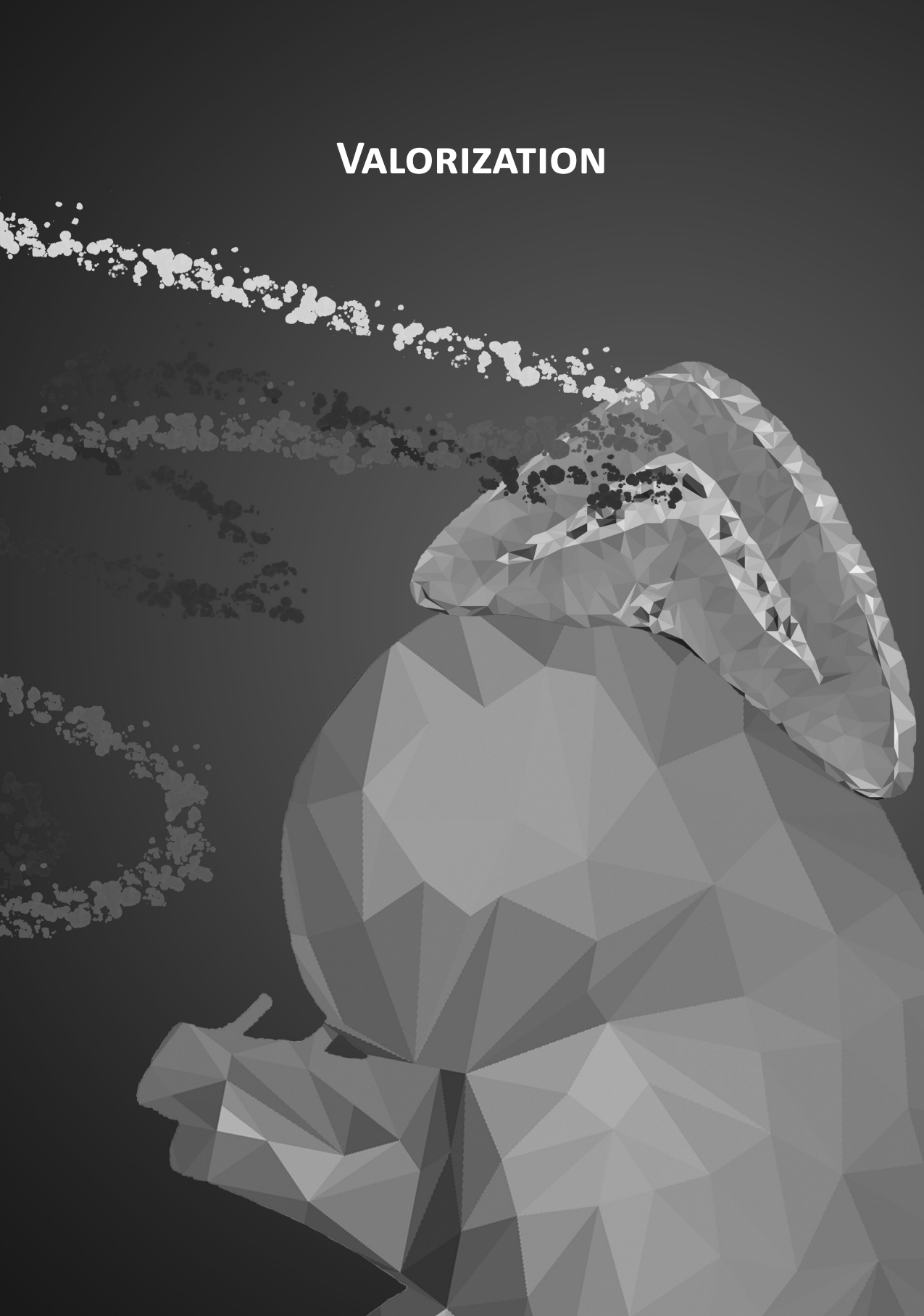
Adrenocortical carcinoma : a study on epidemiology diagnostics and treatment of a rare endocrine malignancy

Valorization



Valorization

It is important to translate academic results to societal or economic benefit and also to suggest routes of implementation to achieve this. This chapter discusses the potential societal or economic benefit of the presented findings.

Part I: Epidemiology

The population-based studies on the epidemiology of adrenocortical carcinoma in children and in adults confirmed the rarity of the disease (**chapter 1 and 2**). With an incidence of one patient per one million inhabitants and an estimated prevalence of 0.5 to 2 patients per hundred thousand inhabitants, ACC is not very interesting from a commercial point of view. After all, investments in new treatment options are difficult to redeem. For this reason, increasing international collaboration and globalization are welcome developments. The European Network for the Study of Adrenal Tumours (ENSAT), founded in 2002, is an expanding collaboration formed by researchers and clinicians. It holds a database with clinical data of >2200 ACC patients (as of June 2015), which is of great potential for future studies. It is expected that this international platform of collaboration will spark future large-scale research projects. The FIRM-ACT trial, launched in 2004 and published in New England Journal of Medicine in 2012, was the first proof that a large, international, multicenter trial could succeed, even if initiated by a non-commercial sponsor. Building on existing networks and infrastructure laid out by the FIRM-ACT trial, the GALACCTIC trial from 2009 demonstrated that a large commercial study on ACC is feasible. In this trial, the inclusion goal of 135 patients was met within the pre-defined enrollment period of 2 years. These undertakings prove that rare diseases are rare, but rare disease patients are numerous.

Part II: Diagnostics

A much discussed matter in management of patients with a non-functioning adrenal adenoma is the frequency and duration of follow-up evaluation. According to current guidelines, it is recommended to repeat adrenal imaging by CT-scan in patients with non-functioning adenomas smaller than 4 cm within 6-12 months after the initial discovery to detect size changes. In addition, annual repetition of hormonal work-up is recommended during 4 years of follow-up. The rationale behind this is mainly to recognize lesions with malignant potential that have escaped detection on primary analysis, and also to identify changes in size or functionality of the adrenal adenoma.

Based on a critical appraisal of the literature as well as on clinical experience of healthcare professionals involved in analysis and follow-up of patients with adrenal incidentaloma, there is a strong impression that adherence to the guidelines results in a substantial amount of unnecessary additional investigations. However, this impression has not yet been underpinned by prospective data that are needed to revise current guidelines. In September 2013, physicians from the University of Groningen conducted a survey among all members of the Dutch Society

of Endocrinology (NVE) in order to examine the current clinical practice with respect to the management of adrenal incidentaloma. With a response rate of 52%, it was shown that a large majority of the respondents follows the guidelines with regard to follow-up investigations including medical imaging with repeat CT-scans.[1] A minority of the internist-endocrinologists ordered even more repeat CT-sans than advised by the guidelines.

Our study on urinary steroid profiling (**chapter 6**) suggests that the diagnostic value of this single laboratory examination is at least similar to repeat imaging studies with CT-scans. These findings will have to be confirmed in a prospective trial, which is already launched (Structured Evaluation of adRENal Tumors Discovered Incidentally - Prospectively Investigating the Testing Yield [SERENDIPITY-trial], NCT02324647). If successful, this is expected to change clinical management of patient with adrenal incidentaloma. USP has several potential advantages over repeat CT-scanning. Collection of a 24-hour urine sample is part of standard care. Consequently, USP does not require an extra effort of the patient. Obviously, USP is much more patient friendly than repeat CT-scanning with its associated extra hospital visits, waiting and procedure time and administration of intravenous contrast. In addition, the patient would no longer be exposed to the potential health risks of CT-scanning (i.e. ionising radiation, contrast nephropathy, contrast allergy). Also, costs of USP (€70,-) are much lower than of CT-scanning (single CT-scan € 200,-). Implementation of urinary steroid profiling after prospective confirmation of our findings is expected to result in an 80% decrease in CT-scan orders.

Part III: Treatment

Concentration of care in a limited number of specialized hospitals aimed at improving outcomes is an important concept in general healthcare, but particularly in oncological care, high risk surgical care and rare diseases.[2] Regarding ACC, increasing evidence suggests that establishment of (inter)national collaborative networks of expert centres has a favourable effect on survival (**chapter 7**).[3, 4] The concept that rare diseases should be treated in a limited number of specialized hospitals seems intuitively logical. Interestingly, a better outcome of oncological treatment in specialized centres is not necessarily correlated with volume requirements.[5] Similar observations were reported in high-risk surgical treatment.[6] Moreover, common minimum volume requirements as instituted for other cancers are hardly feasible for ACC due to the low incidence. For example, the number of new patients with ACC per year in the Netherlands is about 20 (median 21, range 13-26 between 1993 and 2010, **chapter 2**). In reality, the number of surgical procedures for suspect adrenal malignancy will be higher as some pathologies might mimic ACC pre-operatively (**chapter 5**). Nonetheless, the grand total is expected to be too low to institute meaningful minimum volume requirements. In bigger countries this number will be higher, but with 1 patient per 1 million inhabitants it is questionable whether geographical spread would allow for concentration of care on this scale. Quality criteria other than volume are expected to be of greater importance in rare diseases. It seems more important that centres adhere to current state-of-art treatment concepts, which in turn seems best feasible in specialized centres with dedicated physicians. Experience with multidisciplinary oncologic surgery and preferably adrenal/endocrine surgery is a strong recommendation and maybe even

a prerequisite.[2] In addition, participation in international networks and clinical trials should be encouraged to facilitate research on a larger scale, as discussed above in part I.

Chapters 8 to 10 focused on the application of the drug mitotane in clinical management of patients with ACC. Primary aim of this research was to investigate how mitotane dosing can be optimized in order to reach therapeutic plasma levels as early as possible. Also, individually tailored dosing regimens prevent excessive dosing and an overshoot to potentially toxic plasma levels. This is expected to reduce the need for symptom-alleviating drugs and even hospital admissions due to drug toxicity and improve quality of life for patients on mitotane.

Future research aimed at pharmacogenetics of mitotane is expected to further facilitate personalized medicine. For example, patients with genotype 'A' might benefit from a high-dose regimen, whereas in patients with type 'B' a low-dose regimen might result in similar mitotane plasma levels in the same time. By including results on treatment efficacy, it might become clear that some patients do not benefit from mitotane at all and other treatment options should be instituted.

In conclusion, potential societal and economic benefits of this research are numerous and varied, both through direct and indirect effects. The most important items of societal and economic benefit in this thesis are:

- Arguments in favour of increasing international collaboration in clinical trials and basal research due to the rarity of the disease in both adults and children.
- Arguments in favour of less expensive and less invasive follow-up of patients with adrenal incidentaloma.
- Arguments in favour of specialized care in adrenocortical carcinoma, resulting in better treatment outcome.
- First steps towards personalized medicine in mitotane treatment, aimed at more accurate dosing regimens, less drug toxicity and improved quality of life.

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