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

Trigt, V.R. van

CHAPTER 10

General Discussion and Future Perspectives

Prolactinomas are the only type of pituitary adenomas for which treatment is primarily medical with dopamine agonists (DAs). Although it is the most common type of pituitary adenoma, there has long been little scientific interest (**Chapter 8**), as the clinical phenotype was considered mild, and DAs are safe, and effective in restoring normoprolactinemia. Consequently, side effects, persisting symptoms, low medical remission rates and impaired health-related quality of life (HR-QoL) were frequently overlooked, causing the disease burden to be unrecognized.

Emerging evidence on disappointing medical outcomes, and improved surgical techniques prompted our group to perform a systematic review and meta-analysis, which indicated prolactinoma surgery yields high remission rates with a low risk of complications in non-invasive prolactinomas [1]. Moreover, a survey on treatment satisfaction and willingness to undergo prolactinoma surgery was distributed through the Dutch Pituitary Association, indicating patients were keen on participating in research regarding prolactinoma treatment and were interested in surgical options. Consequently, the ProlaC and PRolaCT studies were initiated in 2017 and 2019, respectively, which are currently still open for inclusion [2]. The PRolaCT study, comparing medical treatment to neurosurgical counseling in patients with non-invasive prolactinoma was initially highly controversial because surgery used to be reserved for emergency situations or patients with severe intolerance or resistance to medication (**Chapter 4**). However, after elaborate discussion with pituitary experts during (inter)national conferences, and more publications on surgical results, the global perspective on prolactinoma treatment started to change, and now - approximately six years later - increasing numbers of referrals for counseling and prolactinoma surgery have enabled our knowledge of prolactinoma treatment, counseling, and outcome evaluations to grow, opening our eyes for unmet needs in prolactinoma diagnosis and treatment. This thesis was composed of studies that aided in understanding this disease entity and identified areas for improvement of prolactinoma care by highlighting the patient's perspective.

Outcome evaluation – What should we aim for?

Outcome evaluation is complex in prolactinoma care, due to the heterogeneity of disease manifestations (**Chapter 2**). Standardized outcome parameters are essential to enable comparison of results between treatment modalities and pituitary centers of excellence (PTCOEs). Ideally, all outcome parameters should be objective and universal, although, in reality, objective outcome parameters such as serum prolactin levels, and the gonadal status do not suffice to evaluate treatment success. For instance, some patients with marginally elevated prolactin levels are free from prolactinoma-related symptoms and have an excellent HR-QoL. This result would be classified as unsatisfactory when restricting the definition of treatment success to biochemical remission (i.e., normalization of serum prolactin) despite these patients not having an indication for further treatment. Hence, objective outcome parameters are essential for evaluation of outcomes across treatment modalities and pituitary care centers, nevertheless, the

individual patient sometimes requires a more individualized approach. Using the term *clinical remission* (i.e., resolution of typical prolactinoma-related symptoms, and recovery of the gonadal axis, without a clear remnant on MRI) may contribute to holistic patient-centered care (**Chapter 2**).

The complex relationship between prolactin levels, clinical symptoms and HR-QoL

Our findings showed patients with active prolactinoma were most burdened by psychological and cognitive complaints, improving significantly after disease control (**Chapter 3, 5** and **7**) - in agreement with a recent systematic review by Castle-Kirszbaum et al. [3]. Although HR-QoL is associated with disease activity (**Chapter 3**) [3], it varies considerably between individuals (**Chapter 3** and **5**). Besides issues with measurement of HR-QoL due to PROM-related issues (**Chapter 2**), true variations of HR-QoL may be multifactorial. Firstly, the severity of symptoms does not always correlate with prolactin levels, i.e., some patients become hypogonadotropic with only mild hyperprolactinemia, whereas others may become pregnant with more severe hyperprolactinemia. Secondly, the impact of symptoms on the individual may vary. For instance, subfertility may severely impact HR-QoL in a patient trying to conceive, whereas patients with a completed family may not be impacted at all.

Another explanation for varying HR-QoL might be mild co-secretion of tumors. As mentioned in the introduction, histopathologically different tumors may lead to the clinical presentation of a prolactinoma, with some tumors co-secreting growth hormone (GH) (or more rarely thyroid-stimulating hormone) to varying degrees. When the tumor excretes large amounts of GH, an abnormal oral glucose tolerance test will confirm the concomitant diagnosis of acromegaly. However, when co-secretion is only mild the biochemical diagnosis may not be evident. We hypothesize that some patients with poor HR-QoL might have whispering GH co-secretion and may benefit from surgical removal or additional treatment with somatostatin analogues or GH receptor antagonists. Naturally, this hypothesis requires further investigation. Taken together, HR-QoL is highly variable and underlying reasons for impaired HR-QoL should be explored individually.

Changing perspectives on prolactinoma treatment

Data on treatment outcomes is largely derived from mostly retrospective, small studies at a high risk of bias. These studies indicate cabergoline induces normoprolactinemia in 95% (95% confidence interval (95%CI) 85%-96%) of patients and tumor shrinkage in 88% (95%CI 82%-94%) of patients [1]. Remission rates after DA withdrawal depend on tumor size and duration of medical treatment, with the highest rates in cases showing evident tumor shrinkage on low doses of medication. A recent meta-analysis showed a disappointing 21% pooled remission rate in microadenomas and 16% in macroadenomas [4]. Surgical remission rates were found to be 82%-83% and 44%-60% in micro- and macroprolactinomas, respectively, with the highest rates in adenomas with lower Knosp

grades [1, 5]. These findings induced an interesting change in perspective amongst prolactinoma experts, with the 2023 Pituitary Society Consensus Statement suggesting primary surgery should be discussed with patients harboring non-invasive prolactinoma [5]. **Chapter 5** provided additional prospective evidence for this standpoint. This Chapter describes the first large prospective cohort study reporting on surgical outcomes and HR-QoL in surgically treated patients with prolactinoma, indicating surgery in a Pituitary Center of Excellence (PTCOE) is safe and effective, and induces improvement of HR-QoL - measured by the Leiden Bothers and Needs Pituitary (LBNQ-Pituitary). Remission rates exceeded 90% in patients with non-invasive prolactinoma (Knosp ≤2), which was similar in patients undergoing their first and repeat surgeries. Thus, emerging evidence points towards surgery being a good primary treatment option for non-invasive prolactinomas alongside medical treatment. Nevertheless, these findings should be confirmed in large prospective cohorts comparing surgical and medical outcomes.

Who should be offered prolactinoma surgery?

Digitalization and the rise of artificial intelligence (AI) have improved the availability of information for patients on prolactinomas and treatment options. Increasingly, patients are taking control of their own healthcare by requesting second opinions for multidisciplinary neurosurgical counseling in our PTCOE after having read about the PRolaCT study online. In our experience, especially the group of young females (20-30 years old) preferring surgery over long-term medical treatment is expanding. Although this group may benefit from surgical intervention, it is essential to thoroughly assess the need for surgery and expectations of surgical intervention and ensure their understanding of the associated risks, as is the case for all patients considering pituitary surgery.

The most recent Pituitary Society Consensus Statement suggests primary surgery should not be offered to tumors with Knosp grades 2 or higher due to lower remission rates in this group [5]. However, our prospective cohort study illustrated remission rates were >90% in patients with Knosp 2 tumors, with a low complication rate (**Chapter 5**). This implies the Knosp cut-off may be applied more liberally when surgery is performed by pituitary neurosurgeons who have experience with opening the medial wall of the cavernous sinus. Moreover, the adenoma's localization with respect to the posterior lobe, its visibility and potential fibrosis due to medical pretreatment are equally important to evaluate (**Chapter 4** and **5**). Who should be offered prolactinoma surgery depends on the need for surgical intervention, probabilities of achieving the surgical goal and the surgical risks – all depending on the individual patient, tumor characteristics and the neurosurgeons' abilities.

Surgery - when is the time right?

The question regarding surgical timing is multifaceted. From one point of view, surgery should not be preceded by medical therapy, as primary surgery seems to yield the best remission rates [6-9], because DAs may cause fibrosis, calcifications, and tumor

shrinkage, rendering harmless total resection more complicated [7, 8]. In accordance, the surgical goal was achieved in all patients undergoing primary surgery in our cohort (**Chapter 5)**. However, the number of patients was small, and selection bias must be taken into account, as physicians may be less inclined to perform primary surgery when surgical probabilities are suboptimal. With the change in Expert Consensus (Pituitary Society) concerning surgical treatment, patients are being referred for surgery earlier in their disease. This will enable better comparison of the histopathological and surgical effects of DA pretreatment.

From another point of view, medication is safe and usually well-tolerated, inducing remission in some patients without the risk of surgical complications. Moreover, medication is more cost-effective than surgery in patients who do achieve remission after two years of treatment [10-13]. Hence, the answer to this question is not straightforward and requires additional investigation. Adequately assessing the effects of pretreatment on remission rates requires either randomized controlled trials or large prospective cohorts to enable stratification for tumor characteristics.

Identification of complex prolactinoma remnants

Small prolactinoma (remnants) may not be visible on conventional MRI. **Chapter 6** showed [^{18}F]fluoro-ethyl-L-tyrosine PET co-registered with MRI ([^{18}F]FET-PET/MRI^{CR}) may be useful for shared-decision making and treatment planning in patients with unclear lesions on conventional MRI. Because indication setting and interpretation of the results is complex, this technique should only be used in centers with experienced multidisciplinary teams. In our center, [^{18}F]FET-PET/MRI^{CR} supported the decision to proceed with surgery in approximately half of patients with a high need for surgical treatment - achieving treatment goals in almost 90% of these cases. This tracer has an advantage over the more widely used ^{11}C-methionine ([^{11}C]MET) tracer because of its longer half-life, which enables its use in centers lacking a cyclotron. Although [^{18}F]FET-PET/MRI^{CR} is more complex to interpret because of its washout in the cavernous sinus, this did not seem to hamper its interpretability by an experienced team and outcomes correlated well between the two modalities in two patients undergoing both. Based on tracer characteristics, we hypothesize that [^{18}F]FET-PET/MRI^{CR} may be more sensitive for small intrasellar lesions due to lower background signals of the normal pituitary, whereas [^{11}C]MET-PET/MRI^{CR} may be more sensitive for lesions with parasailer invasion, however comparison of the tracers within patients is required to draw definitive conclusions.

It should be stressed that evaluation of the added value of functional imaging was challenging, as surgical outcomes depend largely on the neurosurgeon's skill, and it remains unknown if the same outcomes would have been reached without functional imaging. While awaiting large prospective studies, restrictive use of functional imaging within a dedicated pituitary care pathway is advisable due to their costly and time-consuming nature.

Recovery after treatment - more than meets the eye

Despite improvement after treatment, HR-QoL does not always normalize compared to healthy individuals [3] (**Chapter 3, 5** and **7**). Naturally, the timing of measurement is important, as recovery is a process that may require many months (**Chapter 3**) [14]. Moreover, physicals symptoms were shown to improve earlier than psychological symptoms [14], and the time to recovery may vary from patient to patient.

Persisting psychological complaints and subtle cognitive impairments may be factors contributing to impaired HR-QoL after biochemical control (**Chapter 3** and **7**). Despite the cognitive impairments found in **Chapter 7** being categorized as subtle, some patients articulated these impairments impacted their personal and professional life significantly and they felt these symptoms were not always acknowledged by their physician. Pretreatment and consecutive posttreatment measurements may provide insight into (partial) reversibility of symptoms, yet full recovery can only be judged by the patient, and subjective complaints should prompt referral for rehabilitation or self-management programs [15].

Methodological lessons learned from prolactinoma research

When performed correctly, randomized controlled trials (RCTs) provide the most reliable scientific evidence by eliminating bias through random assignment of the intervention of interest. In large cohorts, RCTs can balance measured and unmeasured variations of group characteristics, providing high internal validity [16]. However, RCTs are not free of post-randomization bias e.g., due to potential loss to follow-up and missing data [17]. Initially, the PRolaCT study was an RCT, randomizing patients to either standard care with DA or neurosurgical counseling with shared decision making potentially leading to surgical intervention. During the study, we encountered a few randomization-related problems. Firstly, physicians were hesitant to refer patients for participation in the study, as prolactinoma surgery was highly controversial at that time. This led to referral of only a subgroup of eligible patients, in whom surgery was very likely to be successful, thereby inferring selection bias. Secondly, patients were generally already on medical treatment and their experience with DAs caused them to have strong preferences for one of the treatment options, thereby rendering them unwilling to randomize. Thirdly, we found there is a fine line between adequately informing patients about the study, and neurosurgical counseling as part of the intervention, and it was unethical to hold back information to enable randomization. Lastly, increasing experience with prolactinoma surgery taught the pituitary team that the eligible group of well circumscribed non-invasive prolactinoma (<25mm) was very heterogeneous, often causing one of the treatment options to be more suitable. The combination of these factors led to disappointing inclusions rates.

An alternative methodological approach is the observational cohort study. Observational studies can estimate causal effects when RCTs are not feasible or ethical. Conceptualizing observational studies to emulate RCTs may limit bias and improve transparency

concerning study design and analytical decisions [18]. The observational PRolaCT arm (PRolaCT-O) that was opened in 2019 included patients with a preference for one of the treatment modalities, enabling evaluation of treatments in a larger population under real-world conditions and without the complex ethical considerations that come with randomization. The large cohort enables stratification for variations in baseline patient- and tumor characteristics. Although bias cannot be eliminated completely, we are convinced that the observational trial will provide reliable high-quality data [19].

Future perspectives

In spite of increasing scientific interest in prolactinomas, there is a long road ahead concerning improvement of prolactinoma care. Being a rare disease, establishment of national and international collaborations to share experience and data is essential. Collaborations such as the Dutch Prolactinoma Study Group, and European Reference Network for Endocrine Disorders (Endo-ERN) support national and global scientific research to improve knowledge, diagnosis, and treatment of prolactinomas and other pituitary diseases. Initiatives such as development of a prolactinoma-specific module for Endo-ERN's Core Registry are essential to make fast progression in this field. Efforts should be made to establish consensus on relevant outcome parameters and their definitions, as this is a prerequisite for high-quality international data collection.

Funding prolactinoma research is complicated. This disease is not prioritized in the selection process for either dedicated endocrine or neurosurgical grants because sits in between the neurosurgical and endocrinological field. Additionally, it is not a commercially attractive field for the pharmaceutical industry as prolactinoma medication is no longer patented. Although prolactinomas are rare, research in the field can yield relevant information for more prevalent diseases such as psychiatric disorders and Parkinson's disease, in which dopaminergic medication is used as well. Moreover, research aiming to improve HR-QoL contributes to cost-effective healthcare, as HR-QoL has been shown to predict healthcare usage in patients with prolactinoma [20]. Therefore, funding by non-commercial organizations such as semi-government foundations is important.

With the rapid developments in the field of AI, new opportunities arise to improve the efficiency and quality of care. Recent systematic reviews indicated AI has potential to improve pituitary surgery by assisting preoperative planning, surgical strategies, and risk assessments [21, 22]. Future research should aim to further improve learning models [21]. Potential AI-related research topics include AI-assisted transcription of patient notes, predictive modeling of chances of true cavernous sinus invasion on MRI, probabilities of achieving total resection and complication risks.

As shown, prolactinomas come with heterogeneous clinical manifestations (**Chapter 2, 3, 4, 7, 8**). Consequently, prolactinoma care involves evaluating symptoms that may be atypical and non-specific to determine their relationship with the prolactinoma and

the likelihood of these symptoms receding with treatment, informing patients about risks and possibilities concerning treatment, shared decision making, and honesty about areas of uncertainty. It is inevitable that the knowledge and experience is most elaborate within a dedicated care pathway in a PTCOE. However, treating all patients with prolactinoma in PTCOEs is not feasible due to limited capacity and financial considerations. Moreover, medically treated patients with good HR-QoL may not require highly specialized care. Identifying patients who benefit most from referral to a PTCOE is, therefore, essential.

Furthermore, fertility is a relevant topic as prolactinomas are frequently diagnosed in (female) patients of reproductive age. DAs have been shown to restore fertility in 80-90% of patients [23, 24] and surgery was also reported to restore fertility in most patients [6, 25-28], however large prospective cohort studies on fertility are lacking. Additionally, it would be interesting to assess post-surgical fertility in patients who remained subfertile under DA treatment.

Other relevant areas of research include histopathological and cell culture studies to gain insight in DA-induced structural changes that could be detrimental to surgical success and can offer prognostic information on tumoral response to DA treatment, respectively. Histopathological analyses may also provide insight in co-secretion, which may explain differences in symptomology and disease burden among patients. Pharmacogenetic studies may aid in prediction of DA effectivity and side effects, and as mentioned above, longitudinal analyses of cognitive impairments and effectivity of cognitive rehabilitation require further research.

Lastly, the long-awaited prospective comparison of treatment modalities in the PRolaCT study [2] will shed light on long-term biochemical, clinician- and patient-reported outcomes of medication and surgery and will provide insight into cost-efficacy of treatments, thereby promoting Value Based Healthcare. The ProlaC study will provide information about healthcare usage, and determinants of HR-QoL and psychological complaints in the diverse population of patients with prolactinoma, identifying areas of care that require improvement.

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