Registry and Biobank of the European Network for the Study of Adrenal Tumours (ENS@T)

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A core part of the scientific efforts of ENS@T researchers bases on the establishment of a common registry and associated collection of biomaterials. Patients with adrenal tumours prospectively included in the ENS@T registry will be asked to provide...

Ethical review	Approved WMO
Status	Will not start
Health condition type	Adrenal gland disorders
Study type	Observational invasive

Summary

ID

NL-OMON40333

Source
ToetsingOnline

Brief title
ENS@T data- en biobank

Condition

- Adrenal gland disorders
- Endocrine neoplasms benign

Synonym
adrenal tumours

Research involving
Human

Sponsors and support

Primary sponsor: Universitair Medisch Centrum Sint Radboud
Source(s) of monetary or material Support: SP7 ENSAT CANCER

Intervention

Keyword: biobank, databank, paraganglioma, pheochromocytoma

Outcome measures

Primary outcome

Collection of biomaterial will be performed to provide the basis for the identification of novel biomarkers to improve individualized therapeutic regiments. Specifically, the following parameters will be taken into account:

1. Prognostic markers: An increasing number of adrenal masses are detected incidentally during imaging (*adrenal incidentalomas*), but the assessment of the malignant potential of these tumours by imaging procedures is difficult. Even in patients operated on, both adrenocortical carcinoma and malignant pheochromocytoma can often not be definitely distinguished from benign adrenal tumours based on histomorphological features alone, and within both entities a phenotypic range exists that impairs consistent prognostic classification. Reliable and sensitive screening tools for early detection and risk stratification of adrenal cancers are currently lacking, which makes the development of such tools a clinical priority. Similarly, benign adrenal tumours can be associated with significant morbidity and mortality due to their endocrine activity. Definition of patient subgroups with increased cardiovascular risk profile would enable initiation of close follow-up and justify more aggressive treatment.
Newly applied genomic techniques including expression analysis, microRNA profiling, methylation pattern, chromosomal gains and losses, proteome

techniques and exon sequencing will refine a set of markers that identify subgroups of tumours with defined biological behaviour. Lymphocytic DNA will be utilized for comparison of genetic markers identified during mutation analysis. Validation of identified marker genes will be performed by immunohistochemical approaches on paraffin embedded and frozen tumour material. Furthermore, functional characterization of fresh tumor specimen will be included in in vitro (primary cell culture) and in vivo (xenotransplantation model) assays. Secreted markers will be assessed by metabolome techniques in blood and urine samples and from functional in vitro and in vivo assays. In all cases correlation with disease free survival and overall survival as most significant clinical endpoints will be included.

2. Markers of treatment response: Similarly, markers that would predict outcome after a specific therapeutic intervention are being sought. Based on molecular, genetic, biochemical and functional analyses as described above markers will be defined that are associated with a beneficial or unfavourable response after specific therapy. Examples for malignant tumours (adrenocortical carcinoma and malignant pheochromocytoma) include markers of recurrence free survival after complete surgical resection (R0) or treatment response in patients without resectable disease after chemotherapy, radiotherapy or targeted therapy. In patients with benign hormone secreting tumours markers will be identified that correlate with treatment response (e.g. surgery or medical therapy) and cardiovascular endpoints.

3. Follow-up markers: A significant problem in the follow-up of patients with malignant adrenal tumours is the timely detection of persistent or recurrent disease following an apparently complete surgical resection. Delay in detection can often translate into postponed initiation of treatment and, thus, worsening of prognostic outlook. Biomarkers for detection of persistent or recurrent disease will be identified on the basis of the above defined *omic and functional technologies.

Secondary outcome

no applicable

Study description

Background summary

Adrenal tumours
Tumours of the adrenal glands arise from the cortex or the medulla part of the adrenal gland. Clinical manifestations arise because of symptoms from excess secretion of hormones by the tumours. The tumours from the adrenal cortex can produce excess of steroid hormones including cortisol and aldosterone and tumours from the adrenal medulla can produce excessive amounts of catecholamines. Malignant adrenal tumours can also manifest through local mass effects or symptoms related to distant metastatic spread. Adrenal tumours can be benign or malignant. Often this separation is difficult to make and long-term close follow up is necessary after surgical removal to detect recurrences early in patients who have adrenal cancer. While malignant tumours of the adrenal gland are rare, up to 3.5% of the population have so called adrenal incidentalomas - tumours of the adrenals found incidentally during investigation for an unrelated condition. The majority of these do not secrete hormones (1).

Aldosterone Producing Adenoma
Primary aldosteronism is the most frequent form of secondary hypertension accounting for more than 11% of referred hypertensive patients (2). Although it is usually held to be caused by bilateral idiopathic hyperplasia in approximately two-thirds of cases and aldosterone-producing adenoma (Conn's syndrome) in one-third, these relative rates are reversed when adrenal vein

sampling is systematically used (2). Hence, primary aldosteronism due to adrenal tumours is likely the most common form of the disease. However, many experts now contend that there could be a continuum between bilateral adrenocortical hyperplasia and unilateral aldosterone-producing adenoma. Of note, notwithstanding the high prevalence of primary aldosteronism the molecular mechanisms underlying excess aldosterone production in this continuum remain totally unknown. Therefore, the availability of a large collection of aldosterone-producing tumours would be instrumental for allowing investigating these molecular mechanisms through application of novel techniques for the analysis of the whole transcriptome (3), the microRNA profile and the proteome.
In its classical form, primary aldosteronism presents with aldosterone excess, low plasma renin activity, while hypokalemia, once assumed to be a hallmark of the syndrome lacks in most cases. Patients with aldosterone producing adenomas have more severe hypertension, more frequent hypokalemia, higher plasma and urinary levels of aldosterone, and are younger than those with bilateral disease. Once primary aldosteronism is confirmed, the subtype needs to be determined to guide treatment. Computed tomography or magnetic resonance imaging are required to detect the adenoma or and aldosterone-producing carcinoma, but give misleading results in terms of identifying the unilateral or bilateral source of excess aldosterone (4, 5). Hence, to pose the indication for adrenalectomy most patients require adrenal vein sampling (5). Optimal treatment for aldosterone-producing adenoma or unilateral hyperplasia is unilateral laparoscopic adrenalectomy.

Pheochromocytomas and Paragangliomas
Catecholamine-producing tumours may arise in the adrenal medulla (pheochromocytomas) or in extra-adrenal chromaffin cells (paragangliomas). Their prevalence is about 0.2% in patients with hypertension (6-8) and 4% in patients with a incidentally discovered adrenal mass (9).
These tumours may be sporadic or may present as part of any of several genetic syndromes: familial pheochromocytoma-paraganglioma syndromes, multiple endocrine neoplasia type 2, neurofibromatosis 1, and von Hippel-Lindau disease. Familial cases are diagnosed earlier and are more frequently bilateral and recurrent than sporadic cases. The most specific and sensitive diagnostic test for the tumour is the determination of plasma or urinary metanephrines. The tumours can be located by computed tomography, magnetic resonance imaging and metaiodobenzylguanidine scintigraphy. Treatment is resection of the tumour, usually by laparoscopic surgery.
About 10% of tumours are malignant either at first operation or during follow-up, malignancy being diagnosed by the presence of metastases at sites where chromaffin cells should be normally absent (i.e., bones, liver, lungs, lymphnodes). Recurrences and malignancy are more frequent in cases with large or extra-adrenal tumours. Treatment for malignant recurrence includes surgery, therapeutic embolization, chemotherapy and metabolic radiotherapy (10). Patients, especially those with familial or extra-adrenal tumours, should be followed-up indefinitely.

Non-aldosterone cortical adrenal adenomas

Non-aldosterone secreting cortical tumours represent the most common benign adrenal tumour. These may be truly non-functioning, that is not associated with any hormonal excess, and are usually detected incidentally in patients undergoing radiological investigations (ultrasound, CT, MRI scanning) for other reasons. Indeed, autopsy studies have shown that up to 5% of the population may harbour so-called adrenal "incidentalomas". Malignancy rate in these lesions is very low - the majority of lesions are less than 3cm in diameter and can be treated conservatively (11).

Rarely the tumours may secrete cortisol. In the most florid example, Cushing's syndrome results because of severe hypercortisolism resulting in central adiposity, muscle wasting, thinning of the skin with bruising, osteoporosis, hypertension and diabetes mellitus. Removal of the adenoma is required to cure the condition. More rarely patients may have a genetic problem that results in autonomous production of cortisol from adenomas within the adrenals (e.g. McCune Albright syndrome or Carney's complex). The adrenals may also become hyperplastic or tumorous when the adrenal glands develop an unusual pattern of receptor expression over and above the normal receptor that controls cortisol production - the ACTH-receptor.

"Sub-clinical" Cushing's syndrome can also be found in patients harbouring adrenal incidentalomas occurring in up to 10% of all cases. These patients may have an increased risk of hypertension, obesity and diabetes.

Adrenocortical Carcinomas

Adrenocortical carcinoma (ACC) is a rare malignancy with incompletely understood pathogenesis and poor prognosis. Patients present with hormone excess (e.g. virilization, Cushing's syndrome) or a local mass effect (median tumour size at diagnosis > 10cm). Tumours typically appear inhomogeneous in both computerised tomography and magnetic resonance imaging with irregular borders, and differ from benign adrenal tumours by their low fat content. Hormonal analysis reveals evidence of steroid hormone secretion by the tumour in the majority of cases, even in seemingly hormonally inactive lesions. Histopathology is crucial for the diagnosis of malignancy and may also provide important prognostic information. In stages I -III open surgery by an expert surgeon aiming at complete resection is the treatment of choice. Local recurrence is frequent, particularly after violation of the tumour capsule. Surgery plays also a role in local tumour recurrence and metastatic disease. In patients not amenable to surgery, mitotane as a substance with adrenolytic properties remains the treatment of choice (12). Monitoring of drug levels is mandatory for optimum results. In advanced disease, the most promising therapeutic options (etoposide, doxorubicin, cisplatin plus mitotane and streptozotocin plus mitotane) are currently being compared in an international phase III trial. Adjuvant treatment options after complete tumour removal (e.g. mitotane, radiotherapy) are urgently needed, as postoperative disease free survival at five years is below 50% (13).

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European Network for the Study of Adrenal Tumours (ENS@T)

With the exception of endocrine inactive adenomas adrenal tumours are rare. Therefore, progress in diagnosis and treatment of these tumour entities can only be achieved by combining the efforts of researchers and clinicians from several countries. To overcome these difficulties and to achieve significant progress benefiting the affected patients a Network on Adrenal Tumours at a European-wide level has been created.
The European Network for the Study of Adrenal Tumours (ENS@T) aims to improve the understanding of the genetics, tumourigenesis and hormonal hypersecretion in patients with adrenal tumours and associated familial syndromes. It intends to improve the prediction of recurrence and the management of malignant adrenal tumours, which are particularly rare. The study of adrenal tumours is likely to reveal new molecular mechanisms of tumour growth and provide insight into the role of hormones as the cause of hypertension.
ENS@T was founded in 2002 by putting together three already existing National Adrenal Networks (COMETE in France, GANIMED in Germany, and NISGAT in Italy) and teams from the United Kingdom all dedicated to the study of adrenal tumours. In 2009, ENS@T became a membership-based society with statutes and bye-laws (www.ensat.org).

Study objective

A core part of the scientific efforts of ENS@T researchers bases on the establishment of a common registry and associated collection of biomaterials. Patients with adrenal tumours prospectively included in the ENS@T registry will be asked to provide blood and urine samples and * as available * tumour material collected during surgical resection.

The scientific aims of the proposed project can be summarized as follows:

1) Improvement of networking in the field of adrenal research in Europe through integration of local and national research efforts
2) Implementation of an European adrenal tumour registry and associated biobank
3) Improvement of differential diagnosis and risk stratification of adrenal tumours
4) Identification and validation of tools for follow-up of patients with adrenal tumours
5) Identification of novel biomarkers for evaluating treatment response in patients with adrenal tumours
6) Screening for molecular mechanisms as the basis to improve treatment response in patients with adrenal tumours

Study design

- study design: European multi-central retrospective and prospective register study and associated biobank.

- study duration: In a first step, patient enrolment and biomaterial collection is planned for 10 years. However, in case of positive interim analysis this timeframe will be extended. The registry will be maintained for at least 20 years.

- proposed number of patients: Participating European Centers will aim to enrol as many patients with adrenal tumours as possible. An upper limit of patients included in the registry is not defined.

Study burden and risks

The benefits of optimized grading, management and potentially better patient treatment decisions based on biomarker results needs to be balanced against the patient burden including providing clinical information, blood and urine samples and surgical tissue specimens. This balance needs to be cognisant of the ethical principles underlying such scientific research. Our belief is that the benefits to the patient (at least in the long-term perspective) far outweigh the burden imposed. Implementing standardized collections of tumour samples and annotations is necessary to achieve the proposed scientific objectives.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

patients with adrenal tumours who have provided written informed consent

Exclusion criteria

no exclusion criteria are defined

Study design

Design

Study type: Observational invasive

Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Diagnostic

Recruitment

NL

Recruitment status:	Will not start
Enrollment:	200
Type:	Anticipated

Ethics review

Approved WMO

Date:	16-07-2014
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
CCMO	NL45486.091.13