accuracy of planar scintigraphy with the medium energy collimator, but previous studies have shown that measurement of the iodine uptake is feasible with the medium energy collimator [53,54]. It is hypothesized that the use of the medium energy collimator in quantitative SPECT/CT may also result in more accurate iodine uptake measurements. To accurately measure the iodine uptake in quantitative SPECT/CT, incorporation of spill-out around the thyroid was needed with the use of the low energy collimator. The medium energy collimator results in less spill-out because it

measures less (low energy) photons and prevents passage of background noise and scattered photons, which may eliminate the need for incorporation of the spill-out region for an accurate iodine uptake measurement. Future studies should focus on the quantitative accuracy of the medium energy collimator in quantitative SPECT/CT, as we hypothesize this would result in more accurate iodine uptake measurements.

The method for delineation of thyroid volume in our quantification workflow for quantitative SPECT/CT was based on a phantom study and was only tested on patients with GD, because we expected that VOI delineation with the maximum voxel value is the same in patients with tMNG. However, in our patient study we found that the optimal threshold for measuring the thyroid volume in tMNG patients was around 15% of the maximum voxel value instead of 25% found in GD. Earlier we hypothesized that in the case of presence of both extreme hot spots and mild hot spots in tMNG, delineation based on 25% of the maximum voxel value potentially excludes the mild spots, because the voxel value within these mild spots is too low. In the patient study, 15% of the maximum voxel value resulted in the most accurate estimation of thyroid volume. Therefore, delineation of thyroid volume in quantitative SPECT/CT was categorized for a homogeneous radiotracer distribution (around 25%) and inhomogeneous radiotracer distribution (around 15%).

6. General Conclusion

Currently, the use of radioiodine therapy for treatment of benign thyroid diseases such as Graves' disease and toxic multinodular goiter often results in life-impacting complications, such as persistent hyperthyroidism and iatrogenic hypothyroidism. Improvement of the accuracy in I-131 dose calculation may contribute to reducing the occurrence of these serious complications. The aim of this study was to improve the accuracy of I-131 dose calculation with quantitative SPECT/CT, to possibly reduce the incidence of persistent hyperthyroidism and iatrogenic hypothyroidism after radioiodine therapy.

Assessment of the workflow in planar scintigraphy resulted in major changes in the protocol. The calibration factor was stable over time, resulting in a reduction of the frequency of calibration factor measurements from weekly to three times per year after maintenance. Furthermore, the threshold for ROI delineation to measure the iodine uptake was changed, because background noise and scatter was incorporated in the measurement.

In this study, a method was proposed for measurement of the iodine uptake with quantitative SPECT/CT based on a phantom study. Although measurements with quantitative SPECT/CT resulted in higher iodine uptakes compared to planar scintigraphy in the patient study, the workflow for quantitative SPECT/CT should be validated in a larger phantom study which also incorporates phantom volumes larger than 50 mL. Furthermore, future studies should focus on assessing the quantitative accuracy in measuring the iodine uptake with the medium energy collimator in quantitative SPECT/CT.

Thyroid volume estimation was more accurate with quantitative SPECT/CT compared to planar scintigraphy, because delineation of the thyroid volume on SPECT is visually examined on the registered low dose CT. Furthermore, thyroid volume measurements in planar scintigraphy heavily depend on interobserver variability, resulting in a clinically relevant differences in calculated I-131 dose for radioiodine therapy. Thyroid volume should therefore be estimated with quantitative SPECT/CT in the future.

In both patients with GD and tMNG, the administered I-131 activity concentration was generally higher in patients who developed hypothyroidism after radioiodine therapy than in patients who developed euthyroidism or had persistent hyperthyroidism. Lowered I-131 doses calculated with quantitative SPECT/CT may be a first step towards reducing the incidence of the development of hypothyroidism after radioiodine therapy.

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Appendices

A. Additional clinical background

A.1 Thyroid physiology

The thyroid is a butterfly-shaped endocrine gland, located in the inferior part of the anterior neck and in front of the trachea (Figure A.1a) [2]. This endocrine gland produces hormones, which control many bodily functions, such as heart rate, cardiac output, bone growth during childhood, fertility, ovulation, lipolysis or lipid synthesis.

The production of thyroid hormones is regulated by the brain [2]. The hypothalamus releases thyrotropin-releasing hormone (TRH) into the hypothalamic-pituitary portal system. In the pituitary gland, thyrotropin cells are stimulated by TRH to produce thyroid stimulating hormone (TSH). Thyroid stimulating hormone is released in the blood circulation, and binds to the thyroid stimulating hormone receptor (TSH-R) on the follicular cells of the thyroid. Binding of TSH to the TSH-R on the follicular cells induces synthesis of thyroid hormones (Figure A.1b). Thyroglobulin is a protein which is produced in the follicular cells and stored in the colloid (the lumen of the follicle). Iodine, in the form of iodide, is actively taken up from the blood by the Na^+I-symporter (NIS) of the follicular cells [13,23]. Iodide (I^-) is oxidized to create iodine (I^+) under the influence of thyroid peroxidase enzyme (TPO) [23]. Through organification, iodine is linked to thyroglobulin resulting in monoiodotyrosine (MIT) and diiodotyrosine (DIT) [2,23]. Subsequently, MIT and DIT are coupled to create the thyroid hormones triiodothyronine (T3) and tetraiodithyronine (T4) [23]. These hormones are stored in the colloid and coupled to a transporter protein before released in the capillary circulation. The thyroid produces 90% of T4, the inactive thyroid hormone, and 10% of T3, the active thyroid hormone [2]. Once released in the blood circulation, T3 and T4 inhibit the release of TSH from the pituitary gland to achieve homeostasis.

A.2 Hyperthyroidism lab results

Hyperthyroidism is diagnosed biochemically based on the TSH, free T4 (fT4) and sometimes free T3 (fT3) serum levels [1,2]. Free levels of T3 and T4 are measured rather than total T3 and T4 levels, as protein bound thyronine (T3 and T4) cannot enter tissues [2]. Normal serum levels for TSH are between 0.3 – 4.8 mU/L, normal fT4 levels are between 12 – 23 pmol/L, and normal fT3 levels are between 3.5 – 6.5 pmol/L. Hyperthyroidism is characterized by a TSH serum lower than 0.3 mU/L and fT4 serum higher than 23 pmol/L. Subclinical hyperthyroidism is a result of partially suppressed thyroid tissue in toxic adenoma or toxic multinodular goiter, and is characterized by

a low TSH (<0.3 mU/L) but normal fT4 and fT3 levels. Thyroid stimulating immunoglobulin serum levels are used for the diagnosis of Graves' disease, where values above 1 IU/L are indicative of this auto-immune disorder.

A.3 Nuclear imaging in hyperthyroidism

Interpretation of planar scintigraphy is performed by a nuclear medicine specialist [23]. A diffusely increased thyroid uptake is indicative of Graves' disease. In toxic multinodular goiter or toxic adenoma, planar scintigraphy shows a focally increased uptake due to the remaining normal thyroid tissue being suppressed and therefore lacking iodine uptake [23,24]. Normal thyroid tissue has an iodine uptake of 20%, while hyperthyroid tissue usually has an uptake of larger than 20% [23,25]. Hyperthyroidism combined with a reduced thyroid uptake (< 20%) usually indicates thyroiditis. A schematic view on planar scintigraphy images in hyperthyroidism causing diseases is shown in Figure A.2.

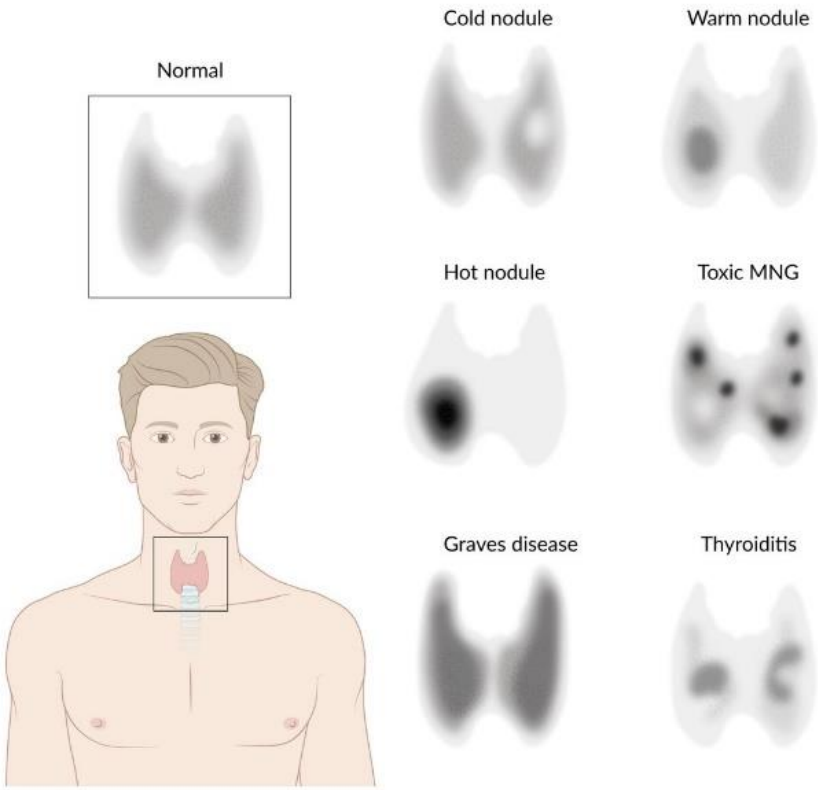

***Figure A.2**: Schematic views of thyroid scintigraphy for several hyperthyroidic diseases* [73].

B. I-131 dose calculation in Hermes

The iodine uptake and volume measurements in planar scintigraphy are performed using HERMES software. The region-of-interest (ROI) is automatically drawn based on the location of measured counts on the planar scintigraphy image. The ROI can be altered manually based on the interpretation of the scintigraphy technician. Accordingly, the thyroid uptake is calculated using Equation (B.1):

$$Thyroid\ uptake = \frac{Thyroid\ counts - Normalized\ background\ counts}{Capsule\ activity\ \cdot Camera\ efficiency} \cdot 100 \qquad (B.1)$$

The thyroid uptake is calculated in %. Thyroid counts are the counts originating from the thyroid and is estimated in counts per second (cps). The normalized background counts are the background counts normalized to the size of ROI drawn for the thyroid, estimated in cps. The capsule activity is the administered I-123 capsule activity after 24h. The calibration factor is calculated in counts per second per MBq cts/s/MBq, using Equation (B.2). The capsule counts are the measured counts originating from the capsule during acquisition. The capsule activity is the known activity after 24h. The acquisition time is determined in seconds (s).

$$Camera\ efficiency = \frac{\frac{Capsule\ counts - Normalized\ background\ counts}{Capsule\ activity}}{Time\ of\ capsule\ acquisition} \qquad (B.2)$$

To estimate the thyroid volume, it is assumed both thyroid lobes are shaped cylindrical and the density of thyroid tissue is 1 g/mL. The scintigraphy technician draws the short axis of the cylinder along the widest part of the thyroid, and the long axis along of the cylinder along the tallest part of the thyroid. The short axis represents the diameter of the cylinder (2 · r), while the long axis represents the height of the cylinder (h). The volumes of both thyroid lobes combined represent the total thyroid volume, which is presented in Hermes in grams (Equation B.3).

$$Thyroid\ volume\ (g) = V_{left\ lobe} + V_{right\ lobe} = (\pi r^2 h)_{left} + (\pi r^2 h)_{right} \qquad (B.3)$$

Patient-specific radioactivity for radioiodine therapy is calculated with Equation (B.4). In this equation, A is the radioactivity in MBq, V is the thyroid volume in mL, U is the radioiodine uptake in the thyroid measured after 24h in %, and k is the conversion factor for the type of thyroid disorder in MBq/mL, which is 3.7 MBq/mL in GD and 7.4 MBq/mL in tMNG.

$$A = \frac{k \cdot V}{U/100} \qquad (B.4)$$

C. Tables

***Table C.1**: The iodine uptake measured using three different threshold (6%, 10%, 11%) for ROI delineation in planar scintigraphy.*

Parameter varying	Measurement nr.	Activity (MBq) (corresponding uptake in patients)	Volume (mL)	Uptake (%) at threshold ROI 6%	Uptake (%) at threshold 10%	Uptake (%) at threshold 11%
Volume	**1**	4.71 (89%)	10	105.74	99.22	98.81
	2	4.54 (86%)	20	104.85	98.79	98.11
	3	4.43 (84%)	30	101.38	95.90	95.21
	4	4.41 (83%)	40	110.04	100.53	99.71
	5	4.29 (81%)	50	108.50	99.15	97.88
Radioactivity (iodine uptake)	**6**	5.46 (100%)	50	111.75	100.06	98.66
	7	4.33 (82%)	50	111.27	101.0	99.38
	8	3.20 (60%)	50	109.36	98.84	97.98
	9	2.46 (47%)	50	106.68	98.47	97.76
	10	1.58 (30%)	50	107.29	99.01	98.18
	11	1.17 (22%)	50	106.80	97.31	96.06
	12	0.68 (13%)	50	105.21	97.51	96.75
Homogeneity	**13**	4.23 (80%)	32	120.25	107.91	107.24

Table C.2: *The differences in thyroid volume on planar scintigraphy between two operators in patients with GD. Difference in calculated I-131 dose is based on an activity concentration of 3.7 MBq/mL and the patient-specific iodine uptake.*

Pt	Thyroid volume (mL) Operator 1	Thyroid volume (mL) Operator 2	Volume difference (mL) (1-2)	I-131 dose difference (MBq)
1	12.45	10.13	2.32	30
2	26.13	24.06	2.07	12
3	21.33	15.80	5.53	90
4	68.75	59.94	8.81	62
5	32.58	21.03	11.55	88
6	24.10	16.96	7.14	57
7	23.02	22.41	0.61	4
8	40.99	24.95	16.04	155
9	20.13	19.71	0.42	2
10	17.95	14.41	3.54	25
11	29.97	21.43	8.54	74
12	24.97	19.35	5.62	44
13	42.42	42.95	-0.53	-3
14	32.70	28.50	4.20	26
15	19.77	20.56	-0.79	-6
16	39.94	29.08	10.86	93
17	21.72	20.38	1.34	11
18	26.42	21.56	4.86	32
19	40.40	35.45	4.95	36
20	28.27	22.89	5.38	51
21	20.11	17.89	2.22	26
22	134.77	150.13	-15.36	-78
23	26.24	19.06	7.18	45
24	20.28	15.21	5.07	27
25	38.41	30.54	7.87	53
26	29.41	20.52	8.89	104
27	102.66	79.85	22.81	127
28	58.89	47.29	11.60	90
29	74.15	61.88	12.27	72
30	67.30	49.24	18.06	106
31	51.43	46.12	5.31	36

Table C.3: *The differences in thyroid volume on planar scintigraphy between two operators in patients with tMNG. Difference in calculated I-131 dose is based on an activity concentration of 7.4 MBq/mL and the patient-specific iodine uptake.*

Pt	Thyroid volume (mL) Operator 1	Thyroid volume (mL) Operator 2	Volume difference (mL) (1-2)	I-131 dose difference (MBq)
1	17.19	17.37	-0.18	-3
2	172.66	116.44	56.22	851
3	41.21	36.80	4.41	236
4	64.31	46.65	17.66	486
5	34.09	48.98	-14.89	-690
6	29.16	20.38	8.78	229
7	70.67	59.82	10.85	217
8	48.11	45.03	3.08	80
9	80.04	77.46	2.58	77
10	19.17	20.33	-1.16	-41
11	25.66	33.82	-8.16	-274
12	169.43	135.05	34.38	830
13	38.87	48.20	-9.33	-371
14	72.79	88.69	-15.9	-648
15	98.12	101.15	-3.03	-87
16	84.76	93.65	-8.89	-153
17	16.26	13.52	2.74	108
18	13.16	20.17	-7.01	-166
19	29.19	37.47	-8.28	-127
20	99.52	130.56	-31.04	-799
21	48.92	52.86	-3.94	-95
22	30.83	27.40	3.43	57
23	7.95	8.53	-0.58	-17
24	38.29	45.23	-6.94	-200
25	49.74	78.44	-28.7	-1384
26	40.78	27.02	13.76	510
27	235.61	228.17	7.44	96
28	93.30	111.09	-17.79	-743
29	18.09	16.69	1.40	39
30	45.97	38.62	7.35	142
31	4.60	4.77	-0.17	-14
32	38.09	44.67	-6.58	-211
33	57.23	50.18	7.05	125
34	27.43	24.61	2.82	84

***Table C.4**: Different thresholds for thyroid volume estimation in quantitative SPECT/CT.*

Measurement nr.	Phantom volume (mL) (Uptake in patient %)	Volume at 20% (mL)	Volume at 22% (mL)	Volume at 25% (mL)	Volume at 27% (mL)	Volume at 30% (mL)
1	10.0 (89)	15.2	14.0	12.7	11.9	10.8
2	20.0 (86)	28.0	26.2	24.3	23.2	21.4
3	30.0 (84)	35.1	33.3	30.6	28.9	26.9
4	40.0 (83)	44.4	41.9	39.0	37.1	34.5
5	50.0 (81)	55.7	52.8	49.1	47.3	43.9
6	50.0 (100)	55.3	52.4	48.8	46.5	42.9
7	50.0 (82)	53.1	50.9	47.3	45.0	41.5
8	50.0 (60)	56.6	53.4	49.3	47.1	43.8
9	50.0 (47)	56.2	53.2	48.6	46.2	42.9
10	50.0 (30)	52.1	49.0	45.7	43.1	39.0
11	50.0 (22)	53.0	50.4	45.4	42.9	40.0
12	50.0 (13)	40.1	38.1	32.8	29.4	24.6
13 (Picker)	35.0 (80)	41.2	38.7	34.3	32.2	29.0

Table C.5: *The differences in planar scintigraphy and quantitative SPECT/CT in terms of iodine uptake, thyroid volume and calculated I-131 dose, with the administered I-131 activity concentration and thyroid function one year after radioiodine therapy in patients with GD. The I-131 dose is calculated with 3.7 MBq/mL.*

Pt	Thyroid function 1y after I-131 therapy	Time between scan and therapy (days)	Activity concentration I-131 (MBq/mL)	Uptake scintigraphy (%)	Uptake SPECT/CT (%)	Volume scintigraphy (mL)	Volume SPECT/CT (mL)	I-131 dose scintigraphy (MBq)	I-131 dose SPECT/CT (MBq)
1	Hypo	7	7.76	28.63	40.00	11.29	7.89	146	73
2	Hypo	12	12.53	61.51	69.00	25.10	18.50	151	99
3	Hyper	19	10.94	22.75	30.20	18.57	10.60	302	130
4	Hypo	47	13.00	52.45	79.10	64.35	58.10	454	272
5	Hyper	7	7.12	48.66	78.30	26.81	25.50	204	120
6	Eu	5	5.20	46.00	52.60	20.53	17.60	165	124
7	Hypo	5	8.35	57.07	63.70	22.72	25.80	147	150
8	Eu	5	4.50	38.26	48.00	32.97	24.00	319	185
9	Hypo	5	4.89	70.92	81.10	19.92	24.20	104	110
10	Eu	5	8.84	51.50	59.30	16.18	10.40	116	65
11	Hypo	5	6.40	42.66	55.30	25.70	19.70	223	132
12	Hyper	56	5.49	47.04	61.90	22.16	20.30	174	121
13	Hyper	5	10.92	59.05	67.80	42.69	25.40	267	139
14	Hypo	5	8.83	59.45	78.60	30.60	21.80	190	103
15	Hyper	12	7.13	48.02	61.50	20.17	16.30	155	98
16	Eu	5	6.86	43.03	50.70	34.51	24.10	297	176
17	Hypo	5	5.18	47.14	57.50	21.05	18.00	165	116
18	Hyper	5	4.46	56.07	65.40	23.99	22.30	158	126
19	Hypo	61	7.45	51.24	76.00	37.93	30.80	274	150
20	Eu	8	4.03	38.93	41.10	25.58	20.20	243	182
21	Hypo	5	5.18	31.77	36.90	19.00	15.80	221	158
22	Hyper	54	4.21	72.41	92.60	142.45	128.10	728	512
23	Hypo	16	6.72	59.67	68.90	22.65	16.10	140	86
24	Hypo	5	9.90	68.63	75.20	17.75	12.00	96	59
25	Eu	5	4.12	54.71	69.50	34.48	31.70	233	169
26	Hypo	5	7.81	31.69	33.30	24.97	12.70	291	141
27	Eu	5	5.62	66.39	84.30	91.26	60.60	509	266
28	Eu	5	9.14	47.79	62.00	53.09	30.60	411	183
29	Hyper	5	3.66	62.80	78.30	68.02	64.80	401	306
30	Eu	5	7.95	63.21	80.50	58.27	39.80	341	183
31	Hyper	5	6.13	54.39	65.70	48.78	69.70	332	393

Table C.6: *The differences in planar scintigraphy and quantitative SPECT/CT in terms of iodine uptake, thyroid volume and calculated I-131 dose, with the administered I-131 activity concentration and thyroid function one year after radioiodine therapy in patients with tMNG. The I-131 dose is calculated with 7.4 MBq/mL.*

Pt	Thyroid function 1y after I-131 therapy	Time between scan and therapy (days)	Activity concentration I-131 (MBq/mL)	Uptake scintigraphy (%)	Uptake SPECT/CT (%)	Volume scintigraphy (mL)	Volume SPECT/CT (mL)	I-131 dose scintigraphy (MBq)	I-131 dose SPECT/CT (MBq)
1	Hypo	5	5.64	45.80	54.70	17.28	26.20	279	354
2	Hyper	5	8.37	48.90	70.60	144.55	170.90	2187	1791
3	Eu	5	4.34	13.80	21.10	39.01	35.60	2092	1249
4	Hypo	25	24.71	26.87	35.70	55.48	28.10	1528	582
5	Hypo	68	11.42	15.98	27.50	41.54	46.90	1923	1262
6	Eu	23	4.73	28.33	36.50	24.77	27.70	647	562
7	Hyper	103	3.14	36.98	55.50	65.25	69.30	1306	924
8	Hypo	103	11.72	28.52	31.40	46.57	36.90	1208	870
9	Eu	75	8.52	24.76	31.90	78.75	63.70	2354	1478
10	Eu	99	11.11	20.86	24.30	19.75	14.90	701	454
11	Hypo	48	10.22	22.04	32.20	29.74	36.50	999	839
12	Eu	229	5.68	30.64	40.70	152.24	149.00	3677	2709
13	Hyper	33	4.94	18.59	47.80	43.54	38.30	1733	593
14	Eu	152	9.28	18.15	34.30	80.74	73.90	3292	1594
15	Eu	82	6.09	25.91	38.00	99.64	111.60	2846	2173
16	Hypo	68	10.20	42.94	56.00	89.21	73.80	1537	975
17	Eu	26	6.18	18.72	26.70	14.89	17.70	589	491
18	Hypo	61	10.32	31.18	39.30	16.67	15.80	396	298
19	Eu	69	7.45	48.31	57.20	33.33	41.30	511	534
20	Eu	48	9.62	28.73	44.70	115.04	98.70	2963	1634
21	Eu	76	12.13	30.56	45.90	50.89	55.30	1232	892
22	Eu	9	4.22	44.84	57.70	29.12	26.00	480	333
23	Eu	33	10.07	25.29	40.00	8.24	15.10	241	279
24	Eu	117	8.76	25.63	33.00	41.76	43.80	1206	982
25	Hypo	41	5.42	15.34	23.90	64.09	92.60	3092	2867
26	Eu	68	8.16	19.96	24.90	33.90	33.70	1257	1002
27	Hyper	27	10.29	57.10	71.70	231.89	146.20	3005	1509
28	Eu	61	4.42	17.73	38.50	102.20	173.40	4265	3333
29	Hypo	33	14.17	26.90	35.60	17.39	25.00	478	520
30	Eu	5	14.16	38.39	41.10	42.30	25.40	815	457
31	Eu	190	11.09	8.82	14.80	4.69	10.50	393	525
32	Eu	117	5.62	23.03	26.00	41.38	34.40	1330	979
33	Hypo	77	10.43	41.71	56.20	53.71	48.50	953	639
34	Eu	30	8.68	24.74	31.70	26.02	27.40	778	640