MEDIRAD

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Protocol for epidemiological study (WP3)

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Abbreviations

Computed tomography – CT

Differentiated thyroid cancer – DTC

Nuclear Medicine – NM

Molecular Radiotherapy – MRT

Radioiodine – RAI

Secondary primary malignancy – SPM

Single-photon emission computed tomography – SPECT

Time integrated activity coefficients – TIACs

Tumour-node-metastases – TNM

Volumes-of-interest – VOIs

Whole-body – WB

1. Background

Thyroid cancer represents about 3% of all cancers worldwide.[1] Differentiated thyroid cancer (DTC) accounts for more than 90% of thyroid cancer. Based on our pilot data and published research, approximately 3700 new thyroid cancers were detected each year in the UK from 2013 to 2017,[2] while approximately 58000 cases were identified in the European Union in 2020.[3] Approximately, 84% of patients have a survival of 10 years or longer.[2] For 80 years, radioiodine (RAI) has been used to treat patients with thyroid cancer following thyroidectomy. Guidelines from different professional societies concerning optimal treatment provide contradictory advice and a wide vaRAItion is observed in the administered activities. This controversy is in part due to the controversial evidence in the literature with respect to the potential risks of RAI treatment.[4, 5]

Salivary disorders are a potential side effect of radioiodine and have been reported as early as weeks or months after treatment.[6] These findings have been supported by systematic reviews and meta-analysis with respect to salivary and lacrimal gland dysfunction. However, due to major methodological differences between studies, the reported incidence of these disorders ranges from 16-72%.[7] Patients treated with RAI also complain of dry eyes in the years following treatment, indicative of lacrimal gland dysfunction.[8] Nevertheless, only a few studies included lacrimal dysfunction assessment, showing an incidence between 11-53% (with low level of evidence).[7] In addition, the dose-response relationship with absorbed doses of ^{131}I to salivary glands or lacrimal glands has never been studied.

Controversy remains over the risk at low dose levels, which typically occur in Nuclear Medicine (NM) procedures and Molecular Radiotherapy (MRT) treatments.[9, 10] Long-term side effects such as second primary malignancy (SPM) have been investigated in several epidemiological studies. Increased risks of SPM in patients presenting a diagnosis of thyroid cancer have been shown in a meta-analysis.[11, 12] Retrospective epidemiological studies trying to address the risk of SPM after radioiodine treatment for thyroid cancer have provided contradicting results.[13, 14] Several studies have reported that patients receiving RAI are at an increased risk of SPM, both when compared with the general population and with thyroid cancer patients not receiving RAI.[15-17] Further research is required to assess if the increased rate of SPM in thyroid cancer survivors is linked to a specific genetic or environmental background or to the effect of RAI. None of the epidemiological studies have considered individual dosimetry for target organs. As such organ-specific relationships between exposure to RAI and the incidence of SPM have not been investigated. A review of previous research and the pilot data acquired as part of MEDIRAD indicate that a wide range of radiation absorbed doses are delivered to thyroid remnant, healthy organs and the whole-body.[18-22] The use of population averages for organ absorbed doses is therefore inadequate and individualised dose estimates are required.

The advantages of investigating SPMs in thyroid cancer patients treated with RAI are that (i) the method of administration ensures a whole-body irradiation (ii) patients are expected to have a normal life span and (iii) there are few confounding factors from additional therapeutic procedures. One objective of the MEDIRAD project, within Work Package 3, was to develop the methodology to collate patient-specific dosimetry from RAI treatment of low and intermediate risk thyroid cancer acquired in multiple sites according to a common protocol. The dosimetry analysis of pilot MEDIRAD data allowed the calculation of absorbed organ doses for the patients recruited. Those calculations require patient specific data and imaging data obtainable from participating hospitals.

The methodologies for standardised quantitative imaging[23] and dosimetry have been developed as part of MEDIRAD WP3 and are summarised in Deliverable D3.8 (Guidelines and recommendations for quantitative I-131 imaging and dosimetry). SPECT images are quantified and corrected for dead time. If WB, CT and SPECT DICOM images are anonymised for a study, all header data describing the

SPECT(/CT) system used to acquire the data will need to remain. This will be required to apply the correct calibration factors.

Dosimetry is either performed for volumes-of-interest (VOIs) or on a voxel-by-voxel basis. For VOI-based dosimetry, the outlining techniques must be well defined and should be based on anatomical imaging in conjunction with visible uptake on the SPECT images. Outlining by a trained radiologist is advised. Dosimetry methodologies should include appropriate uncertainty analysis and should either be standardised across centres or carried out at a central dosimetry hub.[24]

The aims of Task 3.5 is to consider a large-scale, multi-national, epidemiological study of people who have undergone RAI therapy to assess the risk of secondary malignancies, and other side-effects on healthy tissues such as salivary and lacrimal dysfunctions. To assess the feasibility to perform an epidemiological study incorporating collection of standardised dosimetry data, the first European network of centres able to perform standardised quantitative imaging of RAI has been established.[23]

2. Aims and objectives

Aim: To estimate the short, mid, and long term side effects of the treatment of thyroid cancer by RAI.

Specific objectives

- To establish an international multi-centre prospective study of patients with a diagnosis of DTC,
- To study incidence and risk factors of salivary and ocular complications following RAI treatment,
- To study incidence and risk factors of SPM after RAI treatment,
- To assess the dose-response relationships between absorbed dose to salivary glands and the occurrence of salivary/lacrimal gland dysfunctions,
- To assess the dose-response relationships between absorbed dose to WB and specific organs and SPM incidence.

3. Methods

3.1 Definition of study population

The cohort will be prospectively established from patients over 18 of age, diagnosed with thyroid cancer in the European Union and the UK. Data on initial treatment with RAI following thyroidectomy and further treatments with RAI will be collected from hospitals participating to this multi-centre international cohort. Approximately 60000 thyroid cancer patients are diagnosed in the European Union and the UK each year with the majority undergoing RAI treatment.

The cohort data will be stored in a relational database. This allows identifiable data to be stored in separate tables to the dosimetry and cancer-related data. Data linkage using hospital or national insurance numbers will uniquely identify individuals having repeated procedures and those undergoing procedures at more than one hospital. Where unique hospital or national insurance numbers are missing, a combination of other identifiers, including full names and date of birth will be used to identify these individuals.

A restricted group of patients will be invited to participate in an individual salivary and ocular complications survey with a thorough follow-up, where saliva samplings and questionnaires about risk factors and symptoms will be conducted.

3.1.1 Exclusions

- Non-residents in the country will be excluded. This is required as non-resident patients cannot be followed up for cancer risk by a national cancer registry.
- Patients who have previously been treated with RAI, radiotherapy, chemotherapy will be excluded to reduce bias due to previous exposure.
- Patients who are likely to be treated with multiple ^{131}I therapies within 18 months of inclusion will be excluded from the salivary and ocular complications survey.

3.1.2 Follow-up period

Start date: at the diagnosis of DTC

End date: at the diagnosis of SPM, death, end date of follow-up (15 years), date of last follow-up

The sample of patients included in the salivary and ocular complications survey will be followed for 18 months, with 3 visits (immediately before RAI intake (T0), 6 (T6) and 18 (T18) months later).

3.1.3 Endpoints

Vital status: All patients will be followed-up for mortality using appropriate national vital statistics databases.

Cancer incidence: Linkage will be made with national/regional cancer registries as appropriate. National cancer registries will provide information on cancers and deaths occurring in the cohort. All cancer diagnoses must be provided in electronic form in ICD-O-3 coding.
In France or other countries, where cancer registration is complete only for children, attempts will be made to use national health insurance database of reimbursement of medication for cancer incidence in adults.

Cause of death: Linkage will be made with national/regional cancer or mortality registries as appropriate. Details of deaths, including coded cause of death will be uploaded directly into the study database, allowing linkage between radiation dose data and cancer diagnosis and mortality data.

Salivary and ocular complications: Objective (saliva flow rates) and subjective (symptom questionnaires) endpoints will be used to assess gland dysfunctions.

3.2 Data collection

3.2.1 At enrolment

As part of MEDIRAD, pilot data have been collected of patients undergoing RAI therapy for thyroid cancer in a multi-centre setting. From these data, we know that the following patient information and NM imaging data for standardized absorbed dose estimates can be collected at the inclusion time:

- patient details (first name, last name)
- date and place of birth
- gender
- address
- National/hospital patient identification numbers
- Thyroid cancer diagnosis (Date of surgery, type of surgery, date of diagnosis, histological type, tumour-node-metastases (TNM) staging system)
- Date of RAI treatment
- Type of procedure

- Administered activity & Administration times
- Dosimetry scan details
- Dosimetry scans (SPECT, SPECT/CT or WB) to calculate radiation absorbed doses to thyroid remnant, healthy tissue and whole-body

Additional data about comorbidities will be collected at the inclusion time. Cancers diagnosed among cohort members may be associated with the condition for which the patient was treated or with other coexisting congenital anomalies, rather than ionising radiation. These confounding factors will be identified through an extensive review of the literature and the collection of confounding factors be included in the data collection from participating hospitals and relevant national databases.

3.2.2 During follow-up

For all the patients included in the international multi-centre cohort, new data should be collected during follow-up:

- Occurrence of new treatments including RAI, radiotherapy and chemotherapy (numbers of treatments, cumulative dose) and date of treatment,
- Relapse of the thyroid cancer, including metastases (date of metastases, anatomical localizations) and date and type of treatment of the metastases,
- Date of last follow-up,
- Vital status at the end of follow-up,
- Date of second cancer diagnosis, type of cancer , histological type, TNM

For the sample of patients included in the side-effects survey, the whole saliva before and after stimulation of the salivary glands will be collected at T0 and T6, using standard methods.[25] At T0, T6, and T18, patients will be invited to complete validated questionnaires about salivary and eye dry complaints, quality of life, nutrition, and anxiety and depressive symptoms, and will be questioned about potential risk factors.

3.3 Definition of the outcomes

- Salivary and lacrimal complication outcome will be based on a composite criterion combining objective (salivary flow dysfunctions with or without stimulation) and subjective criteria (difficulty swallowing, dry mouth feeling or eyes dry) at T6,
- SPM occurring more than 5 years from exposure to radioiodine (1 year for leukaemia) will be considered as potentially radiation induced (these are standard lag times used within radiation epidemiology to avoid non-radiation-induced cancers being associated with radiation exposures), though cancers occurring within this latency period will still be recorded and used in the modelling process.

3.4 Dosimetry assessment

Methodologies developed within the MEDIRAD WP3 will be used to calculate individual absorbed organ doses. Guidelines and recommendations for quantitative radioiodine imaging and dosimetry have been published as MEDIRAD deliverable 3.8 and elsewhere.[23, 26]

Dosimetry data will be stored together with imaging data in a dose bio-bank similar to the database developed as part of MEDIRAD.

4. Ethics and Research Governance

Approval for use of patient identifiable data will require ethics committee approval in each participating country and/or centre based on national/regional legislation. No contact will be made with most of the patients during this study, except for the restricted group of patients included in the individual survey who will be required to complete and sign a consent form.

5. Statistical analysis

5.1 Power Calculations

The relationship between radiation dose and sample size required to achieve the required statistical power follows an inverse square law.[27]

Dosimetry within MEDIRAD has helped to identify the organs receiving the highest absorbed doses and the range of absorbed doses to these organs. Absorbed doses per administered activity of 0.2 mGy/MBq (Range 0.1 – 0.9 mGy/MBq) and 0.05 mGy/MBq (0.03 – 0.08 mGy/MBq) were estimated for salivary glands and red bone marrow, respectively. Median effective dose per administered activity was found to be 0.05 mSv/MBq (0.03 – 0.11 mSv/MBq).

Sample size calculations have been carried out in order to estimate the number of patients required to show a statistically significant difference between (1) RAI patients and the general population for total SPM, leukaemia and salivary gland cancer, and (2) RAI patients and non-RAI patients with DTC.[28] Baseline risk are taken from the most recent ONS data for secondary cancer incidence and mortality in the UK (2017). Required number of patients were estimated assuming 15 years of follow up. α = 0.95 and β = 0.2 were chosen. Results are provided in Tables 1 and 2.

Organ specific relationships could be investigated using dose-response models from BEIR VII. [27]

Site	Baseline Risk (Cancers/10000 people/year)	SIR (Observed/Expected) (RAI/General Population)	N Required	Expected Excess Cancers
Total SPM	567.4	1.30 [1.10 – 1.50] [29]	3347	85
Leukaemia	14.4	3.14 [1.89 – 4.91] [16]	5141	24
Salivary Gland	0.9	3.84 [1.66 – 7.56] [30]	53458	21

Table 1: Required sample size (N) to detect SIR as published in the literature in RAI patients vs. general population. Baseline risk taken from ONS 2017 England Cancer Statistics. Expected excess secondary cancers = expected cancers in RAI group – expected cancers in general population.

Site	Baseline Risk (Cancers/10000 people/year)	Relative Risk (RAI/Non-RAI)	N Required	Expected Excess Cancers
Total SPM	567.4	1.19 [1.04 – 1.36] [15]	7244	128
Leukaemia	14.4	2.50 [1.13 – 5.33] [15]	7042	29
Salivary Gland	0.9	7.50 [1.20 – 143] [29]	35005	16

Table 2: Required sample size (N), based on published estimates of relative risk, to show an increased risk of cancer in DTC patients receiving RAI vs. patients not receiving RAI. Baseline risk taken from ONS 2017 England Cancer Statistics. Expected excess secondary cancers = expected cancers in RAI group – expected cancers in non-RAI group.

The calculation of the number of patients required for the individual side effects survey is based on a statistical power of 80% with an alpha risk of 5%, and with theoretical relative incidences of salivary and lacrimal dysfunctions of 15%. Estimating that dysfunctions would occur during the first 6 months after RAI, and using a self-controlled design, we calculated a requirement for 1372 patients. To allow for a drop-out rate of 5%, 1400 patients will be needed.

5.2 Planned analyses after data collection

For descriptive purposes, external comparisons will be made with the general population of the country/region and standardized incidence ratios (SIR) / standardized mortality ratios (SMR) will be calculated by computing the ratio of the observed to expected cases of individual disease types.

Dose-response analyses will include (conditional) Poisson or Cox regression modelling in the full cohort study, in order to estimate the relative risk of the specific disease of interest in relation to the estimated organ absorbed dose of ionizing radiation.

Lag periods will be defined for each specific outcome and will *a priori* include 1 year for leukaemia, 5 years for solid tumours and lymphoma. Sensitivity analyses will evaluate other lag periods. All analyses will be adjusted for sex, age, and region. Potential confounding will be assessed. Data analysis will be conducted separately for each study region/country as well as for the combined international dataset.

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