Randomized clinical multicenter trial of small thyroid cancers treated with hemi-thyroidectomy or radiofrequency ablation
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1. List of abbreviations

AS: active surveillance

CRF: case report form

FNAB: fine needle aspiration biopsy

GDPR: general data protection regulation

hypoT: hypothyroidism

HT: hemi-thyroidectomy

RFA: radiofrequency ablation

PET: positron emission tomography

QoL: quality of life

RLN: Recurrent laryngeal nerve

US: ultrasonography

V-RQoL: voice-related quality of life

2 Brief project description

The general metabolism is regulated throughout life by the thyroid gland. The thyroid hormones are essential to all organs and bodily functions. Commonly, the thyroid gland is affected by various diseases and occasionally surgical treatment is needed. In Denmark, the most common operative procedure on the thyroid gland is a hemi-thyroidectomy (HT) with removal of half of the gland. This operation may decrease the thyroid hormones to a degree where the metabolism is negatively affected. Accordingly, many patients with a previous thyroid operation need to take medication daily for the rest of their life.

For patients with small thyroid cancers, the long-term outcome after HT is of specific concern. When thyroid cancers are below 2 cm and there are no signs of dissemination, there patient has a very good prognosis without any significant disease-specific mortality. In these patients, the risk of adverse outcome from a HT should be carefully evaluated. A new possible treatment modality is with radiofrequency ablation (RFA) of the suspected tumor. With RFA, the patient can be treated in local anesthesia. Only the tumor and a small rim of normal tissue is ablated under guidance from ultrasonography. The remaining thyroid is not affected by this treatment. Accordingly, hypothyroidism (hypoT) is very rare after RFA treatments.

In this prospective study, we will include patients with small thyroid cancers or suspicious nodules in a multicenter prospective randomized controlled trial. Patients are included after informed consent and randomized to one of two treatments. One treatment is a standard HT and the second treatment is RFA of the specific tumor. We will evaluate initial outcome of the allocated treatment, thyroid hormonal function, oncologic safety, quality of life (QoL), and treatment costs in a follow-up period of five years after treatment.

3. Lay project description

The metabolism is partially regulated throughout life by the thyroid gland on the neck. The thyroid hormones are essential to all organs and bodily functions. After surgery on the thyroid gland, the thyroid hormones may decrease to a degree where metabolism is negatively affected. Accordingly, many patients with a previous thyroid operation need to take medication daily for the rest of their life. Cancer in the thyroid gland is treated with surgery and small cancers can be treated with a removal of half the gland – a hemithyroidectomy. Even though this is a good operation to cure the cancer, there are side effects of the operation.

In this clinical study we wish to investigate if we can introduce a less invasive treatment for patients with a small cancer in the thyroid gland and hence, minimize the side effects of a treatment. We will include patients with small cancers in the thyroid gland and randomize to one of two treatments. One treatment is a standard resection of half of the thyroid gland and the second treatment is an ablation of the specific tumor (radiofrequency ablation). Patients are followed in a five-year period after treatment.

4. Purpose

The overall purpose of the study is to improve patient's health by reducing the number of operations on small thyroid cancers. In patients with these small tumors, the long-term adverse outcome may be higher than possible benefits from the operation. Accordingly, we will include patients with low-risk thyroid cancers and a need for treatment. These patients are randomized to either standard treatment with HT or the experimental treatment with RFA. For patients undergoing surgical treatment with HT, we will register final histology and both beneficial and adverse outcomes from the operation. For patients undergoing RFA, we will hopefully have reduced need for thyroid hormonal substitutions, reduced surgical adverse outcomes, reduced treatment costs and better QoL without a reduction in oncologic safety and outcome.

5. Background

Small nodules in the thyroid gland are very common and seen in more than one third of the

population after the age of 50. With increasing use of various scans, we identify an increasing amount of asymptomatic thyroid nodules [1]. The vast majority of these thyroid incidentalomas are benign. However, with clinical investigation, we identify an increasing number of small thyroid cancers and a fraction of indeterminate or suspicious tumors. Internationally this increase in thyroid cancer incidence have developed across countries around the world. More and more cancers are identified and treated without any change in the general low mortality after thyroid cancer treatment [1]. Currently, guidelines have altered recommendations from total thyroidectomy in all patients to unilateral (hemi) thyroidectomy in patients with small cancers [1]. Without a change in mortality, other long-term complications are increasingly important. There are several long-term complications seen after thyroid operations. This includes hypothyroidism (hypoT) in about 20% after a unilateral operation [2], risk of nerve damage and voice changes, scar tissue on the neck, and short-term risks with bleeding and infection. Further, the treatment costs are also relevant, and operations are most commonly performed with an overnight stay at the Hospital and follow-up in the outpatient clinic.

New minimal invasive treatments with radiofrequency ablation (RFA) of the thyroid nodule can now be offered for some patients. In benign thyroid nodules, RFA treatment effectively reduces volume and symptoms and improves quality of life [34]. Internationally, RFA are now also a possible treatment in patients with small localized thyroid cancers. The thermal ablation of small cancers offers a 93% volume reduction rate after one year in 468 patients [5]. Further, the risk of complications is much lower than after HT and hypoT is rarely seen [6]. The RFA costs are much lower than operation costs and this treatment also has an excellent cosmetic result. The main issue with RFA is uncertainty about the oncologic outcome with lack of large studies and randomized trials. One recent study with a 5-year follow-up showed good results after RFA compared to surgery [7]. Another study with 414 patients described lymph node metastasis in 1% and recurrence in 2.4% after 24 to 69 months' follow-up [8]. Collectively, these initial data from RFA treatment and follow-up in patients with small thyroid cancers are indeed convincing. There are no randomized controlled trials comparing different treatment modalities, but the number of well-treated patients assure the overall potential and safety of RFA treatments. We have successfully introduced RFA in Denmark for benign thyroid nodules with high success rate and are now expanding indications for this treatment. With mounting evidence on both short-term safety and

efficacy of RFA for these small cancers, RFA may be the optimal minimal treatment for relevant and selected patients with small thyroid cancers.

6. Aims

We aim to perform a randomized clinical multicenter trial with inclusion of patients with small thyroid cancers. Outcomes are described in detail under Methods. Primary outcome: uncomplicated surgical treatment. Secondary outcomes include: oncologic safety, endocrinological results, patient reported outcomes, and health economics.

7. Methods

7.1. Trial design

This is a multi-center, 1:1 randomized, stratified, parallel-group, non-inferiority clinical trial.

7.2 Study setting

Two Danish sites will include patients in the trial, Department of Otorhinolaryngology, Aarhus University Hospital and Department of Otorhinolaryngology, Copenhagen University Hospital, Rigshospitalet. Both centers are tertiary referral hospitals.

7.3 Study population

The patients will be screened in the outpatient clinics by the site investigators.

The inclusion criteria are:

- age of 30 years or older AND
- single tumor in the thyroid gland, with a FNAB suspicious of cancer or diagnostic of cancer (category V or VI in the Bethesda system) AND
- tumor size of less than 2 cm in all dimensions.

Exclusion criteria are:

- suspicion of disseminated disease because of PET-positive lymph nodes; suspect lymph-nodes by ultrasonography (US); or signs of capsular invasion of the tumor OR

- tumor not eligible for RFA treatment because of high-risk location; previous thyroid surgery; concomitant hyperparathyroidism (ionized calcium > 1.32 mmol/L and PTH > 6 pmol//L) OR
- if the patient is pregnant OR
- If the patient is unable to give informed consent.

7.4 Screening log and collection of data without consent from the patient

From study initiation, a screening log will be updated in RedCap. In the out-patient clinic the daily patient lists will be screened by an investigator who is also a clinician at the including site. Patients who have been referred to and examined in the clinic due to suspicion of cancer in the thyroid gland will be screened further in their medical records. From the medical records information on the patient age, the results of the FNAB and the description of the US scan will be passed on to the project. If the patient fulfills the inclusion criteria, they will be added to the screening log with a screening number and the cause(s) for exclusion will be noted. The screening log will not contain sensitive personal information (such as name or personal identification number). We expect 120 patients to be screened in order to include 88 patients in the trial.

7.5 Informed consent and inclusion

The site investigator performing the screening and updating the screening log will identify possible eligible patients. In the out-patient clinic, the investigator will contact the eligible patient and be responsible to provide information orally, provide the written trial information and ensure correct informed consent is obtained before randomization. The oral information will be provided in an undisturbed environment, the patient is informed of the rights to have an assessor and will be given time to consider the participation (24 hours), and the consent is obtained the day after the consultation in the out-patient clinic.

The patient will be orally and written informed, that by giving consent the trial manager and the overseeing authorities will have direct access to health-related data from the medical journals to complete, monitor and control the trial. The control of the trial covers the steering committee's self-monitoring, quality control and external monitoring. The precise data registered are specified in section *7.14 Data collection.*

7.6 Interventions

The standard treatment is HT. Operations with HT must be performed by a specialist in thyroid surgery and at least 2 years of experience with thyroid cancer surgery, which resembles the current clinical recommendations. Timing of the treatment should not exceed current Danish cancer treatment guidelines.

The experimental treatment with RFA can only be performed by an experienced surgeon with at least 2 years of RFA experience. The treatment is performed in the out-patient clinic and in local anesthesia. Guided by US the surgeon places an RFA-electrode in the tumor. An electrical current will pass through the tissue, causing heat and eventually cell death. The treatment is completed after approximately 30 minutes. After an uneventful observation in at least 1 hour, the patient can leave the hospital.

7.7 Risks and adverse effects

The risks of the standard treatment of HT are: hypothyroidism with the need for hormonal supplemental treatment; short- or long-term laryngeal nerve palsy, causing an altered voice; post-surgical bleeding with the need for re-surgery; and post-surgical infection with possible need for re-surgery. All patients undergoing surgery will have a scar on the front of the neck.

Regarding the experimental treatment of RFA, the risks are: local redness and swelling lasting days after the treatment; bleeding in the glandule that may cause the need for surgery, in which case HT will be performed.

There are no additional risks or side effects to participating in the project. The patients will attend an extra follow-up in the out-patient clinic 3 months after treatment, and there will be extra blood samples at the follow-up visits. These extra visits and examinations can be assessed by the patients negatively because of extra time spent, but also positively due to the increased attention and care offered.

7.8 Outcomes

We anticipate no difference between groups in disease specific mortality. Accordingly, the only oncologic outcomes of relevance are risk of recurrence of disease in lymph nodes or in the thyroid

gland. However, such oncologic outcomes are not expected with a high frequency and will only be included and evaluated as secondary outcomes after initial treatment (see oncologic endpoints).

7.8.1 Primary endpoint

The primary outcome is a composite outcome of an uncomplicated initial treatment within the first month after randomization. There is an uncomplicated treatment, if none of the following occurs: 1) short or long-term affection of the recurrent laryngeal nerve (RLN) based on laryngoscopy, 2) infection with a need for surgical treatment, 3) capsule rupture after RFA or bleeding with a need for operation, 4) prolonged hospital stay (more than one night), nor 5) any other reason for a secondary surgical intervention on the neck after initial treatment within the first month.

7.8.2 Secondary endpoints

The secondary endpoints include 1) oncologic, 2) endocrinological, 3) patient reported outcomes, and 4) health economics.

Any oncologic events with either recurrence of disease in the thyroid gland or lymph node metastasis are included. Developing disease in the contralateral side of the thyroid gland will also be described and evaluated and possibly treated. However, contralateral disease will not be classified as adverse outcome after initial treatment but rather classified as new disease. Size and morphology of the thyroid tumor will be evaluated after RFA by US at all follow-up examinations. All patients will have US of lymph nodes and the contralateral thyroid gland at every visit.

Thyroid hormones are evaluated by biochemical measurements at inclusion, after three months and annually. Potential need for treatment with thyroid hormones is included as secondary endpoint.

The patient-reported outcomes are collected with the thyroid specific questionnaire ThyPRO-39 and voice related QoL (V-RQoL). The questionnaires are fulfilled at inclusion, after three months at 1 and 5 years after randomization.

Collective costs for treatment with a HT operation in general anesthesia and an in-hospital stay is much more expensive than RFA treatment in the outpatient clinic. The relation between total

costs for HT versus RFA are close to 5:1 and all treatment related costs will be collected during the trial.

7.9 Follow-up

Follow-up is in the out-patient clinic after 3, 6 and 12 months the first year and annually in a total of 5 years after treatment. This follow-up period resembles the recommendation in the clinical guidelines except for an extra visit at 3 months for the trial participants. All patients will have US performed of lymph nodes and the contralateral thyroid gland at every visit. The participating patients will be followed with two questionnaires at 3 months, year 1,3, and 5 and with a blood sample at 3 months and yearly in the follow-up period. Blood samples and questionnaires are additional examinations for the patients in the project.

In case of suspicion of adverse outcome (lymph node metastasis or cancer recurrence), needle biopsy or surgical removal are recommended to acquire a diagnose of any cancer recurrence. Preferably, all controls are performed by one of the investigators.

All patients included will have the possibility to contact the outpatient clinic throughout the follow-up period.

7.10 Allocation

After inclusion, patients are randomized 1:1 to either RFA or HT. Randomization will be web based. An allocation sequence list with stratification according to study site and age (below 60 years of age or 60 years and older) and varying block sizes is created by RedCap. The list is kept concealed for the investigators. Each patient will be allocated a unique patient-screening number.

7.11 Blinding

It is not possible to blind the assigned treatment for the participants, trial investigators, other care providers or outcome assessors of the primary outcome, because of the choice of intervention and comparator. The intervention of RFA will be performed in the out-patient clinic, with the patient awake, and the assessment of the outcome is a clinical evaluation with US of a patient, who is well aware of the assigned treatment. We plan that the statistician performing the primary analysis is blinded for the treatment assignment.

7.12 Sample size

Primary endpoint: We anticipate a true difference of 6% in the risk of the composite endpoint of adverse outcome after initial treatment with either HT (7%) or RFA (1%). The composite endpoint includes: 1) short or long-term affection of the RLN, 2) infection with a need for surgical treatment, 3) capsule rupture after RFA or bleeding with a need for operation, 4) prolonged hospital stay (more than one night), or 5) any other reason for a secondary surgical intervention on the neck after initial treatment within the first month.

With a significance level of 5% and a power of 80% we will have to include 78 patients (39 in each arm) to exclude a difference in favor of the standard group of more than 5% (absolute risk difference). With a 10% drop out, we will have to include 88 patients in the trial.

Secondary endpoints: We anticipate a 3% rate of adverse oncologic outcome with either cancer recurrence or lymph node metastasis after HT. Further, we anticipate that any adverse oncologic outcome is truly with no difference between groups. With a significance level of 5% and a power of 80% we will have to include 72 patients (36 in each arm) to exclude a difference in favor of the standard group of more than 10%.

For evaluation of hypoT there is an estimated risk of 20% after HT and 0% after RFA. To evaluate this with a 95% confidence level and a power of 80% and a significance of 5% we need to include 68 patients (34 in each arm). HypoT is also estimated to affect QoL. Further, treatment costs will be markedly higher after HT than RFA treatment. Evaluation of these secondary endpoints were not included in power calculations.

7.13 Recruitment

According to local experience and unpublished data, we expect to see 30-40 eligible patients per year at each site. Hence, we find it feasible to anticipate a total of 30 patients per year during the trial enrollment period at the two sites combined.

To ensure adequate enrolment we will ensure thorough implementation of the trial protocol at the two sites, and we plan continuously to educate and update the fellow colleagues, to ensure all eligible patients will be screened.

7.14 Data collection

At inclusion baseline data is collected from the patient's medical records, US scan, questionnaires and biochemical measurements and collected in the electronic case report form (CRF) in RedCap. The data includes: basic patient characteristics (age, gender, height, weight, comorbidities); site of inclusion; tumor description by US (location, size in three dimensions); FNAB results; QoL (ThyPRO-39 and V-RQoL questionnaires); thyroid hormones (TSH, T3, T4); additional biochemistry (Calcitonine, PTH, calcium, creatinine, eGFR, hemoglobin). The amount of blood drawn for analysis is approximately 15 mL.

At every follow-up visit data is collected regarding clinical examination, pathology reports and US. Additionally, during the follow-up visits at 3 months, year 1, 3 and 5 data is collected with questionnaires. At 3 months and yearly data on thyroid hormones are obtained through a blood sample. The amount of blood drawn for analysis at follow-up visits is.3,5 to 11 mL.

All blood samples are destroyed after a maximum of 2 days.

Survival status is collected from the patient's medical journal and registered at 1 and 5 years. All data is registered in the CRF.

7.15 Participant withdrawal

If a patient wishes to withdraw their consent to continue in the trial, they are allowed to do so at all times. The withdraw can include the following:

a) Withdrawal from the intervention and follow up, but we may continue with data registration.

b) Withdrawal from the intervention, follow up, and further data registration, but we may use the already obtained and registered data.

c) Withdrawal from the intervention, follow up and further data registration, and the patient does not wish the registered data to be used.

If a patient wishes to be completely deleted from the records (scenario c), a new patient will be randomized to obtain full sample size.

8. Statistical methods and safety

8.1 Statistical methods

The primary analysis will be an intention-to-treat analysis comparing various outcomes at 1 year between the two treatment groups. We will use a chi-square test and multiple logistic regression with both unadjusted analyses and analyses adjusted for the trial and patient variables (stratification variables, comorbidity, or renal function).

8.2 Data monitoring

One investigator (LR) will be primary investigator (PI) and responsible for outcome data collection, update of screening log, and analysis of adverse events. For each including hospital, there will be one investigator responsible for the oncologic safety for patients in the study (LR and CH) and one investigator responsible for data collection (SR and MK).

The monitoring will take place annually during the inclusion period and include the following issues: documentation of informed consent, CRF completed according to the protocol and the screening and inclusion strategy at the site.

8.3 Data safety and monitoring committee

A monitoring committee will include the Trial Steering Committee (LR, SR, MK and CH) and two independent external supervisors (JM and SB). This committee will oversee the safety of the trial. They will perform and interpret the interim analysis and perform an annual safety evaluation for all included patients. In case of unsuspected and significant high frequency of adverse outcome in the experimental group, the study can be terminated prematurely by the safety committee.

8.4 Interim analysis

An interim analysis will be performed annually. The analysis will include number of patients included, adverse outcomes, and oncologic outcomes. Criteria for ending the trial are findings of statistically higher frequency of adverse outcomes or oncologic outcomes in the experimental group. The analysis will be discussed in the safety committee (7.16) and with all members of the study.

8.5 Treatment quality

Patients can only be treated with RFA by an experienced surgeon with at least 2 years of RFA experience. Further, all treatments of thyroid cancers are centralized to one of the University Hospitals with long experience in treatments of various thyroid cancers. Operations with HT must be performed by a specialist in neck surgery and at least 2 years of experience with thyroid cancer surgery. Timing of the treatment should not exceed current Danish cancer treatment recommendations. Preferably, all controls after treatment are performed by one of the investigators. In case of suspicion of adverse outcome (lymph node metastasis or cancer recurrence), needle biopsy or surgical removal are recommended to acquire a diagnose of any cancer recurrence. Patients are insured similar to all other patients under clinical treatment. Finally, all included patients will have the possibility to contact the outpatient clinic throughout the follow-up period.

8.6 End of study

We aim to have long-term follow-up of at least 88 patients. We will continue to include patients in the study until 88 patients have completed the one-year follow-up. In case of unsuspected and significant high frequency of adverse outcome in the experimental group, the study can be terminated prematurely as described.

9 Ethics and dissemination

9.1 General ethical considerations

The mortality is very low for patients with single, small, well-differentiated thyroid cancers, and the general concern is that the current treatment of HT is causing more harm than the cancer. With the current trial we can introduce a minimal invasive treatment for cancer. With RFA the cancer is not removed, but the cancer is made inactive and at the same time the function of the thyroid gland is preserved. The trial is designed to ensure equal care to all patients despite treatment arm and to ensure timely and adequate additional treatment if needed by the close and detailed follow-up of all trial participants.

9.2 Research ethics approval

We will apply for ethics approval from the local ethics committee. The project will be carried out in accordance with the rules of the Helsinki Declaration II. We will follow the Danish Data protection Legislation, the General Data Protection Regulations (GDPR) and regulations from Danish Research Ethics Committees. Finally, the study has been registered at www.clinicaltrials.gov (NCT06796348).

9.3 Patients' rights

The participants of the project will be able to complaint and apply for a compensation according to the Danish Patient Compensation Act. The participants can apply on patienterstatningen.dk.

9.4 Protocol deviations and amendments

The protocol is completed according to the SPIRIT 2013 statement and checklist. There will be no deviation from the protocol once approved by the local ethics committee. Any amendments to the protocol will be reviewed and approved by the local ethics committee before implementation in the study. The trial protocol will be registered into a public database prior to randomization of the first participant (www.clinicaltrials.gov). A manuscript with summary points of the protocol including design, rationale and analysis plan will be submitted to a peer-reviewed journal before termination of the study.

9.5 Publication and implementation

To make the highest impact, we have planned knowledge sharing with the relevant actors: 1) Patients and relatives, 2) endocrinologists and 3) thyroid surgeons. The main paper will be submitted to a peer-reviewed journal regardless of the results. The primary publication will contain the primary analyses regarding the primary and secondary endpoints assessed 1 year after randomization. Secondary publications will report the outcomes assessed at year 5. All results will be published – both positive, negative and inconclusive results.

We will collaborate with national and international clinicians and researchers to implement the results of the current trial to clinical practice guidelines.

9.6 Collaborations

We will collaborate with several other colleagues from Aarhus and Copenhagen University Hospital, other Hospitals in Denmark and abroad. Patients are commonly referred from General Practice, Ear-, Nose- and Throat doctors in Private Practice, Department of Endocrinology and other clinical departments. The clinical evaluation of thyroid tumors is performed in collaboration with Department of Endocrinology, Department of Nuclear Medicine, Department of Radiology, Department of Biochemistry, and Department of Pathology.

9.7 Involvement of patients and public interests

The study protocol and overall aims and outcome measurements have been evaluated with patient representative CK. Information about the study will be published in a newsletter for patients with thyroid diseases. Finally, results from the study will be disseminated in similar newsletter forms for future patients.

9.8 Declaration of interest

The investigators have no academic or financial conflicts of interest in the trial. LR is the initiator and principal investigator (PI) of the project. LR has received a grant from The Novo Nordisk Foundation of 10 mill DKK. A part of the grant (approximately 4 mill DKK) will cover the salary for the trial manager (SR) and equipment (an ultrasound scanner and RFA needles) for the project. The investigators have no financial affiliation with the sponsor.

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