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Imaging and data collection study protocols

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Abbreviations

HCG	Human chorionic gonadotropin
Bq	Becquerel; MBq: Megabecquerel; GBq: Gigabecquerel
DTC	differentiated thyroid cancer
eGFR	estimated Glomerular Filtration Rate
HEGP	High-energy general purpose
FOV	Field of View
ICRP	International Commission on Radiological Protection
SPECT	Single Photon Emission Computed Tomography
CT	Computed Tomography

1. Introduction

There are no robust multi-centre data available on the radiation absorbed dose delivered to non-target organs in radioiodine therapy. A retrospective collection of such data is not possible due to the omission of scans required.

The primary aim of the present study is to prospectively obtain multi-centre data on the radiation absorbed dose and the range of uncertainty of these data to non-target organs in radioiodine therapy in differentiated thyroid cancer (DTC) patients.

The activity distribution within the patient as a function of time needs to be measured to calculate absorbed dose distributions in the normal organs, thyroid remnants and associated lymph nodes. These activity measurements will be made with a combination of gamma camera SPECT imaging, whole body retention measurements, urine and blood sampling.

Minimum data acquisition requirements will be specified. However, each centre will obtain the maximum level of data possible. This will enable the most significant, yet practical, measurements to be identified to optimise the protocol for use in a large-scale epidemiological study.

Prior to each centre participating in the trial standardised pre-study gamma camera set up and calibration measurements (including dose calibrator and gamma counters) will be made for each camera to be used in the trial. This will ensure that image data collected from each participating centre is harmonised and that the absorbed doses computed based on these images will be comparable between sites.

The contents of this deliverable describes the patient exclusion and inclusion criteria, clinical assessment of the patients, the activity measurements and gamma camera set up protocols.

2. Content

- Clinical Protocol
- Patient Activity Measurements for Dosimetry
- Site Set-up for Quantitative Imaging for Dosimetry

2.1 Clinical Protocol

Patients

In the present study patients meeting following criteria will be included:

- 18 years and older
- Able and willing to give signed informed consent
- Histologically proven differentiated thyroid cancer
- pT1b-pT3, any N
- Clinical indication for ^{131}I therapy
- No distant metastases (patients who will be diagnosed with distant metastases after therapy will be replaced)
- History of total thyroidectomy
- No history of prior therapeutic radiation / radionuclide exposure
- No history of chemotherapy
- No medication known to interfere with iodine kinetics within the last 12 months
- No amiodarone exposure in the last 24 months
- No exposure to iodinated contrast agent in the last six months
- No hemodialysis

Exclusion criteria:

- Pregnancy (to be excluded by serum beta-HCG measurement in women of child-bearing age)
- Lactation within the last 6 months
- Participation in another clinical study within the last 6 months
- Current uncontrolled severe disease
- History of prior malignancy with the exception of low-grade skin cancer
- Inability to tolerate the necessary measurements for the study

Additional exclusion criteria for the biomarker study:

- Diseases of the blood-forming system
- Diagnostic exposure to ionizing radiation within one week of exposure to^{131}I

Patient preparation

- Patients will be advised to follow a low-iodine diet for 2 weeks prior to ^{131}I therapy
- Mode of TSH stimulation at the discretion of the attending physician

Clinical measurements

- Dosimetry-focussed activity measurement protocol as defined in section 2.2
- As a minimum the patient will be weighed and measured for height on the day of ^{131}I administration. If practicable the patient will be reweighed before each imaging time point
- Serum creatinin and eGFR will be measured on the day of ^{131}I administration
- TSH, free T4, thyroglobulin to be measured on the day of ^{131}I administration

2.2 Patient Activity Measurements for Dosimetry

The simple model used by the International Commission on Radiological Protection (ICRP) for estimation of absorbed doses from diagnostic radioiodine imaging of the intact thyroid, includes the stomach, intestines and urinary excretion in addition to the thyroid. The scanning schedule outlined is based on the published ICRP iodide half times. The thyroid uptake phase is assumed to be 6-8 hours. Ideally, this uptake will be determined for each individual patient with a ~4 hour and/or ~8 hours scan. This will be dependent on the level of activity administered and camera dead time characteristics and taking into account staff radiation protection. Modern gamma cameras are capable of quantification of several GBq of ^{131}I. The biological half time of elimination from stomach and small intestine is typically 8 hours. Therefore a scan of this region at 4, 8 and 24 hours is advised for dosimetry in these organs. The biological half time of excretion from an intact adult thyroid is typically 80 days. Due to the physical half-life of ^{131}I this will be effectively 7 days, justifying a scan in the region of 6-8 days. The remaining activity is assumed to be uniformly distributed in the remainder of the body and excreted by the renal system with a biological half time of 8 hours. If there is no particularly visible uptake in the renal system, the remainder body activity could be assessed through whole body retention measurements. Modelling will then be necessary to assess the absorbed dose to the kidneys as all the activity will pass through the kidneys (ICRP 1987).

The uptake in the bone marrow may be estimated through whole body retention measurements in combination with blood sampling, or based on lumbar vertebrae imaging (Hindorf *et al* 2010).

A minimum of 3 measurements are to be made for each patient, but each centre will be encouraged to obtain as many of the following measurements as possible, so that the most important yet practical measurements can be identified to optimise the protocol for use in a large-scale epidemiological study.

- A list of SPECT image time points (ideally SPECT/CT) of the thyroid remnant and patient abdomen is given below:

    - 4±1hrs
    - 8±1hrs
    - 24±2hrs
    - 2 days
    - 3 days
    - 4-5days
    - 6-8 days following administration.

    For radiation protection purposes the first scan should be a SPECT/CT with a low dose CT and subsequently SPECT-only scans could be registered to the first, if necessary.

- Blood samples should be taken at the time of scanning, if this is considered practical. These samples will aid bone marrow dosimetry calculations, but are optional if they are not logistically possible.

- For 20 of these patients, treated at UKW, 5 blood samples will also be acquired and prepared for analysis immediately in the first hours and 3-5 blood samples after 24h and daily up to 7 days after radioiodine administration to enable calculation of the blood absorbed dose and the DNA damage repair rate.

- Whole body retention measurements using an external radiation monitor should be made as often as possible. At least 2 pre- and post-void should be made immediately following the

administration and 3 per day should be made post-void on the remainder of days the patient is in hospital.

- Urine samples will be collected on the day of ^{131}I administration for the measurement of the urinary iodine excretion, where centres are able to perform these measurements.

2.3 Site Set-up for Quantitative Imaging for Dosimetry

The pre-study set up measurements for each site will consist of calibration measurements of the equipment to be used to measure activities for the study.

- The checks in Table 1 will be required prior to the calibration, where possible.

Table 1. Pre-visit checks

Check
Accuracy of radionuclide calibrators and well counters to be used in the trial (Sokole 2010)
Peak checks
^{131}I intrinsic (20 million count) uniformity
^{99m}Tc intrinsic (20 million count) uniformity
Centre of rotation for HEGP collimators
SPECT/CT system alignment checks
Extrinsic HEGP floods
QC of weighing scales used
Regular QC of used dose calibrators

- Patient image acquisition protocols on the SPECT system will be standardised in agreement between participating centres. These will be used for the following calibration measurements and trial patient scans.
- The radiation protection principles of time, distance and shielding should be adhered to throughout these measurements to keep irradiation to staff performing the following measurements as low as possible.

More detailed work sheets will be provided to guide and record all the measurements.

Iodine-131 Dead-Time Factor Measurement

Dead-time factors are to be created and used to correct the acquired ^{131}I image counts for lost counts due to dead-time. On some systems there may be a count rate above which the count losses cannot be corrected. These measurements will also check that the system correctly handles high activities and will identify artefacts that may occur at high count rates.

- A cylindrical phantom, 20 cm in diameter, 20 cm in length, will be filled with clean water and sealed. A static background scan of the phantom will be acquired with the HEGP collimators.
- A vial of known activity concentration of ^{131}I will be prepared; the activity will be measured in a dose calibrator with factors traceable to the national standard.
- Approximately 10 MBq will be added to the phantom. The static scan will be repeated.
- Increasing activities, in successively larger quantities will be added to the phantom and the scan repeated until the phantom activity has reached approximately 3 GBq. Up to 20 static scans will be acquired in total.
- The count rates will be plotted against activity. A dead-time model will be fit to the graph and the resulting equation will be used to correct the patient images for dead-time.
- Count rates at which it will not be possible to correct the scans for these count losses may also be identified.

Iodine-131 Calibration Factor Measurement

Calibration factors will be created to convert image count concentrations to activity concentrations. These factors will vary with object volume due to partial volume and resolution effects.

- Objects with a variety of volumes will be filled with approximately 25 kBq/ml solution of ^{131}I.
- These objects will be imaged positioned in a water-filled torso-shaped phantom to give a similar scattering and attenuation geometry to a patient.
- These will be scanned using the trial imaging protocol.
- The images will be reconstructed using the centre's standard reconstruction software and parameters.
- The anonymised CT, SPECT images and raw projection data will be sent to the lead dosimetry centre, and uploaded where the anonymisation, alignment and attenuation correction will be checked. The reconstruction protocol will also be optimised at this central location in collaboration with all centres.
- The count concentrations in the cylinder images will be measured and used to calculate the factor required to convert the counts to activities for each cylinder volume.

Calibration of Well Counters

- Initial well counter calibration
  - Three 0.2 mL aliquots , prepared from a stock solution with an activity concentration of 100 kBq per mL, will be measured in the well counter.
  - The mean of these three count rate measurements and the initial activity will be used to determine the calibration factor of the well counter.

- Well-counter cross-calibration with SPECT/CT
  - An aliquot of 0.2 mL, taken from the stock solution used to calibrate the SPECT/CT, should be measured in the calibrated well counter.
  - The measurement should be repeated three times within two weeks, with each measurement being at least 3-4 days apart.

- Each measurement of activity with the well counter should be within ± 5% of the decay corrected activity measured on the dose calibrator. Deviations greater than ± 5% will result in recalibration of the well counter.

3. Conclusion

The data collection described in this deliverable will enable the endpoints of this study to be attained:

- Absorbed doses resulting from to ^{131}I therapy of non-target organs such as e.g. heart, kidney, stomach, liver, mammary glands, urinary bladder, salivary glands, blood/bone marrow
- Absorbed doses to target tissue, i.e. thyroid remnant or lymph node metastases.

3.1 Clinical Protocol

The exclusion criteria and clinical data acquisition defined in this document will ensure only patient data is collected that will be suitable for achieving the objectives in this study and that no additional harm will come to the patient in taking part in this trial.

3.2 Patient Activity Measurements for Dosimetry

The measurement schedule allows for the maximum useful data to be obtained for use in this trial to enable identification of the optimal protocol for use in a large-scale epidemiological study.

3.3 Site Set-up for Quantitative Imaging for Dosimetry

Careful site set-up following the methods described in this deliverable will allow dosimetry calculations to be harmonised between all centres, providing robust absorbed dose results.

4. References

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