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Diagnosis and treatment of prolactinomas: the patient's perspective anno 2025

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CHAPTER 1

General Introduction & Outline of the Thesis

GENERAL INTRODUCTION

Prolactinoma

Prolactinomas are generally benign and slowly growing neoplasms of pituitary lactotroph cells or their precursors causing overproduction of the hormone prolactin (i.e., hyperprolactinemia). It is the most common, yet still rare, type of op pituitary adenoma with a prevalence of 50-100 per 1,000,000 patients [1, 2], being more common in premenopausal females than in males (4:1), with a peak incidence around reproductive age (25-40 years old) [3]. After menopause the ratio equalizes [2].

Clinical presentation

Hyperprolactinemia causes a wide variety of symptoms, with the most characteristic being galactorrhea caused by stimulation of the mamillary glands, and menstrual cycle disturbances due to hypogonadism. Hypogonadism is induced by suppression of gonadotroph-releasing hormone (GnRH) via the neuropeptide Kisspeptin and direct inhibitory effects on the sex hormones [4, 5]. Hypogonadism may additionally lead to sexual disturbances, subfertility, fatigue, and decreased bone density in both females and males. Although frequently overlooked, psychological complaints are prevalent, with psychological wellbeing having the largest impact on health-related quality of life (HR-QoL) in patients with active prolactinoma [6]. Cognitive impairments such as impaired attention, auditory and visual memory, processing speed, and executive functioning have consistently been described [7-10]. Moreover, larger prolactinomas may cause mass effects, such as bitemporal hemianopsia and impaired visual acuity due to optic chiasm compression, or pituitary failure due to compression of the pituitary. Figure 1 provides an overview of prolactinoma-related symptoms.

Diagnosis

The diagnosis of a prolactinoma is based on symptomatic hyperprolactinemia providing secondary causes have been excluded and is preferably supported by evidence of a pituitary mass on magnetic resonance imaging (MRI).

Biochemical diagnosis of hyperprolactinemia

Pituitary prolactin secretion is regulated by dopamine, which is produced by the hypothalamus and flows to the anterior pituitary through the hypophyseal portal system, blocking prolactin secretion by binding to the type 2 dopamine receptor (D_2R) on lactotroph cells. Contrarily, thyrotropin-releasing hormone (TRH), vasoactive intestinal peptide (VIP), and estrogen stimulate prolactin production [11]. Figure 2 illustrates the various pathways in prolactin regulation.

Figure 1 Prolactinoma-related symptoms in adults. Symptoms shown in black apply to both females and males, those in pink are specific to females and those in blue are specific to males

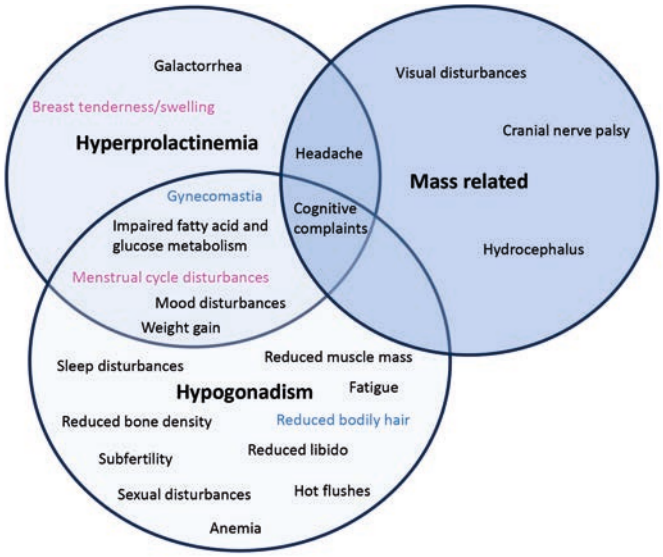
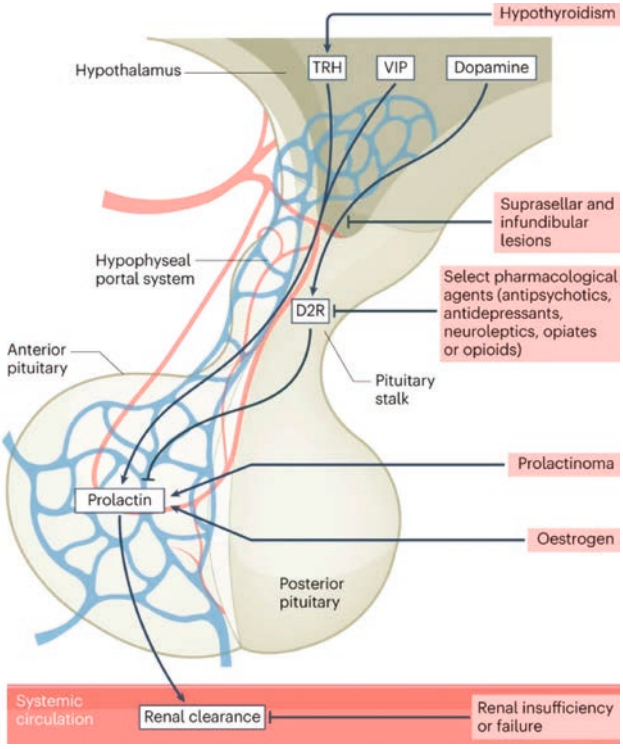


Figure 2 Regulation of prolactin secretion, derived from Petersenn et al. [11]



Although prolactinoma size (*vide infra*) often positively correlates with serum prolactin level [12], exceptions occur. Prolactin levels above five times upper limit of normal (xULN) are highly suggestive of a prolactinoma, yet microprolactinomas may present with only mildly elevated prolactin levels (1.5 to 2 xULN) [11]. In cases with mild hyperprolactinemia, the measurement should be repeated, and other causes of hyperprolactinemia are to be evaluated [11]. Repeated cannulated fasting prolactin measurements during the early follicular phase of the cycle should be performed in relaxed conditions, as (high protein) meals, stress and anxiety may induce mild hyperprolactinemia (two- to fourfold increase) [11]. Moreover, physiological conditions including the luteal phase of the menstrual cycle, pregnancy, nipple stimulation, strenuous activity, and several concomitant diseases including hypothyroidism, adrenal insufficiency, and renal and liver dysfunction can cause prolactin elevation [13, 14]. Hyperprolactinemia may also be induced by dopamine not reaching the pituitary lactotrophs due to pituitary (stalk) compression. Lastly, a thorough medication review is essential, as drugs including dopamine antagonists, antidepressants, antipsychotics, anticonvulsants, opiates, and protease inhibitors may induce hyperprolactinemia [13]. Although the severity of drug-induced hyperprolactinemia varies, more than tenfold increases are rare [11].

In cases of discrepancy between radiologic, clinical, and biochemical findings, assay problems such as high-dose hook effects and macroprolactinemia may be suspected [15]. These phenomena are discussed in Chapter 2 of this thesis.

Imaging (radiological diagnosis)

MRI has been the gold standard for prolactinoma imaging since the 1990's. Prolactinoma size varies from microprolactinoma (<1 cm), to macroprolactinoma (1 cm - 4 cm) and giant prolactinoma (>4 cm), as shown in Figure 3. Due to the lateral distribution of lactotroph cells in the anterior pituitary gland, prolactinomas are frequently localized laterally in the sella, next to the cavernous sinus containing venous channels, cranial nerves, and the internal carotid arteries. On MRI, cavernous sinus invasion can be difficult to distinguish from cavernous sinus compression. In 1993, Knosp et al. published a well-known classification system describing the likelihood of true cavernous sinus invasion based on MRI findings [16]. The initial classification consisted of 4 grades (1 - 4). A subdivision separating grade 3A and 3B was added in 2015 by the same group: the Modified Knosp Classification [17], as illustrated by Figure 4.

As mentioned above, large prolactinomas may compress the optic chiasm, causing visual impairments. The degree of optic chasm compression is described by the Fujimoto classification, varying from no contact with the optic chiasm (Fujimoto 0) to compression of the optic chiasm with deformity of the above cerebral parenchyma (Fujimoto 4) [19].

Figure 3 MRI images of prolactinomas; Image a and b show sagittal and coronal images of an intrasellar microprolactinoma, respectively. Image c and d show sagittal and coronal images of a macroprolactinoma, respectively, and image e and f show sagittal and coronal images of a giant prolactinoma with compression of the optic chiasm. Image a and b were derived from Van Furth et al. [18]

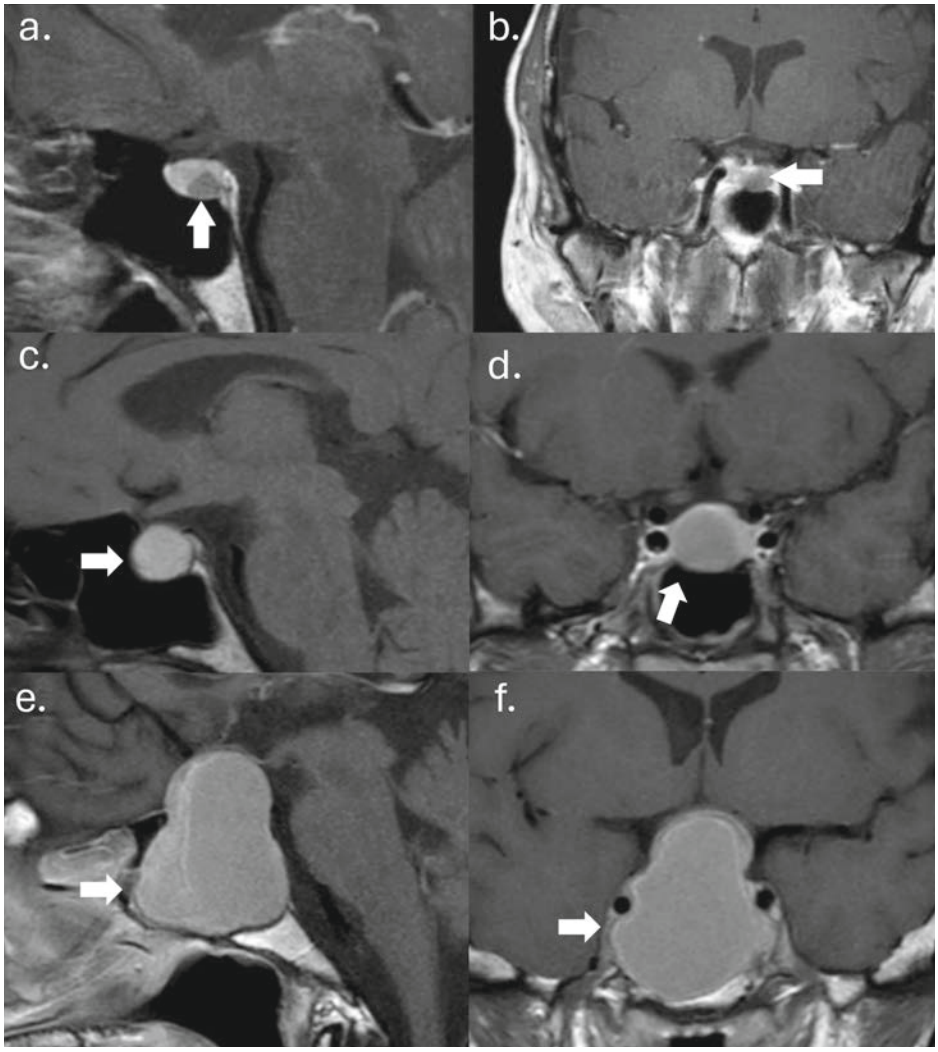
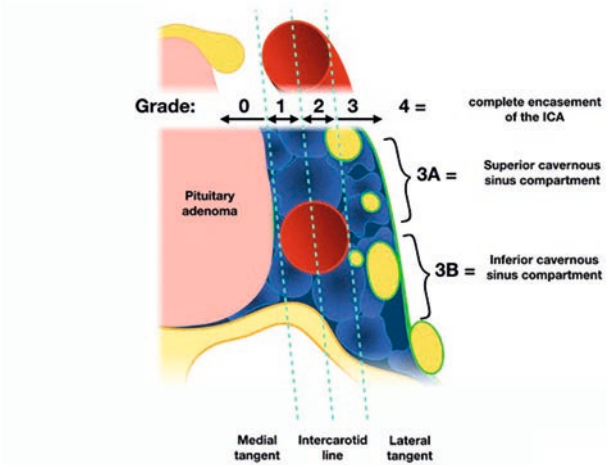


Figure 4 The Modified Knosp Classification, derived from Gaillard et al. [20]



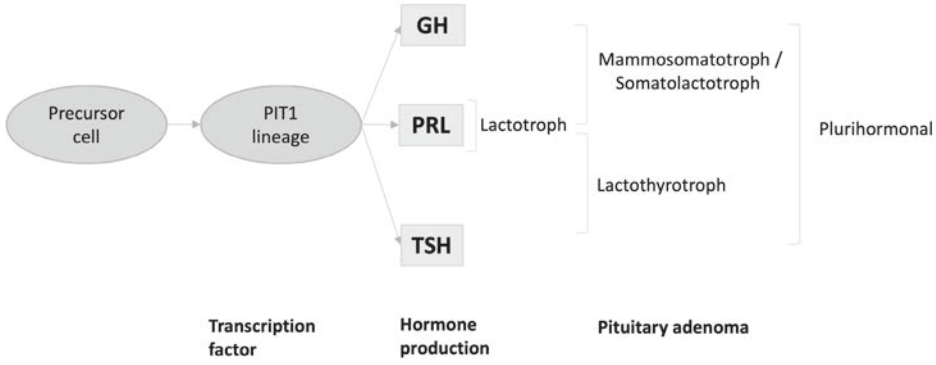
MRI can identify most prolactinomas yet lacks sensitivity for small microprolactinoma (remnants). Functional imaging techniques using positron emission tomography (PET) co-registered with MRI (PET-MRI^{CR}) or direct PET-MRI may be useful in such cases. The most widely used amino-acid based tracer is ^{11}C-methionine ([^{11}C]MET). [^{11}C]MET is preferentially taken up by the pituitary via the L-type amino-acid transporter 1 to be incorporated in proteins, and was shown to be useful for decision making and treatment planning in patients with difficult-to-localize prolactinoma (remnants) [21, 22]. However, its short half-life (20 minutes) complicates its use by requiring an on-site cyclotron (a particle accelerator that is used to produce radioactive isotopes). [^{18}F]fluoroethyl-L-tyrosine ([^{18}F]FET) is an alternative amino-acid based tracer that is taken up by the same transporter which does not require an on-site cyclotron owing to its 110-minute half-life. [^{18}F]FET-PET/MRI^{CR} was shown to be effective for localizing adenomas in acromegaly and Cushing's disease [23-25], however its use in prolactinomas has not yet been described.

Histopathology (confirmation of the diagnosis)

Prolactinoma diagnosis may be confirmed histopathologically in patients undergoing resection or biopsy. Histopathologically, pituitary adenomas are evaluated according to the standardized diagnostic approach of the European Pituitary Pathology Group (EPPG) and classified based on transcription factors and pituitary hormones following the WHO Classification of Tumors (2022) [26, 27]. Prolactin-secreting adenomas are derived from the pituitary-specific positive transcription factor 1 (PIT1) cell lineage and may either produce solely prolactin, i.e., pure lactotroph adenomas (further subdivided as sparsely or densely granulated depending on the number and size of the granules in the prolactin secreting cells), a combination of prolactin and growth hormone, i.e., mammosomatotroph pituitary adenomas, or a combination of prolactin, growth

hormone and thyroid stimulating hormone, i.e., plurihormonal pituitary adenomas. They are closely related to somatotroph and thyrotrophic adenomas, which are also derived from the PIT1 cell lineage [28]. Figure 5 illustrates the PIT1 cell lineage.

Figure 5 Classification of prolactin-secreting adenomas according to the WHO classification (2022) [27]. *GH* growth hormone; *PRL* prolactin; *TSH* thyroid-stimulating hormone



Treatment modalities

Dopamine agonists

Prolactinomas are the only type of pituitary adenomas for which the primary treatment modality consists of medical treatment. Dopamine agonists (DAs) reduce prolactin levels and inhibit lactotroph proliferation by binding to the D_2R on lactotroph cells, inducing normoprolactinemia and tumor shrinkage [29]. In some cases, DAs can even cause the prolactinoma to reside completely. Dopamine agonists induce normoprolactinemia in 88-91% of cases depending on tumor size [30]. Cabergoline, quinagolide and bromocriptine are commonly used, of which cabergoline is first-choice, due to its long half-life, good tolerability, and effectivity [11, 31]. Dopamine agonists are typically used for two years, after which withdrawal may be attempted if normoprolactinemia is sustained on low doses of medication. Remission rates after DA withdrawal, however, are disappointing, with a meta-analysis showing a pooled remission rate of 21% [32]. Although DAs are generally well tolerated, some patients experience side effects, with the most common being mild gastro-intestinal side effects and postural hypotension [11]. A subgroup of patients experiences severe depressive disorders or even devastating impulse control disorders [33, 34]. Furthermore, longstanding high doses of DAs may induce cardiac valvopathy, for which follow-up cardiac ultrasounds are advised [11, 35].

Surgery

Transsphenoidal surgery (TSS), with selective resection of the prolactinoma through the nose, has long been reserved for patients with severe DA intolerance or resistance, patients with mass effects not responding swiftly to DA treatment, cerebrospinal fluid (CSF) leakage or apoplexies [31]. DA resistance is defined as "*lack of normalization*

of prolactin serum levels or lack of relevant mass shrinkage (≥30% reduction in maximum diameter) when treated with standard DA doses (bromocriptine: 7.5–10 mg per day or cabergoline: 2.0 mg per week) for at least 6 months" in the most recent Pituitary Society Consensus Statement [11].

Introduction of endoscopic techniques led to improvement of surgical outcomes. This was illustrated by a systematic review and meta-analysis performed by our group, showing remission rates of 83% (95% confidence interval 76%-90%) in microprolactinomas with complication risks of approximately 5% in retrospective studies [30]. Although these surgical outcomes are promising, high-quality prospective comparison of medical versus surgical treatment is lacking and effects on HR-QoL remain unknown.

Alternative treatments for resistant prolactinomas

Females with microadenomas not desiring pregnancy and males may be treated with sex-hormone replacement to relieve hypogonadotropic symptoms. Alternatively, asymptomatic patients without mass effects may also be left untreated.

The chemotherapeutic drug temozolomide is the first choice in patients with aggressive prolactinomas demonstrating an unusually rapid growth rate or clinically relevant growth despite maximally tolerated DA doses [11]. Furthermore, a few alternative pharmaceutical options not registered for prolactinomas have been shown to be effective in some prolactinomas, such as somatostatin analogues - including octreotide, lanreotide and pasireotide - which bind to the type 2 and type 5 somatostatin receptors present in some prolactinomas [36], as well as selective estrogen receptor modulators like tamoxifen [37]. These treatment options go beyond the scope of this thesis.

Radiotherapy is reserved for patients in whom medical treatment and TSS are unable to control hyperprolactinemia or tumor growth, due to its delayed effect and adverse effects such as hypopituitarism, optic neuropathy, cranial nerve palsy and secondary brain tumors.

Advances in prolactinoma care at the Leiden University Medical Center (LUMC) from 2015 onwards

Around 2015, a joint clinic was opened allowing simultaneous counseling by experienced dedicated pituitary neurosurgeons and endocrinologists. Starting from 2016, a Value Based Healthcare (VBHC) pituitary care pathway was introduced, aiming to increase cost-efficiency by focusing on outcomes relevant to the patient [38]. Prospective data collection of pituitary outcomes commenced following the three VBHC tiers: (1) health status achieved or retained, (2) the process of recovery, and (3) sustainability of health. This approach has previously been described for pituitary care in general but has not yet been specified for prolactinoma care [39].

In 2019, our group initiated two prospective multicenter cohort studies: the ProlaC study - shedding light on HR-QoL and healthcare usage in the heterogeneous patient population, and the PRolaCT study - comparing remission rates and HR-QoL in patients with non-invasive prolactinoma treated medically or undergoing neurosurgical counseling and potential TSS [30]. Referrals for prolactinoma surgery have increased steadily since then. The growing number of prolactinoma surgeries, and designing the prolactinoma studies has shaped the way of thinking about prolactinoma and pituitary care, thereby raising new questions, such as: *which patients are suitable for neurosurgical counseling? What is the best way to counsel patients? How to categorize patients based on probabilities of surgical success and risks - to aid in counseling? What is the best methodology for prolactinoma trials? And which outcome measures are important?*

Towards a clinically relevant classification of prolactinomas to use in counseling

Traditionally, prolactinomas were solely classified based on tumor size (i.e., microprolactinoma, macroprolactinoma or giant prolactinoma). Although this classification provides insight into chances of achieving remission after DA withdrawal, it lacks prognostic value in predicting the probability of surgical success. In 2020, our group introduced a classification system that estimates the probability of harmless total resection to be either *unlikely, potentially* or *likely* based on tumor size, visibility, location with respect to the cavernous sinus, stalk and posterior lobe, and potential tumor shrinkage on DA (as an indicator of potential tumor fibrosis), as illustrated in Figure 6. When the probability of harmless total resection is estimated to be *likely*, surgery may be proposed. However, when the probability is estimated to be either *potentially* or *unlikely*, or when the risk of complications is elevated, surgery is only proposed when the need for alternative treatment to medication is high (e.g., due to severe side effects or resistance to medical therapy). This classification forms the basis of neurosurgical counseling [18].

Towards an integrated way of reporting results: Integrated outcome quadrants

Prospective data collection and registration of treatment goals, and estimations of risks and probabilities of success allowed objective evaluation of treatment outcomes. At the LUMC, on top of classical outcome parameters, treatment is evaluated using integrated outcome quadrants (IOQs), enabling evaluation of treatment based on achievement of the primary treatment goal, combined with the occurrence of adverse effects [40]. This is highly relevant in pituitary surgery because there is a delicate balance between total resection and pituitary damage, however it is also useful to evaluate medical treatment. As depicted in Figure 7, four IOQs are defined: IOQ 1: optimal outcome (intended effect reached without adverse effects), IOQ 2: positive intermediate outcome (intended effect reached with adverse effects), IOQ 3: negative intermediate outcome (intended effect not reached without adverse effects), and IOQ 4: adverse outcome (either intended effect not reached with adverse effects or occurrence of a serious adverse effect, such as death or severe neurological damage - irrespective of achieving the intended effect). This outcome

parameter enhances personalized medicine, as the intended effect (i.e., the treatment goal) can be adapted to each individual patient. Moreover, the goal may be surgical-technical (total resection or debulking) or patient-oriented such as conception, reduction of headaches or improvement of HR-QoL.

Figure 6 Schematic overview of considerations regarding neurosurgical counseling and two illustrative cases. The schematic overview was derived from Van Furth et al. [18]

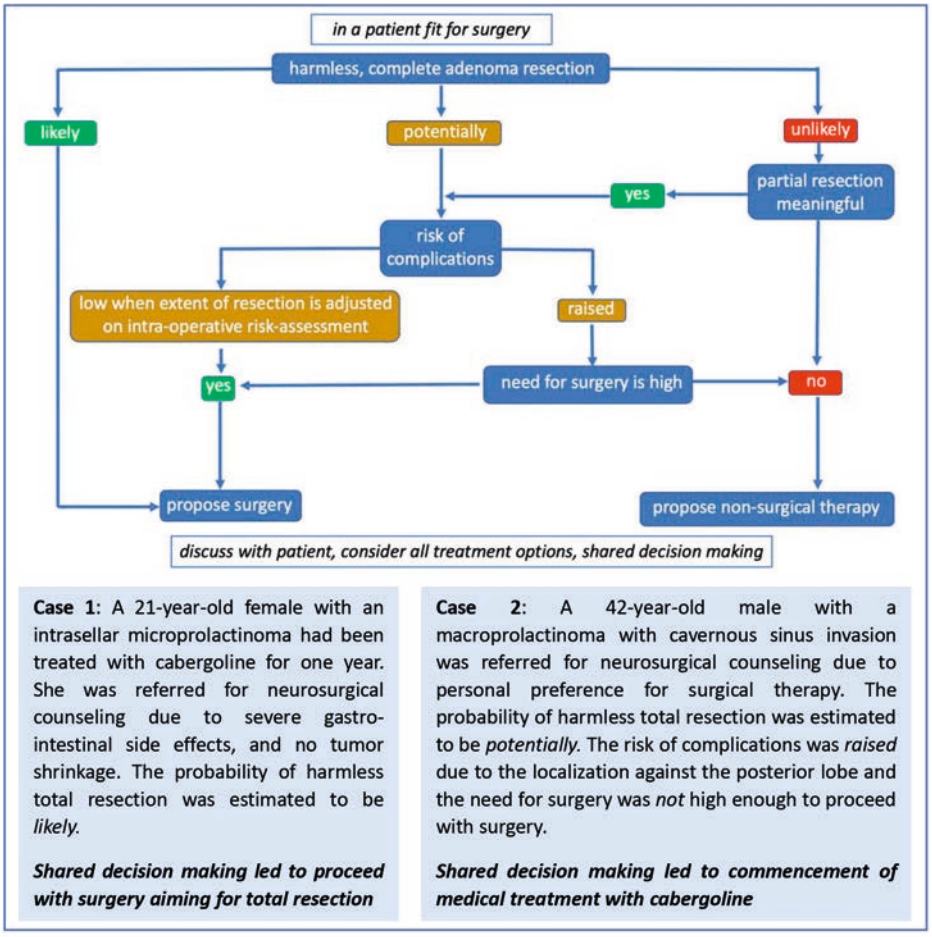
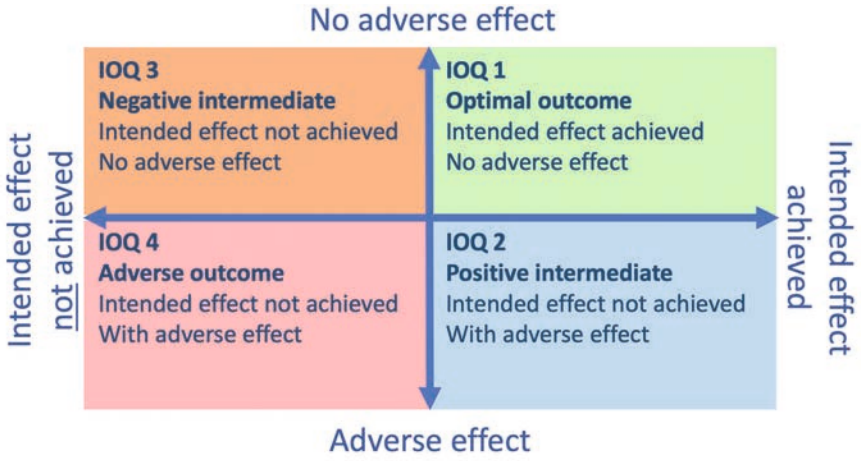


Figure 7 Schematic representation of integrated outcome measures



Towards optimal patient relevant outcomes: Health-related quality of life

Patient-reported outcome measures (PROMs) such as questionnaires, provide direct insight in patients' HR-QoL. PROMs are increasingly being used in endocrinology, offering relevant information, as clinician-reported outcomes are known to frequently be discordant with PROMs [41-43]. It is advisable to use a combination of generic and disease-specific PROMs, because generic PROMs (e.g., Short Form-36 (SF-36) and EuroQoL-5D (EQ-5D)) enable comparison of outcomes across diseases but may lack sensitivity to detect subtle disease-specific impairments. The Leiden Bothers and Needs Pituitary (LBNQ-Pituitary) questionnaire is the only questionnaire that has been validated in pituitary adenomas. No prolactinoma-specific questionnaires have been developed. The LBNQ-Pituitary is a questionnaire that was designed together with pituitary patients and provides insight into the pituitary disease burden [44]. The questionnaire describes the *Bother* that patients experience due to their pituitary disease and the *Need* for attention for these symptoms by their healthcare provider in five domains (mood symptoms, negative illness perceptions, issues in sexual functioning, physical and cognitive complaints, and issues in social functioning). Despite increasing interest in PROMs, HR-QoL data for prolactinomas remain scarce [45]. One recent systematic review identifying only eighteen studies with generally high risks of bias indicated HR-QoL was mostly impacted by mental and psychosocial wellbeing [6]. Nevertheless, high-quality data on HR-QoL outcomes after medical and surgical treatment are lacking, thereby hampering adequate patient counseling. Moreover, interpretation of HR-QoL data is complex as it may be affected by concomitant diseases and life events. Therefore, integration of HR-QoL data in outcome analyses for prolactinomas requires further research.

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AIMS AND OUTLINE OF THE THESIS

Prolactinoma manifestations have long been regarded as mild, yet recent evidence suggests the consequences are more impactful and treatment is less optimal than previously thought. The aim of this thesis was to present novel insights into outcome evaluations, diagnosis, and treatment of prolactinomas. By using patient-reported outcomes alongside the traditional biochemical, radiologic, and clinician-reported outcomes, this thesis aimed to gain a deeper understanding of the patients' disease burden and identify areas of care that require improvement.

Defining success in prolactinoma treatment is complex due to the heterogeneous patient population and disease manifestations. Standardized outcome sets are lacking, and definitions of clinical outcomes are inconsistent, hampering outcome evaluation and comparison of outcomes between patients and pituitary care centers. **Chapter 2** systematically reviewed prolactinoma outcome parameters used in literature and offers suggestions for clinically relevant definitions of *disease remission*, *disease control* and *disease recurrence* based on literature and clinical considerations. Moreover, it provides a suitable outcome set that can be used for evaluation of medical and surgical prolactinoma treatment.

Medical therapy with dopamine agonists has long been the only primary treatment for prolactinomas. Dopamine agonists are effective in achieving normoprolactinemia and tumor shrinkage. However, little is known about patient-reported outcomes in medically treated patients. The PRolaCT and ProlaC study offer a unique insight into the, primarily medically treated, patient population. **Chapter 3** is a cross-sectional analysis using data from the PRolaCT and ProlaC study to gain insight in patient- and disease characteristics, and patient-reported outcomes for female patients with prolactinoma - shedding light on disease burden and its determinants.

Prolactinoma surgery used to be reserved for patients with severe intolerance or resistance to medication, or with an emergency indication due to an apoplexy or cerebrospinal fluid leakage. **Chapter 4** describes the care trajectories of patients who underwent surgery between 2017 and 2019 - a time in which prolactinoma surgery was highly controversial. Over the past decades, surgery has become more accepted due to improved endoscopic techniques, yielding high remission rates with low risks of complications, as described by retrospective studies. **Chapter 5** prospectively describes surgical and patient-reported outcomes of consecutive patients undergoing prolactinoma surgery at the Leiden University Medical Center between 2021 and 2023, aiming for either total resection or debulking – a period in which neurosurgical counseling had become more accepted.

Although MRI is the gold standard for prolactinoma diagnosis, it lacks sensitivity for small microprolactinoma (remnants). With surgery becoming more important in prolactinoma treatment, accurate localization of adenoma (remnants) has become more important. **Chapter 6** describes the utility of [^{18}F]fluoro-ethyl-L-tyrosine PET co-registered with MRI for identification of difficult-to-localize prolactinoma (remnants) with a high need for surgical treatment.

Medication and surgery effectively induce normoprolactinemia, however, their effect on cognitive and psychological complaints were unknown. **Chapter 7** assesses cognitive functioning and psychological complaints in normoprolactinemic patients who have been treated medically or surgically.

A subset of adenomas, among which prolactinomas, do not respond well to primary treatment, for instance due to resistance to medication and/or invasive growth hampering total resection. These patients require additional, often life-long treatment, potentially impairing HR-QoL. **Chapter 8** describes the use of patient-reported outcome measures in patients with difficult-to-treat (i.e., refractory) pituitary adenomas, including prolactinomas.