Evaluation of the role of vibrational spectroscopy in the diagnosis of premalignant and malignant disease of the thyroid
RAFTER (RAman For Thyroid cancER)

Research Protocol
Version 1.4
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Sponsor: Gloucestershire Hospitals NHS Foundation Trust
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Protocol reviewed by: Gloucestershire Hospitals Scientific Peer Review Committee

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Sponsor

Gloucestershire Hospitals NHS Foundation Trust is the main research sponsor for this study. For further information regarding the sponsorship conditions, please contact: Mr Charlie Hall.

Funders

The Biophotonics Research Unit, and Cheltenham and Gloucester Hospitals Charity (FOCUS) funded this project.

Every care was taken in drafting this protocol, but corrections or amendments may be necessary. Problems relating to this trial should be referred, in the first instance, to the Chief Investigator.

This study will adhere to the principles outlined in the NHS Research Governance Framework for Health and Social Care (2nd edition). It will be conducted in compliance with the protocol, the Data Protection Act and other regulatory requirements as appropriate.

Table of Contents

GLOSSARY OF ABBREVIATIONS

LDA	Linear Discriminant Analysis
PCA	Principal Component Analysis
VS	Vibrational spectroscopy
FTIR	Fourier Transform Infrared spectroscopy
RS	Raman spectroscopy
FNA	Fine needle aspiration

KEYWORDS

Raman spectroscopy
Infrared spectroscopy
Spectrum Analysis
Raman probe
Optical
Diagnosis
Cancer
Multivariate analysis
Thyroid cancer
Papillary thyroid cancer
Follicular thyroid cancer
Anaplastic thyroid cancer
Medullary thyroid cancer

STUDY SUMMARY

Title

Evaluation of the role of vibrational spectroscopy in the diagnosis and management of premalignant and malignant disease of the thyroid.

Design

Ex vivo vibrational spectroscopy (VS), including Raman spectroscopy (RS) of thyroid tissue samples, collected from patients undergoing routine diagnostic thyroid biopsies for diagnosis of potential thyroid cancer. Raman spectra are to be correlated with consensus histopathology and clinical outcomes. Multivariate analysis to be used to evaluate the classification accuracy of VS *ex vivo*.

Aims

1. To establish VS signal characteristics across a range of known thyroid cancer types.
2. To evaluate the ability of VS to detect thyroid cancer.
3. To evaluate the ability of VS to detect diseased lymph nodes in patients undergoing surgery for thyroid cancer.
4. To develop a minimally-invasive Raman probe to aid the diagnosis and follow up of patients with thyroid cancer.
5. To investigate thyroid nodules by comparing with histopathological results
6. To further the understanding of biochemical changes in a range of known thyroid cancers.
7. To evaluate the ability of VS to give prognostic information on the progression of thyroid cancer.

Outcome Measures

Measurement of thyroid nodules using the needle probe

Diagnostic performance of VS for differentiation of key thyroid cancer types:

- Papillary thyroid cancer
- Follicular thyroid cancer
  collectively known as the differentiated thyroid cancers
- Anaplastic thyroid cancer
- Medullary thyroid cancer

Diagnostic performance of VS for differentiation between normal and diseased thyroid carcinomas.

Prognostic performance of VS to indicate the risk of thyroid cancer progression.

Population

Patients undergoing investigation of thyroid cancer within Gloucestershire Hospitals NHS Foundation Trust.

INTRODUCTION

Background

Cancer is a major cause of morbidity in the United Kingdom (UK). Each year more than a quarter of a million people are newly diagnosed with cancer. Overall it is estimated that one in three people will develop some form of cancer during their lifetime.

There are more than 200 different types of cancer. Thyroid Cancer is a rare cancer (1% of all new cancer cases) with approximate 3500 new cases in the UK per annum (5/100,000 population). It is more common in females (73%). All age-groups are affected with the peak incidence in women at 35-39 years and men at 65-70 years. Overall the incidence is increasing (150% in 20 years).[1]

There are four main types of thyroid cancer. Papillary and follicular thyroid cancer, known collectively as the differentiated thyroid cancers, carry a good prognosis and are usually curable. Conversely anaplastic thyroid cancer is a very aggressive tumour usually presenting in the elderly with a very poor prognosis. Finally, medullary thyroid cancer is a rare form with a strong genetic preponderance and a prognosis dependent on stage at presentation. Most thyroid cancers metastasize initially to the cervical lymph nodes, however follicular thyroid cancer has a tendency to metastasize via the blood stream to distant sites, commonly lung and bone.

Whist thyroid cancer is rare, the presence of thyroid nodules is extremely common (in around 50% of people, by autopsy).[2] In many cases this represents background multinodular change in an otherwise normal thyroid. Occasionally a thyroid nodule will grow in an otherwise normal thyroid gland to become palpable in the neck, this is known as a solitary nodule. Alternatively, a nodule within a multinodular thyroid can grow or expand to form a palpable “dominant nodule”. In both these situations, the patient will present with a lump in their neck. In most cases a thyroid cancer will also present with a lump in the thyroid or occasionally a cervical lymph node representing a nodal metastasis. There is therefore a clinical need to be able to differentiate between benign nodule and malignant nodules presenting as a neck lump. Around 13% of nodules presented clinically are cancerous.[3]

Currently, patients presenting with a neck lump are assessed with clinical history and examination followed by an ultrasound scan and fine needle aspiration for cytology. This results in a spectrum of outcomes ranging from definitely benign to definitely malignant. However, a large proportion of patients fall into an indeterminate group with lower risk patients requiring interval scanning and higher risk patients a diagnostic lobectomy (removal of thyroid node for diagnosis). The latter is a surgical procedure to remove half the thyroid gland performed under general anaesthetic that usually necessitates an overnight stay in hospital. It is a low-morbidity procedure, but does carry a risk of vocal cord weakness due to nerve damage of up to 5%. In most cases this results in a temporary weak voice that resolves within 6 months.

Every year there are approximately 10,000 thyroid operations performed in England of which 17% are for thyroid cancer. While approximately half of the rest are for patients with symptomatic enlargement of the thyroid (goiter) or for the management of thyrotoxicosis, 20-30% are diagnostic procedures for the evaluation of a thyroid nodule.[4]

There is therefore a clinical and socio-economic need for improved diagnosis of thyroid nodules. The ability to differentiate between malignant and benign nodules in the outpatient setting will shorten diagnostic pathways, reduce the need for diagnostic operative procedures and reduce the cost of managing these patients.

Minimally invasive, near-instantaneous diagnosis of thyroid cancer would relieve patients of the anxiety whist awaiting results and, if required, allow for treatment planning to begin immediately.

Vibrational Spectroscopy

Vibrational spectroscopy (VS) utilises light to probe the composition of tissue. The sample is illumined with a source (often a laser), and the scattered or adsorbed light is measured by a detector. The amount light collected, along with the wavelength can be used to determine the composition and concentration of molecules in of the tissue. Small changes in these values can be used to compare different samples and monitor changes in tissues. The technique is non-destructive and non-invasive.

The potential benefits of VS in the management of thyroid conditions range from initial diagnosis to surveillance and treatment. These are outlined below.

1. VS offers a potential real time non-invasive diagnostic technique which could be used in the outpatient setting to avoid the need for invasive tissue biopsies in the following situations:
    a. The initial diagnosis of thyroid cancers.
    b. The monitoring of malignant changes in women with premalignant thyroid cancer.
2. VS offers a potential real time intraoperative diagnostic tool to detect non-visible disease margins and improve complete excision rates and avoid disease recurrence whist minimising the extent of surgical excisions.
3. In the management of thyroid cancer VS offers a potential tool for intraoperative objective assessment margins and of sentinel lymph nodes.
4. VS offers the potential to give prognostic information that can be used to evaluate the risk of progression of thyroid cancers.

Raman Spectroscopy

Raman spectroscopy (RS) is a non-destructive analytic tool that uses the inelastic scattering of light to identify the molecular composition of different tissues or materials. Incident light of a known frequency interacts with the target tissue and alters the vibration mode of the molecules within it by the transfer of energy. This results in light emitted from the tissue with a frequency dependent on the change in vibrational energy in the tissue. Measuring the frequency of

the emitted light produces a spectra which is unique to the molecular composition of the target tissue.[7] VS has been shown to be effective in the diagnosis of other cancers including colon,[5] lymphoma,[6] skin[7] and prostate.[8]

The Raman Needle Probe

We have previously demonstrated that it is possible to differentiate healthy and diseased tissue in the laboratory by measuring the light emitted when a low power laser is shone upon the tissue; a technique called Raman spectroscopy (RS). Our results have shown it is possible to obtain an "optical biopsy" or fingerprint of disease that can be used to diagnose cancer to a high level of accuracy within 2 seconds. This work was funded by the NIHR i4i and LINC from 2012-2016. We have submitted a second stage application to the NIHR, to fund a single centre *in vivo* trial of our device for lymphoma diagnosis, but would like to collect pilot data using the device for the diagnosis of other cancers.

We (The Biophotonics Research Unit, University of Exeter and University of Bristol) have developed these "smart needle" probes, consisting of fibre-optics within a fine needle for investigating cancer below the skin's surface. It is difficult to create a sensitive probe to fit inside a needle; however, we have demonstrated this approach in lymph node tissue samples from 68 patients in the laboratory, where we showed that our probe could detect cancer with a high level of accuracy.

Following on from our success with lymph nodes we wish to trial our smart needle on excised thyroid to demonstrate the device in another ENT cancer. Earlier studies have shown that thyroid cancer can be diagnosed using RS under a microscope with an accuracy greater than 78%.[9] By eliminating the need for unnecessary surgery by diagnosis with our device, we will minimise the risk to patients, eliminate delays in obtaining results and reduce the cost of surgery and overnight stay in the hospital. We wish to advance this device closer to the clinic for a new cancer to improve the patient care pathway and remove the need for unnecessary surgery, by facilitating the work of the one-stop ENT diagnostic outpatient clinics.

AIMS & OBJECTIVES

1. To demonstrate that the smart Raman needle probe can be used to measure spectra from excised thyroid nodules
2. To establish VS signal characteristics across a range of known thyroid cancer types.
3. To evaluate the ability of VS to detect thyroid cancers.
4. To further the development of a minimally-invasive Raman probe to aid the diagnosis and follow up of patients with thyroid cancer.
5. To further the understanding of biochemical changes in a range of known thyroid cancer types.
6. To evaluate the ability of VS to give prognostic information on the progression of thyroid cancer conditions.

STUDY DESIGN AND METHODS

Study Design

The study consists of measuring spectra of new tissue taken during routine diagnostic surgical thyroid lobectomy.

New tissue for this project will be collected during routine biopsy will be rapidly analysed by a spectrometer before proceeding with conventional histopathological analysis. The new tissue will consist of thyroid and adjacent tissue biopsies. No additional tissue will be taken for this research, we only plan to measure samples taken during routine diagnosis in under 5 minutes, before passing the sections back to the surgical team for routine histopathological analysis.

Patient consent for immediate spectroscopic analysis can be found in Appendix 1 and the participant information leaflet in Appendix 2.

Anonymous background information relevant to known risk factors, family history and details of any treatment, menopausal status, details relevant medical procedures, and any treatment for thyroid cancer will be provided with the samples. An example of the report can be found in Appendix 3. Tissue specimens taken during routine clinical care are to be subjected to *ex vivo* vibrational spectroscopic analysis immediately prior to being sent for routine histopathological analysis. Vibrational spectra are to be correlated with consensus histopathology of adjacent sections. Multivariate analysis is to be used to evaluate the classification accuracy of VS *ex vivo*. The vibrational spectra will be assessed for both prognostic as well as diagnostic information.

Setting and Recruitment of Patients

Identification of Participants

Eligible patients will be identified by any of the clinicians working within Gloucestershire Hospitals NHS Foundation Trust. With the patients consent, the clinicians will contact the Experimental Medicine Research Officer to arrange for the potential participant to be approached for consent to be included in the collection. The consent process will not delay the patient's routine care.

Patients who wish to consider participation in the study are approached by a member of the study clinical team for consent to be recruited. Patients will be given the opportunity to read the participant information sheet (see appendixes) and ask questions about the study.

All patients who will have biopsies taken with consent for inclusion in research studies whist undergoing investigation or treatment for thyroid cancer within Gloucestershire Hospitals NHS Foundation Trust may be considered for inclusion in this study.

The decision that a biopsy is necessary is usually made in the outpatient setting during thyroid examination. These decisions will have either lead to an immediate FNA biopsy in outpatients or arrangements were made for the patient to attend for a specialist clinic appointment or operating list, to have the biopsy taken.

Inclusion criteria

- Patients undergoing biopsy or excision for thyroid cancer as part of their routine clinical care within Gloucestershire Hospitals NHS Foundation Trust.

Exclusion Criteria

- Less than 18 years of age
- Patients unable to consent to the study due to communication difficulties
- Patients unable to consent to the study due to lack of capacity

Handling of Tissue

All tissue samples will be handled in line with Gloucestershire Hospitals NHS Foundation Trust's standard procedures.

For the samples, the fresh tissue will be immediately measured in a room adjacent to the surgical procedure location, in less than 5 minutes, before passing the tissue back to the surgical team for conventional histopathological analysis.

The samples used in this study will be identified with a study identifier number on a pre-printed sticker to be attached to the pathology sample submission form. This will allow the histopathology team to identify the node is involved in this project, and allow them to report the histology back to the research team in pseudo-anonymised form.

In the event of multiple nodules being removed from the patient, the surgical team will position a marker suture identifying the nodule examined using the probe, so the histopathologist can confidently identify the nodule you are interested in (likely to be the nodule of clinical concern in the majority of cases). Only one nodule per case will be used with the probe, to ensure the correct identification and pairing with the correct histology.

"Normal" tissue will be identified as lobes which the histology reports are returned as having no cancer.

Surplus tissue (not required for routine histopathology) from patients undergoing surgical excision of thyroid cancer dissection may be retained by the research team for analysis.

Spectral & Statistical Analysis

The spectral data will be correlated with gold-standard routine histopathology of the biopsy sample. The spectral variance will be explored using principal component analysis. This will facilitate exploration of the biochemical differences between the pathology groups. A multivariate discriminant classification model will then be developed using methods (e.g. Principal Component Analysis and Linear Discriminant Analysis) to extract the subtle spectral differences between tissue types. The background patient information and clinical outcomes will be included within the analysis to further develop the classification model. The classification model will be tested with leave one out cross-validation.

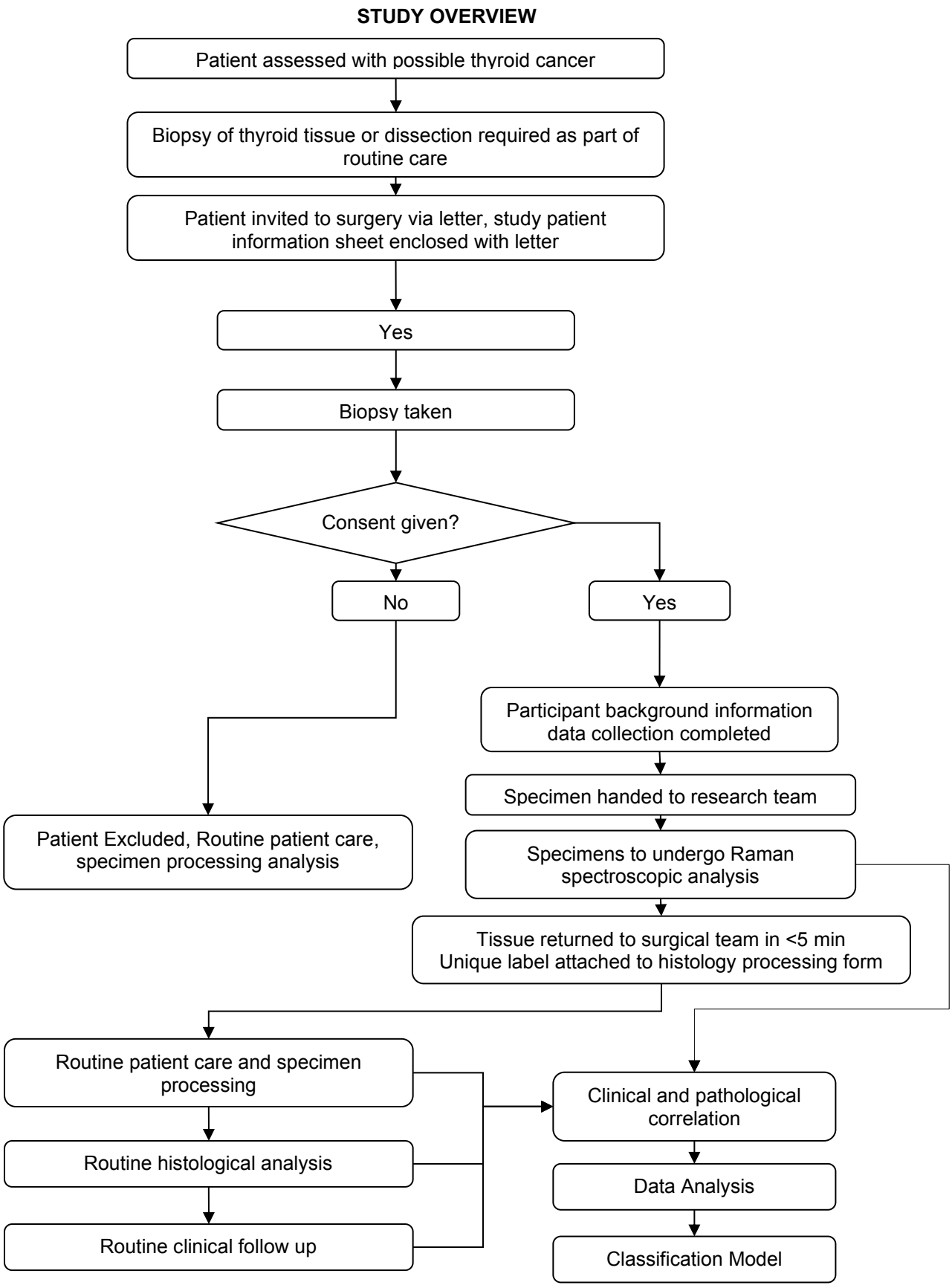

Figure 1 – study overview flow chart

OUTCOME MEASURES

Primary Outcome Measures

Demonstration and evaluation of the spectroscopic measurement of ex vivo thyroid tissue using the Raman needle probe.

Secondary Outcome Measures

Diagnostic performance of VS for differentiation of thyroid cancer vs normal benign (no cancer).

Diagnostic performance of VS for differentiation of thyroid cancer types.

- Papillary thyroid cancer
- Follicular thyroid cancer
- Anaplastic thyroid cancer
- Medullary thyroid cancer

Prognostic performance of VS to indicate the risk of thyroid cancer progression.

REGULATORY ISSUES

Adverse Events

Failure of histological diagnosis due to sample processing errors is not expected and is reportable. All failure of histological diagnosis should be reported to the chief investigator using the form in Appendix 4.

This study is observational and will not alter the routine management of patients, therefore adverse events as a result of treatment received is outside the remit of the study and not reportable.

The histopathology team at Gloucestershire Hospitals NHS FT are aware of this study and its design and propose that there will be little chance of tissue damage (some patients may have undergone an FNA procedure prior to surgery). The histopathologists will inform the research team at once if the use of the probe affects the macroscopic or microscopic assessment of the tissue.

The first 5 biopsy samples will be subject to thorough damage assessment by the histopathology team.

Ethics Approval

The chief investigator has applied for approval from a Research Ethics Committee. The study has been submitted for approval by the Gloucestershire Hospitals Scientific Peer Review Committee.

Patient and public involvement

Patients at Gloucestershire Hospitals NHS Foundation Trust have been contacted. A patient helped review the patient information sheet, and comment on the study. Other patients have been invited to complete a questionnaire after reading the information sheet and being given the opportunity to ask questions. Members of the group commented that they supported this research into the new technique especially if it led to more-rapid diagnosis using a minimally-invasive technique. Several commented on how anxious they felt whilst awaiting results.

Consent

Consent for inclusion in the study will be taken either by the principal investigator, co-investigators or named clinician to whom that duty has been delegated.

Consent to enter the study will be sought from each participant only after a full explanation has been given, an information sheet offered, and time allowed for consideration. Signed participant consent will be obtained prior to analysis of tissue samples. The right of the participant to refuse to participate without giving reasons will be respected.

All participants are free to withdraw at any time from the study without giving reasons and without prejudicing further treatment.

See appendices for participant information sheet and participant consent form.

Confidentiality

The Chief Investigator will preserve the confidentiality of participants taking part in the trial according to the Data Protection Act 1998.

Human Tissue Act

This study complies with the regulations set out in the Human Tissue Act 2004.

Indemnity

Gloucestershire Hospitals NHS Foundation Trust holds standard NHS Hospital Indemnity and insurance cover with NHS Litigation Authority for NHS Trusts in England, which apply to this study.

Audit

The study may be subject to inspection and audit by Gloucestershire Hospitals NHS Foundation Trust as sponsor and other regulatory bodies to ensure adherence to GCP and the NHS Research Governance Framework for Health and Social Care (2nd edition).

Progress reports will be submitted to the bi-annual Gloucestershire Hospitals Research and Innovation Forum.

Publication Policy

Results to be submitted for publication in peer reviewed journals and for presentation at relevant scientific meetings.

REFERENCES

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Gloucestershire Hospitals
NHS Foundation Trust

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Project Title: RAFTER

Project Title (Full): RAman For Thyroid cancER

Appendix 1 **RAFTER Study Consent Form**

IRAS ID: 245612

Participant Identification Number for this trial:

CONSENT FORM

Title of Project: RAFTER (RAman For Thyroid cancER)

Name of Researcher: Dr Alexander Dudgeon

Version 1.2, 04 September 2018

	Please initial box
1. I confirm that I have read the information sheet dated. 04/09/2018 (version. 1.2) for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily.	☐
2. I understand that my participation is voluntary and that I am free to withdraw at any time without giving any reason, without my medical care or legal rights being affected.	☐
3. I understand that the information collected about me will be used to support other research in the future, and may be shared anonymously with other researchers.	☐
4. I agree to take part in the above study.	☐

Name of Participant	Date	Signature

Name of Person taking consent	Date	Signature

When completed: 1 for participant; 1 for researcher site file; 1 to be kept in medical notes.

Gloucestershire Hospitals
NHS Foundation Trust

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Switchboard: 0300 422 2222

Project Title: RAFTER

Project Title (Full): RAman For Thyroid cancER

Appendix 2 **Participant Information Sheet Copy**

Participant Information Sheet: RAFTER

Version 1.2, 04/09/2018

Study Title: RAman For Thyroid cancER

(Developing a new technique for the assessment of swollen thyroid nodule conditions)

You are being invited to take part in a research study. Before you decide it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully and discuss it with others if you wish. Ask us if there is anything that is not clear or if you would like more information. Take time to decide whether or not you wish to take part.

Thank you for reading this.

What is the purpose of the study?

This study is being undertaken to develop a new minimally-invasive method for use in the diagnosis of thyroid cancer. It is hoped that this technique will improve the care of patients by reducing the need for an invasive surgical procedure if no malignant cancer is found.

Why have I been chosen?

You have been chosen to take part in this study because your doctor would like you to have surgery to investigate the lump in your neck. You may have already had a needle biopsy (FNA) and this does not stop you from participating in the study.

What is the technique that is being tested?

The diagnostic technique being tested is called Raman spectroscopy. This technique allows us to determine the biochemical composition of tissues by measuring the changes to specific colours of light shone onto the tissue. This technique is currently also being investigated as a way of diagnosing medical conditions in other parts of the body such as the lymph nodes, breast and oesophagus.

We have not used this technique in the thyroid before and this is an initial study to try and establish if the type of thyroid diseases that can be identified using this technique. If the study were successful, then we would aim to make a device to assess several types of thyroid disease using a fine needle technique without the need for tissue biopsies during invasive surgery.

Do I have to take part?

It is up to you to decide whether or not to take part. If you do decide to take part you will be given this information sheet to keep and be asked to sign a consent form. If you decide to take part you are still free to withdraw at any time and without giving a reason. A decision to withdraw at any time, or a decision not to take part, will not affect the standard of care you receive.

What will happen to me if I take part?

If you decide to take part in the study your normal care will not be affected. The study involves an additional test of your biopsy specimen or tissue removed at the time of surgery. Participation in the study will not significantly affect or delay the results of your routine tests. The research team will then anonymously match the test with your pathology results to identify what type of tissue we are measuring. After completing the consent form, you will not be required to contribute any more of your time to the study. The research team will be provided with your pathology report annonomously , without contacting you further. It will not be possible for the researchers to identify who you are from these results.

If you take part in the study then your tissue sample will immediately be measured with the new diagnostic test, in theatres. The sample will then continue with standard routine diagnosis (histopathology). After the new test has been performed on samples from many different participants, analysis will be carried out to see if the test can be used to diagnose different thyroid diseases without the need for invasive surgical biopsies.

Who else will be taking part?

The research team anticipate that a total of 40 patients will participate in the study.

What are the possible disadvantages and risks of taking part?

We do not anticipate that taking part in this study will affect the care you receive from your doctor. The pathology team do not expect the additional measurements to affect your diagnosis. Samples from participants in the study will be undergo routine testing at the same time as samples from patients not participating in the study. It is therefore not anticipated that participation in this study will cause a delay in the issuing of histopathological results and should not affect the timing of any further treatment you may require.

As we are comparing the new diagnostic technique to the standard analysis the research findings will not affect your care or give additional information on your case, but could contribute to improved diagnostic tests for the future.

What are the possible benefits of taking part?

There is no benefit to your care if you participate in the study, however you will be contributing to the development of a new diagnostic technique. If successful this will give patients access to instant diagnosis of conditions of the thyroid, without the need for invasive surgical tissue biopsies.

Will my taking part in this study be kept confidential?

All information which is collected about your diagnosis during this research will be provided anonymously to the research team, with the linking to pathology reports will be

done with a unique study code. Only your direct care team will have access to your personal data.

What will happen to the results of the research study?

You will not be identified in any report or publication produced as part of this study. Results will be submitted for publication in scientific journals and may be presented at scientific meetings. Initial results will be submitted for publication. If you would like a copy of the results of the study please contact the principal investigator or project supervisor listed at the end of this information sheet.

Who is organising and funding the research?

The study is being organised by the Biophotonics Research Unit at Gloucestershire Hospitals NHS Foundation Trust and is funded by Focus, the charitable fund for the Gloucestershire Oncology Centre the Research and Innovation Forum, part of Cheltenham and Gloucester Hospitals Charity, (registered charity no. 1051606).

Who has reviewed the study?

This study has been reviewed by the London-West Research Ethics Committee.

What if something goes wrong?

Any complaint about the way you have been dealt with during the study or any possible harm you might suffer will be addressed. Please raise your concerns in the first instance with the Principal Investigator (that is the lead researcher), Dr Alexander Dudgeon, his contact details are at the end of this form. If you wish to make a more formal complaint, please contact the hospital's Patient Advice and Liaison Service (PALS) (PALS Office, Gloucestershire Royal Hospital, Great Western Road, Gloucester, GL1 3NN, telephone: 0800 019 3282, e-mail: ghn-tr.pals.gloshospitals@nhs.net).

What could I do to help researchers use my own experience more when they are planning their next project?

Do you want to get more involved and help researchers improve future project ideas and research information leaflets? Please contact "People in Research – Opportunities for public involvement in research" http://www.peopleinresearch.org/. If you would like to help, you can also contact INVOLVE which is a national advisory group, funded by the National Institute for Health Research (NIHR). Its role is to support and promote active public involvement in NHS, public health and social care research. http://www.invo.org.uk/ or INVOLVE, Alpha House, University of Southampton Science Park, Chilworth, Southampton, SO16 7NS, Telephone: 023 8059 5628 Email involve@nihr.ac.uk

Thank you for taking the time to read this information and considering participation in this research study.

Contact for Further Information

Principal Investigator

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Version 1.2 04/09/2018

Appendix 3 **Patient Histology Report**

Example sample information report

SURNAME	FORENAME	SEX	NUMBER TYPE	D.O.B	HISTOLOGY LAB. NO.
[redacted]	[redacted]	[redacted]	MRN [redacted]	[redacted]	[redacted] DATE RECEIVED 09-MAR-2018

ADDRESS OF PATIENT:	SOURCE	ADDRESS FOR REPORT
[redacted]	DAY SURGERY UNIT GRH GLOUCESTER ROYAL HOSPITAL	SEC TO [redacted] GRH GLOUCESTERSHIRE HOSPITAL

CLINICAL SUMMARY:
Cyst on thyroid isthmus.
THYROID ISTHMUS

MACRO:
We have received a pot containing a fragment of thyroid tissue weighing 5.7g and measuring 34 x 24 x up to 15mm thick. External surface inked black. On sectioning the thyroid tissue a cystic area is present filled by thick firm gelatinous material. Associated with this is a solid somewhat nodular appearing proliferation. The entire nodular appearing area is macroscopically 19mm in maximum dimension with a solid component being approximately 13mm in maximum dimension. It abuts margins. Likely inferior portion of thyroid isthmus being taken in A. TS's of rest of nodule being in B&D. E = background/?superior thyroid isthmus. All through.

MICRO:
HISTOPATHOLOGY REPORTING PROFORMA FOR THYROID CANCER -

CORE DATA ITEMS:
SPECIMEN TYPE - ISTHMUSECTOMY

LOCATION OF CARCINOMA - ISTHMUS
SIZE - 19MM

CANCER TYPE - CLASSICAL PAPILLARY THYROID CARCINOMA
ONCOCYTIC VARIANT - NO
MINORITY POORLY DIFFERENTIATED (NOT ANAPLASTIC) COMPONENT - NO

ANGIO-INVASION/VASCULAR INVASION - NOT IDENTIFIED

EXTENT - CONFINED TO THYROID (INTRATHYROIDAL)

EXCISION MARGINS - MACROSCOPIC TUMOUR AT MARGIN (R2)

LYMPH NODES - TOTAL NUMBER OF LYMPH NODES IDENTIFEID - 1 (LEVEL VI LYMPH NODE)
POSITIVE - 0

PATHOLOGICAL CONFIRMATION OF DISTANT METASTASES (pm1) - NO

THYROID ISTHMUS - 19MM CLASSICAL PAPILLARY THYROID CARCINOMA, CONFINED TO THYROID BUT PRESENT MACROSCOPICALLY AT MARGINS, NO LYMPHOVASCLAR INVASION, ONE ADJACENT UNINOLVED LYMPH NODE, pTNM (8th Edition), pT1b, pN0, pMX.

REPORTED BY [redacted]
DIAGNOSIS AGREED BY [redacted]

20-MAR-2018 [redacted] Diagnostic code : T96000;M82603

Histology Gloucestershire Hospitals NHSFT Tel. 0300 4224075

Appendix 4 **Adverse Event Reporting Form**

Study Title - RAFTER (RAman For Thyroid cancER)

Research department use only

Case reference number:

Date report received:

Person making report
Name:
Job title/role in study:
Contact address:
Email address:
Telephone No:
Details of adverse event:

OBJ

Signature of person making report:

_____Date:____/____/____

Please send completed reporting form to:

Dr Alex Dudgeon

Biophotonics Research Unit

Leadon House

GH NHS FT

GL1 3NN

Version 1.0, 7 August 2018

Appendix 5 **Personnel Delegation and Signature Log**

Study title: RAFTER (RAman For Thyroid cancER).

All those involved in the above study must read the protocol (and amendments if applicable) and understand their role as outlined in the protocol

Name (print)	Job title	Signature	Signed Initials	List duty categories	PI signature ONLY & date	Start date	Date of leaving (if appl.)
	Principal Investigator						

Key for list of duty categories:

1. Maintaining investigator file
2. Review & reporting Adverse events & SAE
3. Archiving
4. Resolving data queries
5. Other duties specific to the study, please specify below: