Project outline and justification for data/sample request

1. Investigators

1.1. Recipient Scientist, coordinator of the proposed project

Henri Timmers

1.2. Status of the Recipient Scientist

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1.3. Associated Investigators

Jacques Lenders (Nijmegen/Dresden),
ENS@T registry and eCRF support: Anthony Stell, Richard Sinnott (Melbourne)
PI's of participating ENSAT centres.

2. Project

2.1. Name of Project

Impact of 123I-MIBG scintigraphy on clinical decision making in patients with PPGL ('MIBG impact study')

2.2. Scientific context

In patients with a biochemically established diagnosis of PPGL, imaging is critical for a) primary tumor localization and delineation; b) detection of multiple primary tumors; c) detection of metastases, guiding the optimal choice between curative surgery and palliative treatment options. 123I-metaiodobenzylguanidine (MIBG) scintigraphy is widely used and considered as gold standard for the functional imaging of PPGL, despite limitations such as low sensitivity in extra-adrenal (56-75%), metastastatic (56-83%) and SDHx-related PPGLs (<50%) and false positive results due to physiological uptake by 50% of normal adrenal glands.
In the 2014 Endocrine Society clinical practice guideline on PPGL it is recommended that 123I-MIBG scintigraphy is used as a functional imaging modality in addition to CT/MRI in patients with metastatic PPGL when radiotherapy using 131I-MIBG is planned, and occasionally in some patients with an increased risk for metastatic disease due to large size of the primary tumor or to extra-adrenal, multifocal (except skull base and neck PPGLs), or recurrent disease. The latter recommendation is largely based on expert opinion. There is a lack of studies on the added value of functional imaging as part of the diagnostic evaluation of patients with PPGL when it comes to therapeutic planning and patient outcome.

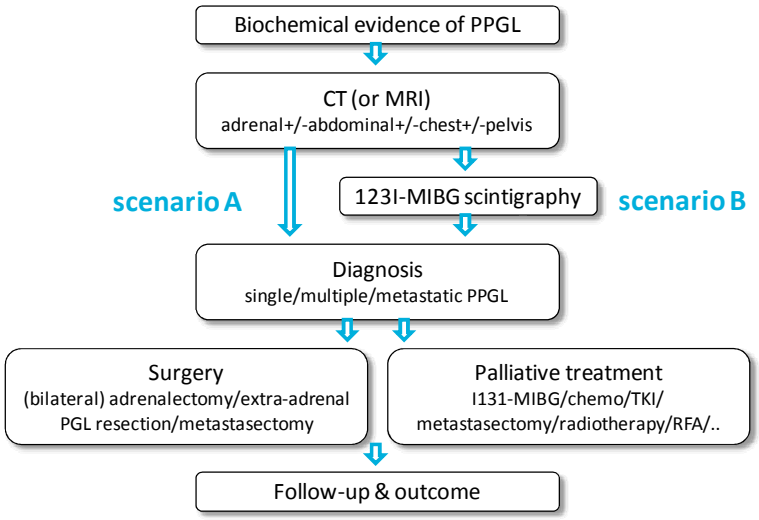
2.3. Aim

To evaluate the yield of 123I-MIBG scintigraphy as part of the diagnostic work up of patients with biochemically established PPGL as compared to routine anatomical

imaging by CT (or MRI) and to determine the impact of 123I-MIBG scintigraphy on clinical decision making regarding surgery and / or palliative treatment.

2.4. Methods

This study entails a retrospective analysis of data entered into the ENSAT registry of patients who each underwent both CT (or MRI) and 123I-MIBG scintigraphy as part of their diagnostic work up of biochemically established PPGL. Imaging results and other data, as detailed below, will be analyzed. Two diagnostic scenarios will be compared (see figure below). According to scenario A, the diagnosis (single/multiple/metastatic PPGL) relies on CT (or MRI) only, whereas in scenario B, additional 123I-MIBG findings are taken into account. The data according to scenario A and B will be evaluated by an independent expert panel separately. In case of scenario A, the panel is blinded to the MIBG results.
The primary outcome measure is the frequency of discrepancies in the diagnosis and ensuing choice of treatment between scenario A and B. The potential added value of 123I-MIBG scintigraphy will be investigated across differences in biochemical phenotype, tumor location(s), tumor size, recurrence and genotype. A sample size of at least 200 patients is warranted.



2.5. Requested clinical annotations (type, justification)

Inclusion criteria:

- proven PPGL (based on histological examination of resected or biopsied tumor material)
- when tumor material is not available for histological examination (i.e., patients with metastatic disease) inclusion may be based on imaging evidence of metastatic disease (including functional imaging evidence) combined with either a past history of a pathologically proven PPGL or biochemical evidence of excess catecholamine production definitive for a PPGL.
- CT and/or MRI performed as part of diagnostic work-up
- Whole body 123I-MIBG performed as part of diagnostic work-up

Minimum clinical annotations:

- Age, sex
- Biochemical phenotype
- Hereditary syndrome / germline mutation
- Imaging evidence for the present prospectively established PPGLs, including imaging modality(ies), 'window' of imaging, tumor location(s), tumor

dimension(s) at least 1 dimension) and any evidence of metastases with details of numbers and locations of metastases.
- If tumors have been resected, date of surgical removal, tumor numbers resected, location of tumor(s), size of tumor(s) in at least 2 of the three x, y, z dimensions at pathological examination, and any evidence of metastases from resected lymph nodes, post-operative biochemical cure, post-operative (metastatic) recurrence, survival
- In case of systemic treatment: MIBG radiotherapy / chemotherapy / other
- In case of local palliative treatment: radiotherapy / RFA / cryoablation

2.6. **Requested samples (type, justification of sample size)**
Not applicable

2.7. Expected results
Currently existing expert-based recommendations regarding the selective use of 123I-MIBG in patients with an increased risk for metastatic disease based on tumor size, location and recurrence could be validated/specified and additional determinants of the relevance of functional imaging could be identified. This could lead to a more efficient and cost-effective diagnostic approach.

2.8. **Projected time frame**
Deadline for data acquisition (i.e. input in ENS@T registry): Nov 2015
Deadline for data analysis: Feb 2016
Expected manuscript submission: May 2016
Targeted Journals (depending on outcome): JCEM

3. Publication policy

1. Recipient scientist formally agrees with the provider(s) - at the time of the request or soon after the provider(s) have accepted the collaboration - the(ir) presence (if any) as co-authors in the publications originating from the collaboration.

2. Number of authors per centre and order of authorships are specified as follows:
1-2 co-authors per centre depending on patient numbers provided as defined in the minimum clinical annotations and projected time frame. Depending on the contribution of each centre or if number of authors has to be limited on the basis of a specific journal style co-authors will be represented as “on behalf of ENS@T” and placed in an appropriate list depending on the Journal format (acknowledgment or collaborators list). In this case the recipient scientist will contact all provider(s) and obtain agreement.
3. The authors agree to acknowledge ENS@T contribution: “This project has been supported by the European Network for the Study of Adrenal Tumors (ENS@T).” (For ENS@T-CANCER related projects: “The research leading to these results has received funding from the Seventh Framework Programme (FP7/2007-2013) under grant agreement n° 259735.”)

4. Conditions of data usage

1. The Recipient scientist will use the data for research purposes only.

2. The data will be used by the Recipient scientist solely in connection with the Research Project as outlined above.

3. The Recipient scientist shall use the data in compliance with all applicable laws and government regulations of the Recipient's country.

4. The Recipient Scientist shall not release the data to any person other than the personnel under the Recipient Scientist's direct supervision.

5. When the Research Project is completed, a detailed description of the use of the data will be made available to the appropriate ENS@T Working Group

6. In the event that a journal publication or scientific article is published based on use of the data, the Recipient Scientist will send a copy of such publication, or the publication cite, promptly after it becomes available to the Recipient, to the appropriate ENS@T Working Group

Date 30/11/14 Signature

5. **Conditions of biomaterial usage**
   Not applicable