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

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CHAPTER 9

Summary and Conclusions

This thesis contains studies that contribute to patient-centered care for prolactinomas. It discusses novel techniques for diagnosis of complex prolactinoma (remnants), gives suggestions for reporting outcomes and describes clinical, radiological, and patient-reported outcomes of surgically and medically treated prolactinomas.

Chapter 1 provides a general introduction to prolactinomas, their diagnosis and treatment.

Chapter 2 illustrates that many prolactinoma outcome parameters were used in literature, part of which were subjective or undefined. Reported definitions of clinical outcomes such as *remission*, *disease control* and *disease recurrence* varied greatly. This chapter offers clear, clinically relevant definitions to use in research and patient care, based on literature and clinical considerations. Moreover, a suggestion was given for an outcome set to evaluate prolactinoma treatment, based on the three-tier Value Based Healthcare (VBHC) principles. Using these definitions and outcome sets improves comparability of outcomes across treatment modalities and pituitary care centers, offering possibilities to improve prolactinoma care.

Chapter 3 cross-sectionally describes a cohort of 450 female patients with prolactinoma derived from the PRolaCT and ProlaC study (2017-2025). It sheds light on epidemiology, disease burden, (psychological) symptoms and HR-QoL. Most patients were diagnosed with microadenomas and were treated with dopamine agonists, whereas only 5% of patients had undergone prolactinoma surgery. Patients with active and controlled disease were most burdened by fatigue, and psychological and cognitive complaints. Patients with active disease reported a higher disease burden and worse psychological HR-QoL with more symptoms of anxiety and depression compared to patients with controlled disease. The disease burden was highest in young patients with active disease. This Chapter underlines the need for improvement of treatment and rehabilitation strategies.

Chapter 4 describes the care trajectories of forty consecutive patients undergoing prolactinoma surgery at the Leiden University Medical Center (LUMC) between 2017 and 2019 – a time in which prolactinoma surgery was unusual. Most patients underwent surgery due to intolerance to medication - a smaller proportion of patients underwent surgery due to resistance to medication, and the patient's or physician's preference for surgery was a rare indication. Most patients received long-term medical pretreatment, and the median disease duration was approximately 4 years. Care trajectories were individualized based on patient- and tumor characteristics. Prior to surgery all patients were discussed in multidisciplinary team meetings in a VBHC care pathway in which the need for surgical treatment, and risks and probabilities of surgical success were thoroughly evaluated. The importance of high-quality imaging and multidisciplinary consultations was stressed.

Chapter 5 reports prospectively on a cohort of one hundred consecutive patients undergoing prolactinoma surgery at the LUMC between 2021 and 2023 – a time in which prolactinoma surgery was becoming more common. Outcomes were described for the entire cohort, and separately for patients undergoing a first surgery with a preoperatively estimated high probability of total resection, and for patients undergoing a reoperation aiming for total resection. High remission rates were achieved in the cohort and subgroups, with long-term complication rates $\leq 4\%$. The most common long-term complication was a mild partial arginine-vasopressin deficiency. HR-QoL improved significantly after surgery (assessed by the Leiden Bothers and Needs – Pituitary). This chapter indicates (repeat) surgery is safe and effective when performed by an experienced pituitary team.

Chapter 6 reports on the use of [^{18}F]fluoroethyl-L-tyrosine PET co-registered with magnetic resonance imaging [^{18}F]FET-PET/MRI^{CR} to identify complex prolactinoma remnants. [^{18}F]FET-PET/MRI^{CR} was used in a cohort of 17 patients to either gain more insight in the exact location or extension of a prolactinoma remnant, or to diagnose prolactinomas in the absence of a (clear) remnant on conventional MRI. We concluded that [^{18}F]FET-PET/MRI^{CR} can be of added value for decision making and treatment planning in complex cases in which conventional MRI does not provide sufficient information. This technique does, however, require an experienced dedicated pituitary team to interpret the results. Moreover, strict indication setting is important because functional imaging is time-consuming and costly.

Chapter 7 describes a cross-sectional study comparing cognitive functioning and psychological complaints in 60 normoprolactinemic patients with prolactinoma to healthy matched controls. Patients with prolactinoma without diagnosed psychopathology were found to have subtle cognitive impairments in verbal memory, selective attention and processing speed compared to controls. Moreover, patients self-reported more fatigue, symptoms of apathy, irritability, anxiety, and depression than controls. Cognitive impairments and psychopathological symptoms were similar in medically and surgically treated patients. These findings emphasize the importance of monitoring cognitive and psychological complaints using validated patient-reported outcome measures, not only in active disease, yet also after biochemical normalization.

Chapter 8 provides a systematic review of patient-reported outcomes in patients with hormone-producing pituitary adenoma not responding to first-line therapy (i.e., refractory patients). The quality of reporting was low, and risks of bias were high in all studies. A wide range of patient-reported outcome measures were used, of which only a quarter was disease-specific. HR-QoL outcomes were inconsistent throughout literature, with refractory patients not always reporting worse HR-QoL than patients in remission. Prolactinomas were the least frequently reported disease entity, despite being the most common type of pituitary adenoma.

Novel insights and future perspectives

This thesis describes novel insights regarding diagnosis and treatment of prolactinomas, with an emphasis on patient-reported outcomes. Firstly, the need for uniformization of outcome reporting was stressed. Future studies should use well-defined standardized outcome sets to improve comparability of results irrespective of study design. Secondly, this thesis emphasizes the importance of shared decision-making and personalized treatment goals. Moreover, multidisciplinary care is of utmost importance for complex cases, including advanced diagnostics such as functional imaging in selected patients. Thirdly, our large multicenter cohort of medically treated female patients revealed heterogeneous prolactinoma-related symptoms, with fatigue, and psychological and cognitive complaints being most burdensome. In our cohort, the disease burden was highest in younger patients with active disease. Male patients require separate evaluation, due to sex-specific differences in disease manifestations. Fourthly, we demonstrated that prolactinoma surgery is safe and effective in a large prospective cohort, resulting in improved health-related quality of life – when performed by an experienced pituitary team. Future studies should focus on the optimal timing of surgery. Lastly, patients had subtle cognitive impairments and psychological complaints compared to matched healthy controlled, despite of medical disease control or surgical remission. Therefore, rehabilitation programs require investigation.

Concluding, this thesis demonstrated that medical and surgical treatment are safe and effective, yet HR-QoL, psychological and cognitive complaints are not always restored. Therefore, treatment and rehabilitation strategies require further research, in which patient-reported outcomes are essential. Studies such as the PRolaCT and ProlaC study will contribute to evaluation of individualized treatment strategies.

