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ORIGINAL ARTICLE

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Randomised comparison of 1.1 GBq and 3.7 GBq radioiodine to ablate the thyroid in the treatment of low-risk thyroid cancer: a 13-year follow-up

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ABSTRACT

Purpose: The optimal activity of radioiodine (I-131) administered for ablation therapy in papillary and follicular thyroid cancer after thyroidectomy remains unknown in a long-term (> 10 year) follow-up. Some, shorter follow-up studies suggest that activities 1.1 GBq and 3.7 GBq are equally effective. We evaluated the long-term outcomes after radioiodine treatment to extend current knowledge about the optimal ablative dose of I-131.

Methods: One hundred and sixty consecutive adult patients (129 females, 31 males; mean age 46 ± 14 y, range 18–89 y) diagnosed with histologically confirmed differentiated thyroid cancer, were randomised in a prospective, phase III, open-label, single-centre study, to receive either 1.1 GBq or 3.7 GBq of I-131 after thyroidectomy. At randomisation, patients were stratified according to the histologically verified cervical lymph node status and were prepared for ablation using thyroid hormone withdrawal. No uptake in the whole-body scan with I-131 and serum thyroglobulin concentration less than 1 ng/mL at 4–8 months after treatment was considered successful ablation.

Results: Median follow-up time was 13.0 years (mean 11.0 ± 4.8 y; range 0.3–17.1 y). Altogether 81 patients received 1.1 GBq with successful ablation in 45 (56%) patients. In the original study, thirty-six patients (44%) needed one or more extra administrations to replete the ablation. Of these, 4 (8.9%) and 5 (14%) patients relapsed during the follow-up, respectively. Of the 79 patients treated with 3.7 GBq 45 (57%) had successful ablation after one administration of radioiodine and 34 (43%) needed several treatments. Of these, 2 (4.4%) and 9 (26.5%) patients relapsed, respectively. The groups did not differ in the proportion of patients relapsing ($p = .591$).

Conclusion: During follow-up of median 13 years, 3.7 GBq is not superior to 1.1 GBq in the radioiodine treatment after thyroidectomy in papillary and follicular thyroid cancer.

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Introduction

After thyroidectomy, patients diagnosed with papillary or follicular thyroid cancer with high or intermediate risk factors, proceed to a radiation ablation to complete the treatment that intends to a curative outcome [1,2]. Radioiodine (I-131) is used to ablate the thyroid remnant after total or near total thyroidectomy to eradicate and control the disease. There is almost always some thyroid tissue left, and thus, potentially also cancer cells. In addition, some microscopic disease might occur in the logoregional lymph nodes, which have not been surgically removed. Radioiodine ablation also improves the specificity of diagnostic scanning [3,4].

The activity of I-131 administered to ablate thyroid tissue, varies considerably between different centres, typically from 1.1 GBq to 7.4 GBq. This is due to the lack of randomised studies with longer follow-up that indicate the optimal activity [5–11]. Some studies suggest that the success of ablation depends on the thyroid tissue left behind from the thyroidectomy, and the I-131 activity should be scaled according to the state of the disease and to the remaining tissue [12,13]. However, this has not been thoroughly investigated. In some studies, lower activities are considered to lead to a less successful outcome of the ablation [10,14,15]. On the other hand, higher activities cause more toxicity, such as taste and smell disturbances, nausea, sialadenitis, haematological toxicities, secondary malignancies and prolonging the duration of radiation isolation required [3,16–22]. In previous randomised studies, activities 1.1 GBq and 3.7 GBq are equally effective for ablation [18,22–24]. However, these studies have follow-up times less than 10 years, which can be considered relatively short, as patients diagnosed with papillary or follicular thyroid cancer tend to have excellent survival and life expectancy.

The ALARA ('as low as reasonably achievable') principle of radiation protection implies the use of the lowest effective activity [25]. This study was initially designed to compare the successfulness of the lower and the higher activities in the treatment of thyroid ablation after thyroidectomy for cancer within this cohort. Considering the late recurrence rate in thyroid cancer, there is a lack of long-term follow-up data from randomised studies extending over 10 years, it is

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necessary to evaluate the long-term follow-up and survival despite the small cohort size. There is still a need for more research determining the optimal activity of I-131 in ablation after thyroidectomy. This randomised study is the first to investigate the long-term outcome of the ablation using a lower (1.1 GBq) versus a higher (3.7 GBq) activity of I-131 in patients with papillary or follicular thyroid cancer.

Materials and methods

Study population

This prospective, phase III, open-label, single-centre study was conducted from January 2000 to October 2004 in the Department of Radiation Oncology in the Helsinki University Hospital, Comprehensive Cancer Centre, Helsinki, Finland. The design, methodology and primary results after 51 months follow-up have been published before [18]. (NCT00115895 at www.clinicaltrials.gov)

Essentially, adult patients diagnosed with histologically confirmed low risk papillary or follicular thyroid cancer without aggressive histological features who performed designated criteria (total or near total thyroidectomy before radioablation, radical operation, no extrathyroideal extension or distant metastases and excluding pregnant women) were randomised to receive either the lower 1.1. GBq or the higher 3.7 GBq activity of I-131 after thyroidectomy. The subjects were stratified according to the presence or absence of histologically verified cervical lymph node metastases at the randomisation to guarantee the similarity of the two treatment groups. The study participants were prepared for ablation using thyroid hormone withdrawal. In the study, no visually assessed uptake in the I-131-whole body scanning (WBS) nor palpable metastases in clinical evaluation and stimulated thyroglobulin concentration less than one ng/mL together with no detectable thyroglobulin antibodies at four to eight months represented successful ablation. Repeated I-131 activities were administered if serum thyroglobulin level became detectable (rising $>$ 1 ng/mL) or abnormal uptake in WBS or SPECT-CT was presented. Patients representing persistent disease had detectable thyroglobulin levels without proven local, locoregional or metastatic recurrence in the radiological or physical examinations. Local ethics committees approved the study, and it was conducted following the Declaration of Helsinki. Written informed consent was obtained from each participant prior to performing any of the study procedures.

For the present follow-up study, patients' demographics, medical history and clinical characteristics were collected and updated. All laboratory measurements (serum thyroglobulin, TSH and T4v), clinical signs, physical examination and ultrasonography findings were recorded at multiple time points by the end of the year 2017 conducted according to the local monitoring protocol to detect cancer recurrence [26]. The patients underwent total or near-total thyroidectomy and were then referred to the Cancer Centre for radioablation. The treatment activity (1.1 GBq or 3.7 GBq) was determined depending on the randomisation, and repeated radioiodine treatments were administrated if necessary. The success of the ablation was evaluated with WBS after the withdrawal of thyroxin 4 – 8 months later. With no evidence of persistent, recurrent or metastatic disease in clinical, radiological or biological control (undetectable or low TSH-stimulated Tg and negative WBS and ultrasound and releasing clinical examination), the patients underwent to the Department of Endocrinology for further follow-up; annual for five years, clinical examination, serum Tg on T4, neck ultrasound at least every second year with prepared biopsy if necessary. Also, more specific radiological examinations (WBS, MRI, CT) were performed to characterise any suspect observation after primary treatment with adverse finding. After five years of follow-up in the Department of Endocrinology in HUCH, patients were referred for further structured follow-up to the community care. The follow-up ended at local, regional or distant thyroid cancer recurrence. The endpoint of this study was the recurrence-free survival by the end of the year 2017. Figure 1 presents the consort diagram and the treatment groups.

Statistical analysis

In the original study, we estimated that one radioiodine treatment would be successful in 40% of the study participants allocated to the 1,1 GBq group and in 60% of those allocated to the 3,7 GBq group. Using power (1-β) 80%, α .05 and a one-sided T-test, 160 participants were to be recruited to the study. An interim safety analysis was carried out when 80 patients had been evaluated for efficacy; a stopping rule was to be applied if a 50% difference in the success rate was observed in favour of the higher administered activity. The data is presented as numbers and percentages, means with standard deviations (SD) or as median and range. We analysed group differences for continuous and for categorical variables using the Fisher's exact test, chi-square test or Mann–Whitney U-test, with Bonferroni corrections as appropriate. We generated survival curves using Kaplan–Meier's method and assessed differences using the Cox regression test. The association with relapse of thyroid cancer was assessed for relevant control variables, such as given activity, age, gender, histopathology of the tumour, size of the tumour, and lymph node status, by the univariate Cox regression. *p* Value of less than .05 was considered statistically significant. Recurrence-free survival and distant recurrence-free survival in this study is defined as time from ablation to detection of cancer recurrence in the neck area or outside locoregional lymph nodes, by radiological imaging, laboratory results and/or by clinical examination by the end of the year 2017. Overall survival in this study is defined as time from ablation to death from any cause of death by the end of the year 2017. We refrained to build a multivariable model since there were no statistically significant variables to include in the model. Statistical analyses were performed using IBM SPSS Statistics for Macintosh, Version 25.0. Armonk, NY: IBM Corp, released 2017.

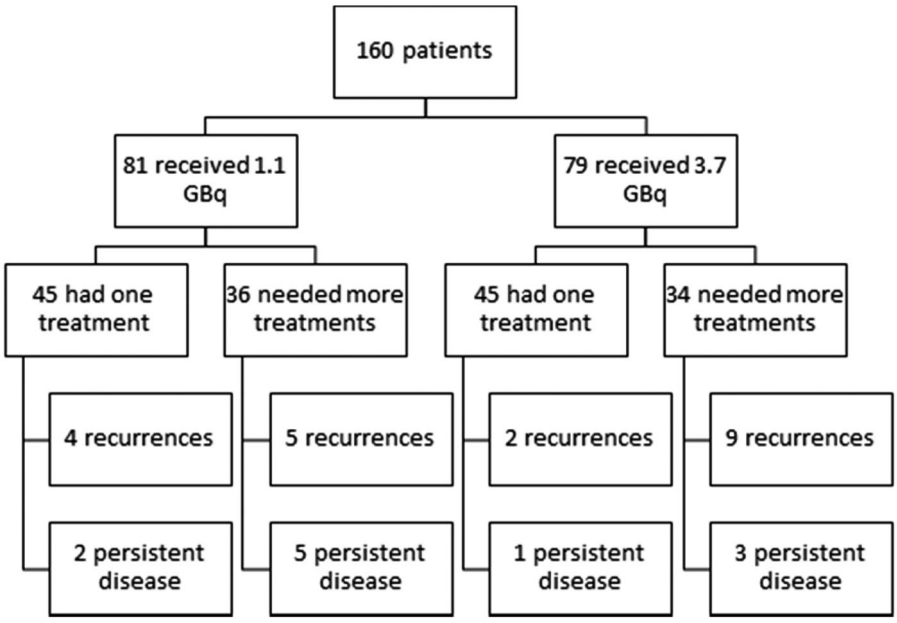

Figure 1. Consort diagram of the low (1.1 GBq) vs. high activity (3.7 GBq) group.

Results

Patients characteristics

One hundred and sixty adult patients (129 (81%) females, 31 (19%) males; mean age 46 ± 14 y, range 18–89 y) were randomised to receive either the lower activity 1.1. GBq ($N = 81$) or the higher activity 3.7 GBq ($N = 79$) of I-131 after thyroidectomy. The lower activity treatment group resembles the higher activity treatment group in all important respects and there were no significant differences between the two treatment groups (Table 1). Median follow-up time was 13.0 years (mean 11.0 ± 4.8 y; range 0.3–17.1 y).

Cancer recurrences by treatment group

Altogether 81 patients were randomised to receive 1.1 GBq of I-131 for ablation. Ablation was successful in 45 (56%) patients after one administration of I-131 and the remaining 36 patients (44%) patients needed one or more extra administrations to complete the ablation (Figure 1). Of the patients with successful ablation after one 1.1 GBq I-131 administration, 4 patients (8.9%) had later recurrence. Of the patients that needed one or more extra administrations of I-131, 5 patients (14%) later relapsed. Biochemically indicated persistent disease occurred in 7 patients. Of the patients with persistent disease, 5 had additional administrations of I-131. Of the 79 patients randomised to receive 3.7 GBq of I-131, 45 (57%) patients had successful ablation after one administration and 34 (43%) patients needed several (maximum of four administrations of I-131) treatments. Of the patients with successful ablation after one single administration, 2 (4.4%) relapsed and of the patients who needed several administrations of 3.7 GBq I-131 9 (26.5%) relapsed during the follow-up. Persistent disease indicated biochemically occurred in 4 patients and three of them had additional treatments. There was no difference between the 1.1 GBq group and 3.7 GBq group in the proportion of patients relapsing ($p = .591$). Persistent disease indicated biochemically by detectable thyroglobulin levels occurred in 7 patients in

Survival and mortality

In our analysis, the recurrence-free survival at the end of the median follow-up time of 13.0 years was 87.5%. Altogether 20 study subjects were diagnosed with thyroid cancer recurrence either as local, regional or metastatic. Of these participants with cancer recurrence, the histology of the primary tumour was papillary thyroid cancer, only one study subject represented follicular histology. With these patients the tumour size ranged from 0.1 cm to 5.0 cm and only two of these patients had primarily positive lymph node status. Local or regional recurrence in the neck area, either in lymph nodes or in the soft tissue, was the most typical recurrence site, in our cohort in 75%, 15 out of 20 patients. Five patients had distant metastases, all of them at least in the lung, one of them had additional locoregional soft tissue metastases in the neck area, and two of them in the lymph nodes. One of these patients with lung and lymph node metastases also had brain metastases. The recurrence free survival and thus follow-up time with these patients ranged from the shortest 10 months to the longest of 12.4 years. Of these participants, 85%, 17 out of 20 patients, were still alive by the end of the follow-up and either in complete remission after later treatments or actively monitored or in treatment because of thyroid cancer.

As shown in Figure 2, there were no differences between the activity groups in survival (Kaplan–Meier survival, log-rank $p = .547$), nor found we any differences between the groups to estimate the survival (Cox regression), Figure 3. We were unable to build a multivariable model that would explain recurrence-free survival.

Table 1. Baseline patient characteristics.

	1.1 GBq N = 81	*3.7 GBq N = 79*
Age (years)		
Median	49	45
Range	23–79	18–89
Gender		
Female	65 (80%)	64 (81%)
Male	16 (20%)	15 (19%)
Initial Thyroglobulin		
$<$ 1 ng/mL	28 (35 %)	20 (37 %)
$\geq$ 1ng/mL	52 (65 %)	47 (59 %)
Not available	0 (0 %)	3 (4 %)
Histology		
Papillary	74	72
Follicular	4	7
Both	3	0
Tumour size (cm)		
Median	1.6	1.7
1st quartile	1.0	1.2
3rd quartile	2.5	2.5
Not available	2	1
Multifocality		
Yes	23 (31 %)	29 (37 %)
No	56 (69 %)	50 (63 %)
T-stage		
T1	51 (63 %)	51 (65 %)
T2	20 (25 %)	20 (25 %)
T3	8 (10 %)	7 (9 %)
Lymph node status		
Nx*	76	72
N1	5	7
I-131 treatment		
One administration	45	45
$>$1 administration	36	34
Repeated activities		
Median activity	3.7 GBq	3.7 GBq
1st Q	1.1 GBq	3.7 GBq
3rd Q	4.18 GBq	7.4 GBq
Recurrence		
After ablation	4	2
After additional administration(s)	5	9
Recurrence site		
Local/locoregional	8	7
Distant	1	4
Persistent disease		
After ablation	2	1
After additional administration(s)	5	3
Death		
Competing causes	7	2
Thyroid cancer	0	3

*No routine lymphadenectomy, clinical N0.

The overall mortality rate was 7.5%, 12 out of 160 participants. Of the participants, three (1.9%) died from thyroid cancer during the follow-up. All of these three patients received the higher, 3.7 GBq activity. These study subjects had recurrence free-time and thus follow-up-time of 0.3, 3.4 and 4.6 years. According to the records, after the detected cancer recurrence, these three patients received multiple new radioiodine treatments, external beam radiation therapy and chemotherapies to treat the metastatic disease locally and systematically before proceeding to the best supportive care. Nine study subjects died of other causes not related to thyroid cancer.

Discussion

Comparison of the two activities of radioiodine with median follow-up of 13 years brings the evidence of the lower activities representing equal effectiveness in ablation of the thyroid remnant into light. Previous studies debate on the optimal effective activity but have not yet established comprehensive suggestions about it in requisite follow-up. Mazzaferri and Jhiang have shown that thyroid cancer can recur even up to 30 years after radioiodine ablation. Thus in previous studies, the follow-up has been insufficient to make definite conclusions about the optimal use of I-131 [11,27–32]. There are two prior randomised studies comparing the two activities with a more significant number of patients but shorter follow-up concluding similar results to us. In the first study with cohort size of 752 patients and follow-up of 8.3 ± 1.6 months showed no significant differences between the lower or, the higher activities [23]. In the second randomised trial, there were 438 patients with median follow-up of 6.5 years resulting in no differences in the recurrence rate between the patients in the lower or higher activity group [22,24]. Our study presents for the first time a long-term outcome of using a low vs. a high activity of I-131 to accomplish thyroid remnant ablation with the measured endpoint of recurrence-free survival.

The lack of generally accepted definition for success of ablation is a recognised issue in various studies and does not stand for an endpoint when reporting the outcomes [32,33]. Because of strict criteria for successful ablation (serum thyroglobulin $<$1 ng/ml and no 131-I uptake) in our cohort study, the results may show lower rate for success of ablation with a single administration of I-131 (overall 44%) compared to other studies [22,23]. Nonetheless, other study groups using slightly different criteria (normal ultrasound of the neck, negative WBS, recombinant human thyrotropin-stimulated serum thyroglobulin $\leq$1 ng/ml or detectable antithyroglobulin antibody if control I-131 WBS was normal, serum thyroglobulin less than 2.0 ng/ml on thyroxin) reported similar findings as represented in this work considering the ablative activity of I-131 [22,23,28]. There are also some difficulties to identify true relapses from persistent disease after initial treatment, since it is not always definite whether a recurrence occurs due to persistent disease after incomplete therapy or not. Therefore, in our study, patients with recurrence truly represent a relapse of thyroid cancer after radioablation with or without additional administrations of I-131.

To eradicate and control papillary or follicular thyroid cancer remnant, radioiodine ablation is the standard procedure after total or subtotal thyroidectomy for high and intermediate risk patients based on current clinical practice guidelines and statements [2,34,35]. These global guidelines describe indications for ablative treatment after thyroidectomy based on risk stratification that have been adjusted on the basis of patient and tumour risk factors. They were not applicable during patient recruitment of our study in 2000–2004. In our study ablation was indicated if papillary or follicular thyroid cancer was more than 10 mm in diameter and the patient was fit for treatment according to the EANM guidelines [36]. Thus, the analysis from our study subjects provide the stated result regardless of current American thyroid Association

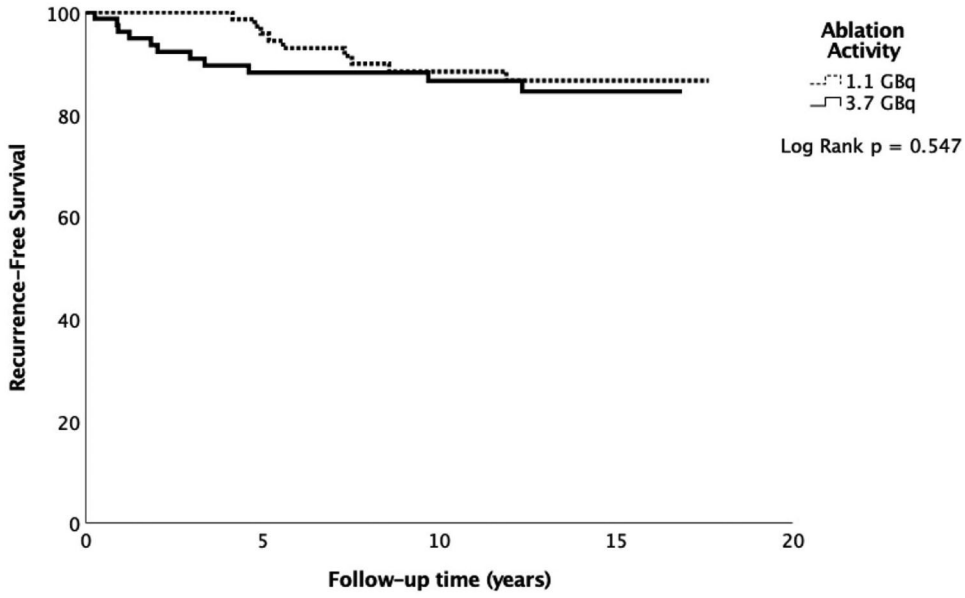

Figure 2. 13-year recurrence-free analysis – a Kaplan–Meier's curve in recurrence-free survival.

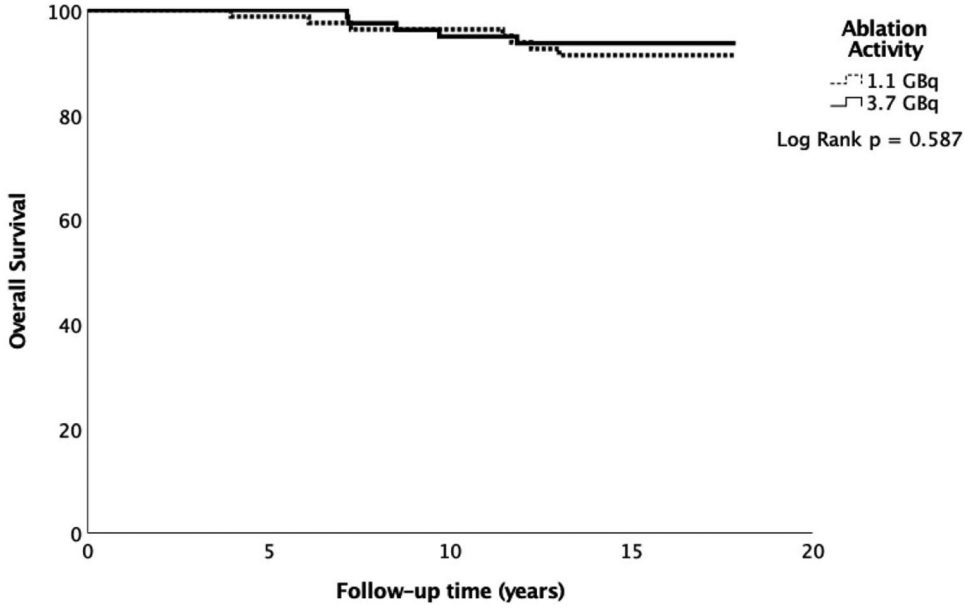

Figure 3. Overall survival – a Kaplan-Meier's curve in overall survival, time from primary treatment to death of any cause or end of follow-up at the end of year 2017.

(ATA) and European Thyroid Association (ETA) risk stratification and risk groups.

The recent trend to expose patients to lower activities of I-131 by recognising the patient and tumour risk-factors, apprehending the impact of underlying gene mutations in a tumour and the role of immune system requires a new mindset in clinical practice. The low-risk patients have a natural tendency to recur extremely rarely, hence, the risk-adapted approach in many centres is to leave these patients entirely without radioablation [37]. Contrarily, some study groups recommend treating low-risk patients with at least 3.7 GBq after thyroidectomy when contemplating treatment in the light of less aggressive surgery and in the absence of long-term studies sustaining evidence to change below this activity with excellent results [10,31]. For intermediate and high-risk patients, the higher 3.7 GBq dose is suggested almost concertedly. Previously, national guidelines and study groups have assimilated the suggestion that regardless of the features of a tumour and despite the possible side-effects, higher-risk patients should be exposed to higher activities for successful ablation because of no data suggesting otherwise [10,14,31]. Currently, ATA and ETA guidelines and research groups increasingly support the use of lower activities and rationalising radioablation in a case of low-risk patient [2,19,34,35]. When deciding the radioiodine activity, the discrepancy in clinical practice and decision making is likely due to important methodological differences and lack of uniform evidence in the various studies. As our study

finds, the low-dose is equally effective for all patients on the groups studied here. Our findings then help to reframe the optimal I-131 activity.

Furthermore, the question of the appropriate I-131 activity is answered by the radiation protection principles, which requires us to use the lowest effective activity [25]. Quantifying the benefits and harms of radioablation in previous studies with comprehensive overview of side-effects, the higher activity represents more toxic dose to patients along with higher costs [14,18–21,38–40]. With current increasing computational capabilities and imaging techniques in everyday use, such as WBS, SPECT-CT and in some centres I-124-PET-CT/MRI-imaging, it is probably feasible in the near future to demonstrate dosimetry calculations and provide estimations of the lowest possible activity needed for successful ablation for individual patients [7,41]. Dosimetry studies could help to quantify as well as verify possible associations in response and side effects in relation to the administrated I-131 and absorbed radiation dose distribution in tumour and healthy tissues such as salivary glands. Also, despite the not yet fully understood phenomenon of thyroid stunning, some studies utilising dosimetry, suggest that along with other factors, the therapeutic activity of I-131 itself might affect to the thyroid tissue uptake and washout. Still, higher activities correlate with lower effective half-life and fractional uptake [42–45]. With imaging methods, we are able to detect patients without I-131 uptake in (macroscopic) malignant lesions and patients with disease progression regardless of significant I-131 uptake [2]. Detecting recurrence or metastases early enough to provide efficient treatment, including surgery, I-131, external beam radiation therapy and tyrosine kinase inhibitors, is naturally of major importance in treating thyroid cancer.

Strengths and limitations

The central issue in treating thyroid cancer with I-131 is the believed association between the thyroid tissue left behind from surgery or the high-risk factors of a tumour and I-131 dose response. In this study, there was no assessment on how much thyroid tissue was left in the patients after surgery, and thus whether there happened to be a difference in this factor between the two groups. However, the patients enrolled in this study underwent the same evaluation protocol to manage the thyroid cancer before the randomisation and thus, the groups should not have differed on this matter. According to the national guidelines, the lymph node dissection was not routinely done in the primary operation. Three deaths occurred during the follow-up in this study population, all in the higher activity group. The size of our cohort is rather small, but the risk factors were studied, and outcome was adequately considered in order to scrutinise the possible differences between the lower and the higher activities as presented in previous publication [18]. Besides, the effects of treatment were measured using strict, objective and validated methods, such as ultrasonography, WBS and single-photon emission computed tomography (SPECT-CT) and stimulated thyroglobulin values in both the treatment groups using the same procedure. This prospective randomised study is a second analysis of the original study and thus underpowered for survival and not able to provide enough evidence to explicitly answer the question of the optimal activity by observing cancer recurrences during the follow-up. Nevertheless, the nature of this research design allows the conclusion regarding the outcome among the variables of interest to achieve increasing knowledge about the optimal I-131 activity to be chosen for the best course of action for our patients.

Conclusion

In this randomised study with median follow-up of 13 years, no difference between the low (1.1 GBq) and the high (3.7 GBq) radioiodine activities was detected in the recurrence-free-survival in low-risk papillary and follicular thyroid cancer. Long-term follow-up is essential before any conclusions because relapses can occur late, even after 10 years. There is a need for more evidence and further investigation regarding ablation treatment approaches and strategies before determining and establishing the appropriate activity for I-131 to ablate the thyroid cancer and remnant. Finally, we conclude that by comparing the two most used activities in radioablation with an adequate follow-up time, the higher activity was not superior to the lower activity in the effectiveness of ablation in a long-term follow-up for low-risk thyroid cancer patients. The interpretation of this study represents a step towards clinically significant implication for truly developing practices.

Disclosure statement

Author Veera Ahtiainen has received research grant from Helsinki University Hospital, Comprehensive Cancer Centre, 9 753,57 €(project code Y1018XHM10). No other conflict of interest to declare from any of the authors.

Ethical approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. This study does not contain any studies with animals performed by any of the authors. Informed consent was obtained from all individual participants included in the study.

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